

Provided for non-commercial research and education use.  
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

## Journal of Theoretical Biology

journal homepage: [www.elsevier.com/locate/jtbi](http://www.elsevier.com/locate/jtbi)

## Schizophrenia—a parameters' game?

Anca Rădulescu\*

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

## ARTICLE INFO

## Article history:

Received 9 November 2007

Received in revised form

18 March 2008

Accepted 2 May 2008

Available online 16 May 2008

## Keywords:

Brain

Pathway

Feedback loop

Dynamical system

Bifurcation

## ABSTRACT

Schizophrenia is a severe, currently incurable, relatively common mental condition. Its symptoms are complex and widespread. It structurally and functionally affects cortical and subcortical regions involved in cognitive, emotional and motivational aspects of behavior. Its diagnosis is based on statistical behavior rather than on its actual cause and its treatment is elusive.

We elaborate a theoretical paradigm that accounts for some of the most important features of this illness. Our nonlinear mathematical model, built upon recent hypotheses of neural vulnerability and limbic dysregulation, addresses the amygdala—hippocampus—prefrontal interactions and their evolution under perturbation. The dependence of the dynamics on the system's parameters offers an analytical context for the “normality/disease” dichotomy. The concept of bifurcation could be the key to understanding the threshold between these two states.

The nonlinearity parameter (Lyapunov number) is responsible in our setup for tuning the limbic vulnerability characteristic to schizophrenia. Studying its effect on the dynamics helps us understand how stressful events and medication can switch the system from a regime of safety to one of instability, and conversely. The approach has potential for pre-symptomatic risk assessments and for long-term predictions.

© 2008 Elsevier Ltd. All rights reserved.

## 1. Introduction

## 1.1. Stress and illness

In the wild, living beings survive by responding to perceived threats with adaptive and appropriate changes in their behaviors and physiological states. Besides the species-specific factors, the nature of these responses depends on the external environment, but also on the internal physiological and emotional conditions. Unfortunately, the neuroendocrine mechanisms that control stress responses based on these environments are poorly understood for most animals (Lowry and Moore, 2006), in particular for humans.

Altogether we know that, via its autonomic effects, sustained stress can severely affect health (Elliott and Eisdorfer, 1982), contributing to a variety of conditions, among which are heart disease, diabetes, growth retardation (Sapolski, 2004), decreased immunity (Manuck et al., 1991) and various eating and digestive disorders (Jones et al., 2007). Through similarly complex mechanisms, stress is also believed to lead to a number of psychiatric disorders, including depression, post-traumatic stress disorder, Alzheimer's disease and other anxiety disorders (Kim and Kim,

2007). This paper addresses in particular the effects of stress on emotional processing in schizophrenia.

## 1.2. Schizophrenia and the limbic dysregulation hypothesis

Schizophrenia is a severe mental disorder with a heterogeneous set of symptoms including paranoia, hallucinations, delusional beliefs, thought disorder, emotional flattening and social withdrawal. The illness is relatively common, affecting at any one time 1.1% of the population, or around 65 million people worldwide (according to NIMH statistics). It is a chronic (Bachrach, 2000; Harding et al., 1992) and neurodegenerative (Ashe et al., 2001; DeLisi, 1999; de Haan and Bakker, 2004) disease, structurally and functionally affecting various cortical and subcortical regions involved in cognitive, emotional and motivational aspects of behavior (Lawrie et al., 2003; Ananth et al., 2002; Staal et al., 2001; Andreasen et al., 1986), and thus having a devastating effect on social functioning.

A main unanswered question in current psychiatry concerns diagnosing and treating this illness. Consensus diagnoses are revised periodically (American Psychiatric Association, 1994), but are based upon observed behavior rather than etiology, which is still unknown. The severity of symptoms cannot be stated in reproducible terms, and is therefore left to clinical interpretation, which increases the potential of misdiagnosis. Furthermore,

\* Tel.: +1303 735 6209; fax: +1303 492 4066.

E-mail address: [radulesc@colorado.edu](mailto:radulesc@colorado.edu)

although progress has been made in understanding some effects and side effects of antipsychotic medication, there is currently no sustainable treatment for schizophrenia, and the drugs that are being used may only treat the effects of the disease rather than its cause.

For example, dopamine and serotonin abnormalities in schizophrenia (Joyce and Milan, 2005; Yamamoto and Hornykiewicz, 2004) constitute today the most established and popular etiological hypothesis (which forms the bases for development of newer antipsychotics (Friedman et al., 2005; Kapur and Mamo, 2003)). However, schizophrenia has many neurobiological features suggesting an underlying dysregulation of emotional arousal, including limbic (Chua and McKenna, 1995; Williams et al., 2004), endocrine (Ritsner et al., 2004; Sapolsky and Plotsky, 1990; Wik et al., 1986; Tandon et al., 1991), and autonomic (Dawson et al., 1994; Zahn, 1997; Mujica-Parodi et al., 2005) abnormalities. It is possible that the neurotransmitter dysfunction may be induced by hyperarousal (Jackson and Moghaddam, 2004; Moghaddam and Jackson, 2004; Finlay and Zigmond, 1997), making it a consequence of dysregulation, rather than its cause (Rădulescu and Mujica-Parodi, 2007).

Interestingly, stress has been noticed to impair healthy individuals in ways surprisingly similar to schizophrenic symptoms. Many cognitive abnormalities (Dirkin, 1983; Blackwood et al., 2001; Mujica-Parodi, 2002) associated with this illness, such as delusions and hallucinations (Hirsch and Weinberger, 1995), impaired memory (Javitt et al., 1995), lowered sensory gating and selective attention (Mathalon et al., 2004; Braff and Light, 2004) are also induced in healthy adults under acute emotional stress (Ghisolfi et al., 2006; Silva et al., 1998; Brugger et al., 1999).

So the question raises itself: Can stress single-handedly cause a mental illness just through its perseverance? And if not, then what is the intrinsic detail that makes the dramatic difference between normality and pathology? Answers to this question range over a large scale, and are not always consistent. Some studies attribute schizophrenic symptoms solely to prenatal stress, or to social and other environmental factors during the patient's childhood and teenage years (Jarvis, 2007). On the other hand, genetic studies reveal a strong hereditary component of the illness (Bearden et al., 2007; Williams et al., 2007). It is likely that the signature of schizophrenia is a combination of the two sides, and that a genetic stress-sensitivity in conjunction with stressful "life events" may lead to a schizophrenic first-break or relapse (Berner, 2002).

Along these lines, Nuechterlein et al. (1992), Dawson et al. (1992a, b) elaborated a "vulnerability/stress" hypothesis, which attributes schizophrenia to a hereditary predisposition that reduces the individual psychological threshold towards 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 observed that this "vulnerability," or lack of inhibition in the threat detection mechanism (Mujica-Parodi et al., 2007), manifests itself as an overt illness only under the impact of stress factors (Ventura et al., 1989), so that schizophrenic disturbances eventually result as an overlap of environmental stress onto the individual's premorbid personality component. Advances in understanding the neurobiology of the stress cascade (Wik et al., 1986; Tandon et al., 1991; McEwen, 2004) led to a plausible model by which this vulnerability occurs through neurotoxic effects on the hippocampus, involving synaptic remodeling (Corcoran et al., 2002; Kim and Kim, 2007; Weinberger and McClure, 2002).

In this context, schizophrenic symptoms may constitute an end stage of a cyclic and neurodegenerative process. Vulnerability to schizophrenia has been correlated to volume reductions in several brain areas: amygdala, hippocampus and prefrontal cortex (PFC)

(Yui et al., 2007). This is not surprising, since the limbic system is primarily associated with the regulation of emotion and arousal, and is also responsible for integrating the internal and external environments via its wide connections with the neocortex (Anand, 2005), as well as with the autonomic (Amann and Constantinescu, 1990), and endocrine (Mason et al., 1961) systems. Recent studies (Medoff et al., 2001; Preston, 2005; Tamminga, 2006) support the theory that the vulnerability to stress in schizophrenia is based on a pre-existing hippocampal/prefrontal deficit. Impaired hippocampal/prefrontal function leads to decreased inhibition of the amygdala, contributing to higher arousal levels, even under minor stress. Via the connections of the amygdala with the hypothalamus, the fear reaction triggers autonomic and endocrine effects (LeDoux, 2003), in particular increased cortisol levels (Sapolsky and Plotsky, 1990). Excessive cortisol leads to brain neurotoxicity (Weinberger and McClure, 2002) and further hippocampus damage (Pavlidis et al., 2002), thus closing the dysregulation vicious cycle. The delay in schizophrenia's onset—late teens in males and early 30s in females (Kessler et al., 2007)—is consistent with a vicious cycling process, in which the neurodegenerative loop would need sufficient time to progress to the point where symptoms become apparent.

The hypothesis of limbic vulnerability to stress in schizophrenia is further supported by the known relationship between stress and first psychotic episodes (Hazlett et al., 1997) or relapses (Ventura et al., 1989). A sympathetic upturn—such as elevated autonomic activation (Dawson et al., 1994), or electrodermal activity levels (Hazlett et al., 1997; Dawson et al., 1992b)—seems to be present pre-symptomatically in as high as 60% of patients. Also, it has been observed that stressful life events and highly critical attitudes toward the patient in the social environment predict relapse (Nuechterlein et al., 1992), while antipsychotic medication reduces relapse rates. This protective factor may operate partially by raising the psychological threshold in the face of environmental stressors (Ventura et al., 1992). Such first outbreak and relapse predictors are currently being used as clinical indicators for schizophrenia, together with more traditional ones, such as paranoia, agitation and sleeplessness (Hirsch and Weinberger, 1995). The possibility of pre-symptomatic treatment (McGlashan, 1998; McGlashan et al., 2003), among other things, motivated a more careful investigation of the factors implicated in producing this "vulnerability."

The dynamical analysis in this paper is based on a control system model described by Sotres-Bayon et al. (2004), in which limbic regions define a negative feedback loop that regulates arousal. The central amygdala (CE) forms the main excitatory component of the arousal response (Davis and Whalen, 2001). The primary inhibitory pathways are the medial PFC (Baxter et al., 2000; Blair et al., 2005; Izquierdo et al., 2005; Izquierdo and Murray, 2005; Phelps et al., 2004; Rosenkranz et al., 2003) and the hippocampus (Corcoran et al., 2002; Sotres-Bayon et al., 2004). Outputs from the limbic system, via the hypothalamus, provide inputs for the endocrine and autonomic nervous systems. In our context, the model explains how limbic dysregulation in schizophrenia could lead to its characteristic behavioral features and could also cause the endocrine and autonomic abnormalities that so often accompany the illness. From a different perspective, the model uses the known mechanisms of fear conditioning and extinction, so our conclusions should agree with the existing results on regulation of arousal (see Section 3).

Henceforth, the paper is organized as follows. Section 3 constructs and analyzes the mathematical model. Section 4 interprets the results of the analysis and discusses the conclusions in a clinical context. Appendix A gives a more detailed review of the known neural pathways that underlie the limbic interactions assumed in the model.

## 2. The mathematical model

Our theoretical, simplified model quantifies the direct and indirect amygdala–mPFC (medial prefrontal cortex) mutual regulation in a way which can be studied and understood analytically. The strengths of these interactions are tuned differently for different individuals. In our model, this tuning is quantified by a set of parameters, so that the time evolution of the system, and ultimately its asymptotic behavior, depend on the choice of the parameter values. While making no claim to illustrate exactly the complex fear reaction, the model should rather be seen as a metaphor of the brain undergoing stress, supporting the limbic dysregulation hypothesis. If explored further, the idea may be clinically very important, as it suggests ways in which a more quantitative approach would be helpful to the field of psychiatry. New clinical paradigms could be developed to test and use this hypothesis (see Section 3).

As we do not consider bilaterality, our model is constructed as a two-dimensional dynamical system in which the variables  $a = a(t)$  and  $p = p(t)$  are levels of activation of amygdala and PFC, respectively. In a data-driven model, one may observe these variables as discrete time series of measurable hemodynamic or electromagnetic responses. One does not expect, in general, for complex phenomena to behave in a linear fashion, since linear systems do not exhibit any “interesting” behavior. The brain in particular is believed to have more subtle and safer regulation mechanisms, which imply the presence of nonlinearities. We have chosen to represent only the direct pathways between regions (including the self-modulation within each region) by linear terms. The indirect (and much slower-acting) hippocampus-modulated influences are expressed as nonlinearities. Nonlinearity in a two-dimensional system introduces an interesting characteristic feature: possible existence of limit cycles (see Fig. 1).

Experimental studies show that high levels of cortisol due to the amygdala stress-reaction have a detrimental effect on the PFC, in two known distinct ways (see Appendix A): its neurotoxic effects on hippocampal cells and its remodeling of synaptic function between hippocampus and the receptive PFC areas. The system, including these nonlinear contributions, will take the form:

$$\begin{aligned} \dot{a} &= -\mu_1 a - k_1 p + I - \gamma_1(H - f(a)) \\ \dot{p} &= k_2 a + \mu_2 p + \gamma_2(H - f(a) - g(a, p)) \end{aligned}$$

where  $I, H, \mu_1, \mu_2, k_1, k_2, \gamma_1, \gamma_2 > 0$ .

The amygdala activation  $a$  is driven by the following terms: the input  $I > 0$  (corresponding to the background environmental stimuli), the self-inhibition  $-\mu_1 a$  (the amygdala “resilience to stress”; see Section 3) and the prefrontal and hippocampal modulations  $-k_1 p$  and  $-\gamma_1(H - f(a))$ . The regular activation of the hippocampus (introduced here through the constant  $H$ ) is decreased by a term  $-f(a) < 0$ , which signifies the structurally detrimental effect that amygdala overactivity and the subsequent hypercortisolemia have on the hippocampus.

The PFC activation  $p$  is driven by the amygdala excitatory input  $k_2 a$ , a self-excitation  $\mu_2 p$ , a hippocampal excitatory afference  $\gamma_2(H - f(a))$  (see above) and a modulation of the hippocampus–PFC interaction at synaptic level  $-\gamma_2 g(a, p)$ .

In the absence of endocrine contributions (nonlinearities), the dynamics would heuristically work as follows: If the amygdala activation level is high, its excitatory effect on the mPFC will drive  $p$  up, which in turn will inhibit  $a$  and make the system converge towards an equilibrium, given by

$$(a^*, p^*) = \left( \frac{k_2 I + H(\mu_1 \gamma_2 - \gamma_1 k_2)}{k_1 k_2 - \mu_1 \mu_2}, \frac{-\mu_1 I + H(\gamma_1 \mu_2 - k_1 \gamma_2)}{k_1 k_2 - \mu_1 \mu_2} \right)$$

The equilibrium depends on the outside stress level and on the hippocampus activation, as well as on the mutual and self excitation and inhibition parameters. In a “brain” with an overactive amygdala (low  $\mu_1$  value), convergence may fail to happen.

To fix our ideas, we will take both nonlinear terms to be of the simplest possible forms:  $f(a) = \gamma(a - a^*)^2$  to reflect the decrement in  $H$  due to excessive amygdala activation;  $g(a, p) = \delta(a - a^*)(p - p^*)$ , to implement the suppression of Hebbian-like synaptic updates in mPFC. The local stability of the nonlinear system near its fixed point  $(a^*, p^*)$  is dictated by the linear part of the system, and could be established by looking at the Jacobian matrix:

$$D = \begin{pmatrix} -\mu_1 & -k_1 \\ k_2 & \mu_2 \end{pmatrix}$$

Its determinant is  $\Delta = k_1 k_2 - \mu_1 \mu_2$ . We will assume that  $\Delta > 0$ , i.e., we work in a regime where the interconnections prevail over self-modulations in the two regions.

Even if we fix  $k_1, k_2$  and  $\mu_2$  (which is what we will do for the rest of this analysis), the behavior of the system can still evolve in a few different ways, depending on the values of the linear parameter  $\mu_1$ , as well as on the degree of nonlinearity. The fixed point  $(a^*, p^*)$  is locally attracting if  $\mu_1 > \mu_2$ , i.e., if the amygdala self-inhibition is strong enough to exceed the PFC self-excitation. However, as  $\mu_1$  decreases, the stability of the fixed point changes, and for  $\mu_1 < \mu_2$  it becomes a local repeller. The degree of nonlinearity, however, has more subtle additional effects on the system’s behavior in the neighborhood of the fixed point.

Indeed, let’s consider the general form of a two-dimensional nonlinear system with a fixed point at the origin:

$$\begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = D \begin{pmatrix} x \\ y \end{pmatrix} + N(x, y) = \begin{pmatrix} d_{11}x + d_{12}y + N_1(x, y) \\ d_{21}x + d_{22}y + N_2(x, y) \end{pmatrix}$$

where  $D$  is the Jacobian matrix and  $N$  is the nonlinear part, both parameter dependent.

The eigenvalues  $\lambda_1$  and  $\lambda_2$  of  $D$  may take real or complex values that satisfy  $\lambda_1 + \lambda_2 = \tau = \text{trace}(D)$  and  $\lambda_1 \lambda_2 = \Delta = \text{det}(D)$ . In general, if  $\Delta > 0$ , then the origin is either attracting (in case  $\tau < 0$ ) or repelling (in case  $\tau > 0$ ). At the parameter values where  $\tau = \lambda_1 + \lambda_2 = 0$ , the system exhibits a bifurcation. In particular, if  $\lambda_1$  and  $\lambda_2 = \bar{\lambda}_1$  are purely imaginary, then we may have a Hopf bifurcation. The way the local dynamics of the system changes at a Hopf bifurcation is described by the Lyapunov number, which depends on both the linear part  $D$  and the nonlinear part  $N$ , as described below (Perko, 1993). If  $N_1, N_2: \mathbb{R}^2 \rightarrow \mathbb{R}$  are analytic, with expansions:

$$\begin{aligned} N_1(x, y) &= \sum_{i+j \geq 2} a_{ij} x^i y^j = (a_{20}x^2 + a_{11}xy + a_{02}y^2) \\ &\quad + (a_{30}x^3 + a_{21}x^2y + b_{12}xy^2 + b_{03}y^3) + \dots \end{aligned}$$

$$\begin{aligned} N_2(x, y) &= \sum_{i+j \geq 2} b_{ij} x^i y^j = (b_{20}x^2 + b_{11}xy + b_{02}y^2) \\ &\quad + (b_{30}x^3 + b_{21}x^2y + b_{12}xy^2 + b_{03}y^3) + \dots \end{aligned}$$

then the Lyapunov number:

$$\begin{aligned} \sigma &= \frac{-3\pi}{2d_{12}\Delta^{3/2}} \{d_{11}d_{21}(a_{11}^2 + a_{11}b_{02} + a_{02}b_{11}) \\ &\quad + d_{11}d_{12}(b_{11}^2 + a_{20}b_{11} + a_{11}b_{02}) \\ &\quad + d_{21}^2(a_{11}a_{02} + 2a_{02}b_{02}) - 2d_{11}d_{21}(b_{02}^2) \} \end{aligned}$$

$$\begin{aligned}
 & -a_{20}a_{02}) - 2d_{11}d_{12}(a_{20}^2 - b_{20}b_{02}) \\
 & -d_{12}^2(2a_{20}b_{20} + b_{11}b_{20}) + (d_{12}d_{21} - 2d_{11}^2)(b_{11}b_{02} - a_{11}a_{20}) \\
 & - (d_{11}^2 + d_{12}d_{21})\{3(d_{21}b_{03} - d_{12}a_{30}) \\
 & + 2d_{11}(a_{21} + b_{12}) + (d_{21}a_{12} - d_{12}b_{21})\}
 \end{aligned}$$

If  $\sigma \neq 0$ , a Hopf bifurcation occurs at the critical value of the parameters where  $\tau = 0$ . More precisely:

(1) If  $\sigma < 0$ , the origin is attracting for  $\tau < 0$ , and the system has no limit cycle. For  $\tau > 0$ , the origin becomes repelling, and a circular stable limit cycle forms around it, whose radius increases with  $\tau$  (Fig. 2).

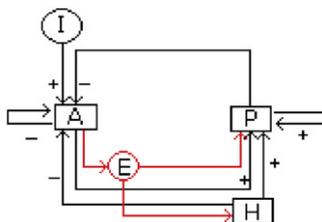
(2) If  $\sigma > 0$ , the system has a unique unstable limit cycle that surrounds the stable origin for  $\tau < 0$ . The radius of the cycle decreases with  $\tau$ . At  $\tau = 0$ , the unstable cycle collapses into the origin, making it unstable for  $\tau > 0$  (Fig. 3).

The change in dynamics is still very sudden at a Hopf bifurcation (even though the parameters change smoothly), but has subtle implications. For the rest of this section, we apply these general results to our particular model, and we show how for different values of the parameters our system can exhibit dramatically different time evolutions: some corresponding to normal physiology and behavior, some corresponding to schizophrenic symptoms. The clinical relevance of these phenomena is further considered in the Section 3.

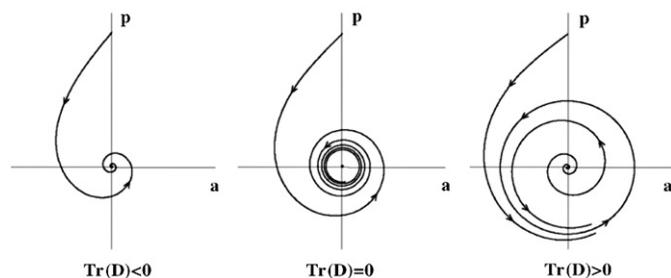
Applying the general theory summarized above, our nonlinear system has a fixed point at  $(a^*, p^*)$ , and exhibits a Hopf bifurcation at  $\mu_1 = \mu_2$  with Lyapunov number

$$\sigma = \frac{3\pi\mu_2\gamma^2\gamma_2^2}{2A^{3/2}} \left( \frac{2\gamma_1 - \delta}{\gamma_2} - \frac{\delta}{\gamma} \right) \left( \frac{k_1 - \gamma_1 - \delta}{\mu_2 - \gamma_2 - \gamma} \right)$$

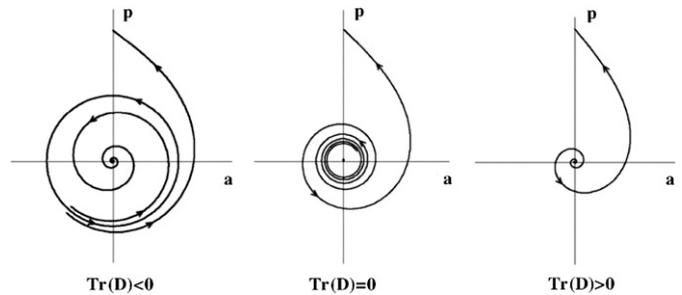
Faithful to the stress/vulnerability hypothesis of schizophrenia, our interpretation regards  $\sigma$  as the “disease-quantifying” parameter: negative values of  $\sigma$  correspond to normal limbic regulation, while positive values of  $\sigma$  quantify risk for developing schizophrenia, and, in more advanced stages, severity of the illness (see Section 3). On the other hand, larger values of  $\mu_1$  correspond to a more stress-resilient amygdala, while smaller



**Fig. 1.** The interactions of the amygdala–hippocampus–mPFC, as described in the text. Legend: A = amygdala, P = prefrontal cortex, H = hippocampus, I = input stimuli, E = endocrine system. Excitatory interactions are marked with (+) and inhibitory interactions, with (–). Nonlinearities and inhibitory contributions to hippocampal and prefrontal functions.



**Fig. 2.** When  $\sigma < 0$ , the system exhibits a supercritical Hopf bifurcation.

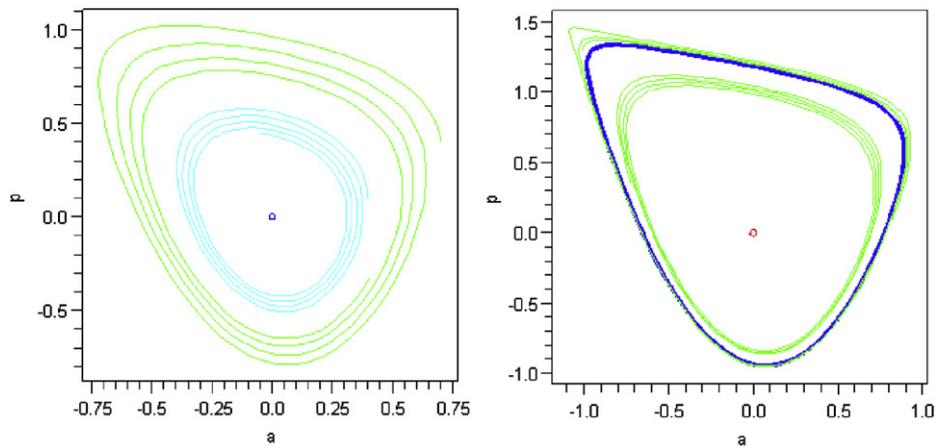


**Fig. 3.** When  $\sigma > 0$ , the system exhibits a subcritical Hopf bifurcation.

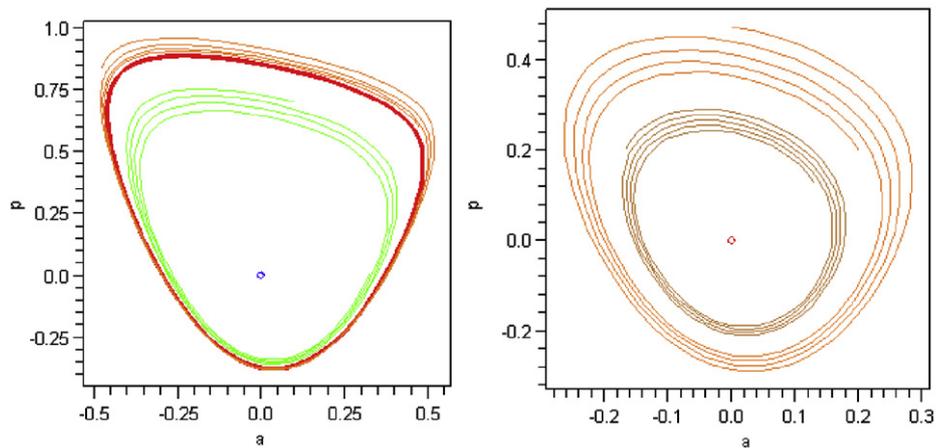
values of  $\mu_1$  signify a more stress-reactive amygdala. We could think of this parameter as quantifying the amygdala responsiveness to stress, which in literature has been related to mental conditions such as depression, or anxiety disorders (Sotres-Bayon et al., 2004), but which is not the signature of schizophrenia. We can verify whether this paradigm is clinically plausible by testing what happens if we apply a brief stress increase to the system (which in real life may come in the form of a traumatic event). We quantify the burst of stress by boosting the amygdala to a high initial state. We observe whether the system returns to homeostasis by checking if the respective trajectory eventually stabilizes (see Figs. 4–6).

Suppose  $\sigma < 0$ . For high amygdala resilience  $\mu_1 > \mu_2$ , all trajectories are attracted towards the fixed point, so the initial condition is irrelevant: the time evolutions converge after any stimulus, if sufficient time is allowed to pass (Fig. 4a). For  $\mu_1 < \mu_2$ , the situation is changed by the formation of an attracting limit cycle (Fig. 4b). After a short stress burst, the duo amygdala–PFC slowly stabilizes towards the cycle. Note that, although dampened in time, the system continues to oscillate in both cases. We will return to this idea in the Section 3. The memorable feature of the  $\sigma < 0$  regime (and of the corresponding subcritical Hopf bifurcation) is that, although stability of the fixed point changes at the bifurcation  $\mu_1 = \mu_2$ , the role of the attractor is assumed by a limit cycle. The fact that the amygdala–PFC pair exhibits in some people wider oscillations that do not seem to dampen in time could be a mark of low amygdala self-inhibition.

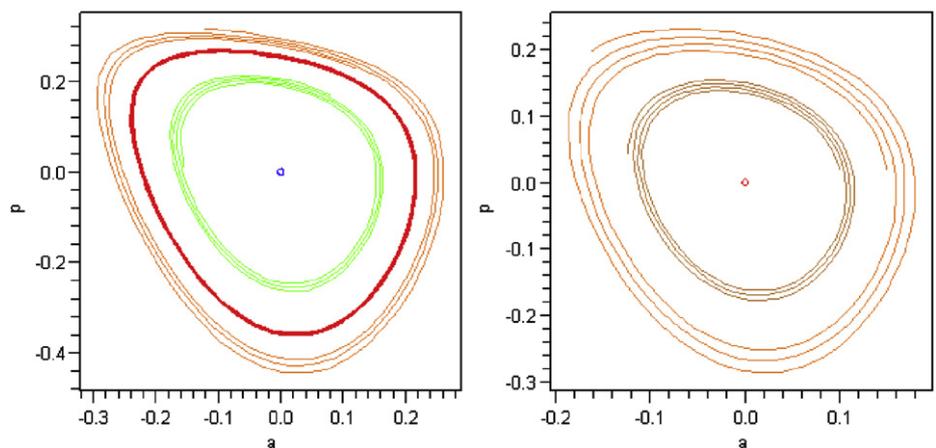
When  $\sigma > 0$ , the situation changes completely. In the regime  $\mu_1 > \mu_2$ , the system has a locally attracting fixed point, surrounded by a repelling cycle, whose radius gets smaller with smaller  $\mu_1$  and with larger  $\sigma$ . The basin of attraction of the stable point is the interior of the cycle: any initial state inside this basin will converge in time towards the fixed point, and any initial state outside will spiral out (Figs. 5a and 6a). When  $\mu_1 = \mu_2$ , the cycle disappears, so when  $\mu_1 < \mu_2$  the fixed point is globally repelling (Figs. 5b and 6b). The behavior of the model in the positive  $\sigma$  regime is representative for schizophrenic dysregulation. A stimulus may elevate amygdala to a value which places the corresponding state outside of the attraction basin, preventing convergence from ever happening. If allowed to follow its natural evolution, the trajectory would perform larger and larger oscillations, corresponding to the cyclic psychotic behavior observed in patients. At some point during this evolution, the patient may enter clinical treatment; antipsychotic medication may succeed to temporarily alter this time-course. It is interesting to note that, as we increase the value of  $\sigma$ , the attraction basin shrinks around the attracting point, so that even weak stressful stimuli may push the state outside the attraction basin. This makes the Lyapunov number  $\sigma$  a good quantifier of the risk and severity of the disease: the larger  $\sigma$ , the more likely it is for the time evolution to be thrown outside of the convergence range even by small perturbations. This relates to the fact that highly vulnerable individuals



**Fig. 4.** Example of the amygdala–PFC system undergoing a supercritical Hopf bifurcation when  $\sigma < 0$ . The Maple software was used to generate the two plots, both for  $\mu_2 = 1, k_1 = 4, k_2 = 8, \gamma_1 = 2, \gamma_2 = 1, \gamma = 2, \delta = 6$ . Left:  $\mu_1 = 1.1$ . The trace  $\tau < 0$ , hence the fixed point is an attractor (blue dot), to which all neighboring trajectories converge (see green and cyan curves). Right:  $\mu_1 = 0.95$ , hence  $\tau > 0$ . The fixed point is repelling (red dot), and instead the stable cycle (blue loop) attracts all local trajectories (green curves).



**Fig. 5.** Example of the amygdala–PFC system undergoing a subcritical Hopf bifurcation when  $\sigma > 0$ .  $\mu_2 = 1, k_1 = 4, k_2 = 8, \gamma_1 = 2, \gamma_2 = 1, \delta = 6$ ;  $\gamma$  was increased to  $\gamma = 5$ . This is sufficient to make  $\sigma > 0$  and enter the “dysregulated” regime. Left:  $\mu = 1.1$ ; the fixed point is attracting (blue dot), but the basin of attraction is bounded by a repelling cycle (red loop). Trajectories inside the attraction basin spiral towards the attracting fixed point (green curve), but the ones outside the attraction basin spiral outwards (orange curve). Right:  $\mu_1 = 0.95$ . Worst-case scenario: the fixed point is unstable (red dot), and all local trajectories are repelled (orange curves).



**Fig. 6.** Example of the amygdala–PFC system undergoing a subcritical Hopf bifurcation when  $\sigma > 0$ .  $\mu_2 = 1, k_1 = 4, k_2 = 8, \gamma_1 = 2, \gamma_2 = 1, \gamma = 2$ ;  $\delta$  was increased to  $\delta = 20$ . Again, this increase made  $\sigma > 0$  and “dysregulated” the system. Left:  $\mu = 1.1$ ; the fixed point is attracting (blue dot), but surrounded by a repelling cycle (red loop). The green curve, as well as all other trajectories inside the cycle, converges to the fixed point. The orange curve spirals away from the cycle. Right:  $\mu_1 = 0.95$ : the fixed point is unstable (red dot), and all local trajectories spiral outwards (orange curves).

may develop psychotic behavior even as a consequence of common daily stress that may appear benign to others.

Our results, as well as the computability of  $\sigma$  from clinical data, make  $\sigma$  desirable and useful as a measure of risk for developing schizophrenia later in life (see Section 3). A  $\sigma$ -based quantitative assessment could be performed prodromally, or even presymptomatically; this is clinically crucial, since it has been proved that early detection and diagnosis greatly improve the prognosis of the illness. On the other hand, in already symptomatic patients,  $\sigma$  and other parameters could help predict relapse times (see Section 3).

A few comparisons of the system's dynamics for relevant parameter values are illustrated in Figs. 4–6. Some interpretations and further speculations on the effect of antipsychotic drugs on the system's parameters and dynamics are addressed in Section 3.

### 3. Discussion

#### 3.1. Parameters

This theoretical model is a “philosophical” as much as a “physiological” illustration of the limbic dysregulation and neurotoxicity hypotheses. It presents the working brain in a light that permits interpretation of its “stress vulnerability,” or “PFC/hippocampal deficit” as parameters that vary continuously, determining its regulation and function. The focus of this interpretation is on the idea that, although these parameters change smoothly over a whole continuum of possible values, there are critical/threshold values, which, when passed, could suddenly and completely change the system's dynamics.

The two parameters on which we focus here, whose tuning determines the behavior of the system, are  $\mu_1$  and  $\sigma$ .

We have interpreted  $\mu_1$  as the amygdala sensitivity to stress, associated it to the capacity of sustaining low amygdala activation under constant background stressors, and further related it to the person's level of trait anxiety. This illustrates a known physiological fact. Some of the excitatory inputs to the amygdala terminate on local inhibitory interneurons which in turn connect with projection neurons, giving rise to feedforward inhibition. It is believed that these connections allow stimulus-driven inhibition to build up and account for the decrease in responses under repeated stimuli (LeDoux, 2007).

We relate the Lyapunov number  $\sigma$  to the individual's limbic vulnerability to stress, described in our model by the two parameters  $\gamma$  (regarding hippocampal sensitivity) and  $\delta$  (regarding PFC synaptic remodeling). Notice that there is typically an interval for  $\delta/\gamma$  for which  $\sigma < 0$ . As mentioned in the Results section, we associate negative values of  $\sigma$  to the well-balanced healthy controls, and positive values of  $\sigma$  to the imbalanced schizophrenic patients. If either  $\gamma$  (Fig. 5) or  $\delta$  (Fig. 6) is too large, the ratio  $\delta/\gamma$  leaves the “safety” interval and produces a positive  $\sigma$ . In other words, if either the hippocampal or the prefrontal vulnerability exceeds certain thresholds, the system qualifies as “dysregulated,” or “diseased,” and its dynamics will reflect that.

One viable way of obtaining the linear coefficients ( $\mu_1$  in particular) from clinical data (such as hemodynamic time series) is by using dynamic causal modeling (DCM) (Friston et al., 2003). DCM is a fairly new identification method of nonlinear input-state-output systems. It uses a bilinear approximation to the dynamics of interactions among states, and delivers information about the system's modulation and effective connectivity. In a data-driven study in collaboration with LSEC,<sup>1</sup> the author is

currently working on using such “interaction strengths” obtained with DCM to validate the theoretical model (Rădulescu and Mujica-Parodi, 2007). The clinical study uses 40 min long fMRI time series of six brain regions (right and left amygdala, right and left hippocampus, Brodman Areas 9 and 45) from two populations of schizophrenic patients and healthy controls. We are also working on elaborating an ideal nonlinear parameter identification technique to quantify the relationship between the hippocampal/PFC activation and stress-produced cortisol (to be measured as salivary concentrations throughout the fMRI scan as well as between scans). The ideal protocol would include periodic (weekly) short scans over a few weeks, accompanied by daily cortisol readings and mood self-assessments. This combination would best capture the longer-term behavior of the system and its behavioral correlates.

#### 3.2. Timelines

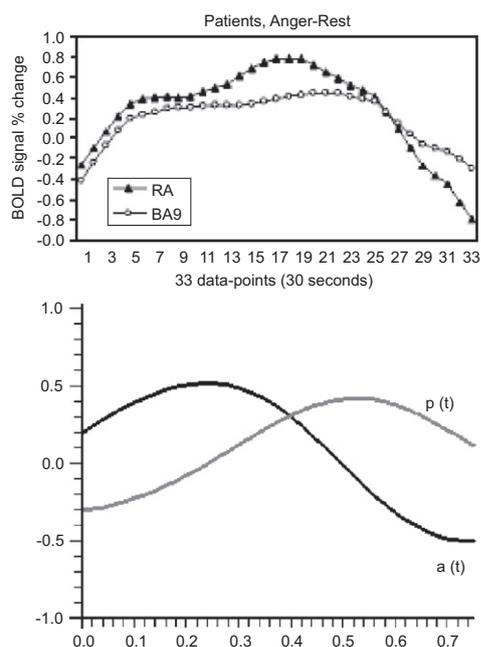
It is important to address here a few time-frame problems. Our model works hand-in-hand with behavioral research that relates stress with neural states and with symptoms over long time periods; in the case of patients, such studies also address first outbreak (Hazlett et al., 1997) and relapse (Ventura et al., 1989) of psychosis. The time frame that the model envisions is thereby of the order of weeks or months, allowing possible psychotic behavior to develop after a stressful event. Here, there are two distinct, although related issues that require consideration:

The first is the amount of time that it takes a cycle (more precisely, an “almost cycle”) to complete. In practice, knowing in advance the length of a few previous cycles may give a good prediction basis for the evolution of the next one, assuming that the external conditions do not change dramatically. Although longitudinal studies of mood (Larsen, 1987; Murray et al., 2002) have been surprisingly overlooked in the past, recent research promotes the idea that mood cycles are not unique to bipolar patients, but appear even in mentally normal individuals, only to a different extent (a feature that perfectly agrees with our model's predictions). In the absence of psychological history or under a dramatically changing environment, clinical predictions could be obtained instead from the proposed theoretical model by analyzing its kinetics with respect to the parameters. (Again, this topic will not be discussed here in more detail.)

The second timeline targets the amount of cycling necessary after leaving the basin of attraction (as consequence of a stressful event), until psychosis becomes apparent. After the original stimulus, the model predicts a slow, but continuous degradation in the state of the patient from one cycle to the next. It may take a long time (years) for the symptoms to establish and for a sustainable diagnosis to be possible; meanwhile, the individual may undergo intermarry diagnoses of “psychosis NOS,” or “bipolar disorder.”

Cycles and oscillations in brain activity, as well as regulation and return to homeostasis have been already the subject of a wide variety of studies, addressing very different time scales. Electrophysiology studies revealed high frequency oscillations in neuronal brain activity, and correlated synchronization of theta rhythms in the amygdalo-hippocampal pathways with retrieval of conditioned fear (Collins et al., 2001; Pelletier and Pare, 2004). It is also known that the brain has a circadian rhythm, so that its activity oscillates according to a daily pattern (Guilding and Piggins, 2007). Additionally, recent imaging studies focus on the dynamics of certain regions of interest in response to visual stimuli (Rădulescu and Mujica-Parodi, 2007; also see Fig. 7). Although our model does not account for such short-scale phenomena, these findings better describe its place as just one level in a more general and complex picture.

<sup>1</sup> Laboratory for the Study of Emotion and Cognition, Stony Brook University Hospital, New York.



**Fig. 7.** Top: fMRI data on amygdala and BA45 activation in schizophrenic patients under visual stimulation with Pictures of Facial Affect. The data has been averaged over all stimulation blocks and over the whole population sample of 11 individuals (Rădulescu and Mujica-Parodi, 2007). Bottom: Long-term oscillations of the amygdala and prefrontal cortex in response to stimuli, as predicted by a Maple simulation of our nonlinear model for  $\sigma > 0$ .

### 3.3. Dopamine receptors and antipsychotics

There is evidence that the hippocampus and the PFC exhibit converging projections to the nucleus accumbens, and that the information between them is likely to be bidirectional via these indirect pathways. Moreover, it has been shown (Goto and Grace, 2005) that the synaptic plasticity within the accumbens is determined by the afferences from the hippocampus and PFC, and involves selectively dopamine D1 and D2 activation and inactivation. In fact, both D1 and D2 receptors have been found in high concentrations in the striatum and particularly in the nucleus accumbens, supporting structural brain studies, which have revealed increases in striatal volumes in schizophrenic patients after antipsychotic treatment (Harrison, 1999). In the context of our model, this evidence suggests that the dopamine-antagonist medication currently in use may lower the prefrontal vulnerability to stress, by counteracting the synaptic remodeling effects of stress. More precisely, medication (without providing a permanent cure) may lower  $\delta$ , and consequentially  $\sigma$ , thus perturbing the system to an artificially maintained better-regulated regime. This could be the reason for the common relapses when medication is forgotten or interrupted. In later work we plan to address the problem of optimizing drug administration and its timing in order to improve symptom evolution.

### 3.4. A wider perspective

Since the model is mainly based on the literature of fear conditioning and extinction, it reproduces its basic characteristics. Indeed, Sotres-Bayon et al. (2004) emphasize the idea that, contrary to common belief, extinction is not equivalent to forgetting, but instead represents new learning, which involves plasticity of the connections between mPFC and the amygdala

(rats with lesions in the mPFC exhibited increased resistance to fear extinction; Morgan et al., 1993). The underlying neural basis of this interaction is, however, still poorly understood. In our model, if the prefrontal control over amygdala decreases (due to reasons such as prefrontal or wiring lesions), the determinant  $\Delta = \mu_1 \mu_2 - k_1 k_2$  gets larger, and with it the time length of a relaxation cycle increases. This may correspond to a delay in the individual's fear extinction response after the stimulus has ceased to exist. More generally, one can compare the impact of  $k_1$  and  $\mu_1$  on the dynamics; since they both comprise the modulation of amygdala, we find it natural that they both be related to the arousal management. We hypothesize that their imbalance may underlie the inability of a person with anxiety disorders to regulate their emotions (by depriving the individual of the ability to emotionally adjust, in reasonable time or at all, to a changing environment). However, their effects on the dynamics are, as mentioned, quite different.

The significance of  $\mu_1$  and  $k_1$  can also be tested by using DCM to compute these coefficients in the control population, and then comparing them against the individuals' trait anxiety scores.

As expected, the model also encompasses neurophysiology and behavior more generic than the collection of schizophrenic symptoms, and agrees with a few known phenomena. However, for a better understanding of the disease, we suggest that a higher-dimensional, more elaborate refinement of this model is required to narrow down and isolate phenomena which are characteristic of schizophrenia, and not to any other conditions. Although our model sheds some light onto the possible mechanisms of the disease, such an extension, if validated by experimental data, would be of direct and crucial clinical use.

## 4. Conclusions

Theoretically, our model shows how two different clinical systems (with very similar underlying rules, and only slightly different parameter values) can exhibit drastically different long-term behavior if started under the same initial conditions. The literature talks about the "continuum" of human behavior and the practical difficulties of establishing a normality/pathology threshold. Such a bifurcation could constitute the needed threshold for clinical evaluations. Practically, if the model proves to be valid, both diagnosis of illness and quantification of its severity can be achieved by calculating the Lyapunov number of a system constructed from clinical measures.

Moreover, the model supports the idea that the dynamics of a diseased system is not driven randomly, but rather only appears to be random over short time periods, due to its complicated behavior. This idea is also very important for clinical treatment, since it suggests that the deterministic behavior of a system can be changed by proper tuning of the parameters. It is possible that medication options could be improved by exploring how drugs can change the parameter values to permanently alter the system and its long-term behavior.

Our future work focuses on using clinical data to validate the model. Although minor corrections are likely, we expect that the model will prove to extract the prototypical behavior and to preserve the important phenomenological features of schizophrenia.

## Appendix A. Connections and pathways

Over the past decade, significant research has been conducted on the role of the prefrontal cortex (PFC), the hippocampus and the amygdala in the fear conditioning and extinction. The

predominant view is that the amygdala is excitatory and the hippocampus and PFC are inhibitory (Sotres-Bayon et al., 2004). More precisely, we believe that the activity of the PFC modulates the amygdala fear reaction to a stressor. In this section, we will briefly describe the internal anatomical organization and the pathways between the regions involved in the stress-reaction. This will be some background and motivation for our mathematical model, although the model itself is much more schematic and tries to avoid detail.

#### A.1. Amygdala

It has been observed, in both human and animal studies, that damage to the amygdala prevents the acquisition and expression of fear. It was thereby concluded that the amygdala may be the underlying site for fear conditioning and extinction. Amygdala is divided into a few physiologically and functionally distinct parts: the lateral amygdala (LA), the central amygdala (CE), the basal nucleus (B) and the intercalated cell mass (ITC). The current hypothesized mechanism of the fear reaction, in a very simplified form, is the following: In the absence of stimuli, the intra-amygdalar connections are suppressing its activation, maintaining it at low levels. When an emotionally potent conditioned stimulus is received, it is transmitted via thalamic pathways to the LA, then to the CE (either directly or via more complex intra-amygdalar connections). Finally, the CE has output connections to a set of regions that control specific autonomic, endocrine and behavioral responses. The role of B is still controversial. Although there is anatomical (Pitkanen et al., 2000) and physiological (Ishikawa and Namura, 2003) evidence that there are strong reciprocal projections of B with the hippocampus and with the medial prefrontal cortex (mPFC), B lesions seem to have no effect on fear extinction. It has been suggested that the role of B may be to integrate information from the LA, hippocampus and mPFC, B being thereby a site of contextual contributions to conditioning. As both the hippocampus and the PFC are believed to be crucial in the dynamics of schizophrenia, and as contextual interpretation of threat has been shown to be impaired in schizophrenic patients, these interconnections are of interest to our present study.

#### A.2. Prefrontal cortex

Damage to the PFC is known to generally induce emotional and cognitive changes. In fact, these changes seem to be very finely tuned and region specific. The PFC consists of several functionally distinct sub-regions, which include the lateral PFC, the orbital frontal cortex and the mPFC (Muller et al., 2002; Seamans et al., 1995; Robbins, 1996). The lateral PFC is involved in working memory and executive control functions, such as motor control (Miller and Cohen, 2001). The orbitofrontal cortex is involved in motivation, reward and emotional decision-making (Damasio, 1990; Berns et al., 2001). The mPFC is itself divided into a few sub-regions: anterior cingulate cortex (ACC) and several more ventral areas (infralimbic, prelimbic). The dorsal part of the ACC is involved in attention and cognitive control, and the ventral part in emotional regulation (Bush et al., 2000). The functionality of the other sub-regions has not yet been clearly established, but the predominant view is that neural activity in the mPFC regulates not only the amygdala-mediated fear responses via direct projections to the LA or the ITC, but also the activity in the hippocampus, via projections to CA1 (see below). Moreover, experimental studies suggest that initiating and sustaining behavior also require mPFC self-stimulation (Mora and Myres, 1977; Ferrer et al., 1993).

#### A.3. Hippocampus

The hippocampus is critical in episodic memory consolidation (Squire and Zola-Morgan, 1991) and for aspects of working memory (Lipska et al., 2002). Unlike the role of the amygdala and PFC in stress processing, which have been confirmed by a wide variety of studies, the potential contribution of the hippocampus remains relatively unexplored.

Structural MRI studies (Caetano et al., 2004) found decreased hippocampal volumes in depressed patients and correlated the volume loss with the length of the illness. The same volume reduction has been observed in schizotypal disorders (Dickey et al., 2007). This is consistent with the hypothesis that hypercortisolism could result in hippocampal neurotoxicity in conditions such as bipolar disorder and schizophrenia.

However, although chronic stress has been shown to structurally damage the hippocampus, this damage is believed to be restricted to particular subfields (Sousa et al., 2000; McEwen, 2001), which is possibly not sufficient to explain psychotic symptoms. Cerqueira et al. (2007a) showed that chronic stress may also impair working memory and behavioral flexibility indirectly, by affecting not the volume or the number of neurons in the hippocampus itself, but rather the synaptic plasticity within CA1 (Kemp and Manahan-Vaughan, 2008) or of the hippocampus–PFC interactions (see the paragraph below on hippocampus–PFC pathways).

#### A.4. Amygdala–PFC

Different amygdala nuclei are robustly connected with different regions in the mPFC, suggesting that the two are functionally coupled. Several studies have shown that the functional mPFC activity is inversely related to amygdala activity (Anand and Shekhar, 2003), and this regulatory interaction is believed to be critical for the organism's ability to adapt to change. Although it has been proposed that mPFC inhibits activity in the amygdala, the mechanisms of this suppression are not yet known. As most mPFC projections to the amygdala are excitatory, it has been proposed that the inhibition occurs by activation of inhibitory neurons within the amygdala (Rosenkranz et al., 2003). However, based on experimental evidence, a new study (Vidal-Gonzales et al., 2007) suggests a more complex, bidirectional modulation of fear, in which PL excites amygdala output (via its projections to B) and IL inhibits amygdala output (through its projections to LA and ITC).

It has been argued that dysfunction of the mPFC–amygdala interaction may trigger the emotional preservation (usually a hyperactive amygdala and a hypoactive PFC) found in depression (Siegle et al., 2003), anxiety (Davidson, 2002) and other fear disorders (Quirk and Gehlert, 2003).

#### A.5. Hippocampus–PFC

Clinical and experimental studies implicate both hippocampus and PFC in several aspects of learning and memory. Not surprisingly, the two units are strongly interconnected and modulate each other's activity in a complex manner. Hippocampal innervation of the PFC is mainly excitatory and originates from the temporal CA1/speculum region and projects to the prelim, medial orbital and inflammable areas (Jay and Witter, 1991). Conversely, hippocampal memory suppression is (at least for nonpsychiatric populations) under the control of prefrontal regions (Depue et al., 2007).

Cerqueira et al. (2007a) show how stress can influence the integrity of the hippocampus–PFC pathway, and thereby explain some of the stress-induced neurobiological deficits that cannot be

attributed to hippocampal lesions. The study correlated stress exposure with an observed volumetric reduction in the upper layers of the mPFC which could not be accounted for by neural loss, but rather by dendritic atrophy and retraction of the pyramidal neurons in layers II and III of the mPFC (also see Cerqueira et al., 2007b). Although the hippocampus–mPFC pathway was shown to be impaired even by a single episode of acute stress (Rocher et al., 2004), this stress-induced atrophy seems to be reversible (Radley et al., 2005).

#### A.6. Amygdala—hippocampus

The amygdala impact on the hippocampus is best represented not by neural pathways, but by the indirect autonomic and endocrine effects initiated in the amygdala in response to stress, which lead to hippocampus impairment and functional reduction (as described above). Conversely however, some studies (Corcoran and Maren, 2001) have opened the possibility that hippocampal projections to the B might be important for contextual contributions in fear extinction.

#### References

- Amann, J.F., Constantinescu, G.M., 1990. The anatomy of the visceral and autonomic nervous systems. *Semin. Vet. Med. Surg. (Small Anim.)* 5 (1), 4–11.
- American Psychiatric Association, 1994. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, fourth ed. Washington, DC.
- Anand, A., 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol. Psychiatry* 57 (10), 1079–1088.
- Anand, A., Shekhar, A., 2003. Brain imaging studies in mood and anxiety disorders: special emphasis on the amygdala. *Ann. NY Acad. Sci.* 985, 370–388.
- Ananth, H., Popescu, I., Critchley, H.D., Good, C.D., Frackowiak, R., Dolan, R.J., 2002. Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphology. *Am. J. Psychiatry* 159 (9), 1497–1505.
- Andreasen, N., Nasrallah, H.A., Dunn, V., Olson, S.C., Grove, W.M., Ehrhardt, J.C., Coffman, J.A., Cosslett, J.H., 1986. Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. *Arch. Gen. Psychiatry* 43 (2), 136–144.
- Ashe, P.C., Berry, M.D., Boulton, A.A., 2001. Schizophrenia, a neurodegenerative disorder with neurodevelopmental antecedents. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 25 (4), 691–707.
- Bachrach, L.L., 2000. Chronicity in schizophrenia. *Hosp. Community Psychiatry* 38 (11), 1226–1227.
- Baxter, M.G., Parker, A., Lindner, C.C., Izquierdo, A., Murray, E.A., 2000. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J. Neurosci.* 20 (11), 4311–4319.
- Bearden, C.E., van Erp, T.G., Thompson, P.M., Toga, A.W., Cannon, T.D., 2007. Cortical mapping of genotype–phenotype relationships in schizophrenia. *Hum. Brain Mapp.* 28 (6), 519–532.
- Berner, P., 2002. Conceptualization of vulnerability models for schizophrenia: historical aspects. *Am. J. Med. Genet.* 114 (8), 938–942.
- Berns, G.S., McClure, S.M., Pagnoni, G., Montague, P.R., 2001. Predictability modulates human brain response to reward. *J. Neurosci.* 21, 2793–2798.
- Blackwood, N.J., Howard, R.J., Murray, R.M., 2001. Cognitive neuropsychiatric models of persecutory delusions. *Am. J. Psychiatry* 158 (4), 527–539.
- Blair, H.T., Sotres-Bayon, F., Moita, M.A., LeDoux, J.E., 2005. The lateral amygdala processes the value of conditioned and unconditioned aversive stimuli. *Neuroscience* 133 (2), 561–569.
- Braff, D.L., Light, G.A., 2004. Preattentive and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology* 174 (1), 75–85.
- Brugger, P., Regard, M., Landis, T., Oelz, O., 1999. Hallucinatory experiences in extreme-altitude climbers. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 12 (1), 67–71.
- Bush, G., Luu, P., Posner, M., 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cognit. Sci.* 4, 215–222.
- Caetano, S., Hatch, J., Brambilla, P., Sassi, R., Nicoletti, M., Mallinger, A., Frank, E., Kupfer, D., Keshavan, M., Soares, J., 2004. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Res. Neuroimaging* 132 (2), 141–147.
- Cerqueira, J., Mailliet, F., Almeida, O., Jay, T., Sousa, N., 2007a. The prefrontal cortex as a key target of the maladaptive response to stress. *J. Neurosci.* 27 (11), 2781–2787.
- Cerqueira, J., Taipa, R., Uyllings, H., Almeida, O., Sousa, N., 2007b. Specific configuration of dendritic degeneration in pyramidal neurons of the medial prefrontal cortex induced by differing corticosteroid regimens. *Cereb. Cortex* 17 (9), 1998–2006.
- Chua, S.E., McKenna, P.J., 1995. Schizophrenia—a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *Br. J. Psychiatry* 166 (5), 563–582.
- Collins, D.R., Pelletier, J.G., Pare, D., 2001. Slow and fast (gamma) neuronal oscillations in the perirhinal cortex and lateral amygdala. *J. Neurophysiol.* 85 (4), 1661–1672.
- Corcoran, C., Mujica-Parodi, L., Yale, S., Leitman, D., Malaspina, D., 2002. Could stress cause psychosis in individuals vulnerable to schizophrenia? *CNS Spectrum* 7 (1), 33–38, 41–42.
- Corcoran, K., Maren, S., 2001. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. *J. Neurosci.* 21, 1720–1726.
- Damasio, A.R., 1990. Synchronous activation in multiple cortical regions: a mechanism for recall. *Semin. Neurosci.* 2, 287–296.
- Davidson, R., 2002. Anxiety and affective style: role of prefrontal cortex and amygdala. *Biol. Psychiatry* 51, 68–80.
- Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. *Mol. Psychiatry* 6 (1), 13–34.
- Dawson, M.E., Nuechterlein, K.H., Schell, A.M., 1992a. Electrodermal anomalies in recent-onset schizophrenia: relationships to symptoms and prognosis. *Schizophr. Bull.* 18 (2), 295–311.
- Dawson, M.E., Nuechterlein, K.H., Schell, A.M., Mintz, J., 1992b. Concurrent and predictive electrodermal correlates of symptomatology in recent-onset schizophrenic patients. *J. Abnorm. Psychol.* 101 (1), 153–164.
- Dawson, M.E., Nuechterlein, K.H., Schell, A.M., Gitlin, M., Ventura, J., 1994. Autonomic abnormalities in schizophrenia. State or trait indicators? *Arch. Gen. Psychiatry* 51 (10), 813–824.
- de Haan, L., Bakker, J.M., 2004. Overview of neuropathological theories of schizophrenia: from degeneration to progressive developmental disorder. *Psychopathology* 37 (1), 1–7.
- DeLisi, L.E., 1999. Defining the course of brain structural change and plasticity in schizophrenia. *Psychiatry Res.* 92 (1), 1–9.
- Depue, B., Curran, T., Banich, M., 2007. Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science* 317, 215.
- Dickey, C., McCarley, R., Xu, M., Seidman, L., Voglmaier, M., Niznikiewicz, M., Connor, E., Shenton, M., 2007. MRI abnormalities of the hippocampus and cavum septi pellucidum in females with schizotypal personality disorder. *Schizophr. Res.* 89, 49–58.
- Dirkin, G.R., 1983. Cognitive tunneling: use of visual information under stress. *Percept. Mot. Skills* 56 (1), 191–198.
- Elliott, G.R., Eisdorfer, C., 1982. *Stress and Human Health*. Springer Publishing Company, New York.
- Ferrer, J.M., Sabater, R., Saez, J.A., 1993. Neurotensin participates in self-stimulation of the medial prefrontal cortex in the rat. *Eur. J. Pharmacol.* 231 (1), 39–45.
- Finlay, J.M., Zigmund, M.J., 1997. The effects of stress on central dopaminergic neurons: possible clinical implications. *Neurochem. Res.* 22 (11), 1387–1394.
- Friedman, J.I., Ocampo, R., Elbaz, Z., Parrella, M., White, L., Bowler, S., Davis, K.L., Harvey, P.D., 2005. The effect of citalopram adjunctive treatment added to atypical antipsychotic medications for cognitive performance in patients with schizophrenia. *J. Clin. Psychopharmacol.* 25 (3), 237–242.
- Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modeling. *NeuroImage* 19, 1273–1302.
- Ghisolfi, E.S., Schuch, A., Strimitzer Jr., I.M., Luersen, G., Martins, F.F., Ramos, F., Becker, J., Lara, D.R., 2006. Caffeine modulates P50 auditory sensory gating in healthy subjects. *Eur. Neuropsychopharmacol.* 16 (3), 204–210.
- Goto, Y., Grace, A., 2005. Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron* 47, 255–266.
- Guilding, C., Piggins, H.D., 2007. Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? *Eur. J. Neurosci.* 25 (11), 3195–3216.
- Harding, C.M., Zubin, J., Strauss, J.S., 1992. Chronicity in schizophrenia: revisited. *Br. J. Psychiatry (Suppl.)* 18, 27–37.
- Harrison, P., 1999. Review: the neuropathological effects of antipsychotic drugs. *Schizophr. Res.* 40, 87–99.
- Hazlett, H., Dawson, M.E., Schell, A.M., Nuechterlein, K.H., 1997. Electrodermal activity as a prodromal sign in schizophrenia. *Biol. Psychiatry* 41 (1), 111–113.
- Hirsch, S., Weinberger, D., 1995. *Schizophrenia*, first ed. Blackwell Science.
- Ishikawa, A., Namura, S., 2003. Convergence and interaction of hippocampal and amygdala projections within the prefrontal cortex in the rat. *J. Neurosci.* 23, 9987–9995.
- Izquierdo, A., Murray, E.A., 2005. Opposing effects of amygdala and orbital prefrontal cortex lesions on the extinction of instrumental responding in macaque monkeys. *Eur. J. Neurosci.* 22 (9), 2341–2346.
- Izquierdo, A., Suda, R.K., Murray, E.A., 2005. Comparison of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in rhesus monkeys. *J. Neurosci.* 25 (37), 8534–8542.
- Jackson, M.E., Moghaddam, B., 2004. Stimulus-specific plasticity of prefrontal cortex dopamine neurotransmission. *J. Neurochem.* 88 (6), 1327–1334.
- Jarvis, G.E., 2007. The social causes of psychosis in North American psychiatry: a review of a disappearing literature. *Can. J. Psychiatry* 52 (5), 287–294.
- Javitt, D.C., Doneshka, P., Grochowski, S., Ritter, W., 1995. Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch. Gen. Psychiatry* 52 (7), 550–558.
- Jay, T.M., Witter, M.P., 1991. Distribution of hippocampus CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris* leucoagglutinine. *J. Comp. Neurol.* 313, 574–586.

- Jones, C.J., Harris, G., Leung, N., Blissett, J., Meyer, C., 2007. The effect of induced stress on the relationship between perfectionism and unhealthy eating attitudes. *Eat Weight Disord.* 12 (2), 39–43.
- Joyce, J.N., Milan, M.J., 2005. Dopamine D3 receptor agonists and therapeutic agents. *Drug Discov. Today* 10 (13), 917–925.
- Kapur, S., Mamo, D., 2003. Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 27 (7), 1081–1090.
- Kemp, A., Manahan-Vaughan, D., 2008. The hippocampal CA1 region and dentate gyrus differentiate between environmental and spatial feature encoding through long-term depression. *Cereb. Cortex* 18 (4), 968–977.
- Kessler, R.C., Amminger, G., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Ustn, T., 2007. Age of onset of mental disorders: a review of recent literature. *Curr. Opin. Psychiatry* 20 (4), 359–364.
- Kim, H.G., Kim, K.L., 2007. Decreased hippocampal cholinergic neurostimulating peptide precursor protein associated with stress exposure in rat brain by proteomic analysis. *J. Neurosci. Res.*, Epub.
- Larsen, R.J., 1987. The stability of mood variability: a spectral analytic approach to daily mood assessments. *J. Pers. Soc. Psychol.* 52 (6), 1195–1204.
- Lawrie, S.M., Whalley, H.C., Job, D.E., Johnstone, E.C., 2003. Structural and functional abnormalities of the amygdala in schizophrenia. *Ann. NY Acad. Sci.* 985, 445–460.
- LeDoux, J., 2003. The emotional brain, fear, and the amygdala. *Cell Mol. Neurobiol.* 23 (4–5), 727–738.
- LeDoux, J., 2007. The Amygdala. *Curr. Biol.* 17 (20), R868–R874.
- Lipska, B., Aultman, J., Verma, A., Weinberger, D., Moghaddam, B., 2002. Neonatal damage of the ventral hippocampus impairs working memory in the rat. *Neuropsychopharmacology* 27, 47–54.
- Lowry, C.A., Moore, F.L., 2006. Regulation of behavioral responses by corticotropin-releasing factor. *Gen. Comp. Endocrinol.* 146 (1), 19–27.
- Manuck, S.B., Cohen, S., Rabin, B.S., Muldoon, M.F., Bachen, E.A., 1991. Individual differences in cellular immune response to stress. *Psychol. Sci.* 2, 111–114.
- Mason, J., Iquta, W.J.H., Brody, J.V., Robinson, J.A., Sachar, E.J., 1961. The role of limbic system structures in the regulation of ACTH secretion. *J. Neural Transm.* 23 (1–2), 4–14.
- Mathalon, D.H., Heinks, T., Ford, J.M., 2004. Selective attention in schizophrenia: sparing and loss of executive control. *Am. J. Psychiatry* 161 (5), 872–881.
- McEwen, B.S., 2001. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann. NY Acad. Sci.* 933, 265–277.
- McEwen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann. NY Acad. Sci.* 1032, 1–7.
- McGlashan, T.H., 1998. Early detection and intervention of schizophrenia: rationale and research. *Br. J. Psychiatry* 172 (Suppl. 33), 3–6.
- McGlashan, T.H., Zipursky, R.B., Perkins, D., Addington, J., Miller, T.J., Woods, S.W., Hawkins, K.A., Hoffman, R., David, S., Tohen, M., Breier, A., 2003. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophr. Res.* 61 (1), 7–18.
- 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.
- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Ann. Rev. Neurosci.* 24, 167–202.
- Moghaddam, B., Jackson, M., 2004. Effect of stress on prefrontal cortex function. *Neurotox. Res.* 6 (1), 73–78.
- Mora, F., Myres, R.D., 1977. Brain self-stimulation: direct evidence for the involvement of dopamine in the prefrontal cortex. *Science* 197, 1387–1389.
- Morgan, M.A., Romanski, L.M., LeDoux, J.E., 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. *Neurosci. Lett.* 163, 109–113.
- Mujica-Parodi, L.R., 2002. Are cognitive symptoms of schizophrenia mediated by abnormalities in emotional arousal? *CNS Spectrums* 7 (1), 58–60, 65–69.
- Mujica-Parodi, L.R., Yeregani, V., Malaspina, D., 2005. Nonlinear complexity and spectral analyses of heart rate variability in medicated and unmedicated patients with schizophrenia. *Neuropsychobiology* 51 (1), 10–15.
- Mujica-Parodi, L.R., Korgaonkar, M., Greenberg, T., Dardo, T., Wagshul, M., Ardekani, B., Guilfoyle, D., Zong, Y., Chon, K., Malaspina, D., 2007. Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Hum. Brain Mapp.*
- Muller, N.G., Machado, L., Knight, R.T., 2002. Contributions of subregions of the prefrontal cortex to working memory: evidence from brain lesions in humans. *J. Cogn. Neurosci.* 14, 673–686.
- Murray, G., Allen, N., Trinder, J., 2002. Longitudinal investigation of mood variability and the ffm: neuroticism predicts variability in extended states of positive and negative affect. *Pers. Individ. Differences* 33, 1217–1228.
- 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., Dawson, M.E., Gitlin, M., Ventura, J., Goldstein, M.J., Snyder, K.S., Yee, C.M., Mintz, J., 1992. Developmental processes in schizophrenic disorders: longitudinal studies of vulnerability and stress. *Schizophr. Bull.* 18 (3), 387–425.
- Pavlidis, C., Nivon, L., McEwen, B., 2002. Effects of chronic stress on hippocampal long-term potentiation. *Hippocampus* 12 (2), 245–257.
- Pelletier, J.G., Pare, D., 2004. Role of amygdala oscillations in the consolidation of emotional memories. *Biol. Psychiatry* 55 (6), 559–562.
- Perko, L., 1993. *Differential Equations and Dynamical Systems*. Springer, New York.
- Phelps, E.A., Delgado, M., Nearing, K., LeDoux, J., 2004. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron* 43 (6), 897–905.
- Pitkanen, A., Pikkariainen, M., Nurminen, N., Ylinen, A., 2000. Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. *Ann. NY Acad. Sci.* 911, 369–391.
- Preston, A.R., 2005. Hippocampal function, declarative memory, and schizophrenia: anatomic and functional neuroimaging considerations. *Curr. Neurol. Neurosci. Rep.* 5 (4), 249–256.
- Quirk, G., Gehlert, D., 2003. Inhibition of the amygdala: key to pathological states? *Ann. NY Acad. Sci.* 985, 263–272.
- Radley, J., Rocher, A., Janssen, W., Hof, P., McEwen, B., Morrison, J., 2005. Reversibility of atypical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Exp. Neurol.* 196, 199–203.
- Rădulescu, A., Mujica-Parodi, L.R., 2007. A systems approach to schizophrenia and limbic dysregulation. *Schizophr. Res.*, unpublished work.
- Ritsner, M., Maayan, R., Gibel, A., Strous, R.D., Modai, I., Weizman, A., 2004. Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *Eur. Neuropsychopharmacol.* 14 (4), 267–273.
- Robbins, T.W., 1996. Dissociating executive functions of the prefrontal cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 351, 1463–1470.
- Rocher, C., Spedding, M., Munoz, C., Jay, T., 2004. Acute stress-induced changes in hippocampal-prefrontal circuits in rats: effects of antidepressants. *Cereb. Cortex* 14, 224–229.
- Rosenkranz, J.A., Moore, H., Grace, A.A., 2003. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. *J. Neurosci.* 23 (35), 11054–11064.
- Sapolski, R., 2004. *Why Zebras Don't Get Ulcers*, third ed. Henry Holt and Co.
- Sapolski, R.M., Plotsky, P.M., 1990. Hypercortisolism and its possible neural bases. *Biol. Psychiatry* 27 (9), 937–952.
- Seamans, J.K., Floresco, S.B., Phillips, A.G., 1995. Functional differences between the prelimbic and anterior cingulate regions of the rat prefrontal cortex. *Behav. Neurosci.* 109, 1063–1073.
- Siegle, G., Konecky, R., Thase, M., Carter, C., 2003. Relationships between amygdala volume and activity during emotional information processing tasks in depressed and never-depressed individuals: an fMRI investigation. *Ann. NY Acad. Sci.* 985, 481–484.
- Silva, J.A., Leong, G.B., Harry, B.E., Ronan, J., Weinstock, R., 1998. Dangerous misidentification of people due to flashback phenomena in posttraumatic stress disorder. *J. Forensic Sci.* 43 (6), 1107–1111.
- Sotres-Bayon, F., Bush, D., LeDoux, J.E., 2004. Emotional perseveration: an update on prefrontal–amygdala interactions in fear extinction. *Learn. Memory.* 11, 525–535.
- Sousa, N., Lukoyanov, N.V., Madeira, M.D., Almeida, O.F., Paula-Barbosa, M.M., 2000. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience* 97, 253–266.
- Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. *Science* 253, 1380–1386.
- Staal, W.G., Hulshoff Pol, H.E., Schnack, H.G., van Haren, N.E.M., Seifert, N., Kahn, R.S., 2001. Structural brain abnormalities in chronic schizophrenia at the extremes of the outcome spectrum. *Am. J. Psychiatry* 158 (7), 1140–1142.
- Stamm, R., Buhler, K.E., 2001. Concepts of vulnerability of psychiatric diseases. *Fortschr. Neurol. Psychiatry* 69 (7), 300–309.
- Tamminga, C.A., 2006. The neurobiology of cognition in schizophrenia. *J. Clin. Psychiatry* 67 (Suppl 9), 9–13 discussion 36–42.
- Tandon, R., Mazzara, C., DeQuardo, J., Craig, K.A., Meador-Woodruff, J.H., Goldman, R., 1991. Dexamethasone suppression test in schizophrenia: relationship to symptomatology, ventricular enlargement, and outcome. *Biol. Psychiatry* 29 (10), 953–964.
- Ventura, J., Nuechterlein, K.H., Lukoff, D., Hardesty, J.P., 1989. A prospective study of stressful life events and schizophrenic relapse. *J. Abnorm. Psychol.* 98 (4), 407–411.
- Ventura, J., Nuechterlein, K.H., Hardesty, J.P., Gitlin, M., 1992. Life events and schizophrenic relapse after withdrawal of medication. *Br. J. Psychiatry* 161, 615–620.
- Vidal-Gonzales, I., Vidal-Gonzales, B., Rauch, S., Quirk, G., 2007. Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn. Mem.* 13, 728–733.
- Weinberger, D., McClure, R., 2002. Neurotoxicity, neuroplasticity and magnetic resonance imaging morphometry. *Arch. Gen. Psychiatry* 59, 553–558.
- Wik, G., Wiesel, F.A., Eneroth, P., Sedvall, G., Astrom, G., 1986. Dexamethasone suppression test in schizophrenic patients before and during neuroleptic treatment. *Acta Psychiatr. Scand.* 74 (2), 161–167.
- 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. *Am. J. Psychiatry* 161 (3), 480–489.
- Williams, H.J., Owen, M.J., O'Donovan, M.C., 2007. Is COMT a susceptibility gene for schizophrenia? *Schizophr. Bull.* 33 (3), 635–641.
- Yamamoto, K., Hornykiewicz, O., 2004. Proposal for a noradrenaline hypothesis of schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 28 (5), 913–922.
- Yuii, K., Suzuki, M., Kurachi, M., 2007. Stress sensitization in schizophrenia. *Ann. NY Acad. Sci.* 1113, 276–290.
- Zahn, T.P., 1997. Autonomic nervous system markers of psychopathology in childhood-onset schizophrenia. *Arch. Gen. Psychiatry* 54 (10), 904–912.