

MODELING THE DYNAMICS OF DISEASE STATES AND MEMORY FUNCTION IN DEPRESSION

by

Selver Demic

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Chair:

1st Internal Examiner: Prof. Dr. Sen Cheng

2nd Internal Examiner: Prof. Dr. Rolf Heumann

External Examiner:

Non-Specialist:

Date of Final Examination:

PhD Grade Assigned:

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III. List of Abbreviations

MDD	Major depressive disorder
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorder, 4th edition, text revision
DE	Depressive episode
OR	Occurrence rate
RR	Recurrence rate
MTL	Medial temporal lobe
AN	Adult neurogenesis
CRH	Corticotropin-releasing hormone
HPA	Hypothalamic-pituitary-adrenal axis
Ads	Antidepressants drugs
SSRIs	Selective serotonin re-uptake inhibitors
CBT	Cognitive behavioral therapy
DG	Dentate gyrus
CA1	Cornu Amonis 1
CA3	Cornu Amonis 3
EC	Entorhinal cortex
TA	Temporoammonic pathway
SC	Schaeffer collaterals
MF	Mossy fibers
EM	Episodic memory
NDE	Number of depressive episode
AA	Memories stored and retrieved in asymptomatic state
AD	Memories stored in asymptomatic and retrieved in depressive state
DD	Memories stored and retrieved in depressive state
ps	Pattern separation

III. Abstract

Major depressive disorder (MDD) is a common and costly disorder associated with considerable morbidity, disability, and risk for suicide. The disorder is clinically and etiologically heterogeneous. Despite intense research efforts, the response rates of antidepressant treatments are relatively low and the etiology and progression of MDD remain poorly understood. Here I use computational modeling to advance our understanding of MDD.

First, I propose a systematic and comprehensive definition of disease states, which is based on a type of mathematical model called a finite-state machine. Second, I propose a dynamical systems model for the progression, or dynamics, of MDD. The model is abstract and combines several major factors (mechanisms) that influence the dynamics of MDD. I study under what conditions the model can account for the occurrence and recurrence of depressive episodes (DEs) and how I can model the effects of antidepressant treatments and cognitive behavioral therapy within the same dynamical systems model through changing a small subset of parameters. My results suggest several predictions about MDD. Patients who suffer from MDD can be divided into two sub-populations: a high-risk sub-population that has a high-risk of developing chronic depression and a low-risk sub-population, in which patients develop depression stochastically with low probability. The success of antidepressant treatment is stochastic, leading to widely different times-to-remission in otherwise identical patients.

Depression is not only a heterogeneous disorder, it may be fatal due to high rate of suicides associated with depression. Also, depression increases mortality for several physical diseases, which has negative impact on life expectancy in MDD patients. Therefore, I develop a Markov model and study the dynamics of depression and influence of depression on the average life span. Like the dynamical systems model, the Markov model reproduces occurrence and recurrence rates reliably, but only if two sub-populations were included, demonstrating that this prediction is valid regardless of the particular model used. The Markov model suggests that patients with MDD have a shortened life span by about 5 years. The fraction of the people with shortened life span is higher in the

population that had at least one DE than in the population that did not have any.

Interestingly, low- and high-risk subpopulations showed qualitatively different correlation between life span and the number of depressive episodes.

Finally, I develop a computational model of episodic memory storage and retrieval and study the potential memory impairments in MDD. Although memory dysfunction in MDD has been in the focus of interest of neuroscientists in the last decades, the causes remain unclear. There are several suggestions for the potential causes of certain types of deficits, but each type of deficit is generally treated as separated from the others. Here, I aim to account for the episodic memory deficit as well as over-general memories observed in MDD patients in a single unified model. I propose that episodic memory in MDD might occur due to deficit in adult neurogenesis (AN) and/ or change in theta power. Results of the model suggest that there is an optimal level of AN for episodic memory retrieval. I suggest that episodic memory dysfunction might also account for over-general memories observed in depressive patients, causing a shift in the retrieval episodic memories to the retrieval of semantic memory.

While the specific details of my models might be subjected to criticism and revisions, my approach shows the potential power of computational modeling of MDD and the need for different type of quantitative data for understanding depression.

Keywords: Major depressive disorder, finite-state machine, dynamical systems model, Markov chain model, memory

1. Introduction

1.1. Overview of Major Depression

Mood disorders are among the most common and debilitating psychiatric disorder (Hollon et al., 2002). The most common mood disorder is major depressive disorder (MDD), which is estimate to affects around 20% of the population at some point during the life time of an individual (American Psychiatric Association, 2000; Blazer et al., 1994; Hasin et al., 2005; Kessler et al., 2005). MDD is a serious and costly disorder that is usually associated with severe and persistent symptoms leading to important social role impairment, poor health, increased medical co-morbidity and mortality (Angst et al., 2002; Hasler, 2010; Insel & Charney, 2003; Murray & Lopez, 1997). MDD can strike anyone regardless of age, ethnic background, socioeconomic status or gender (Nolen-Hoeksema, 2001; Weissman, 1996). The prevalence of this disorder is important considering the individual as well as societal costs. Accordingly, the social and economic consequences of these conditions are huge; according to the World Health Organization, MDD is currently the leading cause of disease burden in North America and the 4th leading cause worldwide (Greenberg et al., 2003; Hasselmo et al., 1995; Kessler et al., 2003; Murray & Lopez, 1996).

The onset of MDD is usually between the ages of 20 and 30 years and peaks between 30 and 40 years (Kessler et al., 1994a; Kessler & Bromet, 2013). Whereas there is no laboratory test for MDD, the diagnosis of MDD is based on the patient's self-reported experiences, behavior reported by relatives or friends, and a mental status examination. According to the Diagnostic and Statistical Manual of Mental Disorder, 4th edition, text revision (DSM-IV-TR), the standard for the diagnosis of mental disorders, a depressive episode (DE) is characterized as a period lasting at least 14 days, during which the patient is consistently within the symptomatic range of a sufficient number of symptoms (Table 1) (American Psychiatric Association, 2000; Frank et al., 1991). In addition to these symptoms, depressive person may report multiple somatic complaints or in severe cases may have symptoms of psychosis (delusions or hallucinations)(Nestler et al., 2002).

Table 1. DSM-IV-TR Criteria for Major Depressive Disorder (American Psychiatric Association, 2000)

Five or more of the following symptoms should be present daily for most of the day for at least 2 weeks
At least one symptom is either depressed mood or anhedonia
Changes in appetite or weight
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of guilty or worthlessness
Difficulty with thinking, concentrating, or making decisions
Suicidal ideation or suicidal attempts

1.2. Influence of MDD on the life span

Depression is not only widespread and common, it may be fatal. About 90% of suicides are associated with mental illness, most commonly with MDD (Insel & Charney, 2003). Among depressive patients, about 15% die after committing suicide (Gonda et al., 2007; Vahia et al., 2000). Hence, suicide is up to 20 times more likely in depressive patients than in the general population (Semple & Smyth, 2013). MDD also increases mortality for many physical diseases such as heart failure, HIV/AIDS, renal disease, cancer and diabetes, and following myocardial infarction and stroke (Cook et al., 2004; Herrmann et al., 1998; Jiang et al., 2001; Lin et al., 2009). The overall death rate for patients with MDD is higher than in the general population, with the premature death usually due to suicide, drug and alcohol problems, accidents, cardiovascular disease, thyroid disorders (Semple & Smyth, 2013). Consequently, patients with MDD die five years earlier than people without MDD (Marcus et al., 2012; Zivin et al., 2012).

1.3. Memory deficits in MDD

MDD is characterized by a constellation of behavioral, emotional, and cognitive symptoms especially in the domain of memory (Gotlib & Joormann, 2010). Indeed, patients with MDD often report attention and memory deficits (Goeldner et al., 2013). Memory function is critical to daily life, and enables information to be stored and retrieved over variable periods, ranging from seconds to days to years, as well as, planing the future. It is now well recognized that there are multiple forms of memory. These are largely divided into kinds of memory that are typically expressed explicitly, often called declarative memory, and other kinds of memory called non-declarative memory that are expressed implicitly through changes in behavioral or physiological responses (Dickerson & Eichenbaum, 2010).

1.3.1. Episodic memory deficits in MDD

Since there is no evidence that non-declarative memory is impaired in depressed subjects (Austin, 2001; Bazin et al., 1994; Denny & Hunt, 1992; Hertel & Milan, 1994), I focus on declarative memory function in MDD patients, which differs from that in healthy controls in a number of interesting ways. There are several suggestions for the potential causes of certain types of memory deficits in MDD patients, but each type is generally treated as separated from the others. In the following sections I will review the results of these memory deficits in MDD.

Many studies reported mild to moderate declarative memory impairment in patients with MDD (Airaksinen et al., 2007; Airaksinen et al., 2006; Bierman et al., 2005). There are two forms of long-term declarative memory that both involve retrieving earlier stored information: semantic memory and episodic memory. Numerous studies have reported an impairment of episodic memory, memory of personally experienced events together with information about the time and place of the events (Dickerson & Eichenbaum, 2010; van Eijndhoven et al., 2013), during depressive episode (Burt et al., 1995; Clark et al., 2009; van Eijndhoven et al., 2013; Zakzanis et al., 1998). The ability to describe the details of a recent travel or family gathering that took place in the previous days or months, for example, depends heavily on intact episodic memory function. It has been reported that

episodic memory performance is correlated with scores on a depression rating scale, resulting in an almost linear relationship (Bierman et al., 2005; Dere et al., 2010).

Another type of the declarative memory is semantic memory, which is general knowledge about the world that we have accumulated throughout our lives (Dickerson & Eichenbaum, 2010). Unlike episodic memory, semantic memory is not impaired in the patients with MDD (Brunet et al., 2011; Söderlund et al., 2014).

1.3.2. Over-general memories in MDD

Another type of memory impairment observed in the patients with major depressive disorder is over-general memory (Conway & Williams, 2008; Mackinger et al., 2000; Söderlund et al., 2014; Spinhoven et al., 2006; Williams et al., 2007). When subjects are asked to recall a specific event that is related to a given cue word, MDD patients respond mostly with a general memory that summarizes a category of similar events instead (Söderlund et al., 2014; Williams et al., 2007). For instance, when cued with “enjoy” patients tend to give more general answer, e.g., “I always enjoy a good party”. “I enjoy Jane's party last Friday” would be more appropriate.

(Williams et al., 2007) suggested that the over-general memory effect could be accounted for in the theory of autobiographical memory of Conway and Pleydell-Pearce. In this model, autobiographical memories are arranged in a hierarchical structure with three levels of representation: the highest level (lifetime periods), intermediate level (general event descriptions), the lowest level (event-specific knowledge or episodic memory) (Conway & Pleydell-Pearce, 2000). Retrieval of autobiographical memories, the model stipulates, is initiated at the highest level and then descends via the intermediate level to the lowest level to retrieve a specific event. Williams et al. (2007) suggest that autobiographical memory in the patients with MDD may be over-general, because patients stop the retrieval process at the intermediate level to avoid retrieving specific events that are unpleasant or traumatic (Williams et al., 2007). In addition to this functional avoidance, two other mechanisms (capture and rumination, and impaired executive capacity and control) contribute to over-general memory either independently or through their combined effect (Williams et al., 2007).

The numerous findings of a relationship between the MDD and the over-general memory have led some authors to conclude that over-general memory is a stable marker of clinical depression, independent of mood state (Van Vreeswijk & De Wilde, 2004). Furthermore, the over-general memory persists in formerly depressed individuals even when mood is undisturbed (Mackinger et al., 2000; Spinhoven et al., 2006).

1.4. Other cognitive deficits in MDD

In addition to the episodic memory impairment and the over-general memory, MDD is characterized by impairments in other cognitive domains such as executive functions, attention, working memory and psycho-motor speed (Austin, 2001; Basso & Bornstein, 1999; Castaneda et al., 2008; McDermott & Ebmeier, 2009; Reppermund et al., 2007). There is also evidence of mood-congruent sensitivity and bias towards negative or affective stimuli among individuals with MDD (Beck, 1976; Bower, 1981a; Ellis et al., 1997). Despite numerous studies describing cognitive impairments in MDD, there is no agreement upon a conclusive neuropsychological profile characterizing MDD. There is no single cognitive function that is impaired in all the patients with MDD, and not all the patients are impaired in the same degree (Hammar & Ardal, 2009).

However, there are several hypothesis that offer an explanation of the cognitive impairment in MDD. A global-diffuse hypothesis postulates that MDD patients are characterized by a generally lowered cognitive profile, suggesting a global-diffuse impairment on a range of cognitive domains (Landrø et al., 2001; Veiel, 1997). On the other hand, hypothesis of specific cognitive impairment, postulate that MDD is associated with pronounced impairment within specific cognitive domains, primarily in memory and executive function (Austin, 2001; Elliott, 1998). Another hypothesis, known as the cognitive effort hypothesis, claims that regardless of domain MDD patients show impairments on tasks that require attention and cognitive capacity, whereas functioning on automatic tasks is normal (Hammar et al., 2003; Rohling & Scogin, 1993).

The research over the past decade have yielded diverse findings. In any case, cognitive deficits in MDD lead to a decreased quality of life (McCall & Dunn, 2003), but do not seem to afflict all individuals with MDD.

1.5. Etiology of MDD

The understanding of the nature and causes of MDD has evolved over the centuries, though this understanding is incomplete and has left many aspects of MDD as a subject of discussion and research. The heterogeneity of MDD implies that multiple neural substrates and mechanisms contribute to its etiology (Nestler et al., 2002). Proposed causes include psychological, psychosocial, hereditary, evolutionary and biological factors. Furthermore, MDD has a highly variable course, responds inconsistently to treatment, and has no established mechanism. In the following sections, I will review the major theories of the mechanisms of MDD.

1.5.1. Genetics

Family, twin, and adoption studies provide evidence that genetic factors might account for some risk of developing MDD (Flint & Kendler, 2014; Kendler et al., 2006; Sullivan et al., 2000). According to the diathesis-stress theories of MDD, genetic liability (diathesis) interacts with negative life experiences (stress) to cause depressive symptoms and disorders (Hornung & Heim, 2014; Monroe & Simons, 1991). Indeed, there is some evidence that specific genes and gene-by-environment interactions are involved in the pathogenesis of MDD, even though they cannot account for all occurrences of MDD (Hasler, 2010). Some aspects of personality such as anxiousness, pessimism, and avoidance of harm, are also partially heritable (Bouchard, 1994). In addition to heritable depression-prone personality traits, it has been reported that MDD is due in part to heritable factors that are independent of personality (Kendler et al., 2006).

Family studies of a recurrent MDD have shown that first-degree relatives of MDD subjects are at increased risk of MDD compared with first-degree relatives of control subjects (Lohoff, 2010; Weissman et al., 1993). There was a two- to fourfold increased risk of MDD among the first-degree relatives of MDD subjects (Lohoff, 2010). MDD forms with early-onset (i.e., before age 30), high severity, a high recurrence, and psychosis may have higher heritability than other forms of MDD (Belmaker & Agam, 2008; Kendler et al., 1999). Family studies with multiple cases of MDD have identified chromosomal regions with linkage to the disorder, however, no single chromosomal region has been replicated in every family study of genetic linkage in MDD (Belmaker & Agam, 2008; Kessler et al.,

2003; Nolen-Hoeksema, 2001). Hence, it is clear from the family studies that MDD is not caused by single gene, but is a disorder with complex genetic characteristics.

1.5.2. Stress

Epidemiological studies have demonstrated that stress is a risk factor for the development and persistence of depression and anxiety (Laucht et al., 2009). It has been reported that daily-life stress sensitivity represents a behavioral expression of genetic risk of MDD (Wichers et al., 2007, 2009). Furthermore, the higher the stress sensitivity is, the greater association with later depressive symptoms is (Wichers et al., 2009). Environmental factors also moderate the effect of stress sensitivity. Accordingly, negative life events moderate the effect of stress sensitivity on follow-up depressive symptoms (Kendler & Gardner, 1998). Thus, the higher the level of stress sensitivity is, the higher the influence of negative life events on future MDD will be. However, it is still unclear why certain individuals exposed to specific environmental pathogens develop MDD while others do not.

Other evidence for the role of stress in the MDD comes from studies of the stress hormone cortisol and its central releasing factor also known as corticotropin-releasing hormone (CRH) (MacMaster & Kusumakar, 2004; Merali et al., 2004). Altered stress hormone secretion appeared to be most prominent in MDD patients with a history of childhood trauma (Pitchot et al., 2005). Patients with MDD have elevated cortisol levels in plasma (Burke et al., 2005), elevated CRH level in cerebrospinal fluid (Merali et al., 2004), and increased levels of CRH messenger RNA and proteins in limbic brain regions (Merali et al., 2004). Elevated levels of glucocorticoids can reduce neurogenesis, and this has been suggested to be the cause for the decreased size of the hippocampus in magnetic resonance images of the brain in many patients with MDD (MacQueen et al., 2003). CRH-receptor antagonist show antidepressant activity in animal models (Louis et al., 2006), but the results of large clinical trials have been disappointing. A compound that blocks glucocorticosteroid receptor has been reported to be efficacious in MDD, but only in the most severe and psychotic types (Flores et al., 2006).

Although MDD is considered a stress disorder, most subject treated for MDD have no evidence of dysfunction of a hypothalamic-pituitary-adrenal axis (HPA). However, some

subjects with MDD do show abnormalities of that axis and of the extra-hypothalamic CRH system (Svenningsson et al., 2006).

1.5.3. Amygdala hyperactivity

Multiple findings have tied amygdala hyperactivity to MDD (Siegle et al., 2007; Surguladze et al., 2005). Hyperactivity of the amygdala is associated with increased sensitivity to negative stimuli (Munafò et al., 2008) and leads to a negative bias in the processing or interpretation of emotional stimuli (Dannowski et al., 2007; Monk et al., 2008). Hence, greater amygdala response to emotionally arousing stimuli in the MDD is associated with enhanced memory for those stimuli (Hamilton & Gotlib, 2008).

Since the amygdala is involved in the evaluation and storage of emotionally charged events (Ledoux, 1998), its hyperactivity to negative stimuli in predisposed individuals would appear to represent a neurophysiological correlate of cognitive bias. However, some studies fail to find an explicit mood-congruent memory bias in MDD (Bazin et al., 1996; Calev, 1996a; Ellwart et al., 2003). Amygdala hyperactivity has been interpreted as a valence specific effect, which causes a negative memory bias (Hamilton & Gotlib, 2008; Ramel et al., 2007), but the hyperactivity is also a common finding during baseline conditions in MDD (Drevets et al., 2002). However, only about one-half of the patients with MDD have increased amygdala activity (Siegle et al., 2007).

1.5.4. The mono-amine-deficiency hypothesis

One major theory about the biological etiology of MDD suggests that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, nor-epinephrine or dopamine in the central nervous system (Belmaker & Agam, 2008; Lopez-Munoz & Alamo, 2009; Morilak & Frazer, 2004). The serotonergic and noradrenergic systems originate deep in the brain and spread out over almost the entire brain, suggesting a system suitable of modulating many areas including areas of feeling, focusing, thinking, and behaving. A strong argument of the monoamine theory is its predictive power. Almost every compound that has been produced for inhibiting re-uptake of serotonin or norepinephrine is clinically effective in the treatment of MDD (Belmaker & Agam, 2008).

Although most antidepressants drugs (ADs) produce a rapid increase in extracellular level of the monoamines, the onset of an appreciable clinical effect usually takes at least 3-4 weeks (Machado-Vieira et al., 2008; Quitkin et al., 1993; Santarelli et al., 2003; Segman et al., 1995; Stassen et al., 1993; Thompson, 2002). This delayed onset of action, or response, which is usually defined as a 50% reduction in depression rating scale score compared to baseline (Macedo-Soares et al., 2005), suggests that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Furthermore, experimentally depleting serotonin and nor-epinephrine in humans does not induce MDD in healthy subjects, but will cause relapse in the patients who have been successfully treated with a selective serotonin re-uptake inhibitor (SSRI) (Ruhé et al., 2007).

Although ADs are currently used as the initial or "first-line" therapies for MDD, their success rate is relatively low. The most frequently used medication for MDD, SSRIs, have success rates of 50% to 60% in daily practice (Anderson & Tomenson, 1994; Fava, 2000; Nelson, 1998; Ruhé et al., 2006; Walsh et al., 2002). In some studies, ADs even fail to show superiority over placebo (Ellis et al., 1997; Kirsch, 1998; Thase, 1999). More precisely, the response to inert placebos is approximately 75% of the response to active AD medication (Kirsch, 1998; Perry & Cassagnol, 2009). The high rate of inadequate treatment of the disorder remains a serious concern. Research comparing AD medication to cognitive behavioral therapy (CBT) has found that both are equally effective for non-psychotic forms of depression (Nemeroff et al., 2003). These findings suggest that serotonin and nor-epinephrine have critical roles in the mechanisms of these AD treatments of MDD, but that additional neurochemical mechanisms are necessary to cause MDD.

1.5.5. Alteration in the hippocampal morphology and adult neurogenesis

The hippocampal region has recently received significant attention in mood disorders research. Although almost certainly not solely responsible for the spectrum of symptoms observed in MDD, the highly plastic, stress-sensitive hippocampal region may play a central role in understanding the etiology and maintenance of MDD (Campbell &

Macqueen, 2004). Hence, one of the hypothesis suggest that depression may be related, in part, to reduction in hippocampal plasticity and neurogenesis. In a favor of the hypothesis are results of magnetic resonance imaging studies of the hippocampal volume, which showed that MDD patients had significantly decreased left and right hippocampal volumes compared to controls (Campbell & Macqueen, 2004; Pantel et al., 1997; Zubenko et al., 1990). Volume reductions of the hippocampus might be the result of re-modeling of key cellular elements, involving retraction of dendrites, decreased neurogenesis in the dentate gyrus and loss of glial cells (Campbell & Macqueen, 2004).

Depression and stress are related to a reduction in brain derived neurotrophic factor, which may lead to hippocampal atrophy and inhibited neurogenesis (Jacobs et al., 2000). One of the primary catalysts for focusing on adult hippocampal neurogenesis in MDD is an observation that most antidepressants and environmental interventions that confer antidepressant-like behavioral effects stimulate adult hippocampal neurogenesis. Certain characteristic of neurons generated in adulthood, are in favor of this theory. Newly generated neurons receive excitatory inputs and show a lower threshold for LTP induction as early as 18 days after birth, but show enhanced long term potentiation at 4–6 weeks after birth (Espósito et al., 2005; Ngwenya et al., 2006; Schmidt-Hieber et al., 2004). The time course of maturation of newly generated neurons in the dentate gyrus is generally consistent with the delayed onset of therapeutic action of the antidepressants (Espósito et al., 2005; Ngwenya et al., 2006). Hence, the unique physiological properties of adult-born dentate granule neurons qualifies adult hippocampal neurogenesis as a potential mechanism or substrate underlying antidepressant action (Dranovsky & Hen, 2006; Ge et al., 2007; Kee et al., 2007; Mirescu & Gould, 2006; Ramirez-Amaya et al., 2006; Schmidt-Hieber et al., 2004).

1.5.6. Cognitive theories of depression

Cognitive impairments have been widely reported in patients with MDD (Austin, 2001; McDermott & Ebmeier, 2009), therefore, the DSM-IV-TR lists “diminished ability to think or concentrate” as an important symptom (American Psychiatric Association, 2000). The importance of the cognitive aspects in the etiology and maintenance of MDD has been first highlighted more than 40 years ago in Beck's cognitive model of depression (Beck, 1976). The model postulates that depressed patients process depression-congruent information

selectively, which seems to form part of a vulnerability factor (Beck, 1976; Disner et al., 2011).

Cognitive impairment has been identified across a number of specific cognitive domains, with deficits in attention, processing speed, memory and executive functions being the most typical symptoms (Basso & Bornstein, 1999; McDermott & Ebmeier, 2009; Reppermund et al., 2007). However, regarding individual cognitive functions, contradictory results have been reported for executive functions, and processing speed (McDermott & Ebmeier, 2009). As I described previously (see 1.3.), declarative memories in general and the over-general memory and episodic memory deficits in particular are common symptoms in MDD patients. Conversely, many experiments yielded pursuant results finding no implicit memory impairment (Austin, 2001; Bazin et al., 1994; Denny & Hunt, 1992; Hertel & Milan, 1994).

Another large body of research examined the effects of MDD on explicit and implicit memory for emotional material, finding that depression-congruent stimuli are favored in attention, learning, and memory compared to other materials (Beck, 1976; Bower, 1981b; Ellis et al., 1997). In contrast, there are studies that did not find an explicit mood-congruent memory bias in MDD (Bazin et al., 1996; Calev, 1996b; Ellwart et al., 2003). Moreover, cognitive impairments often persist after recovery from psycho-pathological symptoms, indicating that cognition and mood are separable in MDD.

1.6. Lack of consistency in definition of the disease states

MDD tends to occur episodically with a highly variable course and complex transitions between several disease states. A DE can be interrupted by a remission, which is defined as an asymptomatic period of at least 14 days (American Psychiatric Association, 2000; Frank et al., 1991). Remission and a recovery are accompanied by the same behavioral symptoms and, at the behavioral level, distinguished only by their duration. A remission that lasts for 6 months or longer is called recovery (Frank et al., 1991). This term refers to the recovery from the episode, not from MDD per se. The appearance of a new DE after recovery is called a recurrence (Frank et al., 1991). A relapse is a return of the symptoms satisfying the full syndrome criteria for the DE during the period of remission, but before recovery (American Psychiatric Association, 2000; Frank et al., 1991).

According to a population-based study among MDD patients, about 15% of first lifetime onsets have unremitting course, and 35% recover but have one or more future episodes (Eaton et al., 2008; Hardeveld et al., 2010). These cases may represent chronic and more severe forms of MDD (Eaton et al., 2008; Torpey & Klein, 2008). About 50% of first lifetime onsets recover and have no future episodes (American Psychiatric Association, 2000; Eaton et al., 2008). However, the disease states in MDD are not defined consistently by different investigators, thus making it difficult to interpret the results and precluding comparisons between different studies.

1.7. Hippocampus, adult neurogenesis and memory

Neural structures in the medial temporal lobe (MTL) have long been implicated in the acquisition of new memories (Beck, 1976; DeRubeis & Crits-Christoph, 1998; Moore & Fresco, 2012). There is now a consensus that the hippocampus, a deep lying neural structure in the MTL, is heavily involved in the storage and retrieval of episodic memory (Scoville & Milner, 1957), yet its precise role remains elusive.

The hippocampus is made up of multiple subregions — the dentate gyrus (DG), the Cornu Amonis 1 (CA1) and Cornu Amonis 3 (CA3) subfields, and the subiculum (Fig.1) (O'Keefe & Nadel, 1979; Squire & Zola-Morgan, 1991; Vargha-Khadem et al., 1997).

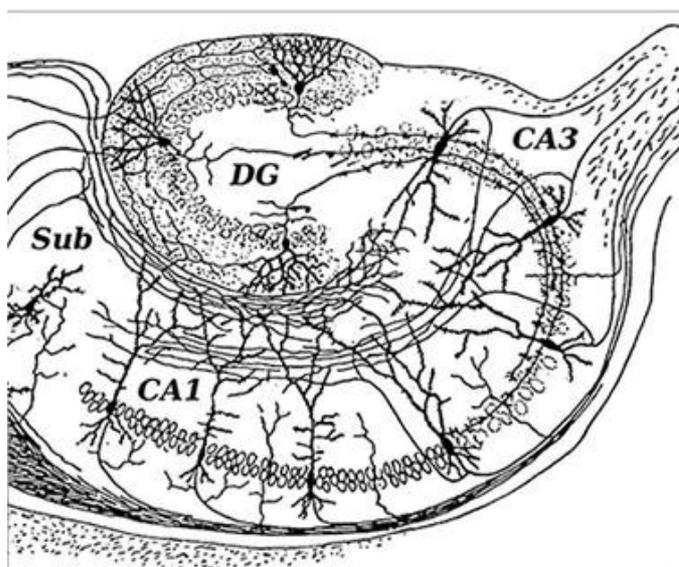


Figure 1. Drawing of the neural circuitry of the rodent hippocampus [from (Ramón y Cajal, 1911)].

The synaptic circuit connects the DG to the CA3, to the CA1 and to the subiculum (see Fig. 2). The entorhinal cortex serves as the gateway into the hippocampal formation and receives monosynaptic input from numerous brain regions. Layer II of entorhinal cortex projects to the DG through the perforant pathway, and the DG connects to the CA3 via mossy fibers (Amaral & Witter, 1989; Small et al., 2011). CA3 neurons interconnect with the other CA3 through auto-associative tracts, or with the CA1 through the Shaffer collateral's (Amaral & Witter, 1989; Small et al., 2011). Finally, the CA1 connects to the subiculum (Amaral & Witter, 1989; Small et al., 2011).

In addition to this pattern of connectivity, layer II and III of the EC cortex project to the CA3 and to the CA1/subiculum, respectively (Amaral & Witter, 1989; Small et al., 2011). CA1 and primarily the subiculum provide the main hippocampal outflow, back to the deep layers of the EC and also to a range of the other brain regions (Amaral & Witter, 1989; Small et al., 2011).

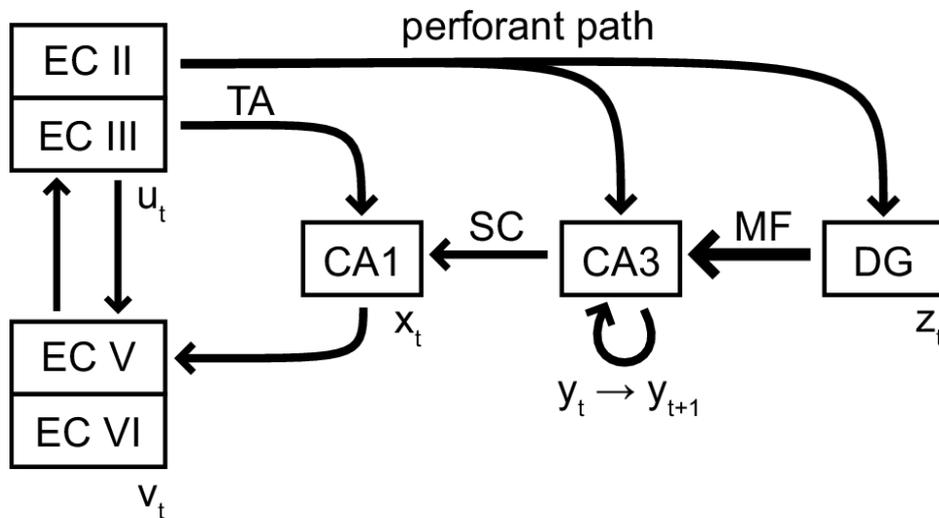


Figure 2. Schematic of the excitatory connectivity between subregions of the hippocampal formation [from (Cheng, 2013) with permission].

EC, entorhinal cortex; TA, temporoammonic pathway; SC, Schaffer collaterals; MF, mossy fibers; DG, dentate gyrus. The vectors u , v , x , y , and z represent the activity pattern at a given time in the appropriate subregion. The arrangement of the subregions emphasizes the hierarchical stacking of CA1, CA3, and DG.

The hippocampal neural network is highly dynamic, with the capacity to modify its connectivity by changing the number and strength of synaptic contacts. Models of the hippocampal function have proposed that the hippocampal sub-regions, i.e., CA1, CA3, and DG, perform specialized functions (Cheng, 2013; Duman, 2004; Madsen et al., 2000; Malberg et al., 2000; Perera et al., 2007; van Praag et al., 1999). It has been proposed that CA1 performs a match–mismatch comparison of memory retrieval with sensory input (van Strien et al., 2009) and pattern completion (Hasselmo, 2005b).

CA3 has recurrent connections and is well suited to generate neural sequences intrinsically, i.e., without external inputs (Cheng, 2013). The DG is proposed to play a role in pattern separation (Becker, 2005; Clelland et al., 2009), which ensures that novel inputs that are similar to established memories are stored as distinct memories, since similar patterns would interfere in CA3. This pattern separation process is facilitated by the sparse activity in DG, its sparse but strong projections to CA3, and synaptic plasticity.

A unique property of the hippocampus is that new neurons continue to be generated in the DG throughout life, providing this region of the hippocampus with exceptional plasticity (Marr, 1971; McNaughton & Morris, 1987; Treves, 2008). The continuous addition of new neurons into the DG has been demonstrated in rodents, primates and humans (Altman & Bayer, 1990; Eriksson et al., 1998; Shapiro & Ribak, 2005). Since newborn cells have lower thresholds for excitation and plasticity, it has been suggested that the newborn neurons might contribute further to pattern separation, thereby minimizing interference between highly similar memories (Jacobs et al., 2000).

Although pattern separation was initially introduced as network process, it is widely interpreted as predicting an impairment in behavioral tasks requiring discrimination of similar events or places, in which correct and incorrect target show a high level of interference. Consistent with this definition of pattern separation, mice with impaired neurogenesis are slower in distinguishing highly similar context but are unimpaired when contexts are very different (Cameron & Glover, 2015; Déry et al., 2013). Inversely, mice with increased adult neurogenesis discriminate highly similar contexts faster (Becker, 2005).

Interestingly, MDD and stress are related to reduction in brain-derived neurotrophic factor, which may lead to hippocampal atrophy and inhibits the birth of new neurons (neurogenesis) (Nibuya et al., 1995). In animal models of depression, disruption of adult hippocampal neurogenesis blocks the effect of chronic antidepressant drug treatment (Santarelli et al., 2003), and impairs spatial and object recognition memory (Jessberger et al., 2009). Therefore, it has been suggested that a reduced rate of adult neurogenesis (AN) might be responsible for the episodic memory deficits in MDD.

1.8. Interdependence of episodic and semantic memory

Some 40 years ago, Tulving (1972) first proposed that human long term memory can be divided into at least two subtypes: semantic memory and episodic memory. This distinction has been supported by neuropsychological investigations and advanced our understanding of each type of memory. Patients with damage of the MTL have a severe episodic memory impairment such that they are unable to acquire new episodic memories (anterograde amnesia), and difficulties to access episodic memories for several years prior to the damage (graded retrograde amnesia) (Bayley et al., 2006; Rosenbaum et al., 2008). In some cases, retrograde amnesia covers the entire life span. However, semantic memory that was acquired preceding the damage of MTL is largely spared, except for knowledge acquired in the immediate period before the damage (Manns et al., 2003). Hence, the episodic-semantic distinction suggests that the episodic memory typically relies on MTL structures whereas the semantic memory relies on the neocortex instead.

Although most existing studies focus on the dissociation between different memory systems, several theoretical studies have suggested that these two forms of memory do not necessarily operate in isolation, but rather influence each other. Indeed, in his own work, Tulving (1972) observed that the acquisition of a new episodic memory is affected by information in semantic memory. This notion was elaborated in the SPI model (for serial encoding, parallel storage, and independent retrieval). The SPI model proposes that information is encoded serially, such that information must pass from the perceptual system to semantic memory before it can be encoded into episodic memory. The parallel storage assumption of SPI holds that different aspects of incoming information are stored separately (in parallel) in different systems. The third process in SPI, retrieval, is assumed

to be independent between the systems. Hence, the model specifies different kinds of interdependencies for encoding, storage, and retrieval. However, other models have different view, for example, (Baddeley, 1988) suggested that semantic memory might represent the information that has been abstracted and dissociated from multiple learned episodes. Another model maintains that episodic memory involves a synergy between semantic memory and contextual information (Reder et al., 2009).

Despite different views on the interdependence of semantic and episodic memory, there is a common agreement that this independence exists. In addition, numerous experimental studies have provided evidence for range of interdependence between semantic and episodic memory (Greenberg & Verfaellie, 2010).

1.9. Aims of the study

Depression has been recognized as a clinical syndrome for over 2000 years (Kheirbek et al., 2012; Nakashiba et al., 2012), nonetheless satisfactory explanations of its puzzling features are still missing. There are still major gap in the understanding of its nature, etiology and classification. Currently, there are numerous hypotheses that try to explain the dynamics of MDD, however, all hypotheses have limitations so our understanding what causes MDD is still incomplete. Existing hypotheses are not exclusive, but rather complementary. The question is how to integrate the different hypotheses. Mathematical models are well-suited for this problem.

Here, I aim to systematically define the states in the course of MDD and to study the dynamics of MDD. I developed a single abstract dynamical systems model that is consistent with many existing theories about MDD. Although the model is not mechanistic, it helps us to understand and analyze the etiology and dynamics of MDD. I model the influence of three types of therapies (antidepressant treatment, cognitive behavioral therapy, and life style changes) on the occurrence and duration of depressive episode.

MDD is not only heterogeneous disorder, it may be fatal due to high rate of suicides associated with depression. Also, MDD increases mortality for several physical diseases, which has negative impact on life expectancy in MDD patients. Therefore, I develop

Markov model to study dynamics of MDD and influence of MDD on the average life span.

Finally, I develop a computational model of episodic memory storage and retrieval and study the potential impairments in MDD. Although memory dysfunction in MDD has been in the focus of interest of neuroscientists in the last decades, the causes remain unclear. There are several suggestions for the potential causes of certain types of deficits, but each type of deficit is generally treated as separated from the others. Here, I aim to account for the episodic memory deficit as well as over-general memories observed in MDD patients in a single unified model.

2. Materials and methods

2.1. Dynamical models of progression of disease states in MDD

2.1.1. Dynamical systems model of MDD

To model the dynamics of depression, I first need a way to describe the state of a person, i.e., whether a person is suffering from MDD or not. I adopted the simplest approach possible, which is to describe the state of a person by a single variable. I call this variable M , loosely for mood. $M < 0$ indicates that the person suffers from symptoms associated with MDD; the person is in the symptomatic state.

In my simple model with only one variable, I do not model which precise symptoms patients suffer from. A negative value of the state variable indicates that the person satisfies a sufficient number of symptoms (Table 1) to meet the syndromal criterion for a depressive episode according to the DSM-IV-TR (American Psychiatric Association, 2000; Frank et al., 1991). If this state persists for fourteen days or more, the person is considered to suffer from MDD (American Psychiatric Association, 2000). $M > 0$ indicates that the person does not meet the syndromal criterion for a depressive episode; the person is in the asymptomatic state.

The variable M changes across time to account for changes in the symptoms and progression of MDD. The time evolution of M in discrete time steps is modeled according to this simple equation

$$M(t + \Delta t) = M(t) + \frac{dM}{dt} \Delta t. \quad (1)$$

In each time step Δt , the mood changes by the amount $\frac{dM}{dt} \Delta t$. The crucial issue is

how to model the dynamics of the mood given by $\frac{dM}{dt}$. The dynamics fully determines the behavior of the system and should account for the major empirical observations in MDD as outlined in the introduction. I was looking for a simple model that can capture

many of the important clinical observations related to MDD. The simplest model is a linear one with a single stable point. Preliminary work showed that linear dynamics does not account for many important observations. It was too easy to switch from positive to negative mood and vice versa, which is in contradiction with the phenomenology of MDD. Therefore, I needed a model that has two stable states, one corresponding to a depressive state and the other to a non-depressive state. I therefore chose to model the dynamics with a polynomial of third degree (Fig. 3A), modeled according to this equation

$$\frac{dM}{dt} = -0.01 a (M-b)(M-c)(M-d) + I + \varepsilon, \quad (2)$$

where $a > 0$; b, c, d are parameters to be studied, I is an external input, and ε is a Gaussian noise term with zero mean and a standard deviation of one to set the scale.

In my model, the system is driven both by deterministic intrinsic dynamics (cf. Fig. 3B) and a stochastic noise process (cf. Fig. 3C, D). The intrinsic dynamics is an abstract model of the changes in the mood of a person driven by deterministic physiological processes, processes, which I do not attempt to model mechanistically here. The dynamical system in Eq. (2) has two stable fix points, separated by an unstable fix point (Fig. 3A). The parameters b, c , and d are ordered such that $b \leq c \leq d$ (Fig.3A). Depending on how the parameters affect the dynamics of MDD, I assign them to possible physiological correlates (Table 2). The parameters of the model specify the unique dynamics of a system, which represents a person.

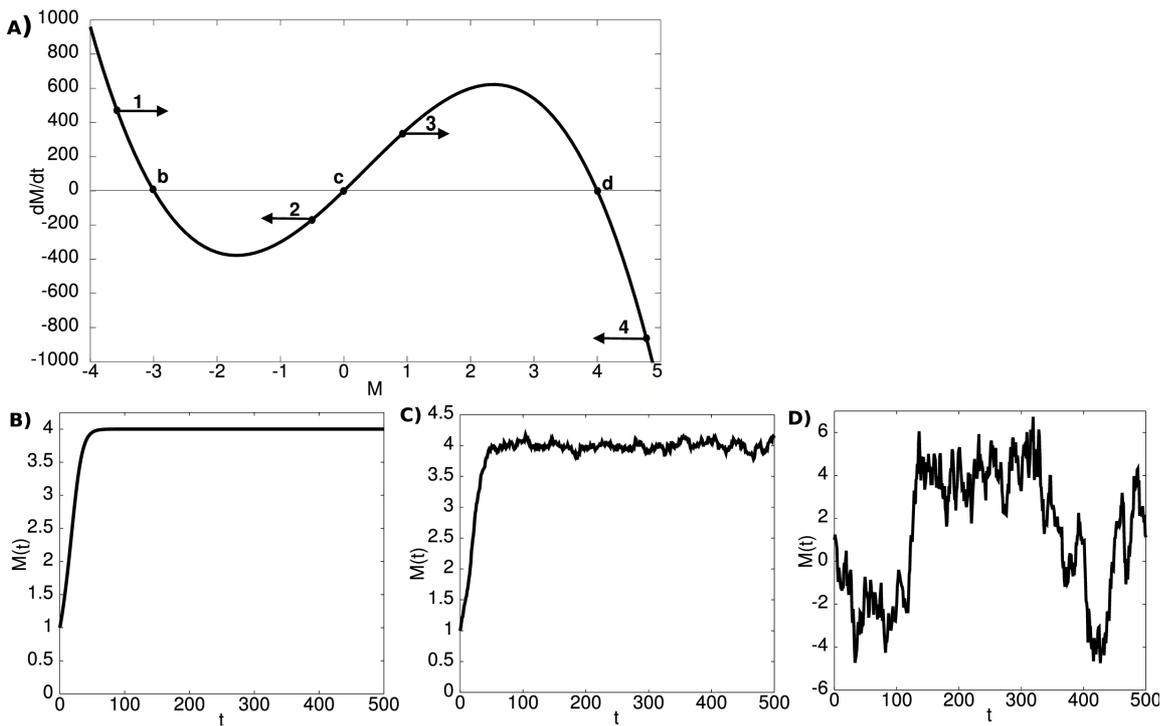


Figure 3. *Dynamical systems model for the dynamics of mood.*

A) A schematic showing the mood change as a function of the state variable M without external inputs and noise ($I=e=0$). The arrows at 1, 2, 3, 4 indicate the direction of change in those states. The points labeled with b , c , and d are fix points. At these points, the value of the change is zero ($dM/dt = 0$). Therefore, when there is no noise, the state will not change once it has reached a fix point. The fix points b and d are stable, meaning that the system will return to these states if slightly perturbed. The fix point c is unstable and has different properties, the system will move further away from point c even if the system is only slightly perturbed. In that case, the system will evolve until it reaches one of the stable fixed points. If $M > c$, the system will move towards the fix point d . The system will evolve towards the other fix point b , if $M < c$. Therefore, the fix point c separates the basins of attraction of the two stable fix points. Samples of the evolution of M over time **B)** without noise, **C)** with a moderate level of noise and **D)** with high level of noise. Note, that with high level of noise the system exhibits stochastic transition between positive and negative values.

Within a sub-population in the model, all individuals share identical parameters. By contrast, the noise process captures stochastic physiological processes as well as external environmental factors. Fluctuations in the mood can be caused, for instance, by random

hormonal changes or by changes due to the circadian rhythm. Also, external changes might cause fluctuation in the mood of a person during the day, i.e., stressful situations at work or rapid weather changes. The name “noise” does not imply that the noise process is irrelevant or unimportant. On the contrary, the noise term is crucial in my model since it introduces unpredictable changes to the mood. This stochasticity is what makes the time-course of the mood of one modeled person (cf. Fig. 3D) different from that of another person.

Table 2. Potential physiological correlates of the model parameters

Symbol	Parameter	Potential physiological correlates
a	Decay rate	Hippocampal volume and rate of adult neurogenesis
b	Negative stable fix point	Level of monoamines (i.e. serotonin)
c	Instable fix point	Pessimistic attitude $c > 0$, optimistic attitude $c < 0$
d	Positive stable fix point	Amygdala activity (higher activity is represented by a smaller d)
I	External input	Environmental influence
ε	Noise	Unpredictable internal or external changes that cause fluctuation in the mood

2.1.2. Markov chain model

I also used a discrete time Markov chain model to describe the dynamics of depression. In a Markov chain, the next state of the system depends only on the present state, not on preceding states. According to the Markov chain definition, there is a set of states,

$$S = \{s_1, s_2, \dots, s_r\}$$

in the Markov chain (Grinstead & Snell, 1997; Kemeny et al., 2012).

The process is initiated in one of the states and moves from one state to another, where each move is called a step. If the chain is currently in state s_i , then it moves to state

s_j , at the next step with a probability denoted by p_{ij} , which is known as the transition probability (Grinstead & Snell, 1997; Kemeny et al., 2012). Also, the process can remain in the same state and this occurs with probability p_{ii} . An initial probability distribution specifies the starting state. Usually this is done by specifying a particular state as the starting state (Grinstead & Snell, 1997; Kemeny & Snell, 1961). Transition probabilities

are represented in a quadratic transition matrix (Eq. (3))

$$P = \begin{pmatrix} p_{11} & p_{12} & \dots & p_{1j} \\ p_{21} & p_{22} & \dots & p_{2j} \\ \vdots & \vdots & \ddots & \vdots \\ p_{i1} & p_{i2} & \dots & p_{ij} \end{pmatrix} \quad (3)$$

with each row summing to 1, so that $\sum_j P_{ij} = 1$.

A state s_i of a Markov chain is called absorbing, if it is impossible to leave it (i.e., $s_{ii} = 1$ and $s_{ij} = 0 \forall i \neq j$). A Markov chain is absorbing if it has at least one absorbing state, and if from every state it is possible to go to an absorbing state (not necessarily in one step) (Kemeny et al., 2012; Kemeny & Snell, 1961).

The Markov chain that I used to model the dynamics of depression is a three-state-model

$S = \{A, S, M\}$ (Fig. 4). “A” refers to the asymptomatic state “S” to the symptomatic state, in which the person shows a sufficient number of symptoms (Table 1) to meet the syndromal criterion for a depressive episode and “M” to the terminal state. The terminal state is entered, if the modeled person dies prematurely due to depression related suicide or other causes, such as, for instance, a car accident or unrelated health issues. Across time, the system changes from one state to another to account for changes in the symptoms and progression of MDD. The step size in the model is one day. The transition are predetermined by the transition probabilities which are stored in a quadratic three-by-three matrix.

$$P = \begin{pmatrix} a_{-r} & a_{2s} & a_{2m} \\ s_{2a} & s_{-r} & s_{2m} \\ 0 & 0 & 1 \end{pmatrix} \quad (4)$$

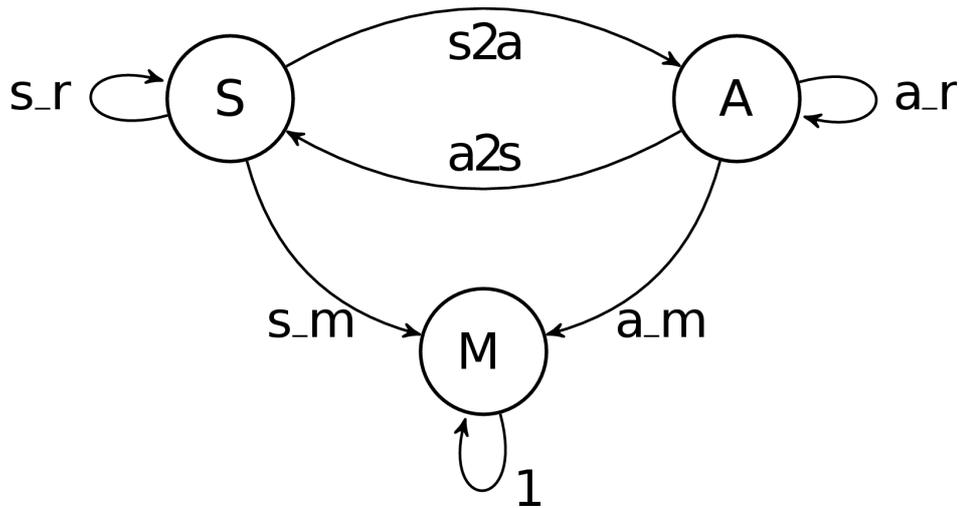


Figure 4. Three state Markov chain model.

Circles represent different states of the disease: asymptomatic (A), symptomatic (S) and terminal state (M) state. Arrow-lines are pointing in the direction of transition, i.e., arrow-lines with an origin in asymptomatic state are indicating direction of transition from asymptomatic to: symptomatic (a2s), terminal (a2m) and recurrent transition to the asymptomatic state (a_r). Similarly, arrow-lines with an origin in symptomatic state are indicating direction of transition from symptomatic to: asymptomatic (s2a), terminal (s2m) and recurrent transition to the symptomatic state (a_s). Terminal state have different properties, hence, there is no transition from terminal to the other states.

For all simulations, the system was initialized in the asymptomatic state and might have transition either to the symptomatic or to the terminal state, or it might remain in the current state. The same rule applies for the symptomatic state. By contrary, there are no transitions from the terminal state to the asymptomatic or symptomatic states. Since the system can not leave the terminal state, it is an absorbing state. Since there are transitions from every state to the absorbing state, the Markov chain can furthermore be classified as an absorbing Markov chain.

2.2. Analyzing the dynamics

2.2.1. Relating occurrence rate and recurrence rates to the distribution of the number of depressive episodes

I use empirical occurrence and recurrence rates to compute the distribution of the number of depressive episodes during an individual's lifetime (NDE) since the latter is rarely reported by epidemiological studies but quite informative. The occurrence rate (OR) is the fraction of the population that suffers from at least one DE during their life time. The OR thus equals the probability of having one or more depressive episodes, i.e.,

$$OR = p[NDE \geq 1] . \quad (5)$$

The rate of first recurrence $RR(1)$ is the fraction of patients who suffer from depression a second time out of those patients who suffered from one previous depressive episode. The rates of second recurrence $RR(2)$, third recurrence $RR(3)$, etc. are defined similarly. In general, $RR(i)$ can be calculated using the following equation

$$RR(i) = \frac{p[NDE \geq i+1]}{p[NDE \geq i]} . \quad (6)$$

The probability of having no depressive episode is

$$p[NDE=0] = 1 - OR . \quad (7)$$

The probability of having exactly one depressive episode is

$$p[NDE=1] = (1 - RR(1))OR . \quad (8)$$

The probability of having two or more depressive episode is computed according to this equation

$$p[\text{NDE} = i] = (1 - RR(i)) \text{OR} \prod_{j=1}^{i-1} RR(j) \quad (9)$$

for $i \geq 1$.

To study the OR and RR in the dynamical systems model, I initialized the system in a positive state $M(0)=1.75$ and simulated the dynamics of MDD for a period of 70 years using a time-step $\Delta t=0.1d$.

To study the OR and RR in the three state Markov chain model, I initialized the system in the asymptomatic state and simulated the dynamics of MDD for a period of 70 years using a time-step one day.

In both models, the analyses are based on simulations of 10,000 individuals. In the two sub-populations model, 93% of individuals belong to the low-risk sub-population while the remaining 7% belong to the high-risk sub-population.

2.2.2. Studying treatment effects

To study the time-to-remission and time-to-response in the dynamical systems model, I initialized the system in a symptomatic state. The initial value was drawn from a uniform distribution. I simulated the dynamics of MDD for a period of 20 years using a time-step $\Delta t=0.1d$. To study the effects of different treatments, I used only simulations of the two-subpopulations model in which a DE occurred. Hence, 63% of the simulations belong to the low-risk sub-population while the remaining 37% belong to the high-risk sub-population.

I initialized the finite-state machine in the rebound depressive episode state and considered the time when M increases above 50% as time-to-response, and the time at which the first remission or recovery occurred as the time-to-remission. Fourteen days were added to the time-to-remission to account for the fact that symptoms have to be present for at least fourteen days to qualify as a DE. In the control group, parameters were identical to those used for the simulation of the occurrence rate. In the experimental group, I changed certain

parameters in order to simulate the effect of various treatments such as AD treatment (change in parameter a , and d or b), CBT (change in parameter c) and life style changes (change in parameter I).

All simulations and analyzes were performed in Matlab R2012a (MathWorks; Natick, Massachusetts, USA) using custom-written software.

2.3. Model of semantic and episodic memory

(Cheng, 2013) suggested that episodic and semantic memory differ in their neural representation and that episodic memories are best represented by sequences of neural activity patterns. The hippocampus was suggested to facilitate the rapid storage and retrieval of neural sequences, accounting for why the hippocampus is crucial for accurate storage and memory retrieval (Agster et al., 2002; Cheng, 2013; Fortin et al., 2002).

Unlike episodic memory, semantic memory is best represented by static neural activity patterns and stored in neurocortex (Dickerson & Eichenbaum, 2010; O'Keefe & Nadel, 1979; Squire & Zola-Morgan, 1991; Vargha-Khadem et al., 1997).

In this study, I adopted the model proposed by (Fang et al., 2015). The model involves three memory systems: sensory, semantic and episodic, which are arranged hierarchically (Fig. 5). Hence, all incoming information must first pass from the sensory to semantic system, than processed by semantic system which generates corresponding semantic representations. Thereafter, sequences of these projections are then eventually encoded as episodic memory and stored into episodic system (Fig. 5).

I adapted the model by introducing adult neurogenesis and pattern separation into the model, and studied how variation in adult neurogenesis influences episodic information encoding, storage and retrieval. The adaptation will be explained in more details in the following.

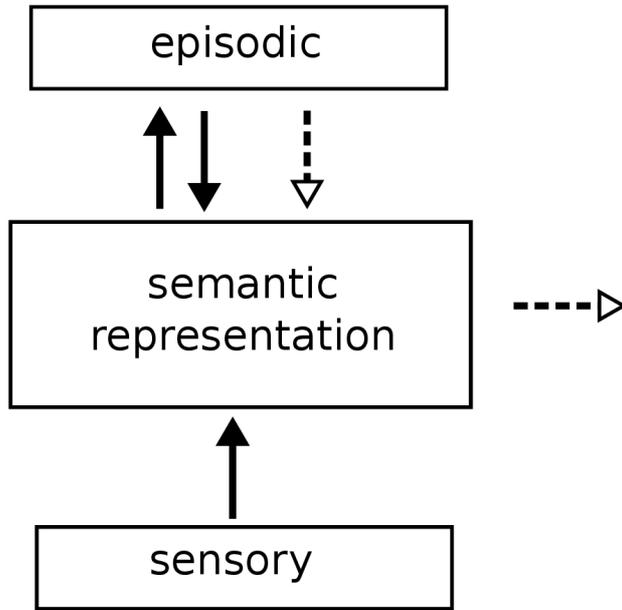


Figure 5. Schematic rendering of the model of memory systems relations [adapted from (Fang et al., 2015)].

The model involves sensory system, semantic representation layer, and episodic memory system. Solid arrows show direction of information encoding encoding, whereas dashed arrows show direction of information retrieval.

2.3.1. Stimuli

The model was trained and tested in distinct simulations with sequences of 30 x 30 pixel gray scale image of different objects (for more details see (Fang et al., 2015)). The objects that were used include letters “T”, “U”, “L”, “I”, “H” (Fig. 6). During the training phase, the model was trained with sequences consisting of tens of thousands of those images, which requires a large network and long training period.

The sequences represent the object moving and rotating in the input space. For the object movement, configuration values were x, y coordinate and orientation which refer to the center point of square area where the object can fit in. In all simulations, moving trajectory

of the object followed Lissajous curve. The ratio $\frac{a}{b}$ of Lissajous curve was set to be irrational so that ideally the moving trajectory would never appear to be close.

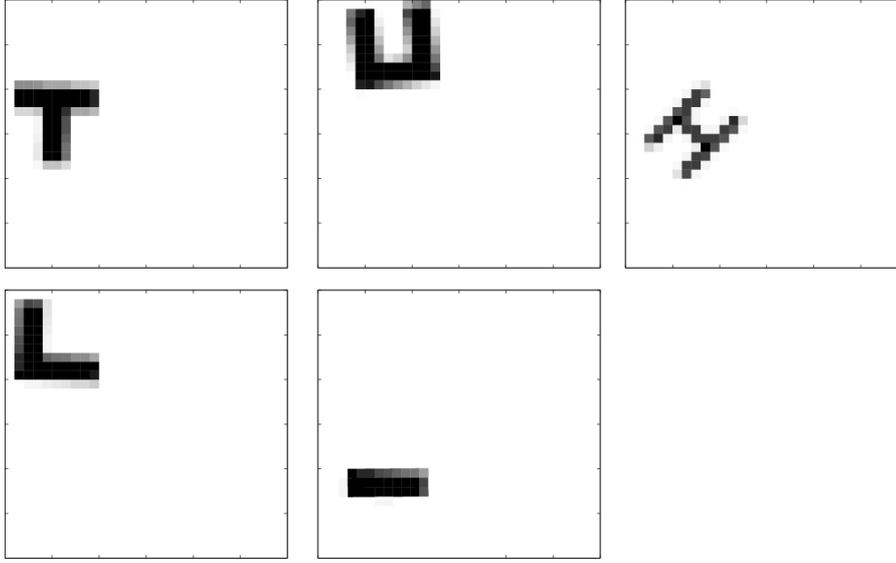


Figure 6. Example of the images of input objects [adapted from (Fang et al., 2015)].

In the simulations input objects “T”, “L”, “U”, “H”, “I” were used.

2.3.2. Semantic representation layer

A hierarchical structure based on Slow Feature Analysis Algorithm (SFA) (for more details, see (Wiskott & Sejnowski, 2002)) was implemented as a semantic representation layer. It is based on the assumption that meaningful information within an input stream varies slowly in time. The algorithm was developed to find instantaneous scalar input output functions that generate slowly varying output signals that vary as slowly as possible but still carry significant information. In a given function space F and multidimensional input signal $x(t)$, SFA finds a set of functions $g_i(x) \in F$ such that the output signals given by following equation

$$y_i(t) := g_i(x(t)) \quad , \quad (10)$$

and derivative of the equation

$$\Delta(y_i) := \langle \dot{y}_i^2 \rangle_t \quad (11)$$

is minimized, under the following constrains:

$$\langle y_i \rangle_t = 0 \quad (\text{zero mean}), \quad (12)$$

$$\langle y_i \rangle_t^2 = 1 \quad (\text{unit variance}), \quad (13)$$

$$\forall j < i: \langle y_i y_j \rangle_t = 0 \quad (\text{decorrelation and order}). \quad (14)$$

The Delta value introduced in Eq. (11) measures the temporal slowness of the signal $y(t)$, where small delta values indicates slowly varying signals. The first two constrains (Eq.(12) and (13)) avoid the constant function that does not change over time to emerge as the slowest feature. The third constraint (Eq.(14)) ensures SFA does not yield the same slow signal twice.

The hierarchical network, implementing the semantic representation layer in the model, consists of a converting hierarchy of layers of SFA nodes. For detailed description of SFA see (Fang et al., 2015). It is important to note that slowness cannot be achieved by low-pass filter, since despite being slowly varying functions g_i are instantaneous function of input. The hierarchical network is implemented in Python. All required building elements for the network are available in the MDP library (Wiskott & Sejnowski, 2002).

2.3.3. Episodic memory storage

After semantic layer has been trained, representations of input episodes are in turn stored into the episodic system. Episodes are not stored or retrieved as a whole, but rather in several subsequent steps. The mechanism of the model is illustrated in Figure 7, where y stands for representation of pattern in a sequence, while their positions in a sequence are represented by time t . Hence, a sequence is divided into a small segments which consists of two patterns, one preceded by the another, except the initial and last pattern of the sequence. More precisely, the second pattern of each segment is identical to the first pattern of its next segment, indicated by the same subscript in the figure. The identical patterns between different segments serves as linkage between patterns in the original sequence.

To initiate retrieval in the model, the first pattern was used as a cue. The model searches for the closest pattern to the cue, or the shortest Euclidean distance between the two patterns. In the next step, the second pattern of the retrieved segment becomes a new retrieval cue (Fig. 7).

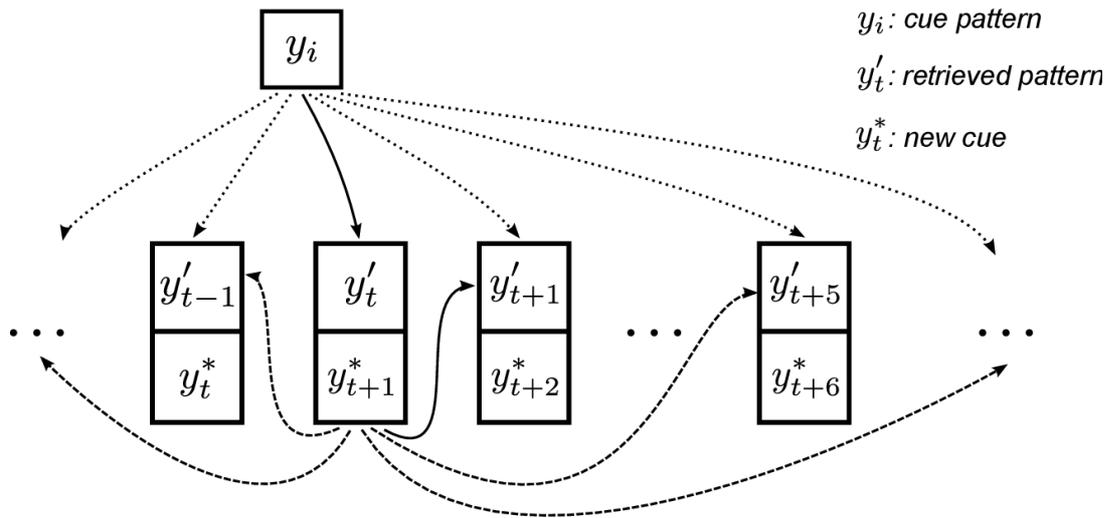


Figure 7. Sequence storage in the model of the episodic memory system [adapted from (Fang et al., 2015)].

One example of determining subsequent element in the sequence is marked by solid arrow line. Hence, retrieval starts with cue-pattern, and sequence learning net identify the most closest pattern. Since pattern are stored as a doublets, second element becomes cue for subsequent pattern. This procedure will be repeated until a sequence is completed.

This process will iterate until the full sequence is retrieved. If there are no identical patterns in the stored sequences and without noise, the retrieval is perfect. To mimic a real life condition, I perturb the system by adding noise to the cue pattern at each retrieval step which might cause that sequence deviate from the original ones.

Hence, if $y'_{t-1} \rightarrow y_t^*$ is retrieved pattern from the last step, then retrieved pattern of current step is

$$y' = \underset{i}{\operatorname{argmin}} \|y_t^* + \varepsilon_t - y_i\| , \quad (15)$$

where y_i stands for any stored pattern, ε for retrieval noise drawn from a Gaussian distribution with mean zero and standard deviation σ .

As a measure of memory retrieval accuracy of the model, Euclidean distance between the original and retrieved sequence were used,

$$e(t) = \|y_t' - y_i\| , \quad (16)$$

where e stands for retrieval error.

2.4. Influence of AN on the episodic memory

It has been suggested that during episodic memory (EM) storage, the input patterns are mapped onto pre-existing intrinsic sequences of neural activity in CA3 as a result of two inputs, one coming from EC and another coming from DG (Cheng, 2013). Since newborn cells integrate themselves into DG network, with normal AN, the input from DG acts as something like a random number generator. Therefore, I hypothesize that y_i corresponds to EC input, while a_i represents DG input in the memory model (Fig. 8), where a_i was drawn from a Gaussian distribution with mean zero and different standard deviation σ_s .

Here I describe an overview of information processing in the memory model (Fig. 5). First process is a sensory driven semantic learning. This stage is general training to the semantic representation layer. Second, semantic representation of some specific input sequences that are the same type as a training data were stored into episodic system. Here I introduce in the memory model mechanisms that corresponds to the adult neurogenesis. To test assumption that adult neurogenesis influences episodic memory, I model episodic memory storage with and without AN (Fig. 8).

where n stands for number of stored sequences Eq. (17).

The last step is a retrieval of a stored episode. By introducing the input pattern whose representation has already been stored as an external retrieval cue, the model is supposed to intrinsically complete stored sequence. Hence, for simulation of the retrieval,

$y_{i1} + a_i + \varepsilon$ was used as the retrieval cue, and the system identified the most similar pattern and completed the rest of the sequence, as it was described above (see 2.3.3). ε is Gaussian noise with mean zero and standard deviation rt .

2.5. Modeling memory functioning in asymptomatic state and depressive state

I modeled the influence of depression on memory through the reduction of AN during depression. Since the term a_i was added to each sequence (see 2.4.) to model a randomizing input from newborn DG cells, it might seem a possibility to model a reduction in AN by setting a_i to zero. However, neurons in DG that were generated during a preceding asymptomatic period continue to be part of the circuit and continue their pattern separation function, albeit less efficiently. I therefore used the following modeling strategy. During an asymptomatic period, newborn neurons in the DG generate a new a_i for each sequence as described above. During a symptomatic period, existing DG neurons recycle one of the previously generated a_i terms to store new sequences.

More specifically, during an asymptomatic state each sequence with $1 \leq i \leq j$ was stored with an newly generated a_i . In the following DE, sequences with $j+1 \leq l \leq n$ were stored by drawing randomly from the one of the previously generated, i.e., $a_l = a_i$ for some $i \leq j$. Due to the recycling of pattern separation vectors, there will be increased interference between the stored sequences, which I hypothesize will give rise to memory deficits in depression.

The parameter j varies depending of the duration of the depressive episode such that shorter depressive episodes will have larger j . During retrieval in the depressive state there are two possible scenarios, either retrieving memories that were stored in the depressive state (sequences with $j+1 \leq l \leq n$ were retrieved) or memories that are stored in the

asymptomatic state (sequences with $1 \leq i \leq j$ were retrieved). In this way, I was able to model memory storage and retrieval in the depressive and asymptomatic state.

All simulations and analyses were performed in Python using custom-written software.

3. Results

3.1. Finite state machine: systematic definition of disease states

I developed a finite state machine (Fig. 9) to systematically define the disease states of MDD: *depressive episode*, *remission*, *recovery*, and *relapse*, which were described above (see 1.6.). This mathematical model analyzes the transitions of M from the asymptomatic to the symptomatic state, and vice versa, and assigns a disease state to each time interval. The disease state changes depending on the length of periods for which M remains positive (T_p) or negative (T_n) (see Fig. 10 for an example). In addition to the disease states of clinical relevance, I had to introduce auxiliary disease states to account for short interruptions of a disease state that are clinically irrelevant. For instance, if a one-month-long depressive episode is interrupted by a 2-day-long period in the asymptomatic state, there is little reason to assume that the short interruption has any relevance. Clinicians frequently make such intuitive judgments without making them explicit (Frank et al., 1991), but such discounting has to be built in explicitly in a mathematical model. In the following, I describe the auxiliary disease states in more detail.

The *null state* is the initial state, before any data is available to make a more specific determination of the disease state. Short periods in the symptomatic state, $T_n < 14$, and any duration in the asymptomatic state, $T_p > 0$, will not change this state (Fig. 9&10). The only possible transition out of the null state is to a DE, if the syndromal criterion is met for at least 14 consecutive days, i.e., $T_n \geq 14$. A *rebound depressive episode* is an interruption of a DE that is shorter than two weeks (Fig. 9&10). The duration in the positive state is added to the duration of the DE (boxes connected to rebound depressive episode in Fig. 9). Similarly, *rebound relapse*, *interrupted remission*, and *interrupted recovery* are interruptions of the relapse, remission and recovery states of MDD, respectively.

The auxiliary disease states are necessary to discount short interruptions of the disease states in my model and have little clinical relevance. I therefore focus my attention on the clinically relevant disease states in the following.

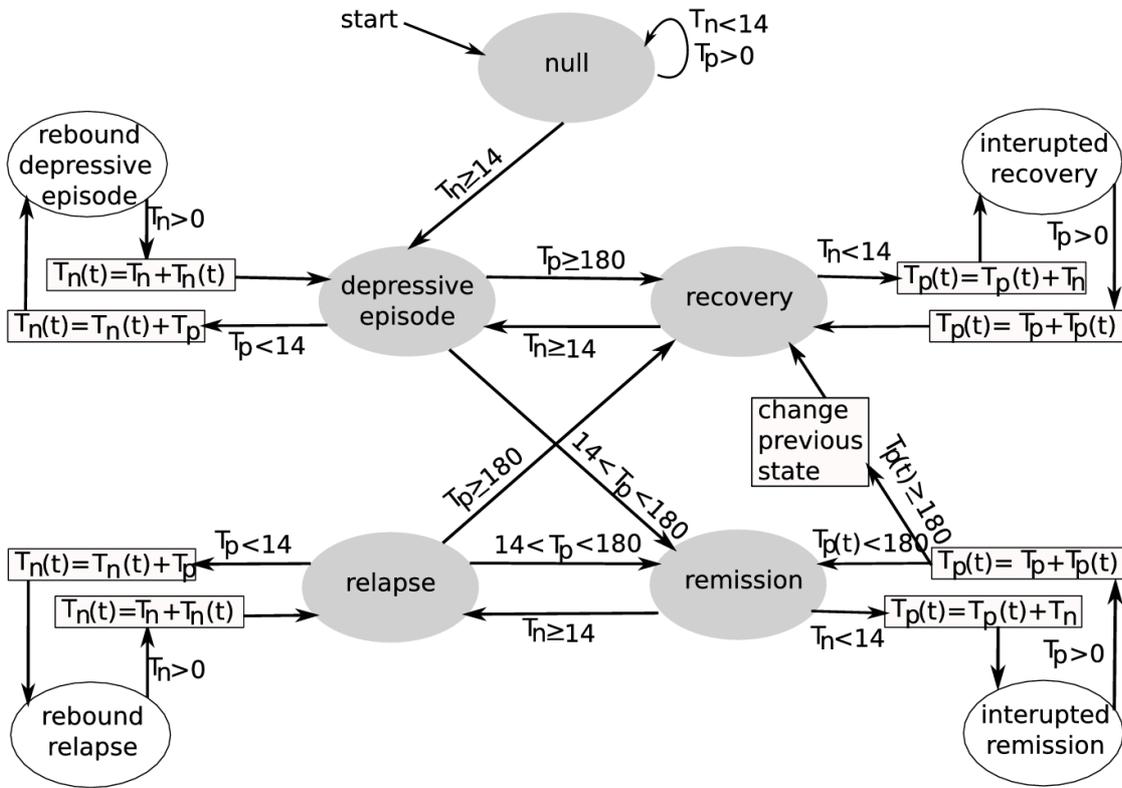


Figure 9. Finite state machine modeling the transitions between the disease states in depression.

State diagram for the finite state machine. Ellipses represent the disease states in depression. Grey filled ellipses are clinically relevant disease states; unfilled ellipses are auxiliary disease states that are needed to discount short interruptions of clinically relevant disease states. The arrows indicate transitions between disease states. Transitions only occur when the state variable M changes sign, i.e., either from positive to negative, or vice versa. Each arrow is labeled by the criteria that trigger the transition. T_n represents the length (in days) of the period during $M < 0$ before transition to a positive value occurred. In other words, T_n is the duration that a person meets the syndromal criterion for a depressive episode according to DSM-IV-TR (American Psychiatric Association, 2000). Accordingly, T_p represents the length (in days) of the period during $M > 0$, i.e., the duration in which a person does not meet the syndromal criterion for a depressive episode. The rectangles indicate a change to previously identified states. Short interruptions of disease states are added to the duration of disease states.

One point requires special attention. Recovery occurs after an asymptomatic period of 6 months or more, even if that period is interrupted by short periods (<14 days) in the negative state. If the first period in the positive state lasts for longer than 14 days and less than 6 month, then the finite-state machine will initially label this period as remission. Short interruptions in the negative state and the following periods in the positive state are added to duration of remission. If the total duration of the “remission” period exceeds 6 months, then the period becomes recovery. To correct the initial classification, I included an action “change previous state” (Fig. 9).

This finite-state machine unambiguously defines the disease states and can be used to track their evolution over the lifespan of patients as well as in my theoretical simulations.

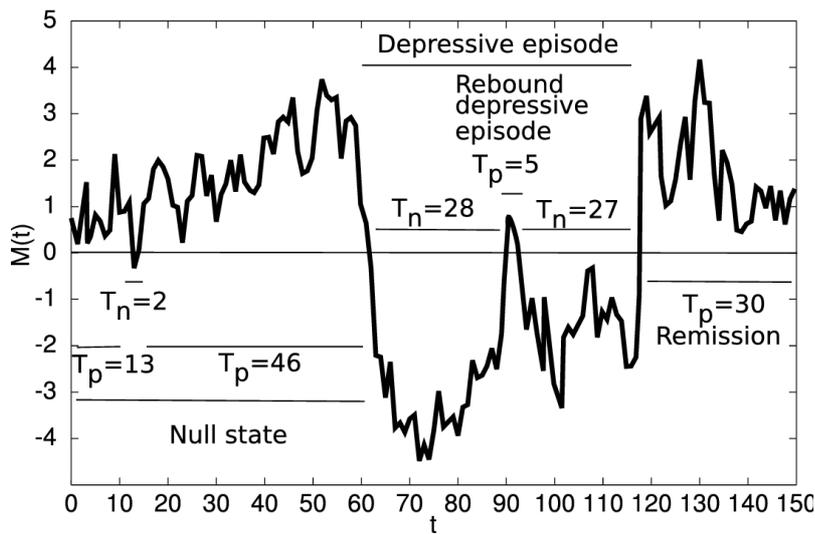


Figure 10. Example of the time course of the state variable M and the disease states identified by the finite state machine.

In this example, a symptomatic period lasting 28d is interrupted by an asymptomatic period of 5d and followed by another symptomatic period of 27d. Therefore, our model identifies the three periods together as a single depressive episode of length 60d. T_n and T_p represent the length (in days) of the period when $M < 0$ and $M > 0$, respectively.

3.2. Dynamical systems model for the dynamics of major depressive disorder

I developed a simple dynamical systems model (see Methods) to simulate and study the progression of disease states over 70 years. If my model captures some aspect of the dynamics of MDD, it should be able to account for the epidemiological data on occurrence and recurrence rates of MDD (see Methods). According to DSM-IV-TR, $OR=20\%$, $RR(1)=50\%$, $RR(2)=70\%$, and $RR(3)=90\%$ (American Psychiatric Association, 2000).

3.2.1. Single population dynamical systems model

In a first attempt, I speculated that perhaps all people share the same dynamics parameters, and thus similar physiological parameters, and that depressive episodes occur stochastically. Hence, I chose a single set of parameters representing a homogeneous population to match the epidemiological occurrence rate. The parameters of the single population model were: $a=4.65$; $b=-3$; $c=0.175$; $d=5$; $I=0.02$.

However, this model does not match any of the epidemiological recurrence rates (Fig. 11A). The mismatch is not simply a numerical issue, the model yields qualitatively different data. Rather than having rates that increase with the number of DE as in epidemiological studies, in my single-population model, the rates decrease. This is not surprising. Since a one-dimensional model has no memory other than the current state, the probability of the second DE (the first recurrence) occurring within a certain time period is the same as the probability of the first DE. However, the first DE can occur any-time within the full 70 years of simulated time whereas the second DE can only occur after the first DE had already occurred. Since the number of DE are proportional to the length of the observation period, the first recurrence rate is lower than the occurrence rate. The same logic applies to the second and third recurrence rates, which are successively lower (Fig. 11A).

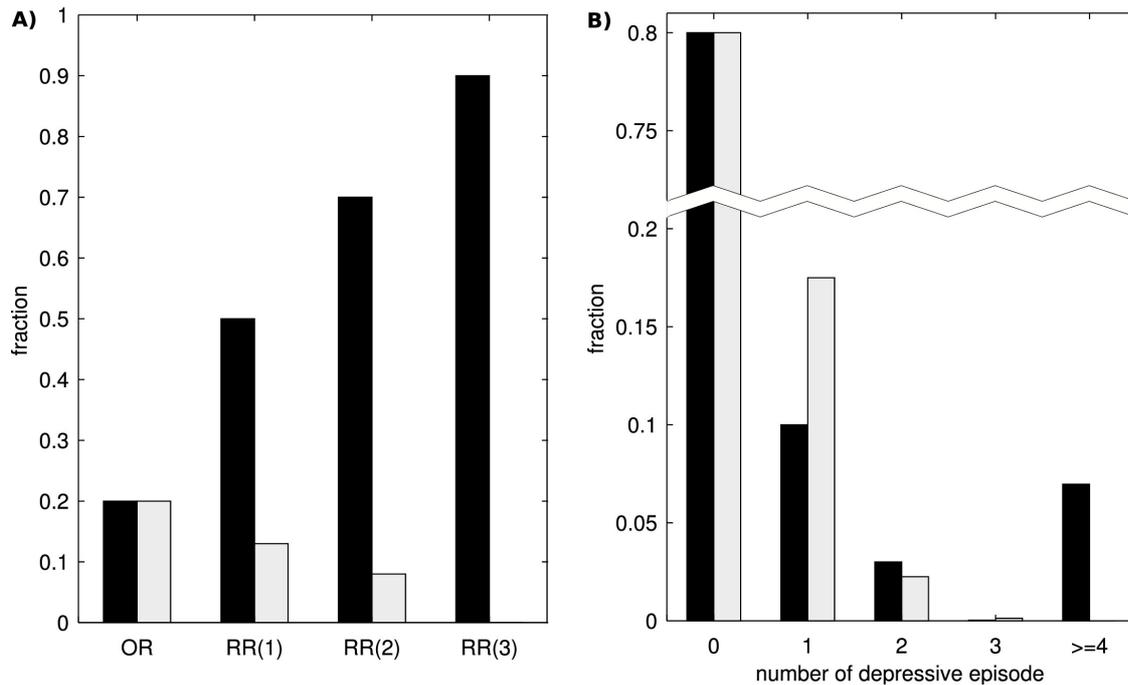


Figure 11: *Single population model can account for empirical occurrence rate but not for recurrence rates.*

A) The occurrence rate (OR) from our simulation (gray bars) was fit to the result from epidemiological studies (black bars). The parameters of the model are: $a=4.65$; $b=-3$; $c=0.175$; $d=5$; $I=0.02$. However, in my simulation, the recurrence rates, $RR(i)$, decrease with the number of prior depressive episodes, which is contrary to epidemiological data. **B)** The distribution of the number of depressive episodes (DE). The probability of zero DE is 0.8. The bars were cut off to show more clearly the smaller probabilities for the higher numbers of DE. The epidemiological distribution is clearly bimodal (black bars), whereas the simulated distribution is unimodal (gray bars).

My argument implies that this property is not specific to the particular parameters that I chose. Indeed, additional simulations show for a range of the parameters a and b that, in the single population model, the rate of first recurrence is lower than the occurrence rate, and the rate of second recurrence is lower than the rate of first recurrence (Fig. 12).

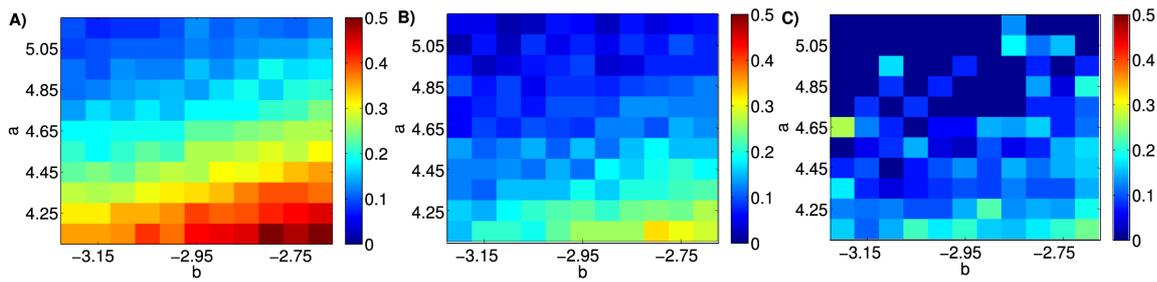


Figure 12: Influence of parameters a and b on the occurrence and recurrence rate in the single population model.

A) Occurrence rate, **B)** first recurrence rate, and **C)** second recurrence rate, each represented by color scales, for a range of the parameters a and b . The remaining parameters are: $c = 0.175$; $d = 5$; $I = 0.02$. Note, that for all combinations of the parameters a and b , the rate of first recurrence is lower than the occurrence rate, and the rate of second recurrence is lower than the rate of first recurrence.

To further investigate how the single population model deviates from the true dynamics of MDD, I calculated the distribution of NDE (Fig.11B). In the simulated data, the likelihood monotonically decreases such that four or more DE are absent from our simulated data. In contrast, the epidemiological data show that four or more DE occur with a substantial probability of around 7% and is even higher than the probability of two or three DE. Since the epidemiological data follows a bimodal distribution, I hypothesized that two sub-populations might be required to account for empirical occurrence and recurrence rates of MDD.

3.2.2. Two sub-populations dynamical systems model

I therefore simulated data for two sub-populations. In this model, ninety-three percent of the population shares low-risk parameters and develops depression with low probability. The parameters of this sub-population were chosen ($a = 5$; $b = -2.85$; $c = 0.175$; $d = 5$; $I = 0.02$) such that $OR = 13\%$. The remaining seven percent of the population belongs to the high-risk sub-population and develops depression with very high probability ($\sim 100\%$). The parameters for this sub-population were: $a = 4.4$; $b = -3.75$; $c = 0.175$; $d = 4.25$; $I = 0$.

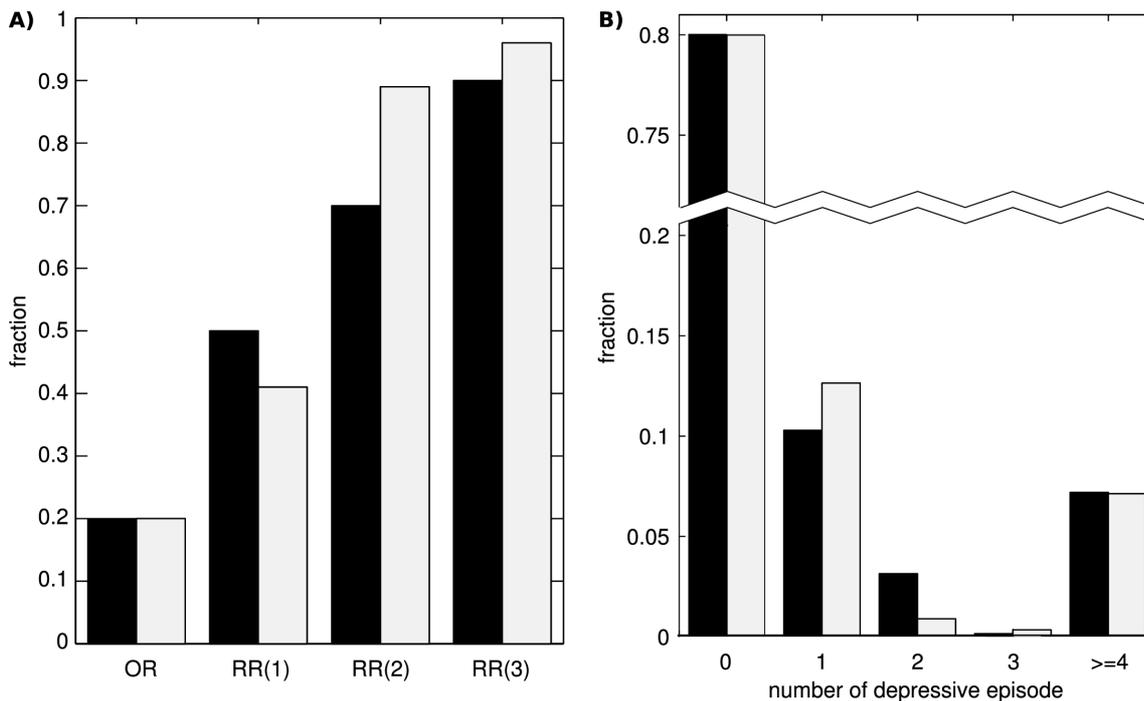


Figure 13: *Two sub-population model can account for empirical occurrence and recurrence rate.*

A) The parameters of the two sub-population model are: $a=5$; $b=-2.85$; $c=0.175$; $d=5$; $I=0.02$ for the low-risk sub-population and $a=4.4$; $b=-3.75$; $c=0.175$; $d=4.25$; $I=0$ for the high-risk sub-population. Our simulation data (grey bars) closely matches the empirical (black bars) occurrence and recurrence rates and **B)** the distribution of the number of depressive episodes.

At this point, I would like to stress that the two sub-populations together represent the entire population, which implies that no one is absolutely immune to depression. By design, the two sub-population model yields a bimodal distribution of NDE (Fig. 13B). With this two sub-population model, I was able to match the empirical occurrence and recurrence rates of MDD (Fig. 13A).

3.2.3. Modeling the effect of antidepressant treatment

The most commonly used antidepressants are those that regulate the metabolism of monoamines in the brain, in particular serotonin. My initial hypothesis was that the parameter d correlates with monoamine levels. Furthermore, it was shown that treatment

with AD increases the rate of adult neurogenesis in the dentate gyrus (Sahay & Hen, 2007) and it has been suggested that adult neurogenesis is important for memory (Cheng, 2013). Since the parameter a determines how quickly the current state is forgotten, I hypothesized that AD treatment increases parameter a . Since the intended effect of AD treatment is to reduce the time that patients suffer from the symptoms of MDD, I decided to use the time-to-remission as the target parameter for AD treatment.

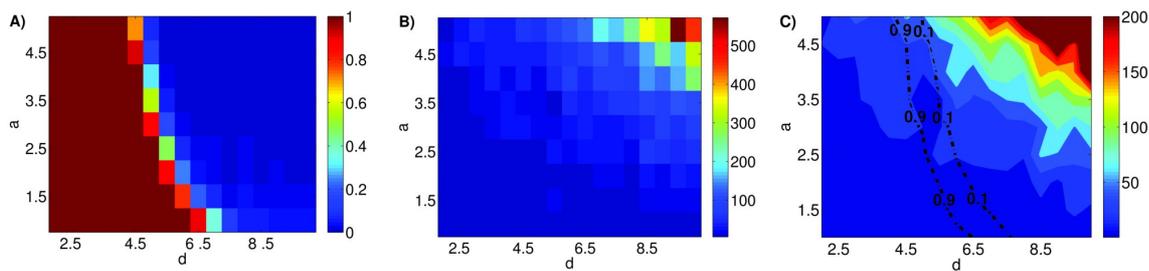


Figure 14: *Modification of parameters a and d cannot account for the effect of antidepressant treatment.*

Shown in the color scales are the occurrence rate (A), the median time-to-remission (B) and the contours of the median time-to-remission (C) in simulated data. Consistent with the assumption that monoamine levels correlate with parameter d and the rate of adult neurogenesis with parameter a , the occurrence rate decreases with increasing parameters a and d (A). However, modeling the effect of antidepressant treatment as increases in parameters a and d would make the paradoxical prediction that antidepressant treatment increases the time-to-remission (B). C) To show this conflict more explicitly we plot both the occurrence rate and the time-to-remission in the same panel. The dashed lines represents contours in the occurrence rate at the indicated values, while the color scale represents median time-to-remission. It is highly unlikely to find parameter combinations of a and d which reduces the time-to-remission while keeping the occurrence rate constant or lowering it.

My simulation results contradict my initial hypothesis, increasing the parameters a and d increases, rather than decreases, the time-to-remission (Fig. 14B&C). One potential resolution could be to assume that I correctly guessed the physiological correlates of the parameters a and d , but the relationship is inverse to my expectation. However, this interpretation is inconsistent with the OR in my simulations. Decreasing parameters a and/or d , increases the OR. Thus if I modeled the effect of AD treatment as a decrease in parameters a and/or d , it would imply paradoxically that AD treatment of healthy patients

increases the OR of MDD (Fig. 14A, C). An extensive parameter search did not yield any parameter changes in a and d that have the desired change time-to-remission and OR simultaneously.

I therefore turned to model the increase in the level of monoamines as an increase in parameter b (Fig. 15). In this scenario, the time-to-remission is reduced by an increase in b , but elevated by an increase in a (Fig. 15 B,E). While the latter outcome is an undesirable property, there are combinations of simultaneous increases in parameters a and b that yield a lower time-to-remission. This is possible because the contour lines are not parallel to the axes or, in other words, the parameters are inter-dependent. Similarly, the OR is reduced by an increase in a , as desired, but elevated by an increase in b (Fig. 15A, C). Again, there are combinations of simultaneous increases in parameters a and b that yield a lower occurrence rate. Importantly for the change of parameters indicated by the black and white points, representing pre- and post-treatment parameters, the change in both the time-to-remission and occurrence rate are in the desired directions. I therefore suggest that parameter a correlates with the rate of adult neurogenesis and parameter b with monoamine levels (Table 2).

It is worthwhile to note that AD treatment in my model does not work like a deterministic switch. Even though AD treatment in my model alters the physiological parameters immediately, remission remains a stochastic process driven by the intrinsic dynamics and the noise term. The results of my model demonstrate that the time required to see a significant effect of antidepressants is about three weeks, which is highly similar to the epidemiological data (see Table 3).

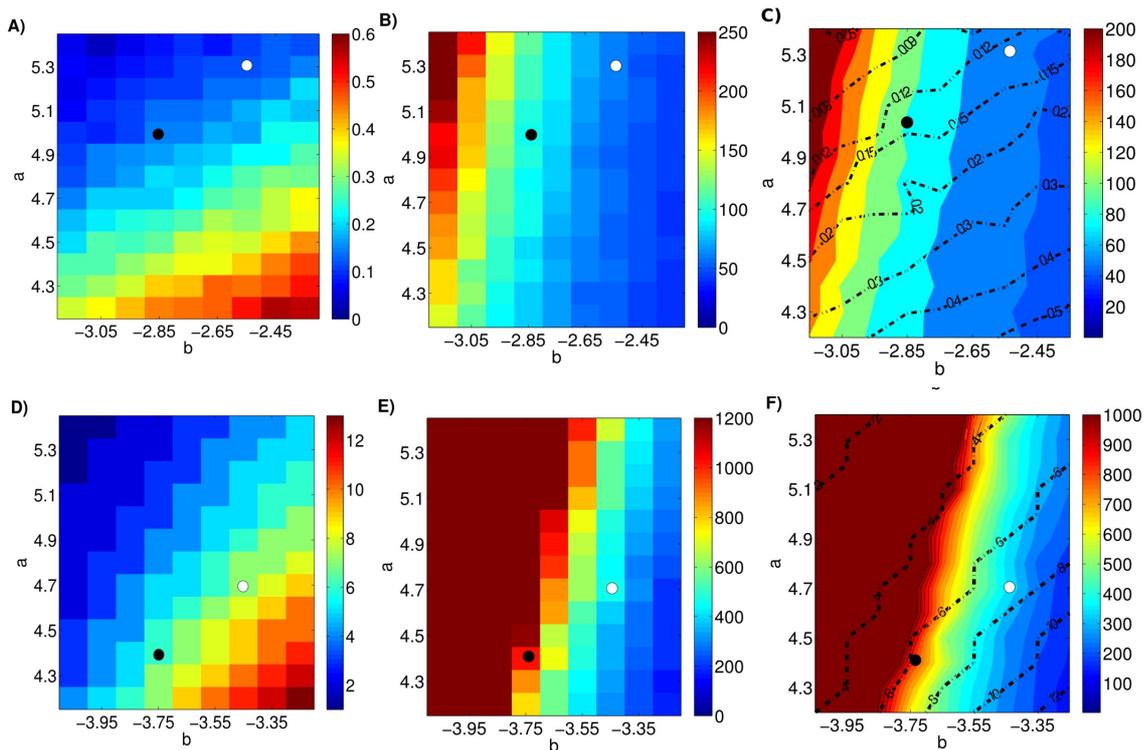


Figure 15: *Increases in parameters a and b are consistent with the effect of antidepressant treatment.*

The first row of panels shows the results of simulations for the low-risk sub-population where the color scales in **A)** and **B)** represent the occurrence rate and median time-to-remission, respectively. Panel **C)** displays the same data using contour lines (occurrence rate) and color scale (median time-to-remission).

The second row of panels shows the results for the high-risk sub-population where the color scale represents **D)** the median number of depressive episodes and **E)** median time-to-remission. Panel **F)** displays the same data using contour lines (median number of depressive episodes) and color scheme (median time-to-remission). The black and white points mark pre- and post-treatment parameters, respectively. For certain parameter combinations an increase in the parameters a and b reduces the median time-to-remission while keeping the occurrence rate (the median number of depressive episodes for the high risk sub-population) constant or lowering it.

Figure 16 shows the distribution of the duration of DEs. Both the treated (Fig. 16D, E, F) and control groups (Fig. 16A, B, C) exhibit distributions with large variances and long tails. This result is somewhat surprising given that within each sub-population all individuals share the same parameters and it underlines the difficulty in understanding the physiological mechanisms of AD treatment.

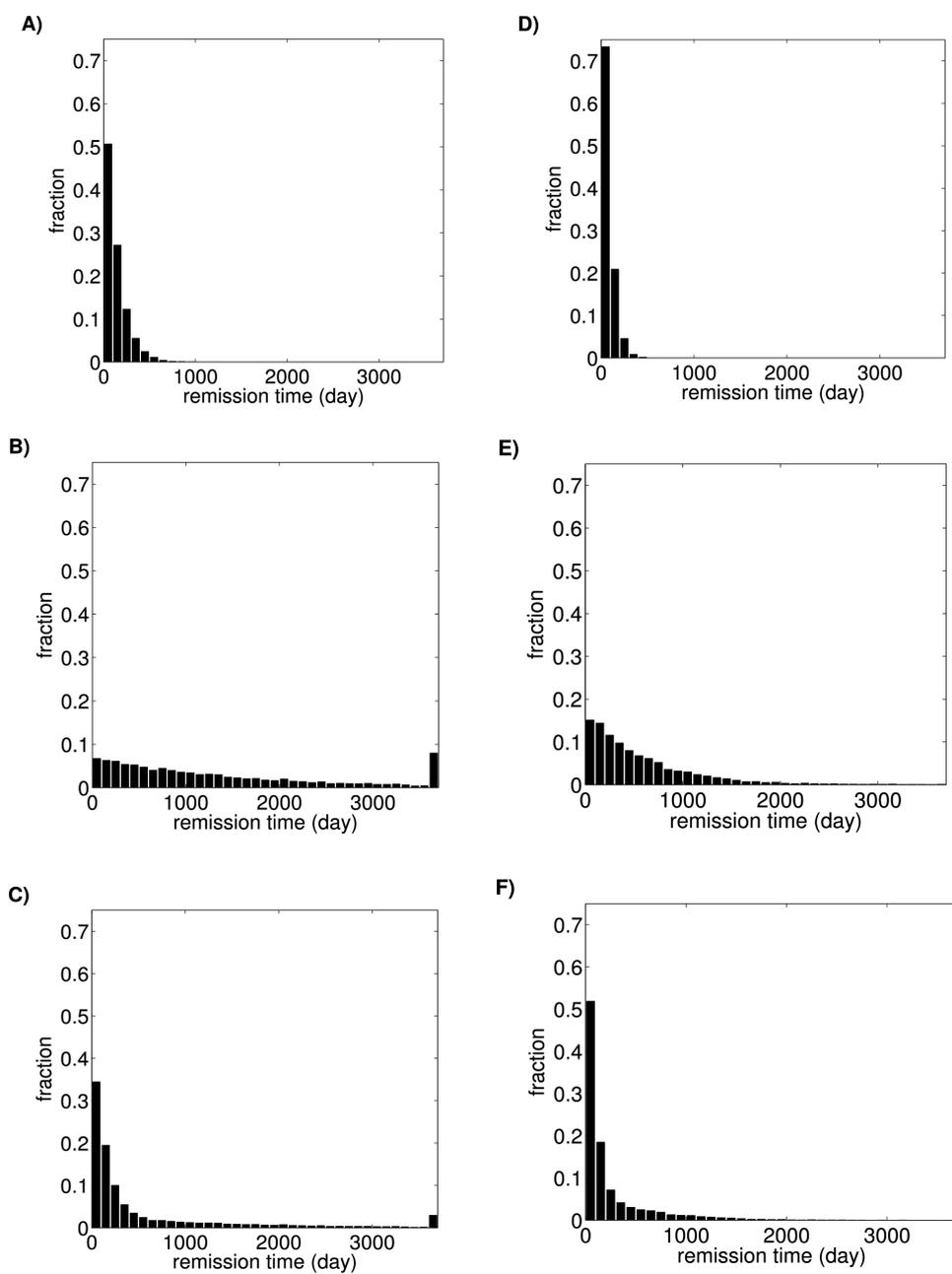


Figure 16: *Distribution of the duration of depressive episodes.*

A), B), and C) show data for control group with pre-treatment parameters. **D), E), and F)** show data for treatment group with post-treatment parameters. The first row (**A, D**) of panels shows the duration of depressive episodes for the low-risk subpopulation, the second row (**B, E**) for the high-risk subpopulation, and the third row (**C, F**) for the joint distribution. Note that the distributions have long tails, indicating that some patients take much longer to improve than others, even though they all share the same parameters.

These highly skewed distributions might explain why the median duration of depressive episodes reported in the literature varies widely from three to twelve months, even if most studies suggest that the median duration of depressive episode is about three months (Angst & Preisig, 1995; Furukawa et al., 2000; Keller et al., 1982; Mueller et al., 1996; Solomon et al., 1997; Spijker et al., 2002) . Overall, I find that my model reproduces rather well other variables which are often used in a clinical and epidemiological studies to examine the efficacy of AD treatment (Table 3)

Table 3. Comparison of quantitative measures of disease progression between model and clinical observation

Variable	Observations	Model
<i>Occurrence rate, OR</i>	20% (American Psychiatric Association, 2000) (Mueller et al., 1999) (Consensus Development Panel, 1985)	20%
<i>1st recurrence, RR(1)</i>	50% (American Psychiatric Association, 2000) (Consensus Development Panel, 1985)	40 %
<i>2nd recurrence, RR(2)</i>	70% (American Psychiatric Association, 2000)	90%
<i>3rd recurrence, RR(3)</i>	90% (American Psychiatric Association, 2000)	96%
<i>Mean time-to-response</i>	2 to 3 we (Stassen et al., 1993) 3 to 4 we (Santarelli et al., 2003) 20 to 31 we (Möller et al., 1996)	20d
<i>DE duration in patients treated with AD (from onset of DE to rem/ rec)</i>		
Mean	8.4 m0 (Spijker et al., 2002)	267d
Median	3 mo (Spijker et al., 2002) 16 we (Mueller et al., 1999) 22 we (1st DE) (Solomon et al., 1997) 19 we (4th DE) (Solomon et al., 1997)	96d
p(TDE<= 90 d)	50% (Spijker et al., 2002) 53% (Hollon et al., 1992)	48%
p(TDE<= 180 d)	63% (Spijker et al., 2002)	68%

p(TDE≤ 360 d)	76%	(Spijker et al., 2002)	80%
p(TDE≤ 630 d)	80%	(Spijker et al., 2002)	87%
p(TDE>720 d)	12%	(Andrade et al., 2003)	11%
	15%	(Eaton et al., 2008)	
	20%	(Spijker et al., 2002)	
	20%	(Keller et al., 1982)	
	22%	(Keller et al., 1986)	
<i>DE duration in patients treated with AD (from onset of AD treatment to rem/ rec)</i>			
Mean	5.6 mo	(Furukawa et al., 2000)	252 d
Median	3 mo	(Furukawa, 2000)	85 d
p(TDE≤ 30 d)	26%	(Furukawa, 2000)	24.5%
p(TDE≤ 90 d)	63%	(Furukawa, 2000)	52%
p(TDE≤ 180 d)	77%	(Furukawa, 2000)	69%
p(TDE≤ 360 d)	85%	(Furukawa, 2000)	80%
p(TDE≤ 720 d)	88%	(Furukawa, 2000)	87%
<i>Median age of onset of 1st DE</i>	early-to-mid twenties	(Andrade et al., 2003)	25 y
<i>DE duration in patients treated with CBT</i>			
p(TDE≤3 m)	50%	(Hollon et al., 1992)	49%
p(TDE≤16 week)	52%	(Luty et al., 2007)	57%

AD: antidepressant; **DE:** depressive episode; **TDE:** duration of depressive episode; **rec:** recovery; **rem:** remission;

3.2.3.1. Robustness of the treatment

It has been suggested that mood-state influence memory recall and that emotion powerfully influencing cognitive processes as free associations, imaginative fantasies, social perceptions, and snap judgments about others' personalities (e.g., angry subjects generated angry associates, told hostile stories, and were prone to find fault with others)

(Bower, 1981a). Hence, when person has depressed mood even before MDD occurred, cognitive and memory functions are going to be influenced already.

In order to model this aspect, I introduce variables Δa and Δc , which capture this mood-related changes in cognitive functioning, where Δa corresponds to memory deficits, while Δc corresponds to cognitive bias. In the Figure 17A & B are show occurrence rate and time-to remission, respectively. However, it was possible to find combination of the parameters Δa and Δc that do not significantly change the occurrence rate nor the time-to-remission. This results are indicating that the model of AD treatment is robust and can account for alteration in the cognitive functioning due to transition from one state to the other.

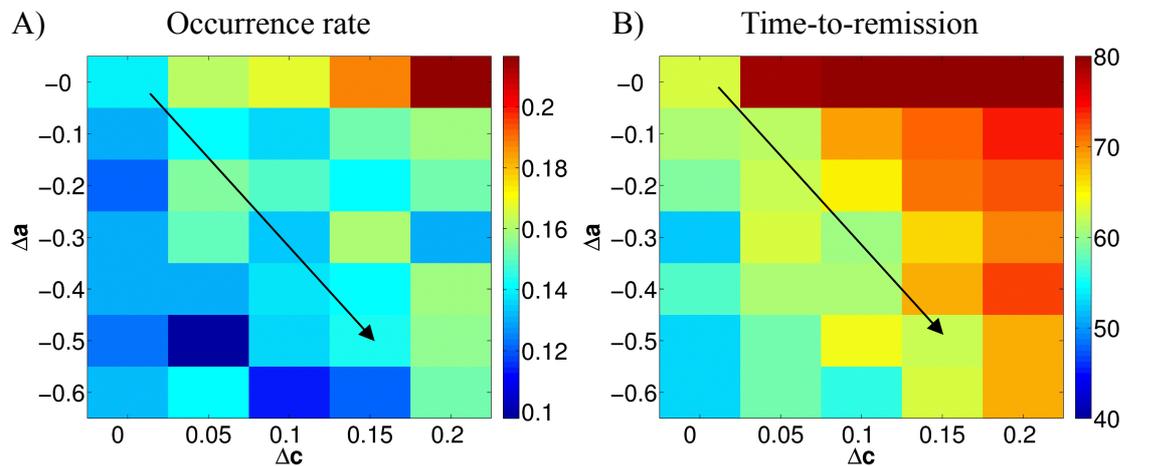


Figure 17. *Robustness of antidepressant treatment.*

Occurrence rate and time-to-remission are represented with color scale in figure A) and B), respectively. The origin of the black arrows mark parameters in asymptomatic state. Δa corresponds to memory deficits, where higher memory deficits are represented with more negative Δa . Δc corresponds to cognitive bias, where larger cognitive bias is represented with more positive Δc . For certain parameter combinations the median time-to-remission and the occurrence rate are almost identical to those in asymptomatic state.

3.2.4. Modeling the effect of cognitive behavioral therapy and life style changes

CBT instructs patients with MDD to develop a more optimistic approach to life and to detect and transform negative thoughts into positive thinking (Beck, 1995; Hollon et al., 2002; Nemeroff et al., 2003). The effect of CBT is an improved ability to deal with difficult circumstances and shorter durations of DEs (Hollon et al., 1992; Jarrett et al., 1999). A similar effect occurs in my simulations when I decrease parameter c : both the OR and the time-to-remission decrease (Fig. 18, the black and white points represent pre- and post-treatment value of parameter c , respectively).

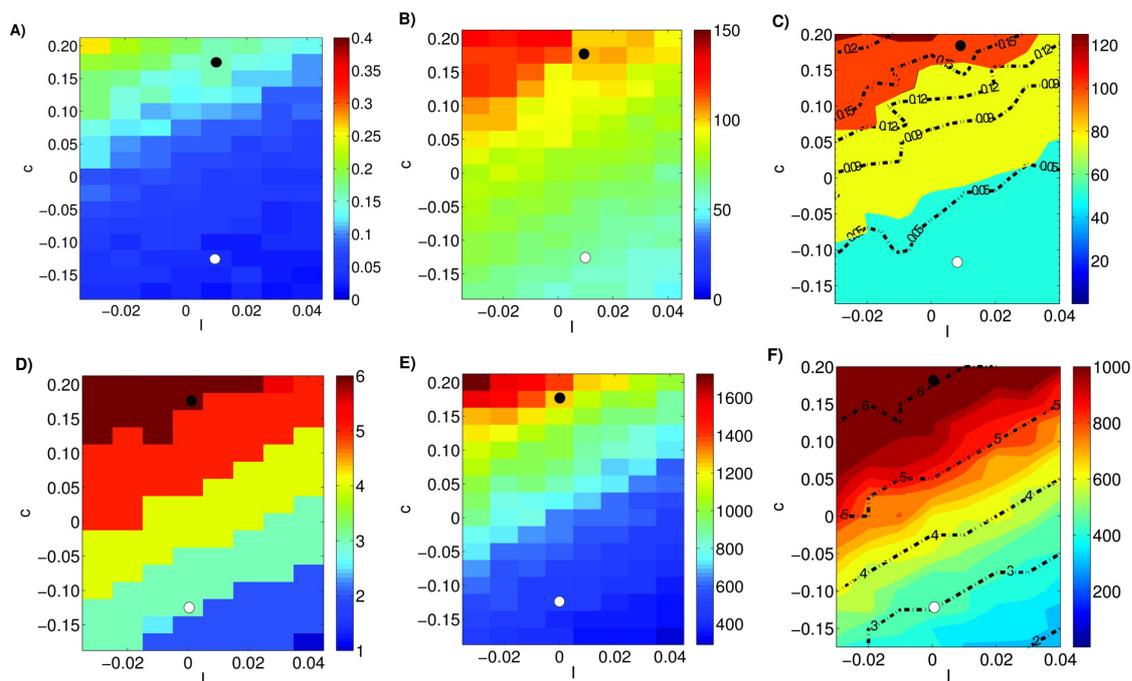


Figure 18: Modeling the effect of cognitive behavioral therapy and life style changes on MDD.

Plotting convention as in Figure 8. An increase in the parameter I and/ or decrease in c reduces the occurrence rate (A) (the median number of depressive episodes for the high-risk sub-population, D) and the median time-to-remission (B and E). These results suggest that smaller values of parameter c correlates with more positive attitude and larger values of I correlate with more positive environmental influences.

Moreover, the results of my model show that about a half of the patients treated with CBT will be in remission after three months of treatment and that the number of patients in remission increases with elapsed time, in line with the epidemiological data (see Table 3).

Hence, I hypothesize that smaller c correspond to optimistic attitude and larger c to pessimistic attitude (Table 2).

Life style changes such as, for instance, exercise, social support, and stress reduction lead to a lower probability of having another DE and to shorter duration of DEs, if they do occur (Blumenthal et al., 2007; Dunn et al., 2005; Martinsen, 2008). Indeed, a recent study compared exercise, antidepressant medication and combined medication and exercise in adults and found that all treatments were effective (Blumenthal et al., 2007; Dunn et al., 2005). Since external factors enter my model through the parameter I , I suggest that the parameter I correlates with environmental influence, where larger I corresponds to positive environmental influence and smaller I to negative influence (Table 2). My simulations confirm that increasing I indeed decreases the time-to-remission and the OR (Fig. 18). In addition, my results suggest that the combination of the two interventions, CBT and life style changes, will yield better results in the treatment of depression and the prevention of relapses and recurrence than their individual application.

3.3. Modified finite state machine

Depression carries a high risk of suicide (Gonda et al., 2007; Insel & Charney, 2003; Vahia et al., 2000). Since the finite state machine described above does not account for people dying prematurely, it was not possible to study the effect of suicide on life expectancy using this model. I therefore modified the finite state machine model by introducing terminal state to account for people that end up their life earlier due to depression triggered suicide or other cause of death (Fig. 19). The rules of systematic definition of the disease state of MDD and transition between the asymptomatic and the symptomatic state are identical to the finite state machine described above (see 3.1.). In the modified finite-state machine, the terminal state is connected with the other states and transitions are possible from the other state to the mortality state, but not in opposite direction (Fig. 19).

The modified finite-state machine unambiguously defines the disease states in MDD and can be used to track their evolution over the lifespan of patients as well as in my theoretical simulations. The modified finite-state machine includes lethal outcome that might occur during depressive or healthy state.

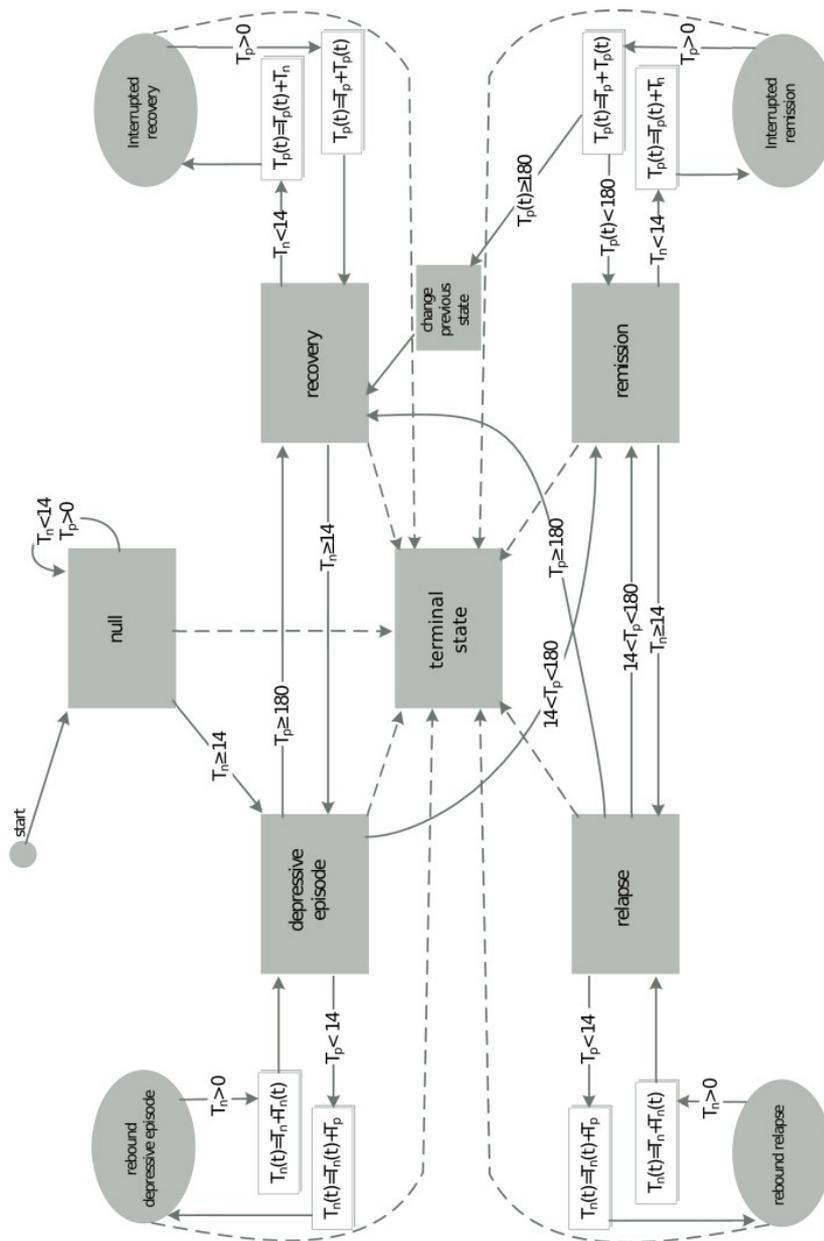


Figure 19. Modified Finite state machine model of the transitions between the disease states in depression.

Squares and ellipses represent the disease states in depression. Grey filled squares are clinically relevant disease states; gray filled ellipses are auxiliary disease states that are needed to discount short interruptions of clinically relevant disease states. The rules of systematic definition of the disease state of MDD and transition between the states are already described above (see Fig.9). The finite-state machine model is extended with mortality state which is connected with the rest of the disease states. There is no transition from mortality state to the other states.

3.4. Markov chain model

I developed a three state Markov chain model to simulate and study the progression of disease states over 70 years and to study influence of suicide on life (see Methods). The model should be capable to captures some aspect of the dynamics of MDD such as occurrence rate and recurrence rates reported in the epidemiological studies (see Methods).

3.4.1. Single population Markov chain model

In a first attempt, I chose a single set of parameters representing a homogeneous population to match the epidemiological occurrence rate. Table 4 shows the parameters of the single population Markov chain model. Like in the single population dynamical systems model, this model does not match any of the epidemiological recurrence rates (Fig. 20A) nor the distribution of NDE (Fig. 20). This result of the model is not specific to a particular set of parameters in the Markov model, but applies to a range of the parameters a_r and s_r (Fig. 21).

Table 4. The parameters of the single population Markov chain model

a_r	a2s	a2m	s_r	s2a	s2m
0.959	0.04099995	$5 * 10^{-8}$	0.525	0.474999	$1 * 10^{-6}$

Regarding the NDE in the simulated data (Fig. 20B), the likelihood monotonically decreases such that four or more DE do not occur. In contrast, the epidemiological data follows a bimodal distribution, such that the likelihood monotonically decreases up to 3rd DE and shows an increase for four or more DE (around 7%). Therefore, this observation indicates that two populations might be needed to match epidemiological data.

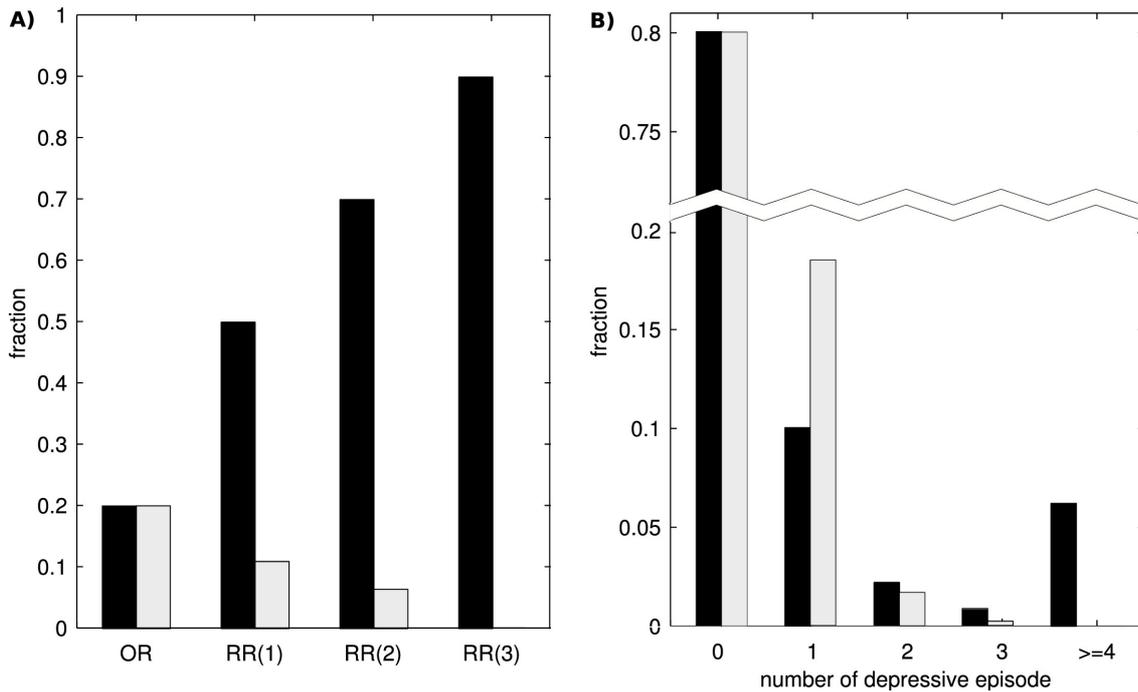


Figure 20. Single population Markov chain model can account for empirical occurrence rate but not for recurrence rates.

The occurrence rate (OR) from our simulation (gray bars) was fit to the result from epidemiological studies (black bars). The parameters of the model are given in the table 4. However, in our simulation the recurrence rates, $RR(i)$, decrease with the number of prior depressive episodes, which is contrary to epidemiological data. **B)** The distribution of the number of depressive episodes (DE). The probability of zero DE is 0.8. The bars were cut off to show more clearly the smaller probabilities for the higher numbers of DE. The epidemiological distribution is clearly bimodal (black bars), whereas the simulated distribution is uni-modal (gray bars).

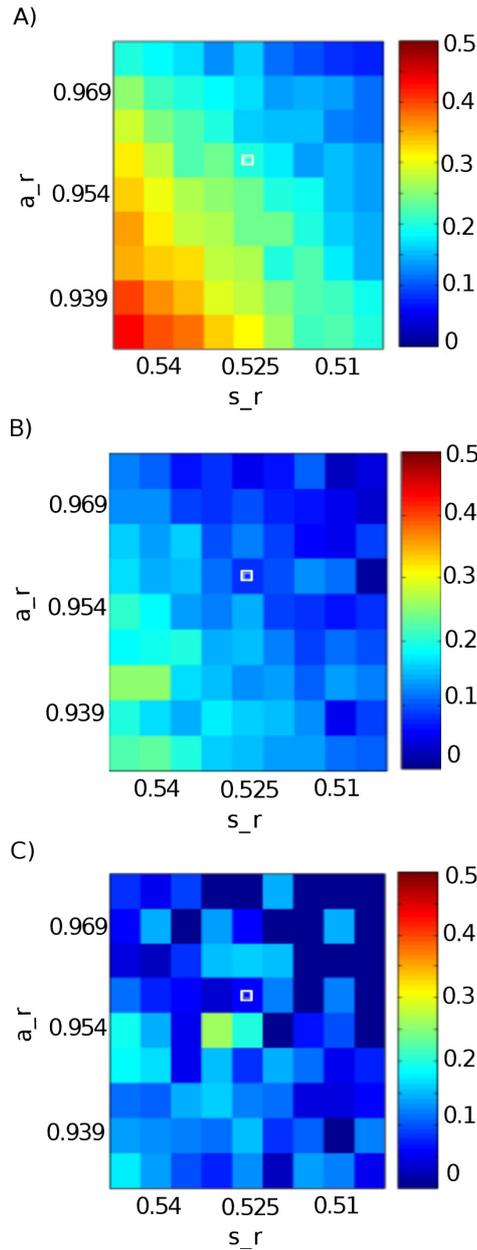


Figure 21. Influence of parameters on the occurrence and recurrence rate in the single population Markov chain model.

A) Occurrence rate, **B)** first recurrence rate, and **C)** second recurrence rate, each represented by color scales, for a range of the parameters s_r and a_r . The remaining parameters are:

$a_{2m} = 5 * 10^{-8}$ and $s_{2m} = 1 * 10^{-6}$, while a_{2s} and s_{2a} are calculated as the remaining difference to the respective row sum of one. Note that for all combinations of the parameters a_r and s_r , the rate of first recurrence is lower than the occurrence rate, and the rate of second recurrence is lower than the rate of first recurrence.

3.4.2. Two sub-populations Markov chain model

Like in the two sub-populations dynamical systems model, I introduced low-risk and high-risk sub-populations. 93% of the population have low-risk parameters (Table 5) and develop depression with a low probability (only 13%) (Fig. 22A). The remaining 7% have high-risk parameters (Table 5) (~100% of the high-risk sub-population develops depression), where most of the population experience four or more depressive episodes (Fig. 22B).

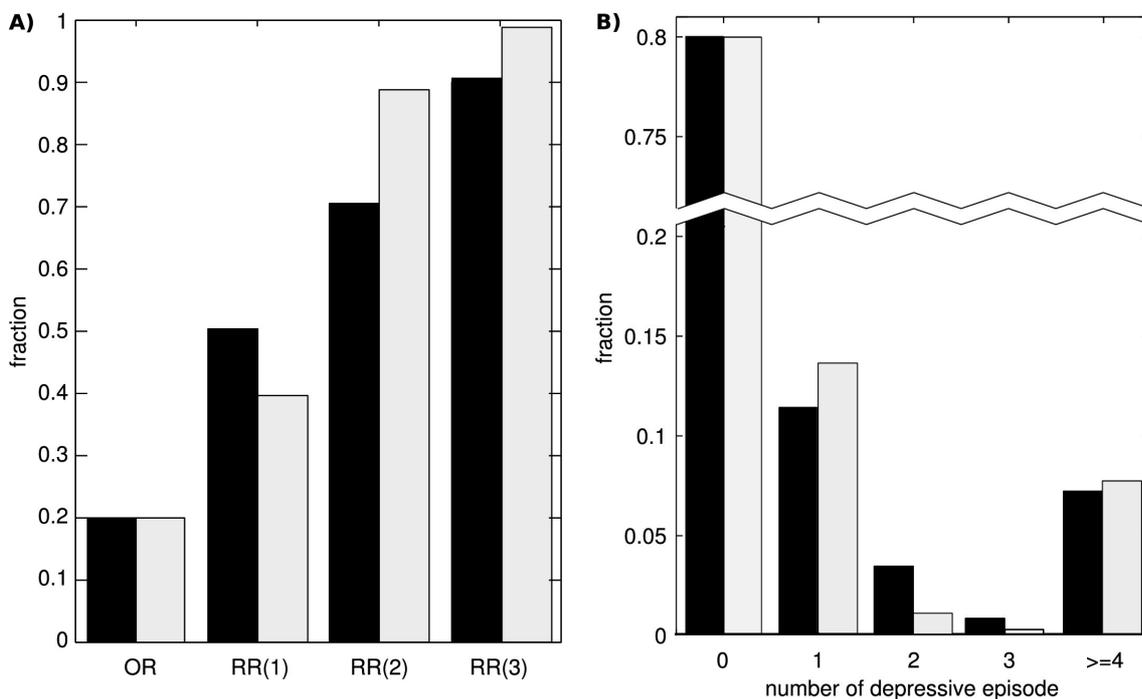


Figure 22. Two sub-population Markov model can account for empirical occurrence and recurrence rate.

A) The parameters of the two sub-population model for the low risk sub-population and for the high risk sub-population are given in the Table 5. My simulation data (gray bars) closely matches the empirical (black bars) occurrence and recurrence rates and **B)** the distribution of the number of depressive episodes.

Table 5. The parameters of the two sub-population Markov chain model

	<i>a_r</i>	<i>a2s</i>	<i>a2m</i>	<i>s_r</i>	<i>s2a</i>	<i>s2m</i>
Low-risk sub-population	0.947	0.02599995	$5 * 10^{-8}$	0.525	0.474999	$1 * 10^{-6}$
High-risk sub-population	0.899	0.1009993454	$6.55 * 10^{-7}$	0.8	0.1999345	$6.55 * 10^{-5}$

Both sub-populations combined give an occurrence rate of 20%. Using this approach with two sub-population, I was able to match the empirical occurrence and recurrence rates of MDD as well NDE (Fig. 22A and B), similar to the two sub-populations dynamical systems model (see above).

3.4.3. Influence of MDD on the average lifespan

To analyze the link between depression and mortality, I studied the relationship between premature deaths and the occurrence of depressive episodes using the two sub-population Markov chain model. In the model, the individuals who suffered from at least one depressive episode during their lifetime had a mean life span that was, on average, five years short than that of individuals who never suffered from depression (Fig. 23A). This result is in line with epidemiological studies that find a similar impact of MDD on life expectancy (Gonda et al., 2007; Vahia et al., 2000).

Consistent with reduced life expectancy in depression, I found that transitions to the terminal state from the symptomatic state are more likely than from the asymptomatic state (Table 6 and Fig. 23E). Therefore, one would expect that mortality increases with the number of depressive episodes and it does up to three DE, but for four or more DE the mortality is lower than for three (Fig. 23B). In order to resolve this puzzle, I calculated the average life time with respect to the number of DE separately for the low- and high-risk sub-populations (Fig. 23C). It is apparent that the low-risk sub-population does not have a reduced lifespan regardless of the number of experienced DE. By contrast, the high-risk sub-population exhibits a marked reduction in lifespan and this reduction is more severe for lower numbers of DE, which is the opposite to what we would have expected and accounts for the unexpected finding in Figure 23B.

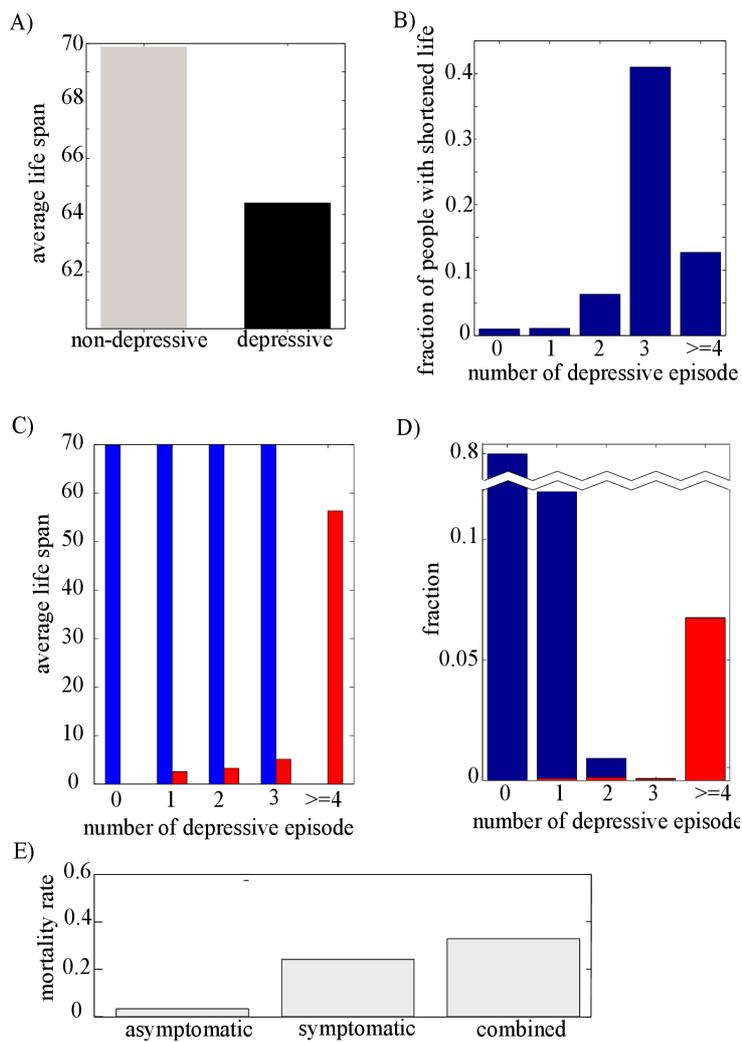


Figure 23. Influence of depression on the lifetime.

A) Average lifespan of people that do not have DE (gray) is longer comparing to the people with one or more DE (black bar). Panel **B)** shows relationship between the NDE and shortened lifespan expectancy. However, fraction of a people with a shortened lifespan expectancy increases with number of DE up to 3rd episode and there is a drop for four or more episodes. Panel **C)** shows average life span versus NDE in low-risk (blue bar) and high-risk (red bar) sub-populations. However, life span does not change with an increase of NDE in low-risk sub-population, while in high-risk sub-population people with four or more DE on average live longer than people with less than four DE. Panel **D)** shows distribution of DE where the fraction of the high-risk sub-population people are shown in red and the low risk sub-population are shown in blue. Panel **E)** shows which state was preceding the terminal state in the people that have shortened lifespan. Accordingly, most of people were in symptomatic state before ending up in the terminal state.

Since almost all individuals with three or more DE belong to the high-risk sub-population (Fig. 23D), these results show that the expected reduction in life expectancy due to depression is entirely due to the high-risk sub-population. This is consistent with the overall rate of premature death being very low (0.26%) in the low-risk sub-population and much higher (20%) in the high risk population.

It remains to be explained why, in the high-risk sub-population, the average live span increases with the number of DE (Fig. 23D). This effect can be explained by the definition of the finite-state machine. In order to count one DE, a minimum of $T_n=14$ days and $T_p=180$ days have to pass. In order to experience higher number of DE, requires more time.

Table 6. Dependence of the number of premature deaths on the number of depressive episodes, broken down by preceding state and sub-population.

<i>Number of depressive episodes</i>	0	1	2	3	≥4
<i>asymptomatic state</i>	100	1	0	0	4
<i>symptomatic state</i>	102	9	13	6	93
<i>Low-risk sub-population</i>	202	2	0	0	0
<i>High-risk sub-population</i>	0	8	13	6	97
<i>total</i>	202	10	13	6	97

3.5. Model of memory functioning

Next, I explored the impact of depression on memory function using an algorithmic model. I hypothesized that depression leads to a reduction in adult neurogenesis, which normally is required for pattern separation to reduce interference between similar patterns. With reduced pattern separation, memory retrieval might become less accurate.

3.5.1. Adult neurogenesis and pattern separation

In order to model the influence of AN on memory, I simulated memory storage and retrieval with AN and compare it to storage and retrieval without AN (see methods). The retrieval of episodic memories stored with AN was superior to that without AN (Fig. 24A).

The difference in retrieval error of the first element of the sequence without and with AN is zero, and increases along with position of the element in the sequence. The result shown in Figure 24A represents the retrieval of a 100 episodes, averaged over 100 repetitions.

To test how a different number of stored episodes affects the retrieval, I performed simulations with a different number of episodes from 30 up to 200. Figures 24 B&C show retrieval performance as a function of retrieval noise and the number of episodes, for the 30th pattern (element) in the memory sequence without and with AN, respectively. Not surprisingly, in both networks with and without AN, the retrieval error is smaller when fewer episodes are stored in the network, and increases with the number of stored episodes. The more interesting aspect is the comparison of retrieval accuracy in the networks with and without AN (Fig. 24D), where positive values indicate that the retrieval error is larger in simulations without AN.

For all combinations of the parameters (retrieval noise level and number of episodes stored) the network with AN was superior to the one without AN. Interestingly, the benefit of AN was larger for higher memory loads, but only if the retrieval noise was not too large. This result makes sense since higher memory loads lead to more interference between different memories and such interference is precisely what AN is hypothesized to reduce. When the retrieval noise is too strong, it dominates the retrieval and counters the beneficial effect of pattern separation and thus AN.

Overall, the results of my model show that AN improves memory retrieval.

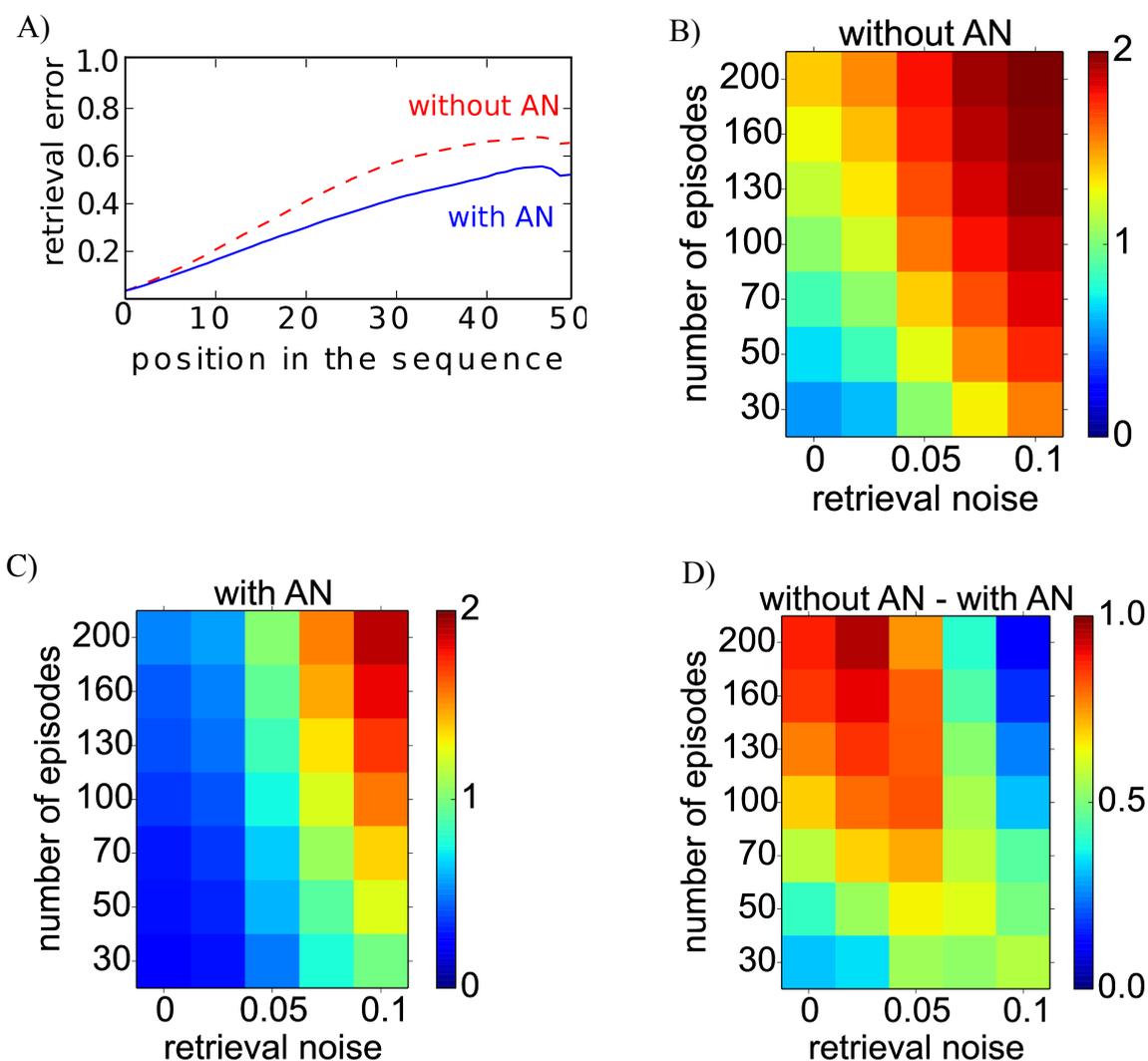


Figure 24: Influence of AN on the memory retrieval.

A) Retrieval error of the memories stored and retrieved with adult neurogenesis (blue line), and memories stored and retrieved without neurogenesis (dashed red line). Parameter values are: $p_s = 0.05$ and $m = 0.025$. Color code in **B)** and **C)** represents retrieval error for memories stored and retrieved without and with adult neurogenesis, respectively. The retrieval error is calculated for the 30th element in the sequence ($n=30$), for a various number of stored sequences and range of retrieval noise. Hence, retrieval error increases with number of stored sequences and with increase of retrieval noise. In panel **D)** color code represents difference in memory retrieval error without and with AN (without AN – with AN). There are only positive values, which indicate that performance was better for simulation with AN, for different amount of noise and number of stored sequences. Please note that for generating results shown in **A)**, **B)**, and **C)** simulations with image sequences of the object “T” was used.

3.5.2. Modeling memory in asymptomatic state and depressive state

To test the idea that an alteration of AN in depression leads to memory deficits, I simulated and compared memory functioning in the asymptomatic and the depressive state. Figure 25 illustrates the setup of the modeling study. AN changes if the state changes. The rate of AN is normal in the asymptomatic state and reduced in the depressive episode.

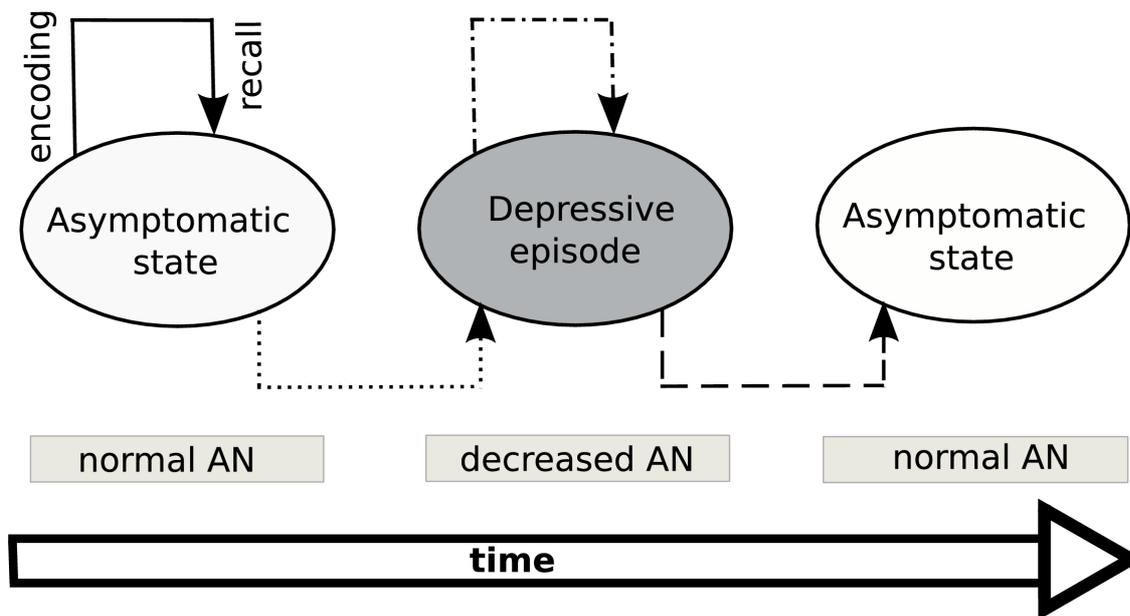


Figure 25. *Adult neurogenesis in asymptomatic and depressive states.*

The empty ellipses are representing asymptomatic state while gray-filled ellipse represents depressive state. Arrow-lines are showing state related memory encoding and retrieval, such that beginning of an arrow-line indicate in which state encoding of memories occurs, while end of an arrow-line indicate in which state memory was retrieved. E.g., dotted line indicate that memory was stored in the asymptomatic state (normal AN) but it was retrieved during the depressive state (decreased AN).

Arrow-lines represent in which state memory encoding and retrieval occur. The origin of the arrow-line indicates in which state the memory is encoded and the arrow indicate in which state the memory is retrieved. Some memories might be stored and retrieved in the

same state, while others might be stored in one state and retrieved in another (Fig. 25).

3.5.3. Dynamic of memory retrieval in asymptomatic and depressive state

Here I test the idea that impaired pattern separation due to reduced AN underlies memory deficits often seen in MDD. To this end, I simulated and compared the retrieval of memories stored and retrieved in the asymptomatic state (AA), memories stored in the asymptomatic and retrieved in the depressive state (AD), and memories stored and retrieved in the depressive state (DD) (Fig. 26). In all three cases, retrieval error is the lowest for the first elements of the sequence and grows as later elements of the sequence are retrieved. Figure 26A shows that the retrieval error in AA, AD and DD are identical for the initial elements but later diverges. The retrieval error is lowest for AA and largest for DD. The latter result is expected given the previous finding that AN benefits memory storage and retrieval and AN is reduced in a depressive episode.

Interestingly, the retrieval error for AD is larger than that for AA, indicating that the recall of episodic memories is impaired during a depressive episode, even if those memories had been stored during a preceding asymptomatic period. The difference between AA and AD is indeed due to the effect of adult neurogenesis, because setting the pattern separation parameter ps , which is linked to adult neurogenesis, to zero abolishes the difference (Fig. 26B, first column). However, too much pattern separation parameter hurts retrieval performance for all three cases and reduces, in some cases inverts, the retrieval deficit of AD relative to AA. When the retrieval error rn is increased, it begins to dominate over other sources of retrieval error and the differences between AA, AD and DD vanishes (Fig. 26B).

These results show that retrieval accuracy depends on the mutual interactions of the retrieval noise and the pattern separation parameters. Pattern separation generally increases retrieval accuracy, but the memory deficit during depressive episode is only seen for certain parameter settings.

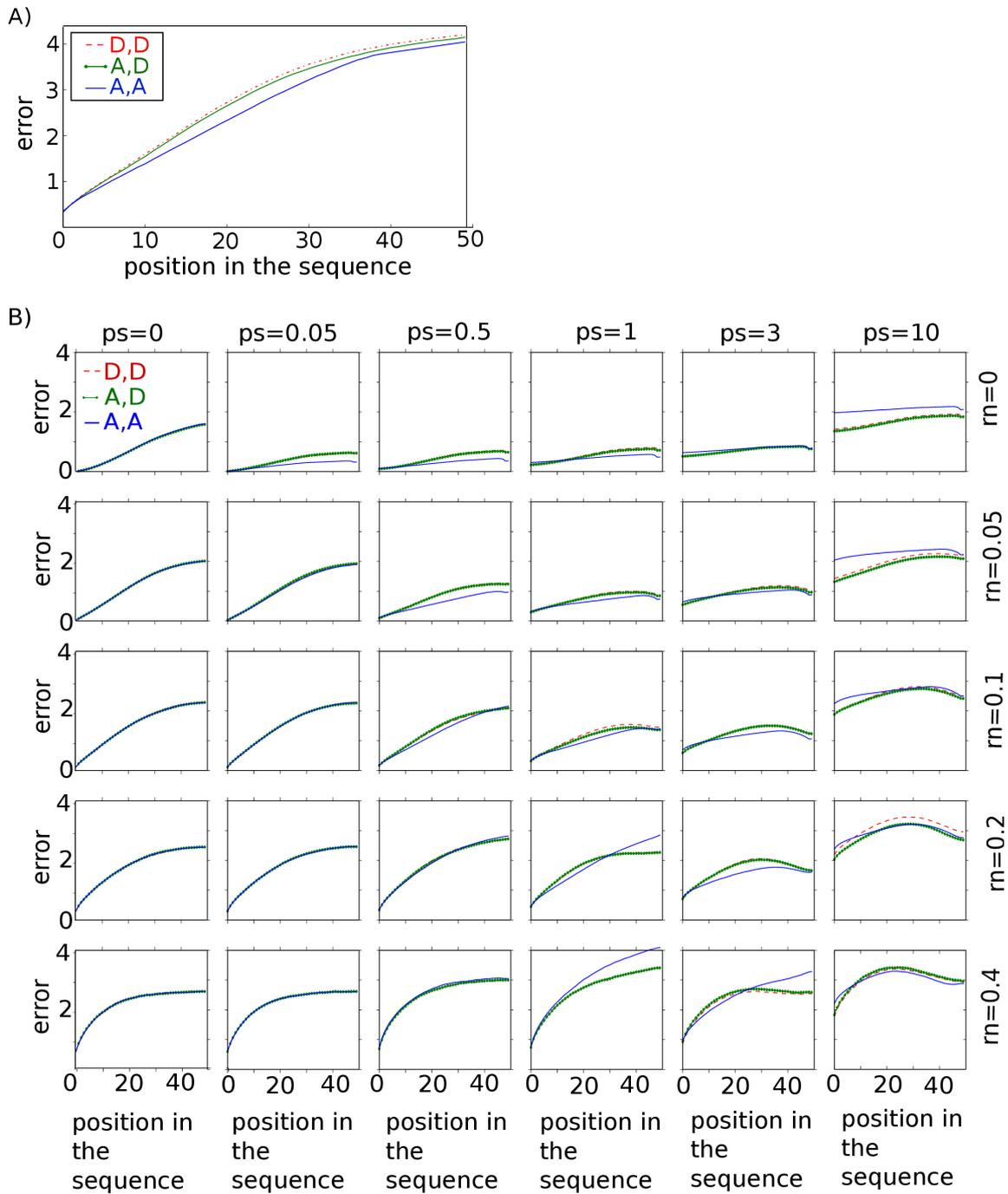


Figure 26. *The Dynamics of memory retrieval*

A) Retrieval error of the memories stored and retrieved in asymptomatic state (blue line), memories stored and retrieved in depressive state (dashed red line), and memories stored in asymptomatic and retrieved in depressive state (green line). Parameter values are: $ps = 0.05$ and $rn = 0.025$. Panel **B)** shows the dynamics of memory retrieval for a range of parameters ps and rn .

3.5.4. Episodic memory retrieval in depressive and asymptomatic state

Since retrieval noise and pattern separation mutually influence retrieval accuracy, I show a summary plot of retrieval error as a function of retrieval noise and pattern separation parameters for the 30th pattern (element) in a sequence (Fig. 27A,B,C). As mentioned in the previous section, the most accurate retrieval occurs when there is no retrieval noise and ps is large, whereas the worst performance occurs when ps is zero and retrieval noise has maximal value. This applies to all three cases.

In order to compare retrieval performance in the asymptomatic and the depressive state, I subtract values of AA from AD (Fig. 27D), and AA from DD (Fig. 27E). Positive values indicate that retrieval error is larger for memories retrieved in the depressive state than for memories retrieved in the asymptomatic state. Naturally, without pattern separation (ps=0) there is no difference in memory retrieval between the groups. In contrast, increases in ps enlarges difference between AA and AD (Fig. 27D) and AA and DD (Fig. 27E). Hence, memories which are stored with more pattern separation in the asymptomatic state tend to be retrieved later more accurately than memories retrieved in the depressive state.

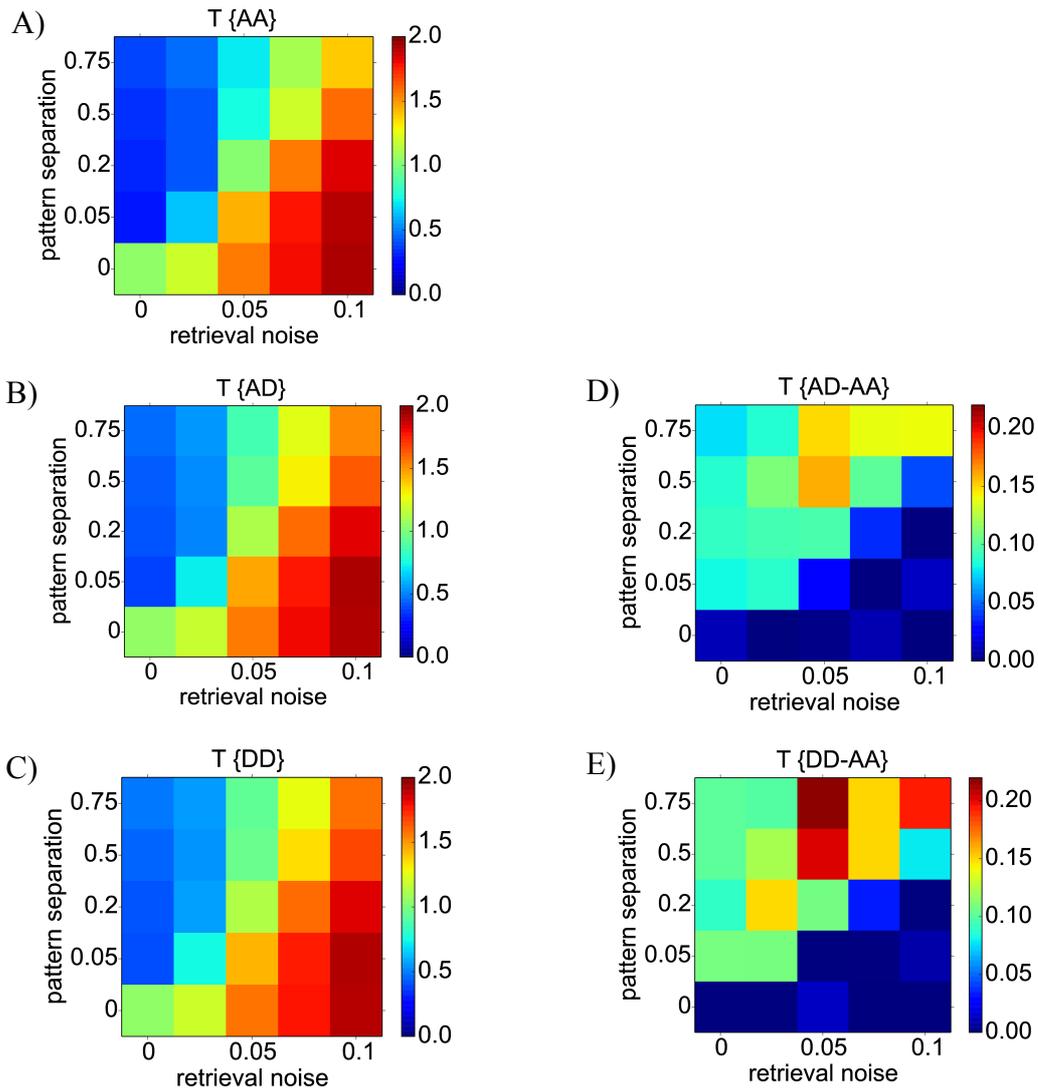


Figure 27. Difference in memory retrieval in depressive and asymptomatic state.

Retrieval error of **A)** memories stored and retrieved in asymptomatic state (AA), **B)** memories stored in asymptomatic and retrieved in depressive state (AD), **C)** memories stored and retrieved in depressive state (DD), is represented by color code, for range of parameters ps and m . **D)** Difference in memory retrieval of the memories stored in asymptomatic and retrieved in depressive state and for memories stored and retrieved in asymptomatic state (AD-AA), whereas color code in panel **E)** represents difference in memory retrieval of memories stored and retrieved in depressive state and memories stored and retrieved in asymptomatic state (DD-AA). Note that for all combinations of the parameters ps and m , in the panels **E)** and **D)**, the retrieval error is lower for memories stored and retrieved in asymptomatic state. The retrieval error is calculated for the 30th element in the sequence ($n=30$), for a range of parameters ps and m , for a simulations with image sequences of the object “T”.

3.5.5. Memory retrieval for different input stimuli

All results shown previously were obtained with the letter 'T'. To examine whether the results are specific to the input stimulus, I used other letters as inputs such as the letters 'U', 'L', 'H', 'I'. The results for these stimuli were similar to those reported above (Fig. 28).

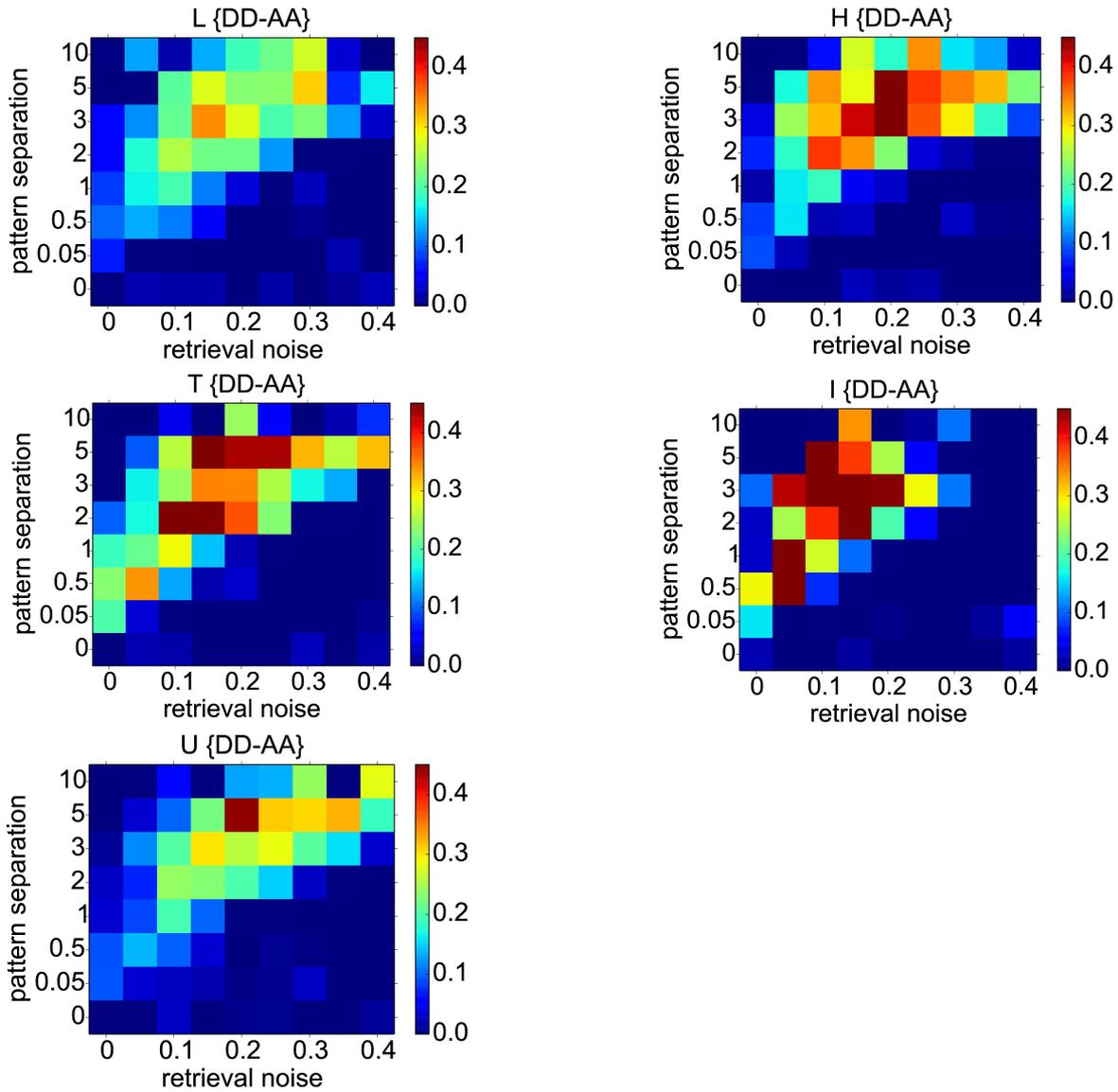


Figure 28. Dynamics of memory retrieval for different stimuli.

Color code represents the difference in memory retrieval for the memories stored in retrieved in depressive state and for memories stored and retrieved in asymptomatic state (DD-AA), for the 30th element in the sequence. Each panels shows the retrieval for a range of parameters ps and m for a particular stimuli “U”, “L”, “T”, “H”, and “I”. Retrieval error decreases with increase of ps parameter for all stimuli and increases with noise.

Figure 28 shows difference in retrieval error between DD and AA scenarios (DD-AA) for range of retrieval noise and ps parameters for the 30th pattern (element) in a sequence. The difference between DD and AA increases with increase in ps parameter, which is true for all objects. Interestingly, the difference in the retrieval error is slightly larger for the letters 'I' and 'H' than for 'U', 'L' and 'T'. This difference might be due to the additional symmetry of the letters 'I' and 'H' that the other letters lack, i.e., a symmetry for a rotation by 180 degrees.

Overall, this finding confirm that less accurate memory retrieval observed in the depressive state is robust and it is not a consequence of selecting a particular object as input.

3.5.6. Impact of depressive episode duration on retrieval performance

fMRI studies have shown that there is a reduction in the hippocampal volume in MDD patients and that this volume reduction increases as the depressive episode continues (Campbell et al., 2004; Pantel et al., 1997; Zubenko et al., 1990). Since the hippocampus plays crucial role in the episodic memory functioning, it would be expected that memory deficits worsen as the DE lingers. I therefore hypothesized that the impairment in AN correlates with the duration of the depressive episode. To test this hypothesis, I varied the duration of the symptomatic period while keep the total number of stored memories constant. As a result the preceding asymptomatic was shortened as the symptomatic period lengthened. This variation was achieved by varying the parameter j (see section 2.5), however, for illustrative purposes, I report the fraction

$$\frac{\text{duration of the symptomatic period}}{\text{total duration}} = \frac{n-j}{n} .$$

I used values of 20%, 50% and 100%, representing short, intermediate and long durations of DEs, respectively.

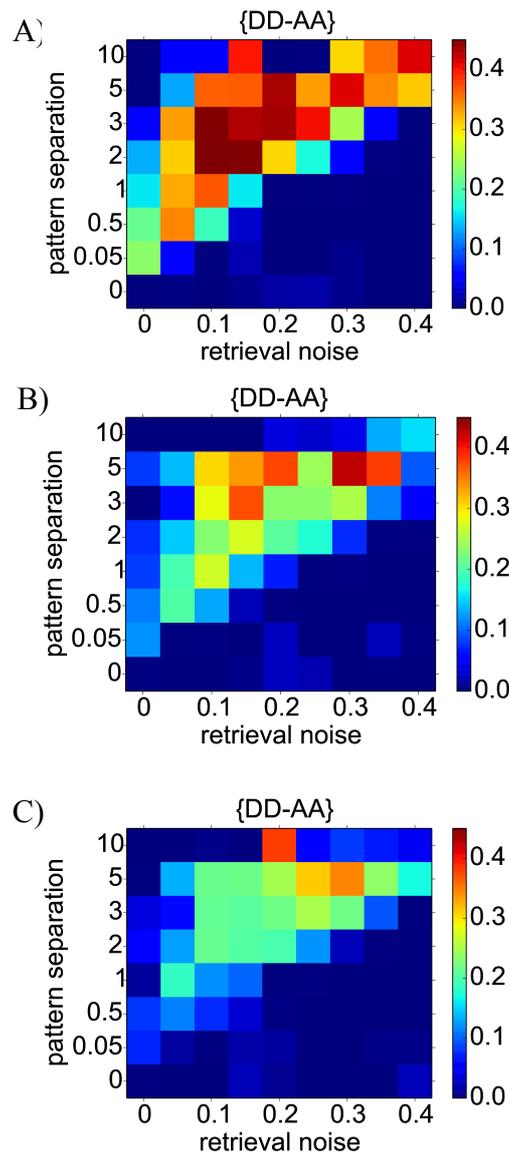


Figure 29. *Depressive episode duration is associated with higher retrieval error.*

Color code represents the difference in retrieval error of memories stored and retrieved in asymptomatic state and memories stored and retrieved during depressive state (DD-AA) with different length of depressive episode: **A)** long DE (100% overlap of AN), **B)** intermediate DE (50% overlap of AN), and **C)** short DE (20% overlap of AN). However, with length of depressive episode decreases retrieval accuracy. The retrieval error is calculated for the 30th element in the sequence ($n=30$), for a various number of stored sequences and range of retrieval noise parameters. The retrieval error is calculated for the 30th element in the sequence ($n=30$), for a range of parameters ps and rn , for a simulations with image sequences of the object “T”.

For all durations of DE, memory retrieval in the asymptomatic state is more accurate than retrieval in the symptomatic state (Fig. 29). Furthermore, memory performance in the model is influenced by the duration of the DE such that the difference in the retrieval was more prominent for depressive episodes with longer duration.

4. Discussion

4.1. Summary

4.1.1. Finite state machine and the dynamical systems model

I have developed a finite-state machine to systematically define the disease states in the course of MDD together with operational criteria for the terms remission, recovery, relapse, and recurrence. I used a simple dynamical systems model to simulate the day-to-day fluctuations in the mood that might correlate with MDD. While this model is not a physiological model, it incorporates several parameters that can be associated with physiological mechanisms. The advantage of this model is that it can incorporate several biological and psychological factors that are thought to affect MDD, and describe their potential interactions.

Combining the finite-state machine and dynamical systems model, I studied the dynamics of disease states in MDD and found that two sub-populations, one high-risk and one low-risk, are required in dynamical systems model to account for the empirical data.

Accordingly, I modeled occurrence and recurrence rates of depressive episodes as well different kind of therapies for major depressive disorder such as antidepressant treatment, cognitive-behavioral treatment, and life style changes. The two sub-populations model is able to reproduce many, though not all, observations quite well.

One parameter, d , I have not associated with a physiological or cognitive roles, yet. The influence that parameter d has on the occurrence rate and time-to-remission suggests that d might correlate partly with amygdala activity. Indeed, other authors have tied the amygdala to depression (Siegle et al., 2007; Surguladze et al., 2005) . Hyperactivity in the amygdala is a common finding during baseline conditions in MDD (Drevets et al., 2002) and has been interpreted as a valence-specific effect that causes a negative memory bias (Hamilton & Gotlib, 2008; Ramel et al., 2007).

4.1.2. Three state Markov chain model

The Markov Chain Model provides a possibility to simulate the dynamics of the mood and to study the effect of MDD on life time expectancy. In order to model the effect of MDD

on life duration, the finite state machine model was modified. Specifically, the terminal state was introduced to account for people that suffer a premature death due to suicide, or other reasons, such as, for example accidents, unrelated medical conditions.

Combining the modified finite-state machine and Markov chain model, I studied the dynamics of disease states in depression and, like in the dynamical systems model, I found that two sub-populations, one high-risk and one low-risk, are required in the three state Markov chain model to account for the empirical data. The two sub-populations Markov chain model is able to reproduce reliably occurrence rate and recurrence rates of MDD as well effect of MDD on life time expectancy. Accordingly, individuals with MDD have a lifespan that is about five year shorter than healthy individuals. Furthermore, the results of my model showed that more individuals suffer a premature death, if they have experienced a DE as compared to those who experienced none. Interestingly, low- and high-risk subpopulations showed different correlations between life expectation and the number of depressive episodes. In addition, the transition to the terminal state is less likely to occur from the asymptomatic state than from the symptomatic state.

4.1.3. Memory model

I have developed a computational model to study the influence of AN on episodic memory storage and retrieval. I found that memories stored with AN were more accurate compared to memories stored without AN. Furthermore, I studied how changes in the number of stored memories influences retrieval and found higher memory load reduces the accuracy of memory retrieval.

Based on the assumption that AN is impaired in MDD, I modeled memory function in the depressive state with reduced AN and compared this with memory function in the asymptomatic state with intact AN. A subsequent switch between the asymptomatic and the depressive state might occur, and it might happened that memories are stored in one state and retrieved in another state. Therefore, three different scenarios regarding episodic memory storage and retrieval were simulated: memory stored and retrieved in the asymptomatic state, memory stored in the asymptomatic and retrieved in the depressive state, and memories stored and retrieved in the depressive state.

I found that episodic memories stored during the asymptomatic state were more accurately retrieved than episodic memories stored and retrieved during the depressive state. Similarly, I found that episodic memories stored during the asymptomatic state were more accurately retrieved than episodic memories stored in the asymptomatic and retrieved during the depressive state. Moreover, I found that accuracy of the episodic memory retrieval increases with the pattern separation, but only until a certain value. Further increase will increase the retrieval error. An increase in the retrieval noise enlarges the retrieval error and blurs superiority of the retrieval in AA in comparison to AD and DD. These results were not specific to the particular input used, and generalized to other inputs, suggesting that this result is robust.

Furthermore, I model and study how the dynamics of memory retrieval depends on the duration of depressive episode changes and found that retrieval error increases with an increase in the depressive episode duration.

4.2. Detailed discussion

4.2.1. Comparison of the dynamical systems model with the three state Markov chain model

My first attempt to reproduce epidemiological data with single populations dynamical systems model, was not successful. However, the two-sub-populations dynamical systems model proved to be suitable for reproducing epidemiological data for occurrence and recurrence rates of MDD. Similarly, a successful approach was found by using two-sub populations in the three state Markov chain model. Table 7 summarizes the comparison of the results of the models and epidemiological data regarding occurrence rate and recurrence rates.

Results of the two models regarding the occurrence rate and the recurrence rates are almost identical. The main difference between the two models is in run-time consumption.

Although simulations of both models are performed in the same program (see Methods), the dynamical systems model was more efficient. A benchmark test for generating a single course of the disease for a period of 70 years indicates a ten times faster performance of the dynamical systems model in comparison to the three state Markov chain model.

Table 7. Comparison of OR and RR of the models and epidemiological data.

Variable	Epidemiological data (American Psychiatric Association, 2000)	Dynamical systems model	Three state Markov chain model
Occurrence rate	20%	20%	20%
Rate of 1 st recurrence	50%	40%	39%
Rate of 2 nd recurrence	70%	90%	88%
Rate of 3 rd recurrence	90%	96%	98%

The necessity of using two sub-populations in both models for reproducing the epidemiological data suggests that this finding is not an artifact and in fact two sub-populations exists in the general population. From a clinical perspective, the existence of the two sub-populations of patients with MDD is of interest because these sub-population might have different etiology and consequently required different treatment. Accordingly, people with MDD can vary widely in terms of symptoms, co-morbidities, clinical course, severity, and treatment responsiveness (American Psychiatric Association, 2000).

In an attempt to make sense of this heterogeneity, different subtypes of depression have been proposed throughout the history of psychiatry (e.g., atypical, melancholic, psychotic). In order for a subtype to be clinically useful, the subtype should be able to predict treatment response and thus have implications for the selection of treatment (Kendler et al., 1996; Lamers et al., 2010; Rush, 2007; Seo et al., 2011).

4.2.2. Comparison between observations and the dynamical systems model outputs

The dynamical systems model offers an account for why AD treatment has only low rates of success and in some studies did not show superiority over placebo (Rush, 2007). In the dynamical systems model, the distribution of DE durations in the treated patients is very broad with a peak at about 3 months and a long tail including episodes longer than 9 years. The properties of this distribution suggests two things. First, many studies were not able to

see an effect of the AD treatment because the time window of observation was not long enough. Second, an effect of AD treatment is highly variable. Note that the parameters are identical for each simulation, so the widely different durations of depressive episodes did not emerge as a result of differences in the parameters.

Furthermore, the risk of relapse seemed similar across heterogeneous groups of patients including those who had recently responded to treatment of an acute episode and those who had been successfully taking maintenance treatment for several months or even years (Kirsch, 1998; Thase, 1999). Similarly, the dynamical systems modeling results indicate that AD treatment does not decrease the probability of developing another DE in the future. Hence, the drugs may lower the probability of the depressed state temporarily, but as the effect in the brain decays, the rate of moving towards a depressed state increases.

4.2.3. Comparison between observations and the three state Markov model outputs

Results of the three state Markov chain model predict that MDD patient will die five years earlier than people without MDD. My results are in the line with epidemiological studies which report that depending on the cause of death, MDD patients died between 2.5 and 8.7 years earlier than non-depressed patients (Marcus et al., 2012; Zivin et al., 2012). In most of the simulations with a history of depression, the symptomatic state precedes the terminal state, which implies that the risk of suicide is higher when a person is in the symptomatic state. Conversely, people without history of MDD die prematurely less frequently.

The sub-populations in the model do not show only differences in terms of occurrence and recurrences rates but also differ regarding life expectancy. Life expectancy in the low-risk sub-population is not influenced by the number of depressive episodes. By contrast, the high-risk sub-population shows decrease in average lifespan, which is not surprising because this sub-population represents more chronic cases, with an average of about 20 experienced episodes. Paradoxically, patients in the high-risk sub-population seem to have a benefit from an increase in the number of depressive episodes. Average life span increases with increase of number of depressive episodes. Note that the parameters are identical within sub-population for each simulation, so the difference in life time

expectancy in high-risk sub-population did not emerge as a result of differences in the parameters.

There are two possible explanation for this paradoxical result. First, individuals with recurrent depression are more willing to seek treatment and help, or family members and relatives were more cautious and supportive. Second, whatever the biological or psychological process that underlies causality between MDD and suicide, it has limit. Hence, most of the changes that occur do so in the first few episodes of the disorder and then, with further episodes, either slows down or stops altogether.

Hence, my results predict that the strength of the association between suicide and depressive episode declines with increasing number of previous depressive episodes. Given the non-experimental nature of these results, additional studies that examine influence of number of episodes on life expectancy are necessary. Furthermore, the results of the model implicate that the number of depressive episodes might not be a good prognostic factor to investigate the impact of MDD on life expectancy.

4.2.4. Dimensionality of the model and history-dependence

DSM-IV-TR, used worldwide as a diagnostic tool, does not define absolute boundaries between mental disorder and no mental disorder. However, the use of a categorical classification is fundamental in everyday clinical practice and research, as well as for health services and insurance purposes. The categories are prototypes, which define certain criteria related to symptoms, i.e., we say that a patient with a close approximation of the ill-prototype is ill. However, it has been argued that MDD should not be treated as a categorical condition and instead be viewed along a continuum (Widiger & Samuel, 2005). Instead of categorizing subjects as ill or healthy, they should be scored on a graded scale according to how many symptoms the subject expressed and/ or how severe the symptoms are. Some authors go even further to suggest that a one-dimensional approach is not sufficient and that multiple dimensions have to be used to capture the multiple facets of depression.

In this study, I reject the view that depression is a categorical condition, and model the dynamics of MDD with a continuous state variable (M) using the dynamical systems

model. However, since virtually all existing observations on MDD have been based on categorical classification and clinical practice depends on it, I developed the finite-state model to translate between the dynamics of a continuous one-dimensional system and the categorical classification of disease states. Since I am at an early stage of the modeling process, it appeared prudent to start with a single state variable to model the dynamics of MDD, especially given the paucity of data that could constrain higher-order systems. In addition, the general approach in modeling is to start with a parsimonious model and to include more complexity only if and when additional mechanisms are required. So far, the simple model I studied has been able to account for a surprisingly wide range of observations. A consequence of the choice of a one-dimensional model is that, at a given point in time, the system's behavior is fully determined by the one state variable. As a result, the system does not depend on the previous history of the system. For instance, the probability of developing a DE does not depend on whether the patient has previously experienced a DE or not.

To allow the history to affect the behavior of the system, one could have included additional state variables, which would imply more complex higher-order systems. I am aware that to fully understand depression, it eventually will be necessary to incorporate such history-dependence. For instance, epidemiological studies have found evidence that adverse experience during childhood, such as sexual or physical abuse, neglect or loss of parents, is associated with substantial increase in the risk of developing depression (Chapman et al., 2004; Edwards et al., 2003; Felitti et al., 1998; Heim et al., 2008). Additionally, childhood trauma can change symptom patterns and the clinical course of MDD. For example, childhood trauma has been consistently associated with an early onset of depression (Bernet & Stein, 1999; Gladstone et al., 2004), as well as larger numbers of depressive episodes or more chronic depression (Zlotnick et al., 2001; Zlotnick et al., 1995). Moreover, childhood adverse experience has been associated with a decreased responsiveness to pharmacological treatment in patients with dysthymia and depression (Hayden & Klein, 2001; Kaplan & Klinetob, 2000).

However, not all forms of depression are associated with childhood adversity, and I may speculate that the high-risk sub-population in my models may partly include the group of

MDD patients with a history of childhood trauma. Indeed, patients within the high-risk sub-population in my model tend to have more episodes, longer duration of episodes as well as more chronic episodes than those in the low-risk sub-population.

4.2.5. Pattern separation, AN and memory

Computational models of the hippocampus and medial temporal lobe have suggested that the DG is especially suited to perform pattern separation, possibly due to adult neurogenesis (Becker, 2005; Marr, 1971; McNaughton & Morris, 1987; Treves et al., 2008). Similarly, in my model AN, pattern separation improves the accuracy of memory retrieval. Interestingly, improvement in memory retrieval increases with the increase in AN, but only until certain value, beyond that value the effect vanishes. This implies that there is an optimal level of AN, which is valuable for memory retrieval.

My result is consistent with experimental results that show that increasing the rate of AN indeed leads to better memory performance in humans. It has been established that new neurons are born in the DG of an adult human brain (Eriksson et al., 1998). Although there is mounting empirical support from rodent studies for the role of the DG neurogenesis in minimizing interference between overlapping memories, unfortunately, it is not possible to directly and non-invasively assess DG neurogenesis in the human brain. However, there is indirect evidence for a role of AN in separating overlapping memory in humans. Studies in animals reported that aerobic exercise stimulates adult hippocampal neurogenesis (Fabel et al., 2009; Olson et al., 2006; Pereira et al., 2007; van Praag et al., 1999). In mice, the increase in adult neurogenesis is accompanied by an increase in DG blood volume (Pereira et al., 2007). MRI studies that follow DG blood volume show that, after 12 weeks of exercise, blood volume increases in both mice and humans. At the same time, memory performance improved (Pereira et al., 2007). A number of other studies, have found that healthy human adults who experienced larger improvements in fitness demonstrated a significantly greater improvement to separate between similar stimuli (Déry et al., 2013). However, the manipulations of the rate of AN have not been made systematically enough to say whether even higher rates of AN will lead to a worsening memory performance, as my results suggest. This aspect is thus a novel prediction of my model.

It has been proposed that with AN each new event is encoded uniquely so that two similar memory sequences that are stored at different times are associated each with a different random DG pattern (Aimone et al., 2009; Cheng, 2013). In this way, the two similar sequences that would interfere when stored in the same network, become more dissimilar (pattern separation), thus reducing interference. In line with these suggestions, the slightly larger difference (DD – AA) in the retrieval error for objects 'I' and 'H', relative to 'U', 'L' and 'T', might be caused by higher interference. The letters 'I' and 'H' has an additional rotational symmetry, so the same shape is repeated during a full rotation. These similar pattern are likely to lead to more interference that can be alleviated by pattern separation. Hence, the larger benefit of AN.

4.2.6. Correlate of the retrieval noise in the memory model

In all simulation of the memory model, I use retrieval noise, however, I did not associate this parameter with a potential mechanism, yet. The influence of retrieval noise on memory function suggests that retrieval noise might be linked to the theta rhythm.

Other authors have suggested that the physiological changes during the theta rhythm may enhance the selective context-dependent retrieval of individual encoded sequences without interference from other sequences (Hasselmo, 2005b, 2005c). During the retrieval process, the activity associated with the first pattern will spread across established synapses to trigger sequential spiking in other patterns, reading out the complete sequences (Hasselmo, 2005a; Levy, 1996; Wallenstein & Hasselmo, 1997). This synchronized activity increases the power of oscillations observable in data recorded using electroencephalography. Increased oscillations in the theta band (3–8 Hz) have been robustly reported during memory processing (Hasselmo, 2005b; Osipova et al., 2006; White et al., 2013), suggesting that theta oscillations play a role in memory processing. Accordingly, in the retrieval session, the theta activity was stronger for recognized items compared with correctly rejected new items (Osipova et al., 2006). Therefore, I hypothesize that an increase in retrieval noise corresponds to a decrease in theta power.

It has been reported that during baseline oscillatory activity (subject awake with eyes closed), depressive subjects show abnormal dynamics in the theta-frequency band (Linkenkaer-Hansen et al., 2005). Moreover, the magnitude of the abnormality was

correlated with the severity of depression in the patients (Linkenkaer-Hansen et al., 2005). Although studies in animals and humans have demonstrated that theta oscillations play a role in declarative memory encoding and retrieval, little has been done to investigate the correlation between memory performance and theta power in depressive patients. It remains to be investigated, whether abnormal theta activation might underlie memory deficits observed in MDD patients. Given this uncertainty, I have opted to compare memory performance between asymptomatic and depressive states using the same level of retrieval noise. If it turns out that the retrieval noise is higher for retrieval in the depressive state (which corresponds to abnormal theta) than in the asymptomatic state, my model would predict an even larger memory deficit in the depressive state.

I found that memory were more accurately retrieved in the asymptomatic state (AA scenario with intact AN) than in the depressive state (DD scenario with impaired AN), which is in line with experimental results. Furthermore, I found that accuracy of memory retrieval is correlated with the duration of the depressive episode. Thus, an accurate episodic memory retrieval requires selective retrieval of one memory without interference from other memories, retrieval error for memories stored during the depressive episode will be extensive.

4.2.7. Over-general memories in depression

In the introduction, I discussed the current research on over-general memory in MDD. From the accumulated research, it is clear that people who suffer from any sort of mood disorder have a decreased ability to recall specific memories from their past and therefore are unable to create specific future memories (Williams et al., 2007). However, I propose that episodic memory dysfunction might also account for over-general memories observed in MDD patients. Episodic memories together with personal semantic information form autobiographical memory. By definition, episodic memories refer to specific events, whereas semantic memories refer to general facts. I suggest that the over-general memory effect can be thought of as a shift from the retrieval of episodic memories to a retrieval of semantic memories.

Episodic memory retrieval will be impaired during a depressive episode, as I found. Therefore, when autobiographical memories formed during a depressive episode is cued,

retrieval is more likely to result in a semantic memory, which in turn results in over-general memories. My suggestion is consistent with previous ideas that over-general memory could result from reduced episodic recall, increased semantic recall, or both (Söderlund et al., 2014). While Williams et al. (2007) were able to explain the origin of over-general memories based on the Conway and Pleydell-Pearce model, my model can account for both over-generality and episodic memory deficits.

4.2.8. Further avenues for studying MDD

I do not claim that my model of the dynamics of depression is the final word. On the contrary, it has several apparent limitations some of which I have discussed above. However, I believe that my model provides some new insights into the complex dynamics of MDD and offer new avenues for studying MDD. Ultimately, I hope that such efforts will lead to a clearer understanding of the nature of MDD.

4.2.8.1. Is the number of depressive episodes a good prognostic factor?

Clinicians mostly use terms such as occurrence rate and recurrence rates, which are based on the number of experienced depressive episodes. As I already mentioned, looking only into number of depressive episodes as prognostic factor for life time expectancy might be insufficient. A better parameter could be the length and/or severity of a depressive episode. Existing epidemiological studies do not provide sufficient data concerning correlation of severity of depression and mortality. The International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification (DIMDI - ICD-10-GM, 2015), which is the official classification for the encoding of diagnoses in inpatient and outpatient medical care in Germany, already proposes to divide MDD according to the severity of the symptoms. Accordingly, the currently valid version is ICD-10-GM 2015 divides MDD in four classes according to the severity, from light depression, moderate depression, severe depression without psychotic symptoms and severe depression with psychotic symptoms (DIMDI - ICD-10-GM, 2015). In the face of the impact of MDD on society and medical health systems, collecting this kind of data in addition to number of depressive episodes, would be beneficial and will lead to further investigation and better understanding of the dynamics of depression.

4.2.8.2. Depression and gender difference

Gender difference in the occurrence and in the course of depression might be responsible for the higher prevalence rates among females. It has been reported that women are twice as likely to be diagnosed with MDD (Kessler, 2003; Nolen-Hoeksema, 2001; Parker & Brotchie, 2010). However, population-based estimates indicate that there are still a significant number of men who suffer from the disorder, and there is evidence that the gender gap is narrowing (Addis, 2008; Kessler et al., 1993). Moreover, researchers have increasingly suggested that MDD can be “masked” in men and that this may produce an underestimate of the true rates at which men suffer from the disorder (Kessler et al., 1993; Wilhelm et al., 1997). Studies of help-seeking behavior for psychiatric disorders consistently demonstrate that, on average, men are less likely than women to utilize mental health services (Kessler et al., 1994b; Kessler et al., 2005; Stoolmiller et al., 2005). For a variety of reasons, men’s mental health has been relatively invisible in the scientific and clinical literature.

Furthermore, women have more often chronic depression such that the ratio for chronic depression is 3 women to one men (Kessler et al., 1993; Nolen-Hoeksema, 2001; Parker & Brotchie, 2010). These findings are, however, controversial, some studies report higher rates of first-onset depression in females rather than a greater number, or longer duration, of episodes others show a female preponderance in recurrent and chronic depression (Addis, 2008; R C Kessler et al., 1993).

Another interesting gender difference regards suicide in depression. Although women are twice as likely to attempt suicide, only 1% women diagnosed with depression commit suicide while 7% of men diagnosed with depression commit suicide (Bracke, 1998; Stefánsson et al., 1994).

Although it would be possible to model gender differences in my model, I decided not to include them due to heterogeneity of the clinical observations and the controversies about the findings.

4.2.8.3. How to model memories that are stored in depressive but retrieved in asymptomatic state?

As I have shown in Figure 25, there are four possible scenarios that might influence memory functioning: memories stored and retrieved in the asymptomatic state (AA), memories stored in the asymptomatic state and retrieved in the depressive state (AD), memories stored and retrieved in the depressive state (DD), and memories stored in the depressive state and retrieved in the asymptomatic state (DA). In my thesis work, I considered the first three cases, but what about memories stored in the depressive state and retrieved in the asymptomatic state?

In this case, adult neurogenesis is impaired during memory storage within a depressive episode, and new inputs are not assigned a unique DG pattern during encoding. In the subsequent asymptomatic state, AN is normal and new sequences are stored with a newly generated random DG pattern. Since the model does not take into account the age of the memory at retrieval, it is inconsequential in which order the asymptomatic and depressive states occurred. In other words, retrieval in the DA case is equivalent to that in AD. Hence, all results reported here for AD would hold equally for DA. To the best of my knowledge, no study to date has examined retrieval in the asymptomatic state of episodic memories that were stored in a depressive state. So there is no basis for a comparison to my model's predictions.

4.3. Conclusions

In summary, computational neuroscience represents a very important column in future research, in the entire field of psychiatry in general and MDD in particular. Mathematical models are quantitatively crisp and concrete, which might help us to close the huge gaps in our understanding of mental illnesses. Computational neuroscience is non-invasive approach to examine neuronal mechanisms and their modifications and possible interaction in complex psychiatric diseases like MDD.

The main goal of my work was to show the potential power of computational modeling of MDD and the need for different quantitative data for understanding MDD. In this work, I have provided a mathematical framework for modeling MDD. I proposed and analyzed

two dynamical models of the time course of MDD and a model of memory function in depression. I hope that my modeling work will promote new empirical studies and/or reexaminations of existing data. In particular, I believe that it is important to monitor the disease progression in MDD on a day-to-day basis. The finite-state machine model that I developed here could be used to define the disease state of MDD more consistently and the operational criteria might lead to improved design, interpretation, and comparison of studies of the natural course and clinical therapeutic trials.

I suggested that episodic memory in depression might occur due to deficit in adult neurogenesis and/ or change in theta power. Furthermore, I suggested that episodic memory dysfunction might also account for over-general memories observed in depressive patients, causing a shift in the retrieval episodic memories to the retrieval of semantic memory.

In this respect, I view my work as an initial step in developing a mathematical framework that ultimately leads to the development of more detailed models of MDD and a better understanding of MDD and its effects on cognitive processes.

5. References

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6. Appendix:

6.1. Curriculum Vitae

Personal information

<i>Name</i>	Selver Demic
<i>Date of birth</i>	22.03.1983
<i>Place of birth</i>	Rozaje, Montenegro
<i>Nationality</i>	Montenegrin
<i>Address</i>	Ruhr-University Bochum Mercator Research Group "Structure of Memory" Faculty of Psychology Universitaetsstr. 150 44801 Bochum Germany
<i>Phone</i>	+49 - 234 - 322 96 16
<i>Fax</i>	+49 - 234 -321 44 63
<i>e-Mail</i>	Selver.demic@rub.de

Education

<i>July 2010</i>	State Examination Medicine <ul style="list-style-type: none">• University Podgorica, Montenegro
<i>Oct. 2002- Mar. 2009</i>	Medical studies <ul style="list-style-type: none">• University Nis, Serbien
<i>Sept. 1998 - July 2002</i>	Diploma in High school „30. September” <ul style="list-style-type: none">• Rozaje, Montenegro

Working experience

<i>Apr. 2015 - July 2015</i>	Teaching Assistantship RUB Research School <ul style="list-style-type: none">• Ruhr University Bochum
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- Apr. 2009 - Apr. 2010* General working experience for the period of one year in the hospitals of Rozaje (DZ Rozaje)
- Rozaje, Montenegro
- July 2009 – Aug. 2009* Internship in the Clinic „La Princesa”
- Madrid, Spain, (IFMSA)
- Aug. 2008 - Sept. 2008* Internship in Clinic „University main hospital”
- Alexandria, Egypt, (IFMSA)
- July 2007 – Sept. 2007* Working as a volunteer to Neurology Department at the Hospital Berane
- Berane, Montenegro
- Feb. 2006 – Mar. 2006* Internship in the Clinic „Santa Casa de Sao Paulo”
- Sao Paulo, Brasilien (IFMSA)

Teaching Experience

- Apr. 2015 – Jul. 2015* Teaching Assistant: “Mathematical Psychology”
- Computer lab for B.Sc. Students, Ruhr-University Bochum
- Jan. 2015 - May 2015* I have supervised B. Sc. Informatics Bachelor Thesis
- Ruhr-University Bochum
- Apr. 2014 – Jul. 2014* Teaching Assistant: “Mathematical Psychology”
- Computer lab for B.Sc. Students, Ruhr-University Bochum
- Apr. 2013 – Jul. 2013* Teaching Assistant: Modeling Cognitive Processes” ,
- Computer lab for B.Sc. Students, Ruhr-University Bochum

Awards

- Oct. 2014 – Dec 2015* Scholarship of the Stiftung Mercator
- Ruhr-University Bochum
- Oct. 2011 – Sept. 2014* Scholarship of the IGSN (International Graduate School of Neuroscience),
- Ruhr-University Bochum

Oct. 2010 – Sept. 2011 Scholarship of the Sonderforschungsbereich (SFB) 874
• Ruhr-University Bochum

Computer skills

Operating systems Microsoft Windows, Linux

Programing MATLAB, Python, Spike 2

Languages

Montenegrian Mother tong

English Excellent command

German Excellent command

French Basic communication skills

Hobbies

From Apr. 2013 Active football referee in “Kreis Bochum”

From Jul. 2012 Member of Football club „FC Sandzak Hattingen” in Hattingen, Germany

Others

Driving license Category **B**

Attended conferences

and seminars

Mar. 2015 11th Göttingen Meeting of the German Neuroscience Society (Göttingen)

Nov. 2014 44th Annual Meeting of the Society for Neuroscience (Washington DC, USA)

Jul. 2014 9th FENS Forum of Neurosicence (Milan, Italy)

May 2013 Computational Cognition Alliance Meeting (Osnabrück)

Dec. 2012 FENS-IBRO-HERTIE WINTER SCHOOL (Obergurgl, Austria)

Dec. 2011 IBRO-UNESCO School on Advanced Theoretical and Computational Neurosciences (Cape Town, South Africa)

Mar. 2009 The 4th International Pirogov Students Scientific Medical Conference(Moscow, Russia)

<i>Sept. 2008</i>	19 th European Students Conference (Berlin)
<i>May 2008</i>	49 th Students Congress of Medical Science of Serbia (Lepenski Vir, Serbia)
<i>Apr. 2007</i>	48 th Students Congress of Medical Science of Serbia (Kopaonik, Serbia)

6.2. List of Publications

- **Demic, S., Cheng, S. (2011).** *The role of adult neurogenesis in depression and memory.* Poster at Cape Town School of Advanced Theoretical and Computational Neurosciences, December 12 – 23, Cape Town, South Africa.
- **Demic, S., Cheng, S. (2012).** *Modelling the etiology of depression.* BoNeuroMed, pages, 12 – 15.
- **Demic, S., Cheng, S. (2012).** *Modelling the etiology of depression.* Poster at FENS-IBRO-HERTIE-WINTER SCHOOL, December 9 – 16, Obergurgl, Austria.
- **Demic, S., Cheng, S. (2014).** *Modeling the dynamics of depression across the life span.* Poster at FENS, July 5 – 9, Mialno, Italy.
- **Demic, S., Cheng, S. (2014).** *Modeling the dynamics of disease states in depression.* Poster at SfN, November 15 – 19, Washington, USA.
- **Demic, S., Cheng, S. (2014).** *Modeling the dynamics of disease states in depression,* PLoS ONE 9(10), e110358, [doi:10.1371/journal.pone.0110358](https://doi.org/10.1371/journal.pone.0110358) [local].
- **Demic, S., Cheng, S. (2015).** *Modeling the dynamics of disease states in depression.* Poster at 11th Göttingen Meeting of the German Neuroscience Society, March 18 – 21, Göttingen, Germany.

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