Journal of Theoretical Biology 259 (2009) 269–279

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

A multi-etiology model of systemic degeneration in schizophrenia

Anca Rădulescu *

Applied Mathematics, University of Colorado at Boulder, UCB 526, Boulder, CO 80309-0526, USA

ARTICLE INFO

Article history:
Received 22 October 2008
Received in revised form
8 March 2009
Accepted 11 March 2009
Available online 27 March 2009

Keywords:
Schizophrenia
Etiology
Stress/vulnerability
Autoimmunity
Modeling
Dynamical system

ABSTRACT

We discuss the possibility of multiple underlying etiologies of the condition currently labeled as schizophrenia. We support this hypothesis with a theoretical model of the prefrontal–limbic system.

We show how the dynamical behavior of this model depends on an entire set of physiological parameters, representing synaptic strengths, vulnerability to stress-induced cortisol, dopamine regulation and rates of autoantibody production. Malfunction of such different parameters produces similar outward dysregulation of the system, which may readily lead to diagnostic difficulties for a clinician.

Techniques that provide a spectrum/profile of neural and steroid functions may be helpful in clarifying these diagnostic dilemmas.

1. Introduction

1.1. Schizophrenia. disease or syndrome?

As defined today, schizophrenia is a serious chronic disorder, affecting about 1.1% of the population (over 65 million people worldwide, according to NIMH statistics). It is a source of unrelenting personal and social drama, and underlies debilitating problems from unemployment and long-time hospitalization to suicide.

As much as it would be beneficial to understand this disease and eliminate the torment it brings to human life, its cause is still unknown by research and its current treatment brings no reliable cure. The definition of schizophrenia itself is elusive, having been created by science (DSM-IV, 1994)—based on statistical behavior, rather than etiology—so as to somehow encompass all the complexities of a syndrome otherwise intractable. Progress has been made in understanding the effects of particular antipsychotics on some of the modules involved in the disease process, such as the dopaminergic or serotonergic brain systems, but the drugs that are being used may still treat the effects of the disease rather than its mysterious cause (Kapur and Mamo, 2005).

Indeed, as of today, the etiology of schizophrenia is still not understood. It clearly affects structurally and functionally various cortical and subcortical regions involved in cognitive, emotional and motivational aspects of behavior (Lawrie, 2003; Ananth, 2002; Staal, 2001; Andreasen, 1986). However, it seems that the days when schizophrenia was labeled as "brain sickness" are over. Its disease process has been shown to have much more extensive physiological effects, including endocrine (Ritsner et al., 2004) and autonomic (Mujica-Parodi and Yeregani, 2005) factors, and has been correlated to a plethora of somatic abnormalities, affecting aspects as thorough as autoimmunity mechanisms, and as simple as "eating your vitamins."

In fact, "schizophrenia's" heterogeneous set of symptoms (hallucinations, delusional beliefs, cognitive dysfunctions, thought disorder, emotional flattening, social withdrawal) is diverse enough to possibly represent a whole collection of diseases in their own right (Bruce and Turetsky, 2002). In addition, most of the illness' signs and symptoms are not unique to schizophrenia and overlap with the symptoms of other mental conditions, such as major depression, bipolar mania, or post-traumatic stress disorder. In this context, newer research is gradually moving in the direction of altering the existing unreliable terminology, even toward entirely replacing it by a physiology-based system, optimizing predictive power (Andreasen, 2000; Jansson and Parnas, 2007; Peled, 2006).

Altogether, the diversity in symptomatology and the intractability of the disease's etiology could in fact have a *bona fide* explanation: there are *multiple etiologies* of schizophrenia (Crow, 1980). It seems sensible to hypothesize that the cognitive and behavioral symptoms of schizophrenia are perhaps a *generic* outward psychopathological manifestation—much like "heart condition" in the somatic context—which could be produced and maintained by any of an entire collection of causes and mechanisms. Each etiology, although producing similar clinical symptoms, has however a different prognosis and should have a different diagnosis and most certainly a different treatment. This

* Tel.: +1 303 786 1616; fax: +1 303 492 4066.
E-mail address: radulesc@colorado.edu

0022-5193/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2009.03.024

is why it is clinically important to make these distinctions, and to strive for a novel organization of the psychiatric terminology (see Section 4.2). The novel criteria and classifications should be constructed to better assist in ascertaining the pathophysiological basis of schizophrenia and of its subgroups.

In order to make it linguistically easier to express clinical distinctions, we isolate a subcategory of the complex physiological abnormalities currently labeled as "schizophrenia." We define "neoschizophrenia" to be a neurodegenerative disorder whose onset of symptoms occurs in the individual's mid-30s and is primarily due to a stress-related vulnerability of prefrontal and limbic regions (as further explained in the next section).

1.2. Vulnerability and prefrontal–limbic dysregulation

Schizophrenia has many neurobiological features suggesting an underlying dysregulation of emotional arousal (Finlay and Zigmond, 1997; Williams et al., 2004; Ritsner et al., 2004). Significant research over the past decade has isolated the amygdala, the hippocampus and parts of the prefrontal cortex as the brain areas most relevant in the mechanisms of fear conditioning and emotion processing, and implicitly in the genesis of psychosis.

More specifically, it has been proposed that schizophrenic symptoms constitute an end-stage of a cyclic and neurodegenerative process, in which a hereditary predisposition ("vulnerability", Nuechterlein, 1994) reduces the individual psychological threshold toward stimuli (Stamm and Buhler, 2001), to the point where even minor daily stresses will directly trigger psychotic experiences (Myin-Germeys et al., 2005). It has been further hypothesized and documented that the critical element in the physiological realization of this degeneration is the dysregulation of limbic regions. Specifically, this manifests as an imbalance between the two components of a feed-back loop: (1) the top-down control provided by the cortical systems over subcortical areas involved in emotion and (2) the control of neuromodulatory systems that in turn affect the cortex. For example, one possible view involves the ability of the hippocampus and prefrontal cortex to contextualize and inhibit activation of the amygdala, the excitatory module (Sotres-Bayon et al., 2004), which in turn drives a portion of the dopaminergic system via the nucleus accumbens. Outputs of the dopamine (DA) system modulate processing in the hippocampus and PFC, thus closing the feed-back cycle (see Section 2). In this context, it is perhaps not surprising that schizophrenia has remained hard to understand, as a system governed by complex limbic interactions.

One line of current thinking (referred to in recent literature as the "stress-diathesis model", Kaplan and Sadock, 1998) is that this vulnerability to stress in schizophrenia is based on a pre-existing prefrontal–limbic deficit (Medoff et al., 2001; Preston, 2005; Tamminga, 2006). More precisely, an impairment in hippocampal/prefrontal function may lead to decreased inhibition of the amygdala and subsequent higher arousal levels, even under minor stress. Through the hypothalamo-pituitary axis, the fear reaction triggers autonomic and endocrine effects (LeDoux, 2003), in particular increased cortisol levels (Sapolsky and Plotsky, 1990). These produce brain neurotoxicity (Weinberger and McClure, 2002) and further hippocampus damage (Pavlides et al., 2002), at the level of neurogenesis (Herbert et al., 2006; Wong and Herbert, 2005) and of hippocampal–PFC synaptic transmission (Cerqueira et al., 2007). This is possibly the main degenerative cycle in neoschizophrenia, which the author has discussed in previous work (Rădulescu, 2008).

This cortisol neurotoxicity hypothesis is gradually gaining ground in current approaches to mental pathology (Walker et al., 2008). However, other mechanisms of prefrontal–limbic vulnerability have been proposed by biological and clinical studies, whose bases do not necessarily reside within the physiology of the brain. A similar central dysregulation (and subsequent outward psychosis) could be the result of a multitude of causes, including genetic dysfunctions, drug abuse, brain trauma, or even lack of proper minerals from food (such as Vitamin B_{12} and folate, Ozcan et al., 2008; Haidemenos et al., 2007). These factors can all work toward altering brain parameters (such as inter-region connectivity/synaptic strengths, Konrad and Winterer, 2007; Seidman and Wencel, 2007), DA receptor dynamics (Laviolette, 2007), or the neuro-immune-endocrine interface (Hafner et al., 2005; Zhang et al., 2005) to a level which places the system in a mode of enhanced vulnerability to environmental pressure. We will argue that, although the outward effects of these factors can be similar to neoschizophrenia's signs and symptoms, they represent distinct pathologies and should be recognized and treated as such.

One of the better known factors of somatic origin which is potentially responsible for psychotic behavior is autoimmunity (i.e., the inability of the body to suppress the production of antibodies aimed against its own structures). In this paper, we extend our previous model of limbic vulnerability to include the effects of autoimmunity on the prefrontal–limbic system. After a short introduction on autoimmunity and psychiatric manifestations of autoimmune conditions, we organize the rest of the paper as follows.

Section 2 describes the brain pathways and physiological mechanisms included in our paradigm, and constructs the mathematical model. Section 3 illustrates, using simulations[1], the behavior of the model and its evolution in a few cases of interest. Section 4 relates this mathematical behavior with the brain pathophysiology, and places it within the context of identifying different potential etiologies for schizophrenia. Finally, Section 4.2 takes a glimpse into a possible future of psychiatric diagnoses and treatment, if based on such a temporal architecture modeling.

1.3. Autoimmunity—a road to psychosis

Basic and clinical experimental data have correlated autoimmune dysregulation to outward psychosis. To fix our ideas, we will consider a standard example of a systemic autoimmune condition: systemic lupus erythematosus (SLE). It affects mainly young people by attacking indiscriminately—with sudden, seemingly unpredictable flares—multiple organ systems, among which the brain. Neuropsychiatric manifestations have a prevalence of up to 75% in SLE (Stojanovich et al., 2007). Conversely, some (but not all) studies counting autoantibodies in the serum of schizophrenia patients have found high proportions of antibrain antibodies (Kuznetoza and Semenov, 1961; Fessel, 1962; DeLisi et al., 1985; Henneberg et al., 1994) (see also the Discussion). However, despite this strong correlation between autoimmune abnormalities and central neurological and psychiatric problems, studies have not consistently proven any causality between the two phenomena, in either direction. It is quite possible that the disease system contains bilateral interactions between the immunity and central nervous subunits (Bongioanni, 1993), as well as other external modulations (e.g., from external stress (Gaughran and Welch, 2007) and the subsequent hypercortisolemia). These back and forth connections, as well as the subsequent overlap in the neuropsychiatric manifestations associated to dysfunctions of the two physiological modules, increase the potential for misdiagnosis (in the sense of misinterpretation of

[1] All simulations were performed in MATLAB.

the symptoms when identifying the mechanisms responsible for them). The focus of this paper is on the possibility and importance of teasing apart the contribution of each such separate module, while still preserving the overall view of the whole functional ensemble.

Although not unexpected, this complexity complicates a possible global analysis that would lead to better understanding of the system. On the other hand, this understanding is clinically very important. Neurobehavioral symptoms of SLE—including depression, anxiety, psychosis, mania, cognitive dysfunction—have been more than once "misdiagnosed" as schizophrenia in a psychiatrist's office (Arthritis Research Campaign, 1998). Clearly, it is of crucial importance to avoid confusions, since in such a case a treatment trial should be planned to match the physiological autoimmune condition, not just to alleviate the outward psychiatric symptoms with antipsychotic medication (Cohen et al., 2004).

As we have already mentioned, in autoimmune conditions such as SLE, the body produces autoantibodies, i.e., antibodies to its own tissues. It is thought that most forms of autoimmunity start up for no obvious reason, apparently by chance (Edwards and Cambridge, 1998), with the production of an autoantibody which, through a vicious cycle, stimulates its own production. One such example in SLE is the autoantibody that targets a complement system molecule called C1q, causing decreased apoptotic cell clearance, and thus facilitating more autoantibody production (Scolding and Joseph, 2002). This and other complexities suggest that lupus may be driven by a whole series of connected such antibody cycles, possibly themselves generated by low C1q levels.

Among the variety of autoantibodies produced in SLE, some are particularly dangerous to the central nervous system (CNS). Several studies have focused on isolating antibodies that target specific brain structures, such as neuronal membrane antigens, ribosomal proteins or endothelial surfaces. For example: anticardiolipin (an antiphospholipid) produces prothrombotic effects which lead to ischemia and infarction and eventually to neuronal death (Gharavi, 2001). Additionally, antiendothelial antibodies (Valesini et al., 2006) contribute to the general damage of vessel wall endothelium, thus weakening the blood–brain barrier and allowing easier penetration of other antibodies or neurotoxic factors from the blood into the CNS. Although most molecular mechanisms of CNS-directed autoimmunity are still under investigation, it is believed that, rather than irreversible cell death, the detrimental effects of some antineuronal antibodies on neural function (Bresnihan et al., 1979) may be only transient. These effects include signaling, myelination (Kipnis et al., 2006; Jovanova-Nesic and Shoenfeld, 2007), synaptic plasticity, neurotransmitters (Moskowitz, 1989) and receptor dynamics.

The antineuronal antibodies most typical to lupus are anti-DNA antibodies, which act at the level of NMDA receptors (Omdal et al., 2005). For example, Kowal et al. (2006) developed a murine model of neuropsychiatric lupus based on autoantibodies that cross-react to the NMDA receptor. They further showed that these autoantibodies, as well as the corresponding ones obtained from the cerebrospinal fluid of lupus patients, impair cognition when they access the CNS through a breach in the blood–brain barrier. Abnormal synaptic remodeling due to this induced dysregulation in NMDA receptor trafficking provides a very plausible explanation for the same neuropsychiatric effects as the ones exhibited in disorders such as Alzheimer's disease, cocaine addiction and schizophrenia (Zhang et al., 2008; Lau and Zukin, 2007). This is why in our model the effects of autoimmunity will be introduced at the synaptic level, as an impairment in transmission in certain neural pathways. Since our study is concerned with the brain dynamics between prefrontal and limbic regions of interest, understanding if and how they are targeted by autoimmunity is very useful. In this sense, we use recent results on the possible selective production of antibodies against specific brain regions (Rothermundt et al., 2001). Indeed, serum antibodies have been reported against a few regions, including the hippocampus (Ganguli et al., 1987; Kelly et al., 1987; Yang et al., 1994), the amygdala and frontal cortex (Henneberg et al., 1994).

Finally, it is very important to notice in our context that the classical SLE treatment plan is based on corticosteroid medication, due to its immunosuppressive effects (Denburg et al., 1994). Severe diffuse CNS manifestations, such as acute confusional state, generalized seizures, mood disorders and psychosis, generally require immediate corticosteroid administration (Sanna et al., 2008), and psychiatric symptoms tend to resolve within three weeks of treatment. On the other hand, hypercortesolemia (possibly through the neurotoxic effects on the prefrontal/hippocampal inhibitory module discussed earlier in the section) could itself cause a variety of psychiatric syndromes such as mania, depression, psychosis, anxiety, dellirium (Cohen et al., 2004). It seems therefore crucial that a medication plan be finely tuned to correspond to the particular needs of each individual patient, since an overdose could lead to exactly the undesired symptoms that it aims to cure. This emphasizes yet again the importance of a sustainable and detailed enough diagnosis that would permit a correct treatment evaluation.

In the Discussion section, we will further interpret the potential interference of corticosteroid medication with the central and endocrine mechanisms that are believed to be responsible for psychosis in neoschizophrenia.

2. Methods—construction of the mathematical model

In our previous work (Rădulescu, 2008), we have related neoschizophrenia to a vulnerability of the inhibitory limbic/prefrontal module reinforced by neurotoxic effects of stress-induced hypercortisolemia. In this section we will describe a phenomenological model which, although still based on this limbic vulnerability, will also reflect some of the more subtle physiological mechanisms discussed in the Introduction. Since neither the stress/vulnerability cycle (described in Section 1.2), nor the effects of autoimmunity on brain function have been yet clearly quantified or understood, it would be very hard to construct an accurate mechanistic model, especially at the level of inter-region connectivity. However, while biologically such simplifications might overlook important detail, a simpler model is mathematically more desirable, since its analysis is actually tractable and potentially insightful. If constructed correctly, our simple model still addresses in a qualitatively plausible way not only the underpinnings of fear conditioning and extinction, but also the impact of autoimmunity on limbic processing and the effects of corticosteroids and antipsychotic medication which are generally prescribed for SLE and schizophrenia, respectively.

We start with a simpler case which does not include the effects of autoimmunity. First, we define our terminology and notations, and we elaborate this preliminary model. We then continue by explaining the underlying set of pathways and physiological rules on which we based our paradigm.

We represent the time activations of the amygdala, the hippocampus and the prefrontal cortex as three distinct variables a, p and h, while a fourth variable δ stands for the activation of the dopamine system, controlled via the nucleus accumbens (NAc) and the ventral tegmental area (VTA). In a data-driven model, one may observe the first three variables as discrete time-series of hemodynamic or electromagnetic responses—with the corresponding units (i.e., percentage BOLD signal change or microvolts, respectively). The fourth variable can be obtained similarly, based implicitly on the activity of the DA neurons in the NAc and VTA; in

animal models, extracellular levels of DA can be also measured, as fractions of the basal level expressed in mg/kg. The interactions between these variables are quantified by a (fairly large) collection of real positive parameters I, M, μ_1, μ_2, k_1, k_2, k_3, γ_1, γ_2, a_1, a_2, α, β, ξ_1, ξ_2 and ξ_3. We have chosen to represent the "direct" glutamatergic and GABA-mediated connections between regions in a linear fashion, consistent with our previous work. The indirect/slower acting influences (such as the neural effects of cortisol, autoimmunity triggered degeneration or dopamine-modulated activity) are all nonlinear terms (Rădulescu, 2008).

$$\dot{a} = -\mu_1 a - k_1 p - \gamma_1 h + I$$
$$\dot{p} = k_2 a - \mu_2(1+\delta)p + \frac{\gamma_2}{a_1 C + 1} h$$
$$\dot{h} = k_3(1+\delta^2)p - a_2 C$$
$$\dot{\delta} = -\xi_1(1+\delta)a + \xi_2(1+\delta)p + \xi_3(1+\delta)h$$

Aside from a self-modulatory inhibition $-\mu_1 a$, the amygdala receives a constant environmental input I via thalamic pathways, and provides excitatory outputs $k_2 a$ to the prefrontal cortex (Sotres-Bayon et al., 2004). Newer findings indicate that the basal lateral amygdala receives a stress-responsive dopamine projection from the ventral tegmental area (Lisman and Grace, 2005), and itself dampens the DA response in the NAc (Stevenson and Gratton, 2003). Outputs from the amygdala, through the hypothalamo-pituitary axis, also provide inputs for the endocrine and autonomic nervous systems, controlling indirectly the cortisol production in response to stress (Sapolsky and Plotsky, 1990).

In our model, we express the amygdala-controlled cortisol as a function $f(\alpha, a) = \alpha e^a/(e^a + 1)$, so that any activation a of the amygdala produces an increase from zero in the production of cortisol. This increase cannot exceed a saturation level α, independently of the level of stress. The stress-induced cortisol, together with corticosteroid-based medication M, determine the levels of blood cortisol $C = M + f(\alpha, a)$, whose known neurotoxic effects influence the structure and activity of the hippocampal/prefrontal inhibitory unit, as shown below.

The prefrontal cortex receives excitatory inputs $k_2 a$ from the amygdala and strong excitatory hippocampal projections $\gamma_2 h$ to the prefrontal prelimbic and infralimbic regions. The synaptic efficacy of this pathway is impaired by increased levels of blood cortisol (Cerqueira et al., 2007); to account for this, we have adjusted the corresponding term to $(\gamma_2/(a_2 C + 1))h$. More recent research reveals the importance of dopaminergic modulation of the mPFC inhibition via GABA interneurons. Projections from the mPFC to the VTA (Brady and O'Donnell, 2004), together with a reciprocal dopaminergic pathway from the VTA to the mPFC, comprise the mesocortical circuit (Harte and O'Connor, 2004; Westerink et al., 1998). More precisely, the glutamate-containing pyramidal neurons, which are the target of VTA DA terminals, make synapses on non-pyramidal GABAergic inhibitory interneurons in the mPFC (Harte and O'Connor, 2004; Seamans et al., 2001). Abnormalities in GABA-ergic interneuron inhibition in mPFC have been related to schizophrenia in recent studies (Volk and Lewis, 2002; Tanaka, 2008). We have expressed this dopamine modulated self-inhibition as the term $-\mu_2(1+\delta)p$.

The hippocampus directly inhibits activation of the amygdala ($-\gamma_1 h$) and reinforces activity in the prefrontal cortex, supporting the process of memory formation and centralization ($\gamma_2 h$). In this process, the contribution of the DA system is again very important. The CA1/ventral subiculum (vSub) sends dense glutametergic projections to the NAc, which are under a powerful DA neuromodulatory influence exerted by the VTA (Floresco et al., 2001). NAc directly projects to the VTA, and, in turn, the dopaminergic input from the VTA is known to enhance long-term potentiation in CA1 (Lisman and Grace, 2005). In addition, the hippocampus receives modulations from both the amygdala (cortisol-neurotoxic inhibition $-\gamma C$) and the mPFC (excitatory modulation through multineuronal entorhinal and perirhinal pathways $k_3(1+\delta^2)p$, where the factor $(1+\delta^2)$ signifies the dopamine-modulated LTP enhancement in CA1).

The dopamine system receives dopamine-modulated inputs from all three prefrontal–limbic areas, as shown by the fourth equation, in which the strengths of these modulations are proportional to the parameters ξ_1, ξ_2 and ξ_3.

As mentioned in the introduction, the large variety of autoantibodies and the complexity of their effects are not very well differentiated by research, and are therefore difficult to capture in all detail. So, in order to conveniently extend our model to encompass autoimmunity, we focused on its effects at the level of amygdalar and hippocampal synaptic transmission, since these structures and areas have been particularly shown to be affected by autoimmunity in SLE (Henneberg et al., 1994; Kelly et al., 1987; Yang et al., 1994). We consider the level of antineuronal autoantibodies to be modeled by an exponential increase in time: $B(t) = e^{\beta t/C}$. Here β is the exponential growth rate that reflects the self-enforcing vicious cycle of autoantibody production, and C is the blood level of cortisol, which slows down (without completely stopping) this production (Ball, 2006; Hong et al., 2007). With these additions, the system becomes

$$\dot{a} = -\mu_1 a - k_1 p - \frac{\gamma_1}{e^{\beta t/C}} h + I$$
$$\dot{p} = \frac{k_2}{e^{\beta t/C}} a - \mu_2 p + \frac{\gamma_2}{e^{\beta t/C}(a_1 C + 1)} h$$
$$\dot{h} = k_3(1+\delta^2)p - a_2 C$$
$$\dot{\delta} = -\xi_1(1+\delta)a + \xi_2(1+\delta)p + \xi_3(1+\delta)h$$

Note that, through the parameters $\mu_1, \mu_2, k_1, k_2, k_3, \gamma_1, \gamma_2, \xi_1, \xi_2, \xi_3 > 0$, the brain region interactions, represented by the linear terms of the system, reflect the excitatory/inhibitory character described earlier in this section.

3. Results—analysis and simulations

Generally, the mathematical analysis of such a system could be cumbersome. Considering the large number of parameters that can be varied independently, we expect the behavior of the system to change with these parameters' variations and exhibit complex transitions (e.g., fold-Hopf or Bautin bifurcations, Guckenheimer and Holmes, 1990; Izhikevich, 2006) at particular critical values. In future work, we plan to focus around such detailed analyses, and on numerical computation of critical bifurcation parameters when theoretical approaches are not possible. However, the purpose of this paper is not to build a complete quantitative analysis of the model we have constructed, especially since the model itself is not uniquely defined physiologically (most pathways, modulations and parameter values are still under investigation). We will instead adopt here a less precise, but rather more descriptive approach, aimed at illustrating basic ideas, such as the possible multitude of etiologies that underlie schizophrenic outward symptoms.

In this section, we fix a set of plausible initial states,[2] and we simulate the time evolution of these states under particular combinations of parameter values. Since we are mainly interested in the levels of prefrontal–limbic activations over time, and since it is convenient to pick a two-dimensional slice for our graphic

[2] We considered a neighbourhood of initial conditions around the ideal "resting state" $(a, p, h, \delta) = (0, 0, 0, 0)$. To fix ideas, we initiated all our plots at the vectors (0,0,0,0.5), (0,0,0.1,0.7) and (0,0,0.2,0.8).

illustrations, we plot all trajectories in the two-dimensional phase-space (a, p).

As promised, we investigate the phase-space transformations of the system under changes of the physiological parameters. Since the parameter space of the model is fairly large, we focus on the parameters which are suspected to be responsible for emotional dysregulation (from mild anxiety to psychosis), while keeping the other parameters fixed. In the context of our model, we equate this dysregulation with an instability in the system, resulting in wide swings of the prefrontal–limbic activation levels, and the corresponding erratic behavior. As in our previous paradigm of emotional dysregulation, we interpret convergent (or at least bounded) trajectories to be the "normal" activation pattern, even when they stabilize to a perpetual oscillation rather than an equilibrium. In our previous work, we considered wide, but stable oscillations to be a sign of trait anxiety rather than a mark of a psychotic mental disorder. It is when these oscillations get more dramatic in time (i.e., when the trajectories are being repelled away from an equilibrium or cycle) that we interpreted the system's behavior to bare the signature of psychosis (Rădulescu, 2008). This is a plausible view, since functional units of the brain will then continue to periodically enter psychotic ranges of hyper or hypo-activation and thus produce the imminent positive or negative symptoms.

3.1. Model behavior without autoimmunity

As a start, we verify that this extended paradigm is consistent with our prior modeling results (Rădulescu, 2008), in which we have considered the behavior of a two-dimensional prefrontal–limbic system under perturbations. In accordance to this prior work, we interpret the strength of amygdalar self-inhibition to be related to the individual's trait anxiety (or the capacity of suppressing arousal under mild constant stressors). In contrast, the nonlinear parameters a_1 and a_2 express the prefrontal/hippocampal sensitivity to cortisol neurotoxicity, hence they can be theoretically regarded as the signature of the stress/vulnerability in neoschizophrenia.

We gradually decrease the amygdala self-inhibition μ_1, while keeping the other parameters fixed. As expected, large enough values of μ_1 force the time-evolutions to converge to a steady state. If we lower μ_1 enough, we cross a critical value where the trajectories seem to stabilize instead to a locally attracting cycle (Figs. 1 and 2). As expected, lower values of μ_1 will not prevent the evolution of states from stabilizing, but rather will force it into a wider stable oscillation. One may plausibly correlate this lower amygdalar self-inhibition to increased trait anxiety (Sanders and Shekhar, 1991; Sajdyk and Shekhar, 2000), and further interpret the corresponding oscillation as one of its clinical signs: increased emotional variability. However, conclusive evidence will still have to be found.

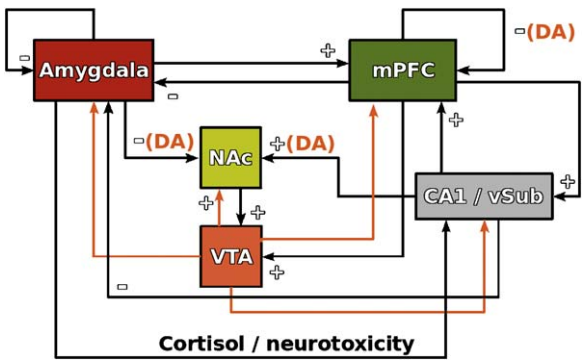

Fig. 1. Simplified schema of the prefrontal–limbic pathways incorporated in our model, as described in Section 2. mPFC = medial prefrontal cortex; NAc = nucleus accumbens; VTA = ventral tegmental area; CA1 = Cornu Ammonis 1; vSub = ventral subiculum; "+" stands for excitatory pathway, "−" for inhibitory pathway and "DA" for dopamine-modulated pathway.

A qualitatively different bifurcation appears to manifest when varying the parameters a_1 and a_2. Indeed, while for small values of these two parameters the system converges to a stable state, when we increase the two values, the place of the stable state is taken by a attracting cycle. For only slightly larger values of a_1 and a_2, the locally attracting cycle itself disappears and the trajectories appear to be spiraling outward, generating the unstable pathological oscillations described before (Fig. 3).

One additional interesting feature is how the prefrontal–limbic dopamine receptivity affects the behavior of the model. Increasing the dopamine modulation parameters ξ_1, ξ_2, ξ_3 augments the amplitude of the oscillations in a normally functioning system (Figs. 4a and b). Conversely, in a pathologically dysregulated system (i.e., with a_1 and a_2 beyond the threshold value that warranties a regime of stability) stability can be regained by lowering the levels of dopamine-sensitivity ξ (Fig. 4c). We believe this result to be very interesting in the context of antipsychotic medication, and we will reopen it for further interpretation in the Discussion section.

3.2. Model behavior including autoimmunity

The synaptic impairment due to autoimmunity, as introduced in this model, depends directly on two quantities: the exponential growth rate of antibody production β and the blood levels of cortisol C, which acts as an immunosuppressor. Figs. 5 and 6 illustrate how corticosteroid medication works to reduce the psychiatric effects of autoimmunity.

For all panels of Fig. 5, the growth rate was fixed to $\beta = 0.01$. Fig. 5a shows that when no medication is administered ($M = 0$) the trajectories do not stabilize. When medication is increased to $M = 3$, the system stabilizes locally, so the effects of autoimmunity are at least temporarily counteracted (Fig. 5b). When M is increased over a certain threshold, the neurotoxic effect of cortisol prevails over its immunosuppressive effect, and the system becomes again unstable. This is shown in Fig. 5c, where the medication has been increased to $M = 6$, which is too high a dose for the respective antibody growth. It seems that for larger growth rates, this critical range—in which medication works toward stabilizing the system—disappears. For $\beta = 0.1$, we have increased dosage up to $M = 15$, with no beneficial effect on the system's behavior at any intermediate stage (not shown). Furthermore, if the system has an *a priori* prefrontal–limbic vulnerability (i.e., for a_1 and a_2 large enough, e.g., $a_1 = 5$ and $a_2 = 2.62$) in addition to the autoimmune overproduction, medication in any quantity does not help either, but rather enhances the already existing instability. These suggest that corticosteroid medication would not only help, but rather further hurt individuals with neoschizophrenia, even though the same medication would be beneficial for treatment of a possible coexisting autoimmune condition.

We finally note that, unlike in the original model (Fig. 3), when introducing excessive autoimmune growth, simply decreasing ξ no longer forces the trajectories to converge (Fig. 6). In other words, while a lower drive of the dopamine systems had a stabilizing effect in the simplified model, in the extended model a similar decrement in dopamine modulation cannot by itself compensate in the long run for the effects of dysregulated autoimmunity. On the other hand, a slight increase in cortisol levels seems to do that successfully, as long as the dysregulation is not excessively pronounced (Figs. 5a and b). This suggests that treating the psychiatric symptoms of an autoimmune condition

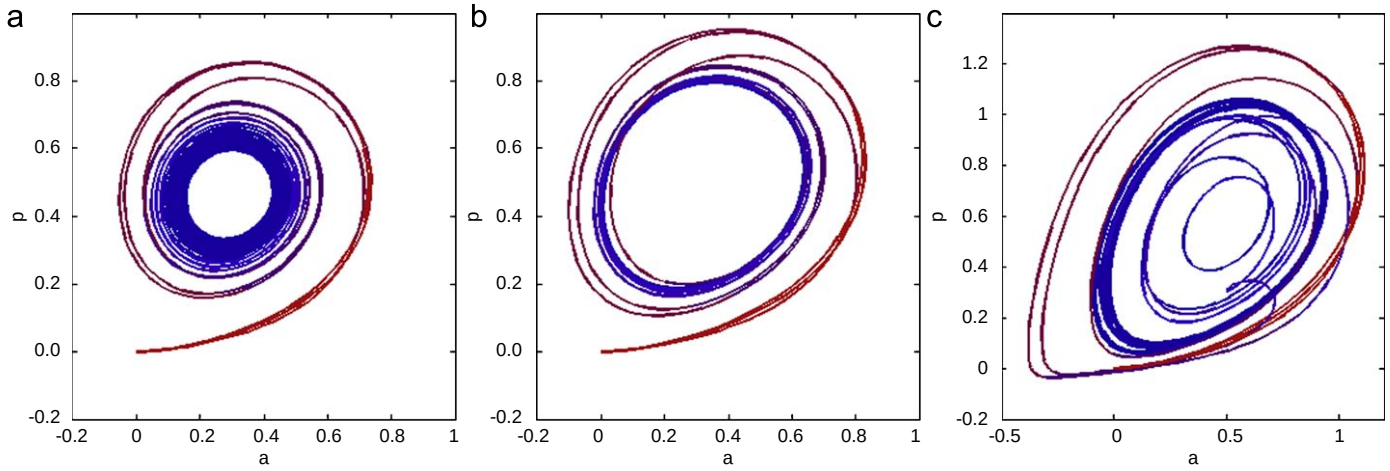

Fig. 2. The three panels show the evolution of the three fixed trajectories in the two-dimensional phase-slice (a, p). The color of the curve changes gradually from red to blue as time progresses. We have fixed: $\mu_2 = 2$, $k_1 = 2$, $k_2 = 2$, $k_3 = 1$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\alpha = 1$, $a_1 = a_2 = 1$, $\xi = \xi_1 = \xi_2 = \xi_3 = 2$, $I = 1$, $\beta = 0$ and $M = 0$ (i.e., no autoimmunity or cortisol-based medication). The parameters correspond to a "normal" functioning regime. (a) $\mu_1 = 1.4$; the trajectories are attracted to a point. (b) $\mu_1 = 1$; the attractor is switching from a point to a cycle. (c) $\mu_1 = 0.21$; the cycle is still locally attracting, although with a slower time constant, forcing the trajectories to stabilize to a regime of oscillations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

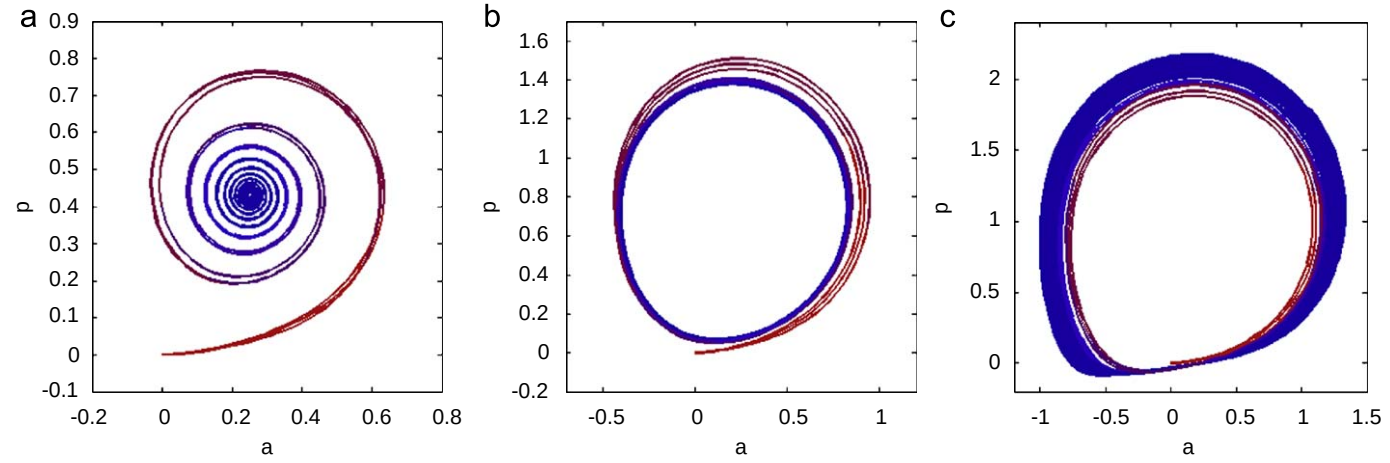

Fig. 3. We plot the trajectories in (a, p) starting at the same initial points, with the same color coding. In all three panels, we fixed: $\mu_1 = 2$, $\mu_2 = 2$, $k_1 = 2$, $k_2 = 2$, $k_3 = 1$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\alpha = 1$, $\xi = 2$, $I = 1$, $\beta = 0$ and $M = 0$ (i.e., no autoimmunity or cortisol-based medication). (a) $a_1 = a_2 = 1$. The trajectories are attracted to a point. (b) $a_1 = 5$ and $a_2 = 2$. The trajectories are attracted to a cycle. (c) $a_1 = 5$, $a_2 = 2.62$. The local stability of the cycle has changed, and the trajectories are now repelled outward.

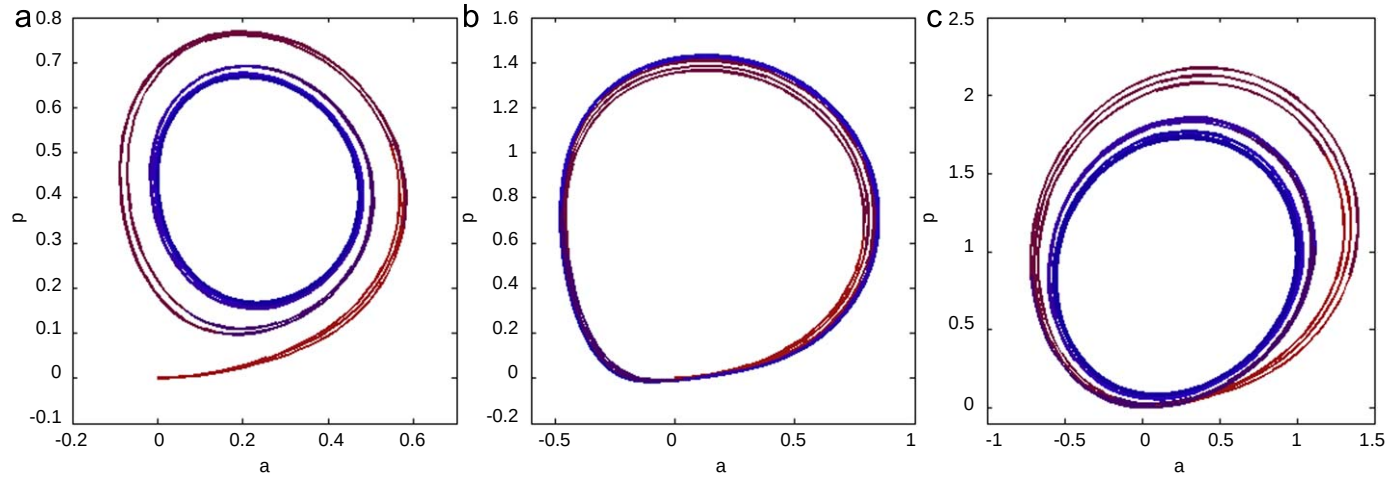

Fig. 4. We plot the trajectories in (a, p) starting at the same initial points, with the same color coding. In all three panels, we fixed: $\mu_1 = 2$, $\mu_2 = 2$, $k_1 = 2$, $k_2 = 2$, $k_3 = 1$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\alpha = 1$, $I = 1$, $\beta = 0$ and $M = 0$ (i.e., no autoimmunity or cortisol-based medication). (a) $a_1 = a_2 = 1$, same as in Fig. 3a, but the dopamine receptivity has been increased to $\xi = 3.5$, causing an increase in the amplitude of the stable oscillations. (b) $a_1 = 5$ and $a_2 = 2$, same as in Fig. 3b, but the dopamine receptivity has been again been increased to $\xi = 3.5$ (c) $a_1 = 5$ and $a_2 = 2.62$, same as in Fig. 3c, but the dopamine receptivity has been lowered to $\xi = 1$, rendering the otherwise dysregulated system more stable.

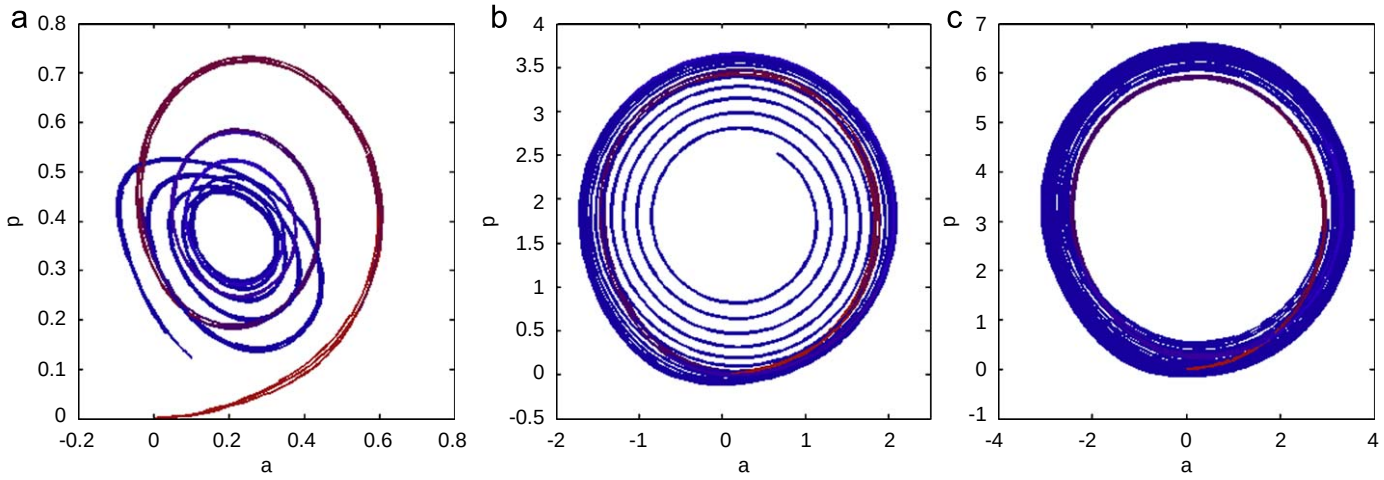

Fig. 5. In all three panels, we fixed: $\mu_1 = 2.2$, $\mu_2 = 2$, $k_1 = 2$, $k_2 = 2$, $k_3 = 1$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\alpha = 1$, $a_1 = a_2 = 1$, $\xi = 2$, $I = 1$, $\beta = 0.01$. This corresponds to a system with no intrinsic psychiatric risk and low anxiety, but affected by an autoimmunity disorder, such as SLE. (a) $M = 0$; the trajectories are unstable (repelled away from the equilibrium). (b) $M = 3$; the trajectories are stabilized by appropriate medication. (c) $M = 6$; the trajectories are unstable again, due to the overmedication-induced cortisolemia.

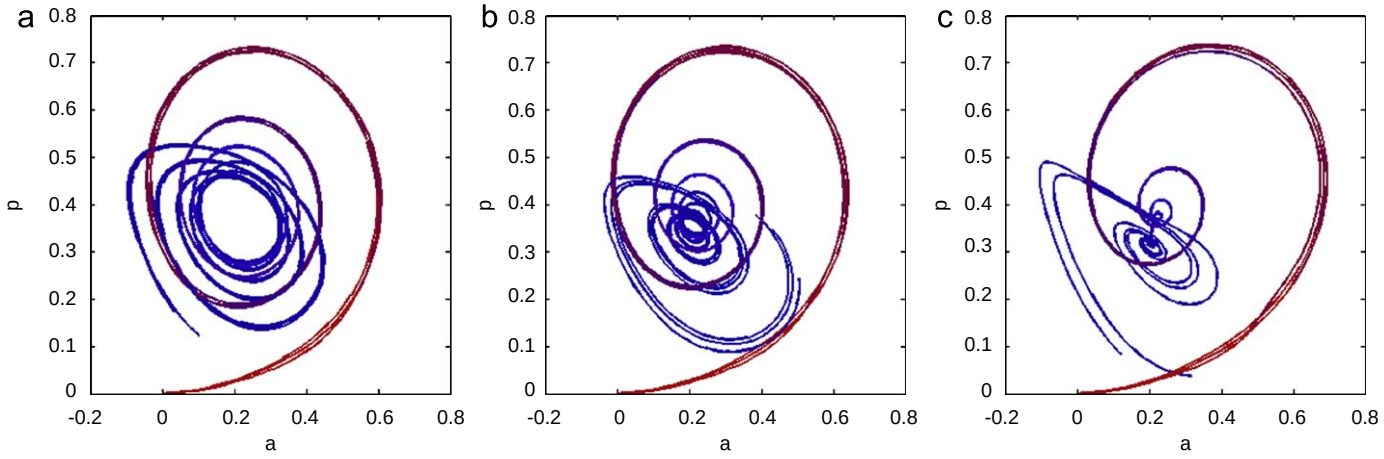

Fig. 6. In all three panels, we fixed: $\mu_1 = 2.2$, $\mu_2 = 2$, $k_1 = 2$, $k_2 = 2$, $k_3 = 1$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\alpha = 1$, $a_1 = a_2 = 1$, $I = 1$, $\beta = 0.01$, $M = 0$. (a) $\xi = 2$ (b) $\xi = 1.5$; (c) $\xi = 1$. Deceasing ξ did not help in stabilizing the unstable trajectories. Combine with Fig. 5 to compare the effects of the two medication options in patients with SLE.

with DA-antagonists (antipsychotics) is irrelevant, and that corticosteroids (increasing M) should be in this case the recommended treatment. In the Discussion section, we offer a more detailed explanation of this phenomenon within the context of antipsychotic and immunosuppressant medication.

4. Discussion

Altough this model's phenomenological nature makes it too broad to directly apply it in clinical situations in its present form, it should be rather viewed as a sign that this approach could become ultimately useful. Current data collection and analysis are advancing toward better quantitative estimates of functions and parameters required for such models. Our theoretical paradigm encourages perfecting such techniques, and—if needed—could suggest new ways of data collection and interpretation. A back-and-forth dynamic combination of theoretical methods—molding the experimental paradigms—and clinical data—validating the theory—could finally lead to a quantitative assessment toolbox for disorders such as schizophrenia. Sections 4.1 and 4.2 will address some of these issues further.

Meanwhile, our model shows how a brain network involved in emotional processing, fear conditioning and extinction can switch from normal to dysregulated behavior when certain functional parameters are changed. More importantly, our paradigm shows how seemingly similar signs of dysregulation could correspond to malfunction of totally different parameters, i.e., they could be manifestations of totally different types of physiological impairment. This goes hand in hand with our hypothesis of multiple etiologies of psychosis, as described in the Introduction section. We would therefore like to interpret here more thoroughly our results that support this idea.

In our previous two-dimensional approach (Rădulescu, 2008), we have already discussed some of the effects of perturbing the amygdalar self-inhibition μ_1 and the cortisol vulnerability coefficients a_1 and a_2. While we associated the linear coefficient with the individual's trait anxiety, the vulnerability parameter reflected the degree of nonlinearity, which we believe to be the key determinator of the disease process. Our new computations confirm and extend these prior results. The loss of stability with the decrease of amygdalar self-inhibition reaffirms the importance of this inhibition in maintaining a well-regulated limbic–prefrontal system. Lack of proper such inhibition may lead to a

less efficient return to baseline after a stressor. On the other hand, a dysregulation in the inhibitory feedback loop produced by increased vulnerability to stress (larger a_1 or a_2) may cause time evolutions to never converge, thus leading to ranges of brain activations compatible with psychotic behavior (Rădulescu, 2008).

As an extension of this paradigm, we introduced here explicitly the effects of the dopamine modules, which are known to be very important in the genesis of psychosis. We observed that an increase in the dopaminergic modulation could produce a dysregulation in the system's evolution which is almost indistinguishable from an increase in vulnerability to cortisol. This effect corresponds to the well-known fact (which lies at the very basis of the pharmacology of antipsychotics, Awouters and Lewi, 2007) that dopamine antagonists alleviate (without definitively curing) psychotic symptoms. In the same direction, we also noted that a dysregulation in our system caused by increased prefrontal/hippocampal cortisol vulnerability can be compensated by decreasing the dopamine responsiveness, i.e., by administration of dopamine antagonist medication. This is also in full accordance with the theory of existing medical treatment for schizophrenia.

The rest of the discussion will focus on the impact of autoimmunity. The game of autoimmune regulation is governed by the exponential growth rate of the autoantibody production. This rate can be effectively decreased by boosting the blood cortisol levels, e.g., by administration of corticosteroids. This slows down the exponential growth and implicitly lowers the detrimental effects of the antibodies on the brain. The corticosteroid treatment of defective autoimmunity works only to some degree, since an excess of cortisol can push the system into the opposite range of instability, due to hypercortisolemia. Indeed, recent studies have revealed that psychosis in SLE can appear as a secondary effect of medication, and that this psychosis is clinically indistinguishable from primary SLE psychosis (Cohen et al., 2004).

In general, however, corticosteroid medication works well if administered correctly in SLE (Shanahan and Kimberly, 2004). A very important message of our model is that, in the case of an actual autoimmune disorder, antipsychotics cannot be regarded as a substitute or alternative to immunosuppressants. This emphasizes once more the importance of teasing apart the different mechanisms underlying psychosis, and of assigning medication customized to fit the particular corresponding malfunction. In our case, misdiagnosing SLE as neoschizophrenia, which probably happens more often than we know (Arthritis Research Campaign, 1998), would lead to administering classical antipsychotic medication to a person suffering from an autoimmune condition. This is very ineffective, even detrimental, given the side effects of all antipsychotics. The consequences of the converse misdiagnosis of neoschizophrenia as SLE would be even more dire, since corticosteroid medication assigned to a person with a vulnerability to cortisol would readily enhance the already manifest psychosis.

Finally, this mechanism provides a good example of an instance where two different drugs, administered to patients with similar outward symptoms, may achieve different clinical outcomes. This is not the only psychiatric context in which such questions have been raised. A more elaborate model could perhaps encompass other such phenomena, such as the similar effects that dopamine agonists and dopamine antagonists seem to have as treatment to certain psychotic symptoms (Strange, 2008).

4.1. Limitations and future work

One specific problem that has been pointed out in both our previous and current paradigms is that the psychotic symptoms we describe and model are not necessarily specific to schizophrenia, and could be considered common to other conditions of central emotional dysregulation. However, this problem is more of a linguistic tautology, since it is the psychiatric diagnostic itself that we are challenging. That is why we chose our own more restrictive, biology-based definition for "neoschizophrenia" in this paper, in which psychosis is a primary result of prefrontal–limbic vulnerability to stress.

A more serious drawback comes from the fact that the physiology described by phenomenological models can only capture a very rough qualitative picture. Our current model in particular does not have the quantitative attributes that would make it applicable as is towards clinical diagnosis. More generally in fact, at this point in psychiatric research, modeling cannot be considered the final answer, but rather only a step towards a better understanding of the problem and its complexity. Clearly, there can always be a better model. A mechanistic model accurate enough to be used for clinical decisions would need to not only be supported with more precise physiological information, but also to address other serious concerns raised by handling biological data (such as subject variability, signal-to-noise ratio, the non-deterministic trends in the system, Paulus and Braff, 2003). Such a model would have to be organized on multiple levels of complexity and comprise several spatial and temporal scales, while remaining mathematically tractable. We believe that this task can only be solved through a cross-talk between experimental research and model theoretical and computational efforts. Psychiatric modeling is a science that should evolve interactively with the progress in experimental methods.

In this context, the state of the current experimental data is at a crossroad. Take for instance our paradigm of immunity-based psychosis. On one hand, research of both physiology of mental illness and autoimmunity mechanisms has accomplished great progress in the past few decades. On the other hand, knowledge of both autoimmunity and schizophrenia—specifically that of antibodies against brain structures of neurons and glial cells—is still controversial. The first steps to understanding how antigen–antibody pathology might play in mental illness has been established by animal research (Williams and Schupf, 1977), which is questionably relevant to human pathophysiology. In clinical research, while some found serum antibrain antibodies in 28–95% of studied schizophrenics (Kuznetoza and Semenov, 1961; Fessel, 1962; DeLisi et al., 1985; Henneberg et al., 1994), others were unable to reproduce these findings (Rubin, 1965; Logan and Deodhar, 1970; Ehrnst et al., 1982).

To end this discussion on a constructive note, we would like to propose here two useful approaches toward a mechanistic model, which are the basis of our future work. They target two different spacial and temporal scales, and rely on two totally different types of datasets: human brain imaging data and neural network dynamics in animal models. Ideally, the results of these two halves would ultimately agree into one whole consistent picture.

On one hand, emerging technologies of measuring physiological parameters such as brain activation (fMRI, NIRS, MEG) or autoimmunity (Rothermundt et al., 2001; Ely et al., 2008) offer novel means of experimental investigation. Such methods have spurred a new culture of parameter-identification and other techniques of quantitative evaluation of imaging data (such as dynamic causal modeling (Kiebel et al., 2007), or computation of dynamical invariants, Rosenstein et al., 1993). These are appropriate to be used and should be used to (1) create and validate more realistic structural models at the ROI level and (2) compute dynamic invariants that characterize in a very compact form the dynamics of ROI interactions. These invariants can be ultimately used for clinical evaluations (see Section 4.2). In most contexts (such as autoimmune dysregulation and its psychiatric effects),

these techniques have not yet been exploited at their fullest (Cohen et al., 2004).

On the other hand, novel animal research has been assembling increasingly better documented models of the mechanisms acting in schizophrenia. For example, the experimental models developed in methylazoxymethanol acetate (MAM) rats by Lodge and Grace (2007) "recapitulate a pathodevelopmental process leading to schizophrenia-like neuroanatomical and behavioral phenotypes". While previous attempts to produce an animal model of schizophrenia had relied on developmental disruption, the model proposed by Lodge and Grace (2007) is based on the administration of a DNA methylating agent (methylazoxymethanol acetate) to pregnant females during gestation. The adult offspring show anatomical changes (thinning of limbic cortices with increased neuronal packing density), disruption of rhythmic activity in frontal cortex and a plethora of behavioral deficits similar to those observed in schizophrenia patients. Among the observed behavioral effects are: decreased prepulse inhibition of startle, disruption in learning new responses, errors in latent inhibition, increased responses to amphetamine, increased sensitivity to stress, executive behavioral impairment, and social impairment. Using this model, the authors further demonstrated the presence of a hippocampal dysfunction that led to DA system hyperresponsivity (Floresco et al., 2001; Lodge and Grace, 2006, 2007).

Altogether, the Lodge–Grace experimental model provides new insights into understanding the role of these systems in the pathophysiology of schizophrenia and is particularly well suited for a dynamical systems analysis. The author's current work includes posing and interpreting this model in a mathematical context. The results could profitably clarify and complement the ones delivered by larger-scale (clinical or theoretical) models in humans.

4.2. The future of diagnosis

Based on the novel quantitative approaches to psychophysiology and psychopathology, one concept which has recently started to gain ground is temporal architecture profiling (Rădulescu, 2008; Peled, 2006). Profiling could complement, perhaps even totally eliminate the current diagnosis assignment, which is not only unreliable and incompatible with multiple etiologies, but also socially undesirable and stigmatizing. This could finally mean assembling a quantitative assessment toolbox for schizophrenia. The dynamical "brain profile" of a particular patient or high risk individual could be created—possibly from a set of clinically measurable parameters—describing physiological features such as brain interactions, or stress vulnerability. This profile could then be compared against a multidimensional, continuous profile chart, constructed based on common statistics. The individual would thus be placed in the right locus of risk/vulnerability, which would facilitate predictions and help assign the most appropriate treatment.

Such theories have already started to emerge in psychiatric literature. Peled (2006), for example, proposed a brain profiling chart based on three dimensions: neural complexity disorders, neuronal resilience insufficiency and context-sensitive processing decline. Relevant equations would be used to calculate and normalize the different values attributed to relevant brain disturbances. The first dimension relates to disturbances occurring to fast neuronal activations and incorporates connectivity and hierarchical imbalances. The second dimension relates to disturbances that alter long-term synaptic modulations, and incorporates disturbances to optimization within neuronal circuitry. Finally the third dimension refers to the level of internal representations.

In the same direction of thinking, our previous work suggests an example of rudimentary profiling based on two dimensions: the amygdalar self-inhibition μ_1 and the level of nonlinearity of the prefrontal–limbic system, measured by the Lyapunov number σ (Rădulescu, 2008). Our current model suggests that a better classification could be obtained from considering a multi-dimensional profile, for example, in the parameter space $(\mu_1, a_1, a_2, \xi, \beta)$.

This view of psychiatric diagnosis is still in its cradle, but it offers great promise and testable predictions about the etiology of mental disorders. It uses time trajectories, which intrinsically encompass the clinical history of the patient. It is also physiology-based, so it relies on brain imaging investigations which are much more precise than behavioral assessments.

Brain profiling diagnosis could be a pioneering step towards a reformed psychiatry. However, much work still needs to be done in understanding the mechanisms and the varieties of schizophrenia. Modeling techniques, based upon combined experimental approaches (from genetics to imaging and endocrine measures) may offer the best long-term pay-off.

Acknowledgments

The author wishes to thank her parents, Doina and Răzvan Rădulescu, for their support and patience while working on this paper in Romania, during the summer of 2008.

References

Ananth, H., et al., 2002. Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. Am. J. Psych. 159.

Andreasen, N., et al., 1986. Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. Arch. Gen. Psych. 43.

Andreasen, N.C., 2000. Schizophrenia: the fundamental questions. Brain Res. Rev. 31 (2–3), 106–112.

Arthritis Research Campaign ⟨http://www.arc.org.uk/news/pressreleases/awareness/deadly.asp⟩. Released January 1998. Accessed 08/17/08.

Awouters, F.H., Lewi, P.J., 2007. Forty years of antipsychotic drug research—from haloperidol to paliperidone—with Dr. Paul Janssen. Arzneimittelforschung. 57 (10), 625–632.

Ball, T.M., 2006. Cortisol circadian rhythms and stress responses in infants at risk of allergic disease. Neuroimmunomodulation 13 (5–6), 294–300.

Bongioanni, P., 1993. The bi- and unilateral correlations between the nervous system and the immune system. Minerva Med. 84 (7–8), 365–381.

Brady, A.M., O'Donnell, P., 2004. Dopaminergic modulation of prefrontal cortical input to nucleus accumbens neurons *in vivo*. J. Neurosci. 24 (5), 1040–1049.

Bresnihan, B., Oliver, M., Williams, B., Hughes, G.R., 1979. An antineuronal antibody cross-reacting with erythrocytes and lymphocytes in systemic lupus erythematosus. Arthritis Rheum. 22 (4), 313–320.

Bruce, I., Turetsky, M.D., et al., 2002. Memory-delineated subtypes of schizophrenia: relationship to clinical, neuroanatomical, and neurophysiological measures. Neuropsychology 16.

Cerqueira, J.J., Mailliet, F., Almeida, O.F.X., Jay, T.M., Sousa, N., 2007. The prefrontal cortex as a key target of the maladaptive response to stress. J. Neurosci. 27 (11), 2781–2787.

Cohen, W., Roberts, W.N., Levenson, J.L., 2004. Psychiatric aspects of SLE. In: Lahita, R. (Ed.), Systemic Lupus Erythematosis, fourth ed. Academic Press, San Diego, CA, pp. 785–825.

Crow, T.J., 1980. Molecular pathology of schizophrenia: more than one disease process? Br. Med. J. 280 (6207), 6668.

DeLisi, L.E., Weber, R.J., Pert, C.B., 1985. Are there antibodies against brain in sera from schizophrenic patient? Review and prospectus. Biol. Psych. 20, 110–115.

Denburg, S.D., Carbotte, R.M., Denburg, J.A., 1994. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 37 (9), 1311–1320.

Diagnostic and Statistical Manual of Mental Disorders, 1994, fourth ed. (DSM-IV), American Psychiatric Association, Washington DC.

Edwards, J., Cambridge, J., 1998. Rheumatoid arthritis and autoimmunity: a new approach to their cause and how long term cure might be achieved ⟨http://www.ucl.ac.uk/regfjxe/Arthritis.htm⟩. Accessed 08/17/08.

Ehrnst, A., Wiesel, F.A., Bjerkenstedt, L., Tribukait, B., Jonsson, J., 1982. Failure to detect immunologic stigmata in schizophrenia. Neuropsychology 8, 169–171.

Ely, L.K., Burrows, S.R., Purcell, A.W., Rossjohn, J., McCluskey, J., 2008. T-cells behaving badly: structural insights into alloreactivity and autoimmunity. Curr. Opin. Immunol. Epub.

Fessel, W.J., 1962. Autoimmunity and mental illness. Arch. Gen. Psych. 6, 320–323.

Finlay, J.M., Zigmond, M.J., 1997. The effects of stress on central dopaminergic neurons: possible clinical implications. Neurochem. Res. 22 (11), 1387–1394.
Floresco, S.B., Todd, C.L., Grace, A.A., 2001. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. J. Neurosci. 21 (13), 4915–4922.
Ganguli, R., Rabin, B.S., Kelly, R.H., Lyte, M., Ragu, U., 1987. Clinical and laboratory evidence of autoimmunity in acute schizophrenia. Ann. N. Y. Acad. Sci. 496, 676–685.
Gaughran, F., Welch, J., 2007. In: Lajtha, A., Galoyan A., Besedovsky, H.O. (Eds.), Handbook of Neurochemistry and Molecular Neurobiology: Neuroimmunology. 3rd edn., Springer.
Gharavi, A.E., 2001. Anticardiolipin syndrome: antiphospholipid syndrome. Clin. Med. 1, 14–17.
Guckenheimer, J., Holmes, P., 1990. Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields. Springer, Berlin.
Hafner, H., Behrens, S., De Vry, J., Gattaz, W.F., 2005. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Eur. Arch. Psych. Clin. Neurosci. 241 (1), 65–68.
Haidemenos, A., Kontis, D., Gazi, A., Kallai, E., Allin, M., Lucia, B., 2007. Plasma homocysteine, folate and B12 in chronic schizophrenia. Prog. Neuropsychopharmacol. Biol. Psych. 31 (6), 1289–1296.
Harte, M., O'Connor, W.T., 2004. Evidence for a differential medial prefrontal dopamine D1 and D2 receptor regulation of local and ventral tegmental glutamate and GABA release: a dual probe microdialysis study in the awake rat. Brain Res. 1017, 120–129.
Henneberg, A.E., Horter, S., Ruffert, S., 1994. Increased prevalence of antibrain antibodies in the sera from schizophrenic patients. Schizophr. Res. 14 (1), 15–22.
Herbert, J., Goodyer, I.M., Grossman, A.B., Hastings, M.H., de Kloet, E.R., Lightman, S.L., Lupien, S.J., Roozendaal, B., Seckl, J.R., 2006. Do corticosteroids damage the brain? J. Neuroendocrinol. 18, 393–411.
Hong, Y., Mager, D.E., Blum, R.A., Jusko, W.J., 2007. Population pharmacokinetic/pharmacodynamic modeling of systemic corticosteroid inhibition of whole blood lymphocytes: modeling interoccasion pharmacodynamic variability. Pharm. Res. 24 (6), 1088–1097.
Izhikevich, E.M., 2006. Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting. MIT Press, Cambridge, MA.
Jansson, L.B., Parnas, J., 2007. Competing definitions of schizophrenia: what can be learned from polydiagnostic studies? Schizophr. Bull. 33 (5), 1178–1200.
Jovanova-Nesic, K., Shoenfeld, Y., 2007. Autoimmunity in the brain: the pathogenesis insight from cell biology. Ann. N. Y. Acad. Sci. 1107, 142–154.
Kaplan, H.I., Sadock, B.J., 1998. Synopsis of Psychiatry, eighth ed. Williams & Wilkins, Baltimore, MD.
Kapur, S., Mamo, D., 2005. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog. Neuropsychopharmacol. Biol. 29 (5), 859–864.
Kelly, R.H., Ganguli, R., Rabin, B.S., 1987. Antibody to discrete areas of the brain in normal individuals and patients with schizophrenia. Biol. Psych. 22, 1488–1491.
Konrad, A., Winterer, G., 2007. Disturbed structural connectivity in schizophrenia primary factor in pathology or epiphenomenon? Schizophr. Bull. doi: 10.1093/schbul/sbm034.
Kowal, C., DeGiorgio, L.A., Lee, J.Y., Edgar, M.A., Huerta, P.T., Bruce, T., Volpe, B.T., Diamond, B., 2006. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. PNAS 103 (52), 19854–19859.
Kiebel, S.J., Kloppel, S., Weiskopf, N., Friston, K.J., 2007. Dynamic causal modeling: a generative model of slice timing in fMRI. Neuroimage 34 (4), 1487–1496.
Kipnis, J., Cardon, M., Strous, R.D., Schwartz, M., 2006. Loss of autoimmune T cells correlates with brain diseases: possible implications for schizophrenia. Trends Mol. Med. 12 (3), 107–112.
Kuznetoza, N.I., Semenov, S.F., 1961. Detection of antibrain antibodies in the sera of patients with neuropsychiatric disorders. Zh. Nevropatol. Psikhiatr. 61, 869–873.
Lau, C.G., Zukin, R.S., 2007. NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. Nat. Rev. Neurosci. 8 (6), 413–426.
Laviolette, S.R., 2007. Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? Schizophr. Bull. 33 (4), 971–981.
Lawrie, S.M., et al., 2003. Structural and functional abnormalities of the amygdala in schizophrenia. Ann. N. Y. Acad. Sci. 985.
LeDoux, J., 2003. The emotional brain, fear, and the amygdala. Cell Mol. Neurobiol. 23 (4–5), 727–738.
Lisman, J.E., Grace, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46, 703–713.
Lodge, D.J., Grace, A.A., 2006. The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. Neuropsychopharmacology 31, 1356–1361.
Lodge, D.J., Grace, A.A., 2007. Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. J. Neurosci. 27 (42), 11424–11430.
Logan, D.G., Deodhar, S.D., 1970. Schizophrenia an immunologic disorder. J. Am. Med. Assoc. 212, 1703–1704.
Medoff, D.R., Holcomb, H.H., Lahti, A.C., Tamminga, C.A., 2001. Probing the human hippocampus using rCBF: contrasts in schizophrenia. Hippocampus 11 (5), 543–550.
Moskowitz, N., 1989. Systemic lupus erythematosus of the central nervous system: 2. Molecular theories and models for mental disease. Mt. Siani J. Med. 56 (1), 23–29.
Mujica-Parodi, L.R., Yeregani, V., et al., 2005. Nonlinear complexity and spectral analyses of heart rate variability in medicated and unmedicated patients with schizophrenia. Neuropsychobiology 51.
Myin-Germeys, I., Delespaul, P., van Os, J., 2005. Behavioural sensitization to daily life stress in psychosis. Psychol. Med. 35 (5), 733–741.
Nuechterlein, K.H., et al., 1994. The vulnerability/stress model of schizophrenic relapse: a longitudinal study. Acta Psychiat. Scand. Supplementum 382.
Omdal, R., Brokstad, K., Waterloo, K., Koldingsnes, W., Jonsson, R., Mellgren, S.I., 2005. Neuropsychiatric disturbances in SLE are associated with antibodies against NMDA receptors. Eur. J. Neurol. 12 (5), 392–398.
Ozcan, O., Ipcioglu, O.M., Gultepe, M., Basogglu, C., 2008. Altered red cell membrane compositions related to functional vitamin B(12) deficiency manifested by elevated urine methylmalonic acid concentrations in patients with schizophrenia. Ann. Clin. Biochem. 45 (Pt 1), 44–49.
Paulus, M.P., Braff, D.L., 2003. Chaos and schizophrenia: does the method fit the madness? Biol. Psych. 53, 3–11.
Pavlides, C., Nivon, L., McEwen, B., 2002. Effects of chronic stress on hippocampal long-term potentiation. Hippocampus 12 (2), 245–257.
Peled, A., 2006. Brain profiling and clinical-neuroscience. Med. Hyp. 67 (4), 941–946.
Preston, A.R., 2005. Hippocampal function, declarative memory, and schizophrenia: anatomic and functional neuroimaging considerations. Curr. Neurol. Neurosci. Rep. 5 (4), 249–256.
Rădulescu, A., 2008. Schizophrenia—a parameters' game? J. Theor. Biol. 254 (1), 89–98.
Ritsner, M., et al., 2004. Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. Eur. Neuropsychopharmacol. 14.
Rosenstein, M.T., Collins, J.J., De Luca, C.J., 1993. A practical method for calculating largest Lyapunov exponents from small data sets. Physica D 65 (1–2), 117–134.
Rothermundt, M., Arolt, V., Bayer, T.A., 2001. Review of immunological and immunopathological findings in schizophrenia. Brain Behav. Immun. 15, 319–339.
Rubin, R.T., 1965. Investigation of precipitins to human brain in sera of psychotic patients. Br. J. Psych. 111, 1003–1106.
Sajdyk, T.J., Shekhar, A., 2000. Sodium lactate elicits anxiety in rats after repeated GABA receptor blockade in the basolateral amygdala. Eur. J. Pharmacol. 394 (2–3), 265–273.
Sanders, S.K., Shekhar, A., 1991. Blockade of GABAA receptors in the region of the anterior basolateral amygdala of rats elicits increases in heart rate and blood pressure. Brain Res. 567 (1), 101–110.
Sanna, G., Bertolaccini, M.L., Khamashta, M.A., 2008. Neuropsychiatric involvement in systemic lupus erythematosus: current therapeutic approach. Curr. Pharm. Des. 14 (13), 1261–1269.
Sapolsky, R.M., Plotsky, P.M., 1990. Hypercortisolism and its possible neural bases. Biol. Psych. 27 (9), 937–952.
Scolding, N.J., Joseph, F.G., 2002. The neuropathology and pathogenesis of systemic lupus erithematosus. Neuropathol. Appl. Neurobiol. 28, 173–189.
Seamans, J.K., Gorelova, N., Durstewitz, D., Yang, C.R., 2001. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J. Neurosci. 21 (10), 3628–3638.
Seidman, L.J., Wencel, H.E., 2007. Genetically mediated brain abnormalities in schizophrenia. Curr. Psych. Rep. 5 (2), 135–144.
Shanahan, J.C., Kimberly, R.P., 2004. Corticosteroid use in SLE. In: Lahita, R. (Ed.), Systemic Lupus Erythematosis, fourth ed. Academic Press, San Diego, CA, pp. 785–825.
Sotres-Bayon, F., Bush, D., LeDoux, J.E., 2004. Emotional perseveration: an update on prefrontal–amygdala interactions in fear extinction. Learn. Mem. 11, 525–535.
Staal, W.G., et al., 2001. Structural brain abnormalities in chronic schizophrenia at the extremes of the outcome spectrum. Am. J. Psych. 15.
Stamm, R., Buhler, K.E., 2001. Concepts of vulnerability of psychiatric diseases. Fortschr. Neurol. Psychiatr. 69 (7), 300–309.
Stevenson, C.W., Gratton, A., 2003. Basolateral amygdala modulation of the nucleus accumbens dopamine response to stress: role of the medial prefrontal cortex. Eur. J. Neurosci. 17, 1287–1295.
Stojanovich, L., Zandman-Goddard, G., Pavlovich, S., Sikanich, N., 2007. Psychiatric manifestations in systemic lupus erythematosus. Autoimmun. Rev. 6 (6), 421–426.
Strange, P.G., 2008. Antipsychotic drug action: antagonism, inverse agonism or partial agonism. Trends Pharmacol. Sci. 29 (6), 314–321.
Tamminga, C.A., 2006. The neurobiology of cognition in schizophrenia. J. Clin. Psych. 67 (Suppl 9), 9–13 (Discussion 36–42).
Tanaka, S., 2008. Dysfunctional GABAergic inhibition in the prefrontal cortex leading to "psychotic" hyperactivation. BMC Neurosci. 9 (41).
Valesini, G., Alessandri, C., Celestino, D., Conti, F., 2006. Anti-endothelial antibodies and neuropsychiatric systemic lupus erythematosus. Ann. N. Y. Acad. Sci. 1069, 118–128.
Volk, D.W., Lewis, D.A., 2002. Impaired prefrontal inhibition in schizophrenia: relevance for cognitive dysfunction. Physiology and Behavior 77 (4), 501–505.
Walker, E., Mittal, V., Tessner, K., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Ann. Rev. Clin. Psychol. 4, 189–216.

Weinberger, D., McClure, R., 2002. Neurotoxicity, neuroplasticity and magnetic resonance imaging morphometry. Arch. Gen. Psych. 59, 553–558.
Westerink, B.H.C., Enrico, P., Feimann, J., de Vries, J.B., 1998. The pharmacology of mesocortical dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and prefrontal cortex of the rat brain. J. Pharmacol. Exper. Therap. 285 (1), 143–154.
Williams Jr., C.A., Schupf, N., 1977. Antigen–antibody reactions in rat brain sites induce transient changes in drinking behavior. Science 196 (4287), 328–330.
Williams, L.M., Harris, A.W.F., Liddell, B.B., Olivieri, G., Phillips, M.L., Peduto, A., Gordon, E., 2004. Dysregulation of arousal and amygdala–prefrontal systems in paranoid schizophrenia. Amer. J. Psych. 161 (3), 480–489.
Wong, E.Y.H., Herbert, J., 2005. Roles of mineralocorticoid and glucocorticoid receptors in the regulation of progenitor proliferation in the adult hippocampus. Eur. J. Neurosci. 22, 785–792.
Yang, Z.W., Chengappa, N.R., Shurin, G., Brar, J.S., Rabin, B.S., Gubbi, A.V., Ganguli, R., 1994. An association between anti-hippocampal antibody concentration and lymphocyte production of IL-2 in patients with schizophrenia. Psychol. Med. 24, 449–455.
Zhang, X.Y., Zhou, D.F., Cao, L.Y., Wu, G.Y., Shen, Y.C., 2005. Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 30, 1532–1538.
Zhang, Y., Behrens, M., Lisman, J.E., 2008. Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex. J. Neurophysiol. 100, 959–965.