Neuroscience and Biobehavioral Reviews 60 (2016) 51–64

Neuroscience and Biobehavioral Reviews

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

Review

Rethinking psychopharmacotherapy: The role of treatment context and brain plasticity in antidepressant and antipsychotic interventions

W. Rief[a,*], A.J. Barsky[b], U. Bingel[c], B.K. Doering[a], R. Schwarting[d], M. Wöhr[d], U. Schweiger[e]

[a] University of Marburg, Clinical Psychology and Psychotherapy, Germany
[b] Brigham and Women's Hospital, Harvard Medical School, Boston, USA
[c] Department of Neurology, University Hospital Essen, University Duisburg-Essen, Germany
[d] University of Marburg, Behavioral Neuroscience, Germany
[e] University of Luebeck Medical School, Luebeck, Germany

ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form 9 November 2015
Accepted 16 November 2015
Available online 23 November 2015

Antidepressants
Antipsychotics
Placebo
Neuroplasticity

ABSTRACT

Emerging evidence indicates that treatment context profoundly affects psychopharmacological interventions. We review the evidence for the interaction between drug application and the context in which the drug is given both in human and animal research. We found evidence for this interaction in the placebo response in clinical trials, in our evolving knowledge of pharmacological and environmental effects on neural plasticity, and in animal studies analyzing environmental influences on psychotropic drug effects. Experimental placebo research has revealed neurobiological trajectories of mechanisms such as patients' treatment expectations and prior treatment experiences. Animal research confirmed that "enriched environments" support positive drug effects, while unfavorable environments (low sensory stimulation, low rates of social contacts) can even reverse the intended treatment outcome. Finally we provide recommendations for context conditions under which psychotropic drugs should be applied. Drug action should be steered by positive expectations, physical activity, and helpful social and physical environmental stimulation. Future drug trials should focus on fully controlling and optimizing such drug × environment interactions to improve trial sensitivity and treatment outcome.

Contents

* Corresponding author.
E-mail address: rief@uni-marburg.de (W. Rief).

http://dx.doi.org/10.1016/j.neubiorev.2015.11.008

1. Introduction

Treatment responses to psychopharmacological interventions are highly variable. The factors contributing to variations in treatment success beyond the drug treatment itself are poorly controlled in clinical trials. Together with strong placebo responses, this has contributed to low trial sensitivity, and a decline in the development of new therapeutic drugs. We summarize how contextual factors and placebo mechanisms contribute to the efficiency of drug interventions via interactions with neurobiological trajectories of drug effects. Contextual factors represent environmental stimulation and include physical stimuli, effects of physical activity, social networks and social interactions (including therapeutic relationships). Placebo mechanisms encompass features of the person and/or the person-environment interaction that contribute to drug efficiency beyond the neurochemical drug effect itself. Typical examples of placebo mechanisms are expectations about treatment success, expectations about side effects (nocebo effects), attributions of mental and bodily changes to drug intake, and pre-experiences with drug treatments via associative learning processes. This paper will summarize evidence for the interaction of drug effects, placebo mechanisms, and contextual factors on the level of brain plasticity in depression and schizophrenia (see Fig. 1). Based on these considerations we propose new recommendations to optimize drug × environment interactions, and maximize treatment effects.

2. The evidence for psychopharmacological drugs: good, but not good enough?

Cochrane meta-analyses have shown that antidepressants and antipsychotics lead to reductions of corresponding affective or cognitive symptoms of depression and schizophrenia (Adams et al., 2013; Arroll et al., 2009; Leucht et al., 2012a). Moreover, discontinuation of drug treatment is frequently associated with relapse and recurrence (Leucht et al., 2012b), which is typically interpreted as indicating the need for continued pharmacological interventions. Based on this strong evidence in particular for short-term effects, medical guidelines clearly recommend the use of these drugs for depression and psychosis.

However, even the most positive summaries about the effectiveness of antidepressants and antipsychotics reveal only small to moderate differences in favor of drugs versus placebos (see below). Placebo responses are high and sometimes they even achieve the same level as drug responses (Barber et al., 2012). The advantage of psychopharmacological drugs over placebos is even smaller when compared to "active" placebos instead of the standard inert placebo pill (Moncrieff et al., 2004). The experience of drug-specific side effects or onset effects can further challenge trial validity. These sensations can trigger improvements based on expectation and other placebo mechanisms rather than through specific drug effects (Rief and Glombiewski, 2012).

One problem in the evaluation of psychotropic drugs is the diffuse boundary of the clinical target conditions, which further reduces assay sensitivity. Depression, schizophrenia and other mental disorders are not distinct entities, but typically overlap. The majority of patients with major depression also fulfill the criteria for another mental disorder (Blazer et al., 1994). Many patients suffer from complex interactions between mental disorders with physical conditions, and the risk of diabetes, cardiovascular diseases, a.o., is substantially increased in psychiatric patients (De Hert et al., 2009). Accepting this heterogeneity in clinical trials leads to low trial sensitivity because of large variance, while excluding comorbid patients leads to artificial selections that cannot be generalized to clinical care samples.

The evaluation of the evidence for psychopharmacological treatments is further complicated by publication bias. Few meta-analyses have attempted to integrate non-published trials in the overall evaluation of antidepressants, and reported substantial reductions of overall effect size compared to analyses solely based on published trials (Eyding et al., 2010; Turner et al., 2008). An increasingly positive bias in published trials is also seen in increasing effect sizes of placebo groups over the last 20 years in antidepressant (Rief et al., 2009a; Walsh et al., 2002) and in antipsychotic trials (Rutherford et al., 2014).

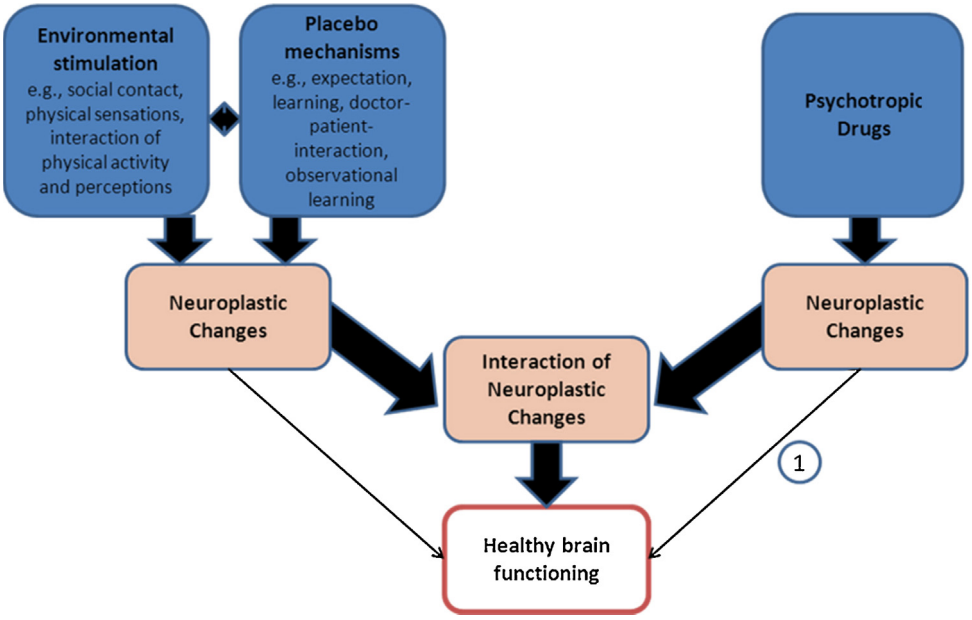

Fig. 1. The interaction of environmental and placebo mechanisms with psychotropic drug treatments on adaptive brain functioning. The influence of psychotropic drugs on brain functions is in continuous interaction with brain plasticity stimulated by environmental influences and placebo mechanisms. While traditional developments tried to isolate direct influences of the drug on brain functions (see (1)), it is hypothesized that future developments should focus on improving the interaction with environmentally stimulated brain plasticity.

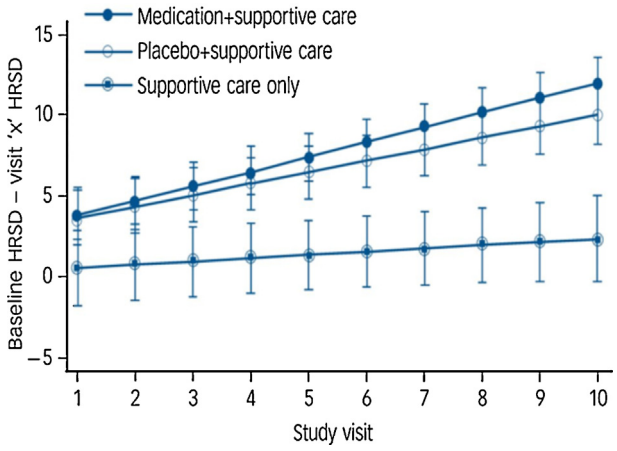

Fig. 2. Results of the study of Leuchter et al. (2014), confirming that positive effects in placebo groups are higher than those in a supportive care only group.

Treatment decisions depend on the expected benefit–risk ratio, but risk assessment (in particular assessment of adverse events) is notoriously unsatisfactory in clinical trials. Both in antidepressant (Rief et al., 2009a) and in antipsychotic trials (Pope et al., 2010), about 80% of trials did not include adequate assessments of side effects, making risk evaluation difficult and delaying detection of drug-induced adverse events. For the clinician, it is hard to decide whether the frequently reported symptoms during drug treatments are genuine side effects of the drug or nocebo effects (Rief et al., 2009b). Besides more general symptoms, further critical adverse events for antidepressants and antipsychotics are reduction of life expectancy in elderly mainly caused by falls or strokes (Brown et al., 2010; Sørensen et al., 2013), type II diabetes mellitus (Wu et al., 2014), reduction of brain volume in antipsychotics (Frost et al., 2010; Ho et al., 2011), or damaging effects in the offspring if the mother is taking antidepressants during pregnancy (Ansorge et al., 2004; Ross et al., 2013; Weikum et al., 2012). Critical effects of long-term treatment before adulthood that were observed in animals (e.g., increased risk of anxiety and depression; the selective serotonin reuptake inhibitors (SSRI) paradox; Homberg et al., 2010; Iniguez et al., 2014) are understudied in humans. The clinical implications for risk-benefit evaluation of these effects need further investigation (Bourke et al., 2014).

Taken together, despite the clear and positive evidence for the use of antipsychotics and antidepressants that have informed corresponding treatment guidelines, there are substantial reasons to search for ways to improve treatment effectiveness, and to reduce negative effects or the absence of expected positive effects. A deeper understanding of how genuine drug effects on the brain interact with those arising from placebo mechanisms and context factors, promises to develop improved treatment regimes.

3. Placebo response: clinical effects and neurophysiological underpinnings

Major psychological mechanisms contributing to placebo responses are expectations, learning mechanisms (e.g., pre-experiences with similar treatments), observational learning, and aspects of the therapeutic relationship (Enck et al., 2013; Rief et al., 2011). Mediators and moderators of placebo responses in psychiatry mainly based on clinical trials have been summarized (Rutherford and Roose, 2013; Weimer et al., 2015). The strong improvements in placebo groups contribute to a small placebo-drug group difference. The incremental effect of antipsychotics over placebo corresponds to a pooled effect size of Cohen's d/Hedges g of .51 (Leucht et al., 2009), which is at the edge of small to moderate effect sizes, while effect sizes above .80 are considered high and clinically meaningful. Moreover, these small to moderate estimates of the beneficial effect do not acknowledge the problem of "publication bias" ("file drawer problem"; see above). The difference of responder rates between antipsychotic versus placebo treatment in psychosis is 18% (42% and 25% respectively; Leucht et al., 2009), further confirming that more powerful intervention approaches are needed. For antidepressants, about 50–80% of the positive drug effects are already reported for the placebo groups (Kirsch and Sapirstein, 1998; Rief et al., 2009a), and some overviews are even more skeptical (Spielmans and Kirsch, 2014).

The first question is whether these effects are in fact not based on placebo mechanisms, but result from factors like regression to the mean, repeated measurements, general symptom fluctuation, etc. Ideally, an untreated control group is needed to juxtapose the natural course of the disease and the placebo improvement in a given trial. However, no-treatment control groups are rarely used in psychopharmacological trials due to ethical reasons (Krogsboll et al., 2009; Laughren, 2001).

Only three trials were identified that directly compared antidepressants with placebo and a no-treatment control group or a

Box 1: Implications of natural course and placebo responses for clinical treatment decision

Research on the results on natural course of mental disorders and placebo effects motivate a rethinking of treatment decisions (see Table 1). Longitudinal investigations reveal that about half of the patients in primary care and the general population suffering from depression recover independently of treatment type (Steinert et al., 2014). Under specific circumstances, antidepressants seem to even block improvements in mental disorders (Andersson et al., 2015). Some people improve under placebo treatments, and the benefit-risk-ratio could be better for them under placebo than drug treatment. For example, using mathematical modeling of treatment trajectories with antidepressants, about 20% in the drug group treated with duloxetine had worse trajectories than comparable patients in the placebo group (Gueorguieva et al., 2011). Together with the demonstrated improvements in natural course groups, we could conclude that for some patients with depression, "watchful waiting" could be the best clinical option. Indication rules are urgently needed to define characteristic patient features for these three treatment options (see Table 1).

Table 1
Clinical decision making for treatments in depression and psychosis.

	Received treatment		
Best treatment	Drug	Placebo	"Watchful waiting"
Drug	Adequately treated	Treatment potential not used	Treatment potential not used
Placebo	Negative treatment effects predominate	Adequately treated	Treatment potential not used
"Watchful waiting"	Negative treatment effects predominate	Negative treatment effects predominate	Adequately treated

Current knowledge on natural course, placebo and drug responses in psychosis and depression indicates that for many patients, drug treatment is the best option, while for some patients, placebo treatments or "watchful waiting" would be better options. As long as clear indication rules are missing, the benefit-risk-ratio is undetermined, and clinical decision making leads to wrong treatment allocations. Frequency/cell sizes are subject to estimations.

minimal intervention group (e.g., supportive care). Strong evidence for better improvement in the placebo group than in a supportive care group stems from a recently published trial (Leuchter et al., 2014). The authors reported that supportive care was significantly less effective than both medication application and placebo application along with supportive care (see Fig. 2). Therefore, the benefits in the placebo groups in antidepressant trials do not seem to be mere results of statistical artifacts and natural course, but are genuine results of placebo mechanisms. Thus, treatment recommendations should factor in positive effects in placebo groups and sometimes even in natural course groups (see Box 1).

4. Neurobiology of placebo responses in mental disorders

Considering the efficacy of placebo effects, their associated neurobiological underpinnings should be further specified. To date, few studies have investigated the neurophysiology of placebo effects related to mental disorders, using experimental designs addressing crucial mechanisms such as emotion regulation or anxiety.

Petrovic et al. (2005) were one of the first groups investigating the neurophysiological effects of expectation manipulation on emotional perception in healthy volunteers, and they compared these processes with well-established processes on placebo analgesia. Using fMRI, they found a shared modulatory network involving the rostral anterior cingulate cortex (ACC) and the lateral orbitofrontal cortex during both placebo effects on emotion and placebo analgesia. These effects were correlated with the subjective placebo effect and were predicted by the amount of treatment expectation. A recent study corroborated the observation that anxiolytic placebo responses in healthy subjects are associated with decreased activity in brain areas relevant for emotional processing, such as the amygdala and insula, and increased activity in areas involved in decision making and reward, such as in the subgenual ACC (Zhang et al., 2011).

Furmark et al. (2008) studied the neural correlates of anxiety reduction resulting from sustained placebo treatment in patients with social anxiety disorder. Brain activity was assessed during a stressful public speaking task by means of positron emission tomography (PET) before and after an 8 week treatment period. Placebo-induced reductions in anxiety were accompanied by attenuated amygdala activity. Intriguingly, this study linked these behavioral and neural findings with serotonin-related gene polymorphisms, since the reduction in stress-induced amygdala activity was only observed in subjects who were homozygous for the long allele of the serotonin transporter-linked polymorphic region (5-HTTLPR) or the G variant of the G-703T-polymorphism in the tryptophan-hydroxylase-2 gene promoter (TPH2, the rate-limiting enzyme in the synthesis of serotonin in the CNS). In the same study, the TPH2 polymorphism significantly predicted placebo responses, whereby homozygosity for the G allele was associated with more pronounced improvement in anxiety symptoms. In patients with social anxiety, connectivity changes between the amygdala and dorsolateral prefrontal cortex with rostral ACC were shown to be associated with the individual anxiolytic response to SSRI treatment and placebo. These observations support the notion that similar expectancy-related mechanisms contribute to improvements in emotion regulation following placebo treatments and anxiolytic drugs (Faria et al., 2014).

While general emotion regulation and anxiety play a role in most psychiatric conditions, the specific neurophysiological processes involved in placebo responses have been reported amongst patients with depression. Leuchter and colleagues have used serial quantitative electroencephalography (qEEG) in patients with major depression enrolled in a 9 week double-blind placebo controlled study in which the SSRI fluoxetine or venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SSNRI), were the active medication. Placebo responders showed a significant increase in prefrontal brain activity early in treatment which was not observed in placebo non-responders or in patients responding or not responding to the medication (Leuchter et al., 2002). An engagement of prefrontal brain areas in placebo responses in depression is substantiated by other brain imaging techniques. Changes in glucose metabolism in depressive male patients were analyzed after 6 weeks treatment with the anti-depressant fluoxetine or placebo using PET (Mayberg et al., 2002). The placebo response was associated with metabolic increases in the prefrontal cortex, but also in the ACC, pre-motor, parietal and posterior cingulate cortex, while decreased activity was observed in the subgenual cingulate cortex, parahippocampus, and thalamus. These results were extended by a PET study investigating depressive patients after receiving placebo pills, with half of the patients being informed that this would be an active antidepressant (Peciña et al., 2015). This later group reported significant decreases in depression scores. These reductions were associated with increased μ-opioid neurotransmission in a network of regions implicated in emotion regulation, namely the subgenual ACC, nucleus accumbens, midline thalamus, and amygdala.

As has been shown for placebo responses in anxiety disorders, genetic variability also contributes to inter-individual differences in placebo responses in depression. Leuchter, for instance, showed that genetic polymorphisms modulating monoaminergic tone (polymorphisms in genes encoding the catabolic enzymes catechol-O-methyltransferase and monoaminooxidase) are related to degree of improvement during placebo treatment of subjects with major depressive disorder (Leuchter et al., 2009).

Although most research of the neurobiological underpinnings of placebo responses in depression is still in an early stage, the available evidence supports the notion that neurobiological trajectories for placebo responses in mental disorders involve expectation, emotion and reward-related circuitry (Benedetti et al., 2005; Murray and Stoessl, 2013; Wernicke and Ossanna, 2010). The latter nicely fits in with the observations that increased subjective reward experience affects treatment efficacy with anti-depressive medication (Wichers et al., 2009). Furthermore, inter-individual variability in the placebo response in anxiety and depression seems to be, at least in part, determined by variability in genes related to monoaminergic tone, particularly serotonin. Future studies will hopefully unravel the neurobiological underpinnings of placebo responses in anxiety and depression and, importantly, their contribution to or interaction with active antidepressant treatments in more detail.

Very little is known about the neurobiology of placebo responses in schizophrenia. Considering the role of dopamine in psychosis, it is relevant that dopamine release is affected by expectation effects and can be triggered by placebo applications (de la Fuente-Fernandez et al., 2001; Schmidt et al., 2014). This is associated with enhanced reward learning and modulations of learning-related signals in the striatum and ventromedial prefrontal cortex (Schmidt et al., 2014). Expectations can also alter dopamine in patients with schizophrenia who received placebo pills. These patients had reduced BOLD activation in the ventral striatum, frontal cortex and cingulate cortex in anticipation of loss, an effect that was associated with dopamine depletion. The findings of reduced dopamine-related brain activity during α-methylparatyrosine (AMPT) were verified by reduced levels of dopamine in urine, homovanillic acid in plasma and increased prolactin levels (Alves et al., 2013). However, despite the confirmation of effects of expectation on dopamine release, in particular under anticipation of losses, it remains unclear whether this affects the same neural circuitries as in psychosis. Finally, Honey et al. (2008) used a ketamine model for psychosis. The brain responses to cognitive

task demands under placebo predicted the expression of psychotic phenomena after drug administration. Fronto-thalamic responses to a working memory task were predictors of the tendency of subjects to develop more negative symptoms under ketamine.

More specific evidence for the interaction of placebo mechanisms such as expectation and neurophysiological processes in schizophrenia is lacking. While initial links between expectation, learning and dopamine release have been established, their functional relevance and overlap with psychosis-relevant circuitries needs further investigation.

5. Excursion: why neuroplasticity processes are crucial for successfully treating mental disorders: a brief overview

In the following sections, we will introduce basic concepts and findings of neuroplasticity in humans, their relevance in depression and schizophrenia, and we will present some illustrative examples of their relevance from animal research. Afterwards (Sections 5–7), we will present specific and more detailed results on neuroplasticity after antidepressant and antipsychotic treatments in animal research, as well as the interaction of these effects with individual and environmental influences.

5.1. Neurogenesis as basis of human adaptation processes

Neural plasticity describes the process of continuous anatomical and physiological restructuring of the brain, governed by a lifelong developmental trajectory, and substantially modulated by (epi-)genetic, neurochemical, endocrine, inflammatory, social, and other environmental stimuli. Neuroplasticity offers the basis for the capacity to adapt permanently to a changing physical and interpersonal environment; therefore adequate neuroplastic processes are a precondition for mental health, and successful drug treatments must be reflected under the perspective of neural plasticity. The conceptualization of human brain functions has changed dramatically after realizing that neurons are in a continuous process of dendritic branching, elongation, and pruning, which is substantially stimulated by brain × environment interactions (Zatorre et al., 2012). Learning and memory trainings can cause such neuroplastic changes (Takeuchi et al., 2013). Such neuroplasticity seems to follow a two-stage process: on a short-term perspective, rapid and transient changes of the functioning of neural pathways occur, which are followed on a long-term perspective by more prolonged changes in the structural organization of neural pathways. Neuroplasticity can contribute to the maintenance of mental disorders (e.g., through continuously distorted information processing), but also to overcoming them (Morris et al., 2014).

A key human adaptation process is contextual learning, i.e., relating important events to a specific spatial, temporal, interoceptive, cognitive or interpersonal context (Maren et al., 2013). Therefore contextual learning can also play a role in the development of placebo reactions, e.g., by linking a specific environment with the expectation of successful treatments. On a neuroanatomical level, a network of structures including hippocampus, prefrontal cortex and amygdala is involved in contextual learning. On a cellular level, adaptation requires plasticity as shown by a wealth of animal research. An important phenomenon of neuroplasticity enabling contextual learning is adult neurogenesis, especially in the hippocampal formation. Neuronal progenitor cells are generated in the subventricular zone and in the dentate gyrus of the hippocampal formation and provide a continuous supply of new neuronal elements (Fuchs and Flugge, 2014). Inhibition of neurogenesis in the hippocampus disrupts contextual learning (Hernandez-Rabaza et al., 2009). The role of adult neurogenesis is not limited to general contextual learning, but it also plays a role in processes such as fear conditioning, recognition, spatial memory, pattern separation, exploratory behavior, behavioral inhibition in dangerous situations, anxious behavior, and regulation of the hypothalamic–pituitary–adrenal axis (Cameron and Glover, 2015).

Positive modulators of neurogenesis are environmental stimuli, exercise, estrogens, and growth factors like vascular endothelial growth factor (VEGF) or brain-derived growth factor (BDNF). Intriguingly, antidepressants have also been shown to modulate neurogenesis (see below). Negative modulators are aging, acute and chronic stress, glutamatergic (NMDA) receptors, and glucocorticoids. Plasticity that is based on neurogenesis introduces a specific time frame, that is, effects are to be expected within weeks but not days.

5.2. Neuroplasticity in patients with depression and during antidepressant treatments

The neurogenesis hypothesis of mental disorders postulates that (a) a decrease in neurogenesis may contribute to the onset or maintenance of mental disorders like depression and anxiety and (b) antidepressant agents require adult neurogenesis in the hippocampus for their effects. These neuroplastic processes can be further influenced by individual factors and environmental processes. Mental disorders are not only characterized by emotional changes, but also by specific deficits in cognition, i.e., attention and memory processes, and expectations (e.g., focus of attention on negative events in depression (Rief et al., 2015). Depression-specific attention and memory processes lead to neuroplastic changes that can further stabilize the depressive state and lead to depression persistence (Armstrong and Olatunji, 2012; Peckham et al., 2010; Sumner et al., 2010). On the other hand, some of the observed neuroanatomical abnormalities of depressed patients can also represent a precondition or risk factor for symptom development (Goodkind et al., 2015). Patients with major depressive disorders have low hippocampal volumes compared to healthy comparison subjects (Zou et al., 2010), and there is electrophysiological evidence that neuroplasticity is decreased in patients with depression compared to healthy controls (Player et al., 2013).

All classes of antidepressants seem to modulate adult neurogenesis as shown in animal studies. These include SSRIs, tricyclic substances, MAO-inhibitors, electroconvulsive treatment (Malberg et al., 2000), SSNRIs (Asokan et al., 2014), and the 5-HT2$_c$ antagonist agomelatine (Banasr et al., 2006). Antidepressants increase neurogenesis in the subgranular zone of the dentate gyrus (Becker et al., 2008; Czeh et al., 2006; Malberg et al., 2000), and neurogenesis appears to be essential for their therapeutic efficacy (Santarelli et al., 2003). Also, increased neurogenesis paralleled reduced depression-like behavior after antidepressant treatment (Becker et al., 2008; Czeh et al., 2006; Santarelli et al., 2003).

As a general model we postulate that antidepressants promote hippocampal plasticity, but that an enriched environment, new experiences and skills training are required to repair maladaptive network function and to foster new adaptive ones. This view of the crucial role of neurogenesis and neuroplastic process during drug treatments and their interaction with environmental influences is supported by detailed and specific evidence summarized in reviews of animal research, which will be provided in a later section.

5.3. Neuroplasticity in patients with schizophrenia and during antipsychotics treatments

Schizophrenia may be conceptualized as a neurodevelopmental disorder, related to genetic and environmental risk factors that interfere with the structural and functional reorganization of neural networks (Meyer-Lindenberg and Tost, 2012, 2014). A

progressive reduction in gray matter volume has been observed in longitudinal trials, especially in the bilateral anterior insula and dorsal ACC, but also variations of dorsal ACC and insula volume are reported in psychosis (Goodkind et al., 2015). These neuroimaging observations are thought to reflect an enduring disturbance of experience-dependent synaptic plasticity, including also dorsolateral prefrontal cortex and hippocampal formation (Meyer-Lindenberg and Tost, 2014). The neural disorganization in long range connectivity circuits seems to be related to illness-typical psychological symptoms, such as cognitive deficits, delusions, and negative symptoms. Finally, the brain is in a state of not reacting to illness-incongruent environmental information (e.g., neglect of a helpful neighbor's behavior in the case of paranoid delusion), but carries forward the delusional interpretation of events, again leading to states of anxiety and mistrust that are associated with corresponding neural plasticity processes. The establishment of a vicious circle of sensitized neural networks maintaining symptoms, and misinterpretation of environmental stimuli supporting these disorder-specific neural plasticity processes can be postulated.

The contribution of antipsychotic treatments to neuroplastic processes became a critical point of discussion after the publication of challenging results indicating that there is a relation between negative brain developments and lifetime drug exposure to antipsychotics (Fusar-Poli et al., 2013; Ho et al., 2011). In contrast, second generation drugs like olanzapine and risperidone seem to be related to increased neurogenesis in the hippocampus and supraventricular zone (Wakade et al., 2002), and in prefrontal cortex and striatum (Wang et al., 2004), compared with haloperidol. Recent evidence indicates that short-term treatment with antipsychotics modulates the connectivity between brain areas differently (Sarpal et al., 2015). Animal research can help to better understand the neurobiological processes during drug treatments, as well as their interaction with environmental influences on neural plasticity. Therefore, these results will be highlighted in the following sections.

6. Neuroplasticity and antidepressant drug treatments: Animal research

Animal models allow more detailed analyses of neurobiological processes, and better control of environmental influences compared to studies with humans. However, their generalizability to clinical applications in humans is rendered difficult given differences in dosage, application form and duration of treatments, limited validity of the "clinical models" for mental disorders in animals, and the fact that "healthy" subjects are often used in animal drug studies aiming at inferring brain reactions in mentally ill patients.

New treatment concepts postulate that the recovery from depression in response to antidepressant treatment is reflected in and due to structural and functional changes in neuronal networks implicated in emotion regulation (Castrén, 2005; Duman and Aghajanian, 2012; Krishnan and Nestler, 2010). These processes have been investigated in animal models of depression, such as learned helplessness, social defeat and inescapable stress. In rats, these states are associated with reduced adult neurogenesis (Ho and Wang, 2010; Lehmann et al., 2013; Malberg and Duman, 2003). Mice, in which neurogenesis is disrupted using irradiation, no longer respond behaviorally to antidepressants. This was shown by Santarelli et al. (2003), who demonstrated that the increase in adult neurogenesis in the dentate gyrus induced by SSRIs is required for their effectiveness in reversing depression-related behavior, and that serotonin auto-receptors are strongly involved in modulating relevant drug-induced neurotrophic and behavioral effects. A related finding suggests that SSRIs lead to a dematuration of mature granule cells in the dentate gyrus, as indicated by a strongly reduced expression of the mature cell marker calbindin (Kobayashi et al., 2010). SSRIs might thus induce a plastic state of the brain that is typically seen in younger organisms (Castrén, 2013). While this result mainly relates to hippocampal structures, antidepressants apparently exert part of their action independent of hippocampal structures (Petrik et al., 2012); however, the effects of antidepressants on neuroplasticity in other areas is less clear (Dringenberg et al., 2014).

Since the seminal work of Hubel and Wiesel (Hubel et al., 1977) the visual system is a well-established model to study environmental effects on neuronal development and plasticity (Hensch, 2005). By means of this system, (Vetencourt et al., 2008) showed that closing one eye in adult rats treated with the antidepressant SSRI fluoxetine led to a strong shift in the responsiveness of visual cortical neurons in favor of the open eye. The observed shift in responsiveness in adult rats was paralleled by increased expression of the neurotrophic factor BDNF, and similar changes were observed in infant rats during the early postnatal critical period, indicating that fluoxetine treatment initiated a process of neuronal plasticity typically not seen in adult controls. Importantly, neuronal plasticity following fluoxetine even allowed functional recovery of a miswired neuronal network in adult rats in which one eye had been closed during early development. However, recovery was only seen when drug treatment and appropriate rehabilitation, in this case patching the better eye, was combined. An effect of antidepressants on neuronal plasticity markers in the visual system has also been reported in humans (Normann et al., 2007). Finally, plasticity induced by antidepressants, electroconvulsive therapy, exercise or environmental enrichment may also include dendritic arborization, synaptogenesis and synaptic strength (Castrén, 2013).

7. Neuroplasticity and antipsychotic drug treatments: animal research

The animal literature on the neurobiological effects of antipsychotics is controversial because several studies have reported neurotoxic effects whereas others have yielded positive neuroplastic results. Part of this ambivalence may be due to the choice of assays (e.g., cell cultures), drugs, and their doses. Neurotoxic effects can include mechanisms such as apoptosis, mitochondrial deficits, excessive glutamate activation, or DNA fragmentation. These effects are more likely in case of, but not exclusive for haloperidol compared to atypical antipsychotics. They are often discussed in the context of neurological side effects, especially tardive dyskinesia (for review see Dean, 2006).

In schizophrenia, special interest was given to neuroplastic processes of the (neo-) striatum, and increased striatal volumes have been reported with haloperidol (Chakos et al., 1998). This effect was most pronounced in case of animals developing vacuous chewing movement, an animal equivalent for drug-induced extrapyramidal symptoms which are attributed to blockade of striatal dopamine D2-receptors and its consequences. The increase of striatal volume was found in case of persistent treatment with haloperidol and clozapine, but not risperidone, and decreased volumes were found with olanzapine (Andersson et al., 2002). Striatal volume increases were reversible by several weeks of drug withdrawal (Vernon et al., 2012).

In the neocortex (frontal and parietal), volume reductions after chronic antipsychotic treatments (haloperidol, olanzapine) prevails (Frost et al., 2010). These volume reductions were not due to loss of neurons or glia, since their densities per volume were actually increased, suggesting that the absolute tissue losses may be due to decreases in axons, myelinisation, dendritic spines, or

blood capillaries. Again, the cortical volume decreases after chronic haloperidol were reversible after several weeks of drug withdrawal (Vernon et al., 2012). Finally, results for the hippocampus are equivocal, including volume increases (haloperidol) (Schmitt et al., 2004), decreases (olanzapine) (Barr et al., 2013), or no changes (haloperidol, clozapine, and olanzapine) (Vernon et al., 2011).

Together, available evidence supports the notion that the neostriatum increases its size with chronic haloperidol and olanzapine treatments, whereas parts of the neocortex seem to decrease in volume. Hippocampal findings are equivocal so far, possibly due to differences in drug treatments and/or anatomical criteria to analyze this rather heterogeneous structure. Initial results indicate that antipsychotics like haloperidol might reduce the connectivity between several brain regions, including prefrontal cortex, hippocampus, and pallidum (Gass et al., 2013), which can further contribute to modulations of brain plasticity.

On a cellular level, antipsychotic treatments (usually chronic haloperidol or chlorpromazine) can lead to increases in axon terminal sizes, postsynaptic densities, and numbers and types of synapses (striatum), and to decreases in dendritic spine density and asymmetric synapses (Benes et al., 1985; Kerns et al., 1992; Uranova et al., 1991). These effects may be specific for longer lasting drug treatments or first-generation antipsychotics (Frost et al., 2010; Klinzova et al., 1990).

The effects of antipsychotics on neurotrophins have been extensively investigated, largely driven by the hypothesis that schizophrenia may be due to early malfunction of neurotrophic factors, resulting in structural disorganisation locally in the brain (Angelucci et al., 2005). Some atypical antipsychotics can increase BDNF and nerve growth factor (NGF) activity in the striatum, hippocampus, and neocortex, whereas haloperidol seems only to promote NGF activity (Horacek et al., 2006). These plasticity-relevant effects can explain the "delayed onset of the antipsychotic effect", suggesting that re-modelling of neuronal structures and circuits is required for this effect (Horacek et al., 2006). More recently, juvenile treatment with the atypical antipsychotic lusaridone was shown to be effective in preventing stress-induced losses of BDNF in a rat model (Luoni et al., 2014). To summarize, the effects of antipsychotics on remodeling of brain structures can be driven via neurotrophin pathways.

Another link between antipsychotic drugs and neuroplasticity is long-term potentiation (LTP). Various antipsychotics with D2 antagonistic properties have different effects on LTP in laboratory animals and humans (Price et al., 2014). The authors concluded in their summary that acute antipsychotics rather consistently impair LTP, both in case of classical and atypical antipsychotics (except for clozapine and olanzapine).

Enhanced cell proliferation is usually not observed in case of haloperidol (prefrontal cortex, neostriatum, subventricular zone, and dentate gyrus) (Halim et al., 2004; Schmitt et al., 2004; Wakade et al., 2002; Wang et al., 2004), in contrast to chronic regimens with the atypical antipsychotics olanzapine, risperidone, clozapine, and quetiapine (Green et al., 2006; Halim et al., 2004; Kodamo et al., 2004; Luo et al., 2005; Wakade et al., 2002; Wang et al., 2004). However, in some studies, where the types of newly formed cells were identified, no evidence of true neurogenesis was obtained (Kodamo et al., 2004; Wang et al., 2004), and it was assumed that enhanced cell proliferation was due to endothelial cells and oligodendrocytes. Kodamo et al. (2004) showed actual neurogenesis in the dentate gyrus with chronic olanzapine, an effect which was comparable to that of chronic fluoxetine treatment. Also, Luo et al. (2005) showed that chronic quetiapine was able to reverse a stress-induced decrease of cell proliferation in the SGZ, and of BDNF levels in the hippocampus. Finally, several findings indicate that the atypical antipsychotics have no effect on cell survival, that is, their outcomes were mainly due to effects on cell formation (Green et al., 2006; Halim et al., 2004; Wang et al., 2004).

8. Interactions of psychopharmacological actions and environmental influences: Animal research

Despite the problems of generalizing animal research to humans, animal studies allow much better control of contextual factors and therefore offer unique insights into the neuroplasticity processes induced by the interaction of drug intake with behavioral and contextual factors of the treatment environment, which will be reviewed in the following.

8.1. Antidepressants

Environmentally triggered experiences can influence the amount and direction of neural plasticity changes. Neuroplastic effects that are similar to those induced by antidepressants have been reported for environmental enrichment (Hendriksen et al., 2010), physical skills training (Curlik et al., 2013), and exercise (Yau et al., 2014). The social context is also of relevance for neuroplasticity, which is confirmed by the finding that successful coping with social stress in monkeys is associated with increased hippocampal neurogenesis (Lyons et al., 2010). The crucial question is how these neuroplastic effects triggered by non-pharmacological aspects interact with the neurobiological effects of the drug. According to the network hypothesis (Castrén, 2013), enhanced neuronal plasticity following antidepressant treatment renders the organism more susceptible to environmental influences, and thus allows the organism to better adapt to alterations in environmental conditions, eventually leading to recovery. This hypothesis is consistent with the delayed emergence of the clinical effects of antidepressants because recovery is not observed as the result from an immediate increase or decrease in a single neurotransmitter level; rather the early neurochemical effects of antidepressants initiate a process of neuronal plasticity through which emotion-regulating brain structures better represent current environmental influences. Environmental factors are thus proposed to interact with drug effects, leading to environment-specific consequences for brain modifications during identical drug treatments.

In order to further investigate the association of neuronal plasticity induced by antidepressants with appropriate environmental stimulation in the context of emotion regulation, Karpova et al. (2011) performed a series of experiments on fear extinction in adult mice. They first exposed mice to a standard fear learning paradigm, in which mice learned to associate a previously neutral tone with foot shock application by using a conditioning procedure, as indicated by an increase in freezing behavior in response to the tone in absence of the shock. Then, mice were repeatedly confronted to the tone alone during extinction trials, similar to exposure therapy for phobias in humans. The authors showed that extinction training led to a reduction in freezing behavior, yet the beneficial effects were short-lasting and spontaneous recovery of the fear response as well as fear renewal were detectable. However, when fluoxetine was administered during extinction training, this combination resulted in a long-lasting reduction in the fear response, with no signs of spontaneous recovery and fear renewal, similar to fear extinction studies in young mice (Gogolla et al., 2009). The positive effect of fluoxetine was due to an enhanced efficacy of extinction training under fluoxetine, since fluoxetine alone did not alter freezing behavior. This suggests a synergetic effect of exposure therapy and fluoxetine treatment.

Consistently with the network hypothesis, fluoxetine was found to induce a plastic state in the basolateral amygdala (Karpova et al., 2011), a key brain structure for fear learning (LeDoux, 2000).

Specifically, fluoxetine was shown to enhance the levels of the neurotrophic factor BDNF while reducing the number of neurons expressing the calcium buffer parvalbumin in the basolateral amygdala. Importantly, both BDNF (Peters et al., 2010) and parvalbumin (Wöhr et al., 2015) modulate the organism's ability to adapt to changes in the environment as assessed by extinction and reversal learning paradigms. For instance, Peters et al. (2010) showed that infusion of BDNF into the prefrontal cortex accelerates fear extinction in rats. Consistently, in BDNF heterozygous mice fluoxetine treatment was less efficient and spontaneous recovery of fear as well as fear renewal were detectable, while BDNF overexpression in the basolateral amygdala led to a long-lasting reduction in the fear response (Karpova et al., 2011). Together, these findings strongly indicate that SSRI treatments render the organism more susceptible to environmental changes through enhanced neuronal plasticity. Of note, evidence for stronger effects of combined therapies was recently also obtained in humans (Schneier et al., 2012).

Subsequent studies confirmed the findings obtained by (Karpova et al., 2011). The combination of fluoxetine and extinction training resulted in a unique change in expression of synaptic proteins involved in excitatory and inhibitory neurotransmission (Popova et al., 2014) consistent with the action of D-cycloserine, which is also known to enhance fear extinction (Walker et al., 2002). Remarkably, fluoxetine was even found to promote fear extinction in a mouse strain characterized by strongly impaired fear extinction (Camp et al., 2012). Moreover, it has been shown that fluoxetine significantly reduces fear reinstatement even after discontinuation of drug treatment (Deschaux et al., 2011) and that post-extinction fluoxetine prevents stress-induced reemergence of extinguished fear (Deschaux et al., 2013). In contrast to fluoxetine, this extinction-facilitating effects was not seen with nortriptyline or mirtazapine (Melo et al., 2012).

The ways in which environmental conditions interact with the pharmacological action of antidepressants was further assessed in a recent study (Dankoski et al., 2014). In this study, the authors measured electrically evoked serotonin release by means of *in vivo* fast scan cyclic voltammetry and compared release rate, net overflow, and clearance in single- and group-housed mice exposed to chronic treatment of citalopram, another SSRI. While chronic citalopram treatment in group-housed mice facilitated serotonin release probably due to serotonin auto-receptor desensitization, no such facilitation was seen in mice exposed to social isolation. Clearance was not affected by drug administration. Importantly, the lack of facilitated serotonin release following chronic citalopram treatment in single-housed mice was paralleled by a lack of drug-induced changes in the marble burying test, a test typically used to assess anxiety-like and repetitive behavior (Thomas et al., 2009). While in group-housed mice, citalopram had an anxiolytic effect, the behavior of mice exposed to single-housing was not altered by drug treatment. In the open field test, however, citalopram treatment resulted in a more anxious phenotype. Consistently, the SSRI sertraline clearly reduces depression-related behavior in the forced swim test in rats exposed to environmental enrichment or standard housing, but less in rats that were single-housed for six weeks as juveniles after weaning from the mother (Yildirim et al., 2012). Initial evidence for this association has been found in human studies suggesting that stress, e.g., absence of social support networks, can contribute to treatment-resistant depression and anxiety (Karelina and DeVries, 2011). These findings show that plasticity in the serotonergic system is responsive to environmental stressors, which can determine the effect of pharmacotherapies using SSRIs.

All these animal studies indicate that the beneficial effects associated with changes in neuronal plasticity induced by antidepressants depend on appropriate environmental stimulation. This has important neuroscientific and clinical implications. Firstly, variable and incomplete efficacy of antidepressants might be explained by the so far mostly neglected interplay between drug treatment and environmental factors. Secondly, a deeper understanding of this interplay offers the potential to improve pharmacotherapy through behavioral interventions. Finally, the network hypothesis predicts that antidepressant treatment under adverse environmental conditions might promote "maladaptive plasticity", resulting in a further deterioration rather than improvement in clinical symptoms (Castrén, 2013). This implies that antidepressant therapy would be strictly discouraged if life circumstances are expected to be negative. In fact, this is exactly what was shown by a pioneering study (Branchi et al., 2013). The authors treated adult mice with chronic fluoxetine while exposing them either to a stressful environment or to an enriched environment after exposure to a chronic stress period for inducing a depression-related behavioral phenotype. If increased serotonin levels elevate mood *per se*, fluoxetine is expected to reduce the depression-related behavioral phenotype in mice irrespective of environmental conditions. However, if fluoxetine leads to increased neuronal plasticity rendering the organism more susceptible to the influences of the environment, SSRIs applied during a stressful environment might lead to more, but not less depression-related behavior, whereas SSRIs applied during enrichment would again be expected to reduce depression-related behavior. The authors found that saccharin preference, an animal paradigm for assessing depression-like anhedonia, showed oppositional results depending on environmental condition: in mice treated with chronic fluoxetine in an enriched environment, anhedonia was reduced, while the depression-related behavioral phenotype was even more prominent if fluoxetine was administered in a stressful environment. The worsening of the behavioral phenotype of depression was paralleled by lower levels of the neurotrophic factor BDNF and increased corticosterone levels. These findings strongly suggest that the effects of SSRIs are driven by the environment and that "unfavourable" environmental factors can impair or even reverse the intended treatment outcome in antidepressants. "Unfavorable" and adverse environmental conditions might be considered contraindications for pharmacotherapies using SSRIs, such as "impoverished treatment environments" (e.g., in socially disadvantaged conditions; Meyer-Lindenberg and Tost, 2012), which are inherently associated with the majority of psychiatric disorders. It is therefore especially important to investigate ways to overcome the negative impact of social isolation on outcomes in mental disorders.

8.2. Antipsychotics

The crucial influence of treatment context and behavior on drug response has also been investigated for antipsychotics. Strong effects on neural processing after drug intake have been shown to be caused by physical activity. This is relevant in the context of cell proliferation and neurogenesis, since physical exercise has repeatedly been shown to enhance these processes in rodents, and these effects are probably due to upregulation in neurotrophic factors, such as BDNF (for review see Zoladz and Pilc, 2010). The studies available so far (Alegre Baptista et al., 2013; Teixeira et al., 2011) show that treadmill exercise or swimming for several weeks can reduce or prevent extrapyramidal symptoms (like catalepsy or vacuous chewing movements) induced by chronic treatment with haloperidol, and that running wheel exercise partly prevented hippocampal volume loss (mainly dentate gyrus and CA1) induced by chronic treatment with olanzapine (Barr et al., 2013). Swimming exercise prevented drug-induced lipid-peroxidation cortically and subcortically (Czeh et al., 2006; Teixeira et al., 2011). The authors of these studies assumed that cardio-metabolic factors (linked to glucose and fat) in case of olanzapine may play a role, for example that olanzapine via enhanced glucose availability may lead to

toxic effects in the hippocampus, which are prevented by exercise-enhanced energy consumption.

Another way of showing the interaction between drug effects and environment effects is the investigation whether drug effects are prone to learning processes. Such an effect would imply that based on Pavlovian conditioning, environmental stimuli have significant impact on drug effects, in particular after long-term treatments. These influences have been shown especially in the context of human placebo mechanism studies (Doering and Rief, 2012). In animals, associative and contextual factors have repeatedly been investigated in case of haloperidol. Catalepsy can be assessed in animals as a behavioral correlate of drug action, which is also relevant for the extrapyramidal side effects of antipsychotics. In rats and mice, haloperidol leads to a dose-dependent effect on catalepsy, since low doses usually induce no or only moderate acute effects, whereas pronounced catalepsy is typical in case of higher doses. However, repeated higher doses can lead to tolerance, whereas sensitization (i.e., enhanced catalepsy) is more typical for low doses. These phenomena can be manipulated via conditioning: cataleptic tolerance to a challenge dose (1.5 mg/kg) occurred in a previously drug-paired environment but not in a distinct saline-paired environment (Jonas et al., 2013). The authors argued "*that cues previously associated with neuroleptic administration are critical for engaging mechanisms that counteract the cataleptic effect of haloperidol in producing tolerance*", that is, such tolerance may be due to classical conditioning (Hinson and Siegel, 1982). Thus, environmental cues paired with drug administration may become conditioned stimuli, which can elicit compensatory responses, thereby reducing drug effectiveness.

The sensitization effect in low doses (Klein and Schmidt, 2003) of haloperidol (0.25 mg/kg) is also subject to conditioning. The first low-dose exposure induced no or only low levels of catalepsy, but led to increased catalepsy with repeated injections. When subsequently challenged with saline (i.e., placebo), substantial levels of catalepsy were observed, arguing for conditioning of this effect (see also (Banasikowski and Beninger, 2012; de Sousa Moreira et al., 1982). This context-dependency of sensitization in haloperidol-induced catalepsy was independent of the novelty of the test context, since it was observed in novel as well as familiar environments (Wiecki et al., 2009). Also, the sensitized response was gradually extinguished by repeated saline experiences in the acquisition context and showed partial renewal after a subsequent haloperidol challenge (Amtage and Schmidt, 2003). It was suggested that catalepsy sensitization may reflect a kind of enhanced striatal "NoGo" learning, which suppresses action execution by disinhibiting D2-dependent striatopallidal projections (Wiecki et al., 2009). This finding can be linked to the fact that chronic haloperidol can promote corticostriatal LTP in animals and humans (Centonze et al., 2004; Waltz et al., 2007). Also, catalepsy sensitization seems to have memory-like properties, since its consolidation is impaired by post-trial administration of a glutamatergic antagonist (Riedinger et al., 2011).

More recently, the effect of environmental cues on antipsychotic outcomes was investigated, using hyperlocomotion to the psychotomimetic phencyclidine as antipsychotic index (Sun et al., 2014). The authors found that "more exposures to the test environment under the influence of haloperidol (but not clozapine or olanzapine) caused a stronger inhibition than fewer exposures, indicating a strong environmental modulation" (see also Zhang and Li, 2012). Finally, maladaptive environments (rearing rats, which are highly social animals, in isolation) affects the prefrontal neurochemical responsiveness to atypical antipsychotics (olanzapine, clozapine), but not to haloperidol (Heidbreder et al., 2001).

To summarize, in animal models there is clear evidence that environmental influences steer the effects of antidepressant and antipsychotic drugs even on a very basic neurobiological level. Maladaptive environmental influences or sedentary behavior can lead to detrimental effects of these drugs on a clinical outcome level, and they can increase the risk of adverse side effects, while supportive environmental influences can ensure the expected positive effects of psychopharmacological interventions (Fig. 3).

9. Implications for treatment regimens

The summarized evidence strongly supports the notion that drug action, placebo mechanisms, and contextual factors such as environmental stimulation contribute to the therapeutic process in mental disorders, and neuroplasticity offers a common platform to understand where and how these processes interact. While many treatment approaches lack a systematic combination of these principles, drug treatments in psychiatry can only develop their full potential if the pharmacological action is supported and steered by environmental and behaviorally-triggered stimulation. First, drug treatment should only be initiated if a positive benefit-risk ratio can be expected under the known environmental conditions (see Box 1). If this cannot be expected, the next question is whether verbal interventions of the psychiatrist/therapist can help to create the environmental conditions necessary for treatment success (Fig. 4).

Research on placebo mechanisms indicates that the start of psychopharmacotherapy should be accompanied by optimizing patient's treatment expectations, addressing past treatment experiences, and establishing a positive therapeutic interaction. During the course of treatment, new learning situations challenging depression-specific or psychosis-specific beliefs, social interaction experiences, and environmental input should be established that support overcoming the mental disorder. Some of these behavioral and contextual factors can be considered to be more general factors (such as physical activity and social contacts). From a psychological point of view, conceptualizations of mental disorders focus on disorder-specific expectations (Rief et al., 2015), and treatment contexts should be created that maximally violate these negative disorder-specific expectations.

Expectations are predictions about future events that are associated with the activation of neural networks, and this process can facilitate the *disorder-specific* perception and interpretation of events (e.g., expectation of pain activates pain-relevant brain structures including the corresponding somatosensory fields; Summerfield and de Lange, 2014). Therefore disorder-specific expectations can be postulated to be crucial factors contributing to the maintenance of mental disorders. Depressed patients expect negative consequences from their behavior, negative feedback from others, and negative events in the future. Following an expectation-violation approach in psychotherapy (see Craske et al., 2014), depressed patients should be encouraged to expose themselves to situations that challenge these expectations, and to focus their attention on whether the negative expectations occur, or whether expectations are violated. A similar approach could be used for patients suffering from psychosis. Eventually supported by antipsychotic drug treatment, patients could be encouraged to expose themselves to situations that allow checking negative expectations, and to experience positive interactions. Recent findings confirm significant incremental effects of such psychological interventions in addition to pharmacotherapy in psychosis (Lincoln et al., 2012; Moritz et al., 2014).

Beyond this disorder-specific expectation modification approach, further interventions should be used in parallel to drug treatments. Physical activity has a proven clinical benefit in depression (Cooney et al., 2014; Cooney et al., 2013), and seems to reduce the risk of side effect development in psychosis. Treatment environments should also include adaptations of "enriched

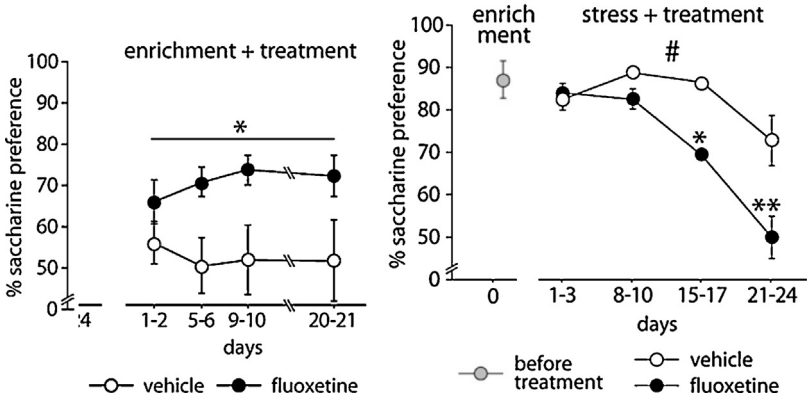

Fig. 3. Environmental influences can inverse SSRI effects. Exposure to stress induces an anhedonic behavioral phenotype ("depression-like behavior") as indicated by reduced saccharin preference. When combining fluoxetine treatment with environmental enrichment, fluoxetine-treated mice showed a significantly higher preference for the saccharin solution compared to control mice, indicating an amelioration of the depression-like phenotype. (left: upper line). However, when stress was imposed during fluoxetine treatment, fluoxetine-treated mice showed a faster and more marked reduction of preference for the saccharin solution compared to control mice, indicating a worsening of the depression-like phenotype (right: lower line). (From Branchi et al., 2013).

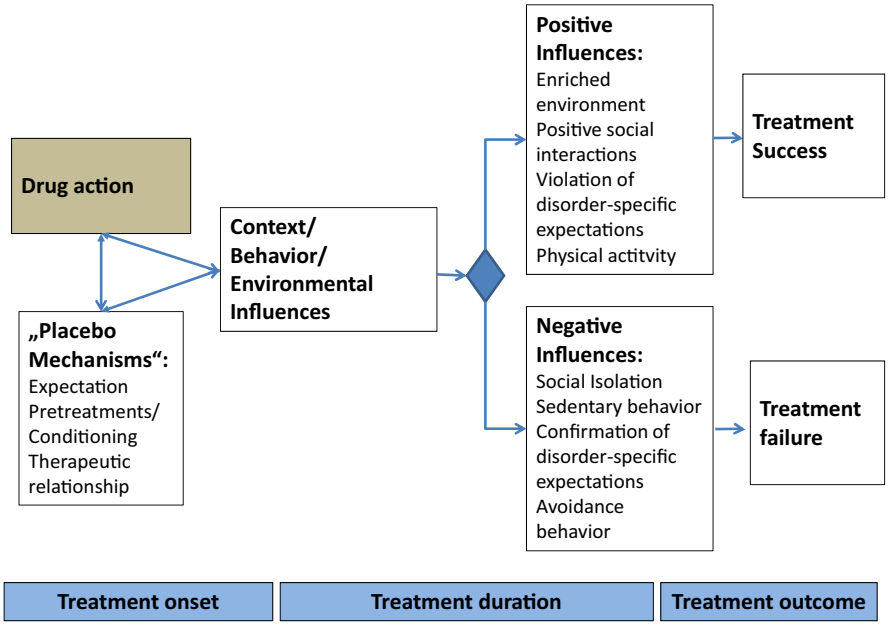

Fig. 4. Determinants of treatment success in psychopharmacological interventions.

environment" conditions, particularly in depression. More generally, environmental enrichment and physical activity can enhance cognitive function, thus contributing to the improvement of other symptoms of depression and psychosis (Pang and Hannan, 2013). The neurophysiological effects of learning are well-known, and should be systematically used after drug treatment starts. These processes are able to interact with pharmacologically induced effects on brain actions, and can steer them into the right direction (see Table 2).

10. Recommendations for clinical trial design

The ability of a trial to detect the potential of a new drug strongly depends on whether the protocol fully controls all the factors that influence treatment success. If expectations, learning processes, and other environmental influences are not controlled, these variables can interact beneficially with the pharmacokinetics in one patient, but these interactions of context factors with psychotropic agents can be detrimental in another patient, thus contributing substantially to large variations in treatment efficiency. All treatment arms should therefore control these effects as much as possible. The assessment of patient expectancies (e.g., whether to attend study visits) can be adjusted for statistically and may be considered in imputation procedures, which can increase the estimated group differences between treatment conditions (Rabideau et al., 2014). At least one treatment arm of clinical trials should aim to optimize all of these influences, to provide information about the maximal efficiency that is possible in a specific clinical condition. While in the past it was assumed that these effects might be additive, more and more evidence shows that these trajectories can interact, which invites more complex study designs for clinical trials. However, considering these interactions switches the focus from developing drugs as an environment-independent stand-alone treatment to drugs that optimize the interaction with behavior change, and drugs that amplify learning, expectation modification and further positive environmental stimulation processes.

Table 2
Recommendations of Drug × Environment Interactions for clinical practice and clinical trial design.

(a) Recommendations for clinical practice
- Education regarding up-to-date pathophysiological and therapeutic concepts of a disease, regarding a treatment's mechanism of action, estimated treatment onset and bio-psycho-social interactions. Remind patients of these concepts throughout the therapy.
- Motivate, plan, initiate and support positive social interactions in the weeks following medication onset.
- Encourage and support regular physical activities in general (especially during antipsychotic treatments).
- Recommend physical activity to cope with symptoms and side effects of treatment.
- Analyze disorder-specific expectations (e.g., fears, catastrophizing cognitions), and encourage exposure to test these expectations (expectation-violation approach; e.g., exposure therapy of CBT).
- Involve the patient in the decision whether a pharmacological or non-pharmacological approach is taken (shared decision-making). Pharmacological approaches should always be combined with non-pharmacologial approaches optimizing environmental influences (see above) (e.g., CBT).
- Exploit placebo mechanisms, e.g.,
  - Assess patient's prior treatment experiences, as well as treatment and outcome expectations, and try to optimize them accordingly.
  - Consider the option of open-label placebo treatments for mild to moderate forms of depression (Schedlowski et al., 2015).
  - Ask the patient to specifically pay attention to the drug intake and to combine drug intake (usually a pill) with distinct sensory or contextual experiences (e.g., drinking a particular juice, or sitting in a particular chair, etc.) to facilitate conditioned pharmacological responses.

(b) Recommendations for clinical trial design
- The major basis for trial sensitivity is the control of any non-pharmacological influencing factors!
- Assay sensitivity is always associated with ascertainment quality. Use systematic and standardized instruments to ascertain not only drug efficacy, but also contextual influences and side effect assessments.
- Verification of comparability of prior treatment experiences and outcome expectancies between patients in different treatment arms.
- Assessment of social and environmental factors and of physical activities that can influence treatment outcome.
- Use of these variables to improve statistical analyses of clinical trials (e.g., imputation methods; control of covariates).
- If possible, try to apply a standardized protocol that ensures a) comparability of physical activity, social influences, and other stimulating environmental influences, and that ensures b) effects steering pharmacological reactions to positive outcome.
- Try to include at least one study arm that attempts to optimize the interaction of pharmacological and context factors, to receive an estimate about the full potential of the treatment plan, but note that assay sensitivity is higher if patients believe that the chance to be in a placebo group is 50% (Sinyor et al., 2010). For further recommendations to improve assay sensitivity see Enck et al. (2013).
- Development of new drugs should focus on drugs that improve learning/neuroplasticity.

11. Limitations

The above postulated models should be considered as hypotheses based on experimental observations and inferences from randomized-clinical trials that require further validation in a clinical care environment. We did not aim to summarize the existing literature comprehensively; rather we aimed to bring together different strands of research (neuroplasticity of psychotropic drugs; placebo mechanisms; neurobiology of context/environmental influences). Finally, results on neuroplastic processes must be interpreted with caution. Their functional relevance remains unclear, unless behavioral data are included in the studies. An increase of neurons does not automatically imply an improvement of functionality, but could also indicate an increase of chaotic information processing. This could explain why haloperidol reduces brain connectivity, yet improves the clinical syndrome of schizophrenia (Gass et al., 2013). However, to develop healthy brain functions, brain plasticity processes steered in a helpful direction still seem to be the way of treatment choice.

While traditional understanding postulated additivity of pharmacological effects and placebo/environmental effects, the conclusions of this paper favor models that also consider complex interactions between influencing factors. The interactions of these different factors can further amplify and hamper positive and negative effects. Moreover, some of these effects could be additionally subject to ceiling effects. There is some evidence that antidepressant treatment does not further enhance the beneficial effects of environmental enrichment on a neurobiological level, indicating that antidepressant treatment and environmental enrichment both are effective through the same neurobiological pathways, including the ones involved in adult neurogenesis (Possamai et al., 2015; Simpson et al., 2012; Simpson and Kelly, 2012). Current "western" environments might offer sufficient physical enrichment, yet other aspects mentioned above (e.g., social contacts) could be further optimized to support treatment improvements.

Issues relating to the timeline of these interactions are unclear. Are the effects of positive context stimulation similar, if they occur the first day after drug onset, or if they occur 2 weeks later? These aspects deserve further investigation.

Despite these shortcomings, there is strong evidence to abandon simplistic, monomechanistic models of drug actions for mental disorders. Negative expectations about drug efficiency, anxious expectations of side effects, low physical activity and low external stimulation can interact with drug effects and result in poor outcome; positive expectations, social support and stimulating context factors can amplify positive drug effects and contribute to excellent outcomes. The consideration of these complex drug x environment interactions offers new pathways to improve drug efficiency, new perspectives on drug innovations, and impetus to develop more sophisticated treatment decisions and treatment schemata.

References

Adams, C.E., Bergman, H., Irving, C.B., Lawrie, S., 2013. Haloperidol versus placebo for schizophrenia. Cochrane Database System. Rev. 11, http://dx.doi.org/10.1002/14651858.CD003082.pub3 (John Wiley & Sons Ltd.).

Alegre Baptista, P.P., de Senna, P.N., Paim, M.F., Saur, L., Blank, M., do Nascimento, P., Ilha, J., Moreira Vianna, M.R., Mestriner, R.G., Achaval, M., Xavier, L.L., 2013. Physical exercise down-regulated locomotor side effects induced by haloperidol treatment in Wistar rats. Pharmacol. Biochem. Behav. 104, 113–118.

Alves, F., Bakker, d.S., Schmitz, G., Abeling, N., Hasler, N., van der Meer, G., Nederveen, J., de Haan, A., Linszen, L., van Amelsvoort, D.T., 2013. Dopaminergic modulation of the reward system in schizophrenia: A placebo-controlled dopamine depletion fMRI study. Eur. Neuropsychopharmacol. 23, 1577–1586.

Amtage, J., Schmidt, W.J., 2003. Context-dependent catalepsy intensification is due to classical conditioning and sensitization. Behav. Pharmacol. 14, 563–567.

Andersson, C., Hamer, R.M., Lawler, C.P., Mailman, R.B., Lieberman, J.A., 2002. Striatal volume changes in the rat following long-term administration of typical and atypical antipsychotic drugs. Neuropsychopharmacology 27, 143–151.

Andersson, E., Hedman, E., Enander, J., et al., 2015. D-cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: A randomized clinical trial. J. Am. Med. Assoc. Psychiatry 72, 659–667.

Angelucci, F., Brene, S., Mathe, A.A., 2005. BDNF in schizophrenia, depression and corresponding animal models. Mol. Psychiatry 10, 345–352.

Ansorge, M.S., Zhou, M.M., Lira, A., Hen, R., Gingrich, J.A., 2004. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 306, 879–881.

Armstrong, T., Olatunji, B.O., 2012. Eye tracking of attention in the affective disorders: a meta-analytic review and synthesis. Clin. Psychol. Rev. 32, 704–723.

Arroll, B., Elley, C.R., Fishman, T., Goodyear-Smith Felicity, A., Kenealy, T., Blashki, G., Kerse, N., MacGillivray, S., 2009. Antidepressants versus placebo for depression in primary care. Cochrane Database System. Rev. 3, http://dx.doi.org/10.1002/14651858.CD007954 (John Wiley & Sons Ltd.).

Asokan, A., Ball, A.R., Laird, C.D., Hermer, L., Ormerod, B.K., 2014. Desvenlafaxine may accelerate neuronal maturation in the dentate gyri of adult male rats. PloS One 9, e98530.

Banasikowski, T.J., Beninger, R.J., 2012. Haloperidol conditioned catalepsy in rats: a possible role for D-1-like receptors. Int. J. Neuropsychopharmacol. 15, 1525–1534.
Banasr, M., Soumier, A., Hery, M., Mocaer, E., Daszuta, A., 2006. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. Biol. Psychiatry 59, 1087–1096.
Barber, J.P., Barrett, M.S., Gallop, R., Rynn, M.A., Rickels, K., 2012. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J. Clin. Psychiatry 73, 66–73.
Barr, A.M., Wu, C.H., Wong, C., Hercher, C., Topfer, E., Boyda, H.N., Procyshyn, R.M., Honer, W.G., Beasley, C.L., 2013. Effects of chronic exercise and treatment with the antipsychotic drug olanzapine on hippocampal volume in adult female rats. Neuroscience 255, 147–157.
Becker, C., Zeau, B., Rivat, C., Blugeot, A., Hamon, M., Benoliel, J.-J., 2008. Repeated social defeat-induced depression-like behavioral and biological alterations in rats: Involvement of cholecystokinin. Mol. Psychiatry 13, 1079–1092.
Benedetti, F., Mayberg, H.S., Wager, T.D., Stohler, C.S., Zubieta, J.K., 2005. Neurobiological mechanisms of the placebo effect. J. Neurosci. 25, 10390–10402.
Benes, F.M., Paskevich, P.A., Davidson, J., Domesick, V.B., 1985. Synaptic rearrangements in medial prefrontal cortex of haloperidol treated rats. Brain Res. 348, 15–20.
Blazer, D.G., Kessler, R.C., McGonagle, K.A., Swartz, M.S., 1994. The prevalence and distribution of major depression in a national community sample- The national comorbidity survey. Am. J. Psychiatry 151, 979–986.
Bourke, C.H., Stowe, Z.N., Owens, M.J., 2014. Prenatal antidepressant exposure: clinical and preclinical findings. Pharmacol. Rev. 66, 435–465.
Branchi, I., Santarelli, S., Capoccia, S., Poggini, S., D'Andrea, I., Cirulli, F., Alleva, E., 2013. Antidepressant treatment outcome depends on the quality of the living environment: a pre-clinical investigation in mice. Plos One 8 (4), http://dx.doi.org/10.1371/journal.pone.0062226.
Brown, S., Kim, M., Mitchell, C., Inskip, H., 2010. Twenty-five year mortality of a community cohort with schizophrenia. Br. J. Psychiatry 196, 116–121.
Cameron, H.A., Glover, L.R., 2015. Adult neurogenesis: beyond learning and memory. Annu. Rev. Psychol. 66, 53–81.
Camp, M.C., MacPherson, K.P., Lederle, L., Graybeal, C., Gaburro, S., DeBrouse, L.M., Ihne, J.L., Bravo, J., O'Connor, a., Ciocchi, R.M., Wellman, S., Lüthi, C.L., Cryan, A., Singewald, J.F., Holmes, N.A., 2012. Genetic strain differences in learned fear inhibition associated with variation in neuroendocrine, autonomic, and amygdala dendritic phenotypes. Neuropsychopharmacology 37, 1534–1547.
Castrén, E., 2005. Is mood chemistry? Nat. Rev. Neurosci. 6, 241–246.
Castrén, E., 2013. Neuronal network plasticity and recovery from depression. J. Am. Med. Assoc. Psychiatry 170, 983–989.
Centonze, D., Usiello, A., Costa, C., Picconi, B., Erbs, E., Bernardi, G., Borrelli, E., Calabresi, P., 2004. Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D2L receptors. J. Neurosci. 24, 8214–8222.
Chakos, M.H., Shirakawa, O., Lieberman, J., Lee, H., Bilder, R., Tamminga, C.A., 1998. Striatal enlargement in rats chronically treated with neuroleptic. Biol. Psychiatry 44, 675–684.
Cooney, G., Dwan, K., Mead, G., 2014. Exercise for Depression. J. Am. Med. Assoc. 311, 2432–2433.
Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., McMurdo, M., Mead, G.E., 2013. Exercise for depression. Cochrane Database System. Rev. 9 (CD004366), http://dx.doi.org/10.1002/14651858.CD004366.pub6.
Craske, M.G., Treanor, M., Conway, C.C., Zbozinek, T., Vervliet, B., 2014. Maximizing exposure therapy: an inhibitory learning approach. Behav. Res. Ther. 58, 10–23.
Curlik 2nd, D.M., Maeng, L.Y., Agarwal, P.R., Shors, T.J., 2013. Physical skill training increases the number of surviving new cells in the adult hippocampus. PloS One 8, e55850.
Czeh, B., Muller-Keuker, J.I.H., Rygula, R., Abumaria, N., Hiemke, C., Domenici, E., Fuchs, E., 2006. Chronic social stress inhibits cell proliferation in the adult medial prefrontal cortex: hemispheric asymmetry and reversal by fluoxetine treatment. Neuropsychopharmacology 32, 1490–1503.
Dankoski, E.C., Agster, K.L., Fox, M.E., Moy, S.S., Wightman, R.M., 2014. Facilitation of serotonin signaling by SSRIs is attenuated by social isolation. Neuropsychopharmacology 39, 2928–2937.
De Hert, M., Dekker, J.M., Wood, D., Kahl, K.G., Holt, R.I.G., Moller, H.J., 2009. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur. Psychiatry 24, 412–424.
de la Fuente-Fernandez, R., Ruth, T.J., Sossi, V., Schulzer, M., Calne, D.B., Stoessl, A.J., 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293, 1164–1166.
de Sousa Moreira, L.F., Pinheiro, M.C., Masur, J., 1982. Catatonic behavior induced by haloperidol, increased by retesting and elicited without drug in rats. Pharmacology 25, 1–5.
Dean, C.E., 2006. Antipsychotic-associated neuronal changes in the brain: toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia? Progress Neuro-Psychopharmacol. Biol. Psychiatry 30, 174–189.
Deschaux, O., Spennato, G., Moreau, J.L., Garcia, R., 2011. Chronic treatment with fluoxetine prevents the return of extinguished auditory-cued conditioned fear. Psychopharmacology 215, 231–237.
Deschaux, O., Zheng, X., Lavigne, J., Nachon, O., Cleren, C., Moreau, J.L., Garcia, R., 2013. Post-extinction fluoxetine treatment prevents stress-induced reemergence of extinguished fear. Psychopharmacology 225, 209–216.
Doering, B., Rief, W., 2012. Utilizing placebo mechanisms for dose reduction in pharmacotherapy. Trends Pharmacol. Sci. 33, 165–172.
Dringenberg, H.C., Day, L.R.B., Choi, D.H., 2014. Chronic fluoxetine treatment suppresses plasticity (long-term potentiation) in the mature rodent primary auditory cortex in vivo. Neural Plast., http://dx.doi.org/10.1155/2014/571285.
Duman, R.S., Aghajanian, G.K., 2012. Synaptic dysfunction in depression: potential therapeutic targets. Science 338, 68–72.
Enck, P., Bingel, U., Schedlowski, M., Rief, W., 2013. The placebo response in medicine: minimize, maximize or personalize? Nat. Rev. Drug Discov. 12, 191–204.
Eyding, D., Lelgemann, M., Grouven, U., Härter, M., Kromp, M., Kaiser, T., Kerekes, M.F., Gerken, M., Wieseler, B., 2010. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. Br. Med. J. 341 (c4737).
Faria, V., Ahs, F., Appel, L., Linnman, C., Bani, M., Bettica, P., Pich, E.M., Wahlstedt, K., Fredrikson, M., Furmark, T., 2014. Amygdala-frontal couplings characterizing SSRI and placebo response in social anxiety disorder. Int. J. Neuropsychopharmacol. 17, 1149–1157.
Frost, D.O., Page, S.C., Carroll, C., Kolb, B., 2010. Early exposure to haloperidol or olanzapine induces long-term alterations of dentritic form. Synapse 64, 191–199.
Fuchs, E., Flugge, G., 2014. Adult neuroplasticity: more than 40 years of research. Neural Plasti. 2014, 541870.
Furmark, T., Appel, L., Henningsson, S., Ahs, F., Faria, V., Linnman, C., Pissiota, A., Frans, O., Bani, M., Bettica, P., Pich, E.M., Jacobsson, E., Wahlstedt, K., Oreland, L., Langstrom, B., Eriksson, E., Fredrikson, M., 2008. A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. J. Neurosci. 28, 13066–13074.
Fusar-Poli, P., Smieskova, R., Kempton, M.J., Ho, B.C., Andreasen, N.C., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37, 1680–1691.
Gass, N., Schwarz, A.J., Sartorius, A., Cleppien, D., Zheng, L., Schenker, E., Risterucci, C., Meyer-Lindenberg, A., Weber-Fahr, W., 2013. Haloperidol modulates midbrain-prefrontal functional connectivity in the rat brain. Eur. Neuropsychopharmacol. 23, 1310–1319.
Gogolla, N., Caroni, P., Lüthi, A., Herry, C., 2009. Perineuronal nets protect fear memories from erasure. Science (New York, N.Y.) 325, 1258–1261.
Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. J. Am. Med. Assoc. Psychiatry 72, 305–315.
Green, W., Patil, P., Marsden, C.A., Bennett, G.W., Wigmore, P.M., 2006. Treatment with olanzapine increases cell proliferation in the subventricular zone and prefrontal cortex. Brain Res. 1070, 242–245.
Gueorguieva, R., Mallinckrodt, C., Krystal, J.H., 2011. Trajectories of depression severity in clinical trials of duloxetine insights into antidepressant and placebo responses. Arch. Gen. Psychiatry 68, 1227–1237.
Halim, N.D., Weickert, C.S., McClintock, B.W., Weinberger, D.R., Lipska, B.K., 2004. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. Neuropsychopharmacology 29, 1063–1069.
Heidbreder, C.A., Foxton, R., Cilia, J., Hughes, Z.A., Shah, A.J., Atkins, A., Hunter, A.J., Hagan, J.J., Jones, D.N.C., 2001. Increased responsiveness of dopamine to atypical, but not typical antipsychotics in the medial prefrontal cortex of rats reared in isolation. Psychopharmacology 156, 338–351.
Hendriksen, H., Prins, J., Olivier, B., Oosting, R.S., 2010. Environmental enrichment induces behavioral recovery and enhanced hippocampal cell proliferation in an antidepressant-resistant animal model for PTSD. PloS One 5, e11943.
Hensch, T.K., 2005. Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci 6, 877–888.
Hernandez-Rabaza, V., Llorens-Martin, M., Velazquez-Sanchez, C., Ferragud, A., Arcusa, A., Gumus, H.G., Gomez-Pinedo, U., Perez-Villalba, A., Rosello, J., Trejo, J.L., Barcia, J.A., Canales, J.J., 2009. Inhibition of adult hippocampal neurogenesis disrupts contextual learning but spares spatial working memory, long-term conditional rule retention and spatial reversal. Neuroscience 159, 59–68.
Hinson, R.E., Siegel, S., 1982. Nonpharmacological bases of drug tolerance and dependence. J. Psychosom. Res. 26, 495–503.
Ho, B.-C., Andreasen, N.C., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes a longitudinal study of first-episode schizophrenia. Arch. Gen. Psychiatry 68, 128–137.
Ho, Y.C., Wang, S., 2010. Adult neurogenesis is reduced in the dorsal hippocampus of rats displaying learned helplessness behavior. Neuroscience 171, 153–161.
Homberg, J.R., Schubert, D., Gaspar, P., 2010. New perspectives on the neurodevelopmental effects of SSRIs. Trends Pharmacol. Sci. 31, 60–65.
Honey, G.D., Corlett, P.R., Absalom, A.R., Lee, M., Pomarol-Clotet, E., Murray, G.K., McKenna, P.J., Bullmore, E.T., Menon, D.K., Fletcher, P.C., 2008. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J. Neurosci. 28, 6295–6303.
Horacek, J., Bubenikova-Valesova, V., Kopecek, M., Palenicek, T., Dockery, C., Mohr, P., Hoschl, C., 2006. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. Cns Drugs 20, 389–409.
Hubel, D.H., Wiesel, T.N., LeVay, S., 1977. Plasticity of ocular dominance columns in monkey striate cortex. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 278, 377–409.

Iniguez, S.D., Alcantara, L.F., Warren, B.L., Riggs, L.M., Parise, E.M., Vialou, V., Wright, K.N., Dayrit, G., Nieto, S.J., Wilkinson, M.B., Lobo, M.K., Neve, R.L., Nestler, E.J., Bolanos-Guzman, C.A., 2014. Fluoxetine exposure during adolescence alters responses to aversive stimuli in adulthood. J. Neurosci. 34, 1007–1021.
Jonas, B.S., Gu, Q., Albertorio-Diaz, J.R., 2013. Psychotropic medication use among adolescents: United States, 2005–2010. In: NCHS data brief, no 135. National Center for Health Statistics, Hyattsville, MD.
Karelina, K., DeVries, a.C., 2011. Modeling social influences on human health. Psychosom. Med. 73, 67–74.
Karpova, N.N., Pickenhagen, A., Lindholm, J., Tiraboschi, E., Kulesskaya, N., Ágústsdóttir, A., Antila, H., Popova, D., Akamine, Y., Sullivan, R., Hen, R., Drew, L.J., Castrén, E., 2011. Fear erasure in mice requires synergy between antidepressant drugs and extinction training. Science 334, 1731–1734.
Kerns, J.M., Sierens, D.K., Kao, L.C., Klawans, H.L., Carvey, P.M., 1992. Snyaptic plasticity in the rat striatum following chronic haloperidol treatment. Clin. Neuropharmacol. 15, 488–500.
Kirsch, I., Sapirstein, G., 1998. Listening to prozac but hearing placebo: a meta-analysis of antidepressant medication. Prevent. Treat. 1 (2), 1, http://dx.doi.org/10.1037/1522-3736.1.1.12a.
Klein, A., Schmidt, W.J., 2003. Catalepsy intensifies context-dependently irrespective of whether it is induced by intermittent or chronic dopamine deficiency. Behav. Pharmacol. 14, 49–53.
Klinzova, A.J., Uranova, N.A., Haselhorst, U., Schenk, H., 1990. Synaptic plasticity in rat medial prefrontal cortex under chronic haloperidol treatment produced behavioral sensitization. J. Hirnforsch. 31, 175–179.
Kobayashi, K., Ikeda, Y., Sakai, A., Yamasaki, N., Haneda, E., Miyakawa, T., Suzuki, H., 2010. Reversal of hippocampal neuronal maturation by serotonergic antidepressants. Proc. Natl. Acad. Sci. U.S.A. 107, 8434–8439.
Kodamo, M., Fujioko, T., Duman, R.S., 2004. Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. Biol. Psychiatry 56, 570–580.
Krishnan, V., Nestler, E.J., 2010. Linking molecules to mood: new insight into the biology of depression. Am. J. Psychiatry 167, 1305–1320.
Krogsboll, L.T., Hrobjartsson, A., Gotzsche, P.C., 2009. Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. BMC Med. Res. Methodol. 9, 1.
Laughren, T.P., 2001. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. Eur. Psychiatry 16, 418–423.
LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.
Lehmann, M.L., Brachman, R.A., Martinowich, K., Schloesser, R.J., Herkenham, M., 2013. Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. J. Neurosci. 33, 2961–2972.
Leucht, C., Huhn, M., Leucht, S., 2012a. Amitriptyline versus placebo for major depressive disorder. Cochrane Database System. Rev. 12, http://dx.doi.org/10.1002/14651858.CD009138.pub2 (John Wiley & Sons Ltd.).
Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Davis John, M., 2012b. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database System. Rev. 5, http://dx.doi.org/10.1002/14651858.CD008016.pub2 (John Wiley & Sons Ltd.).
Leucht, S., Arbter, D., Engel, R., Kissling, W., Davis, J., 2009. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol. Psychiatry 14, 429–447.
Leuchter, A.F., Cook, I.A., Witte, E.A., Morgan, M., Abrams, M., 2002. Changes in brain function of depressed subjects during treatment with placebo. Am. J. Psychiatry 159, 122–129.
Leuchter, A.F., Hunter, A.M., Tartter, M., Cook, I.A., 2014. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. Br. J. Psychiatry 205, 443–449.
Leuchter, A.F., McCracken, J.T., Hunter, A.M., Cook, I.A., Alpert, J.E., 2009. Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder. J. Clin. Psychopharmacol. 29, 372–377.
Lincoln, T.M., Ziegler, M., Mehl, S., Kesting, M.L., Lullmann, E., Westermann, S., Rief, W., 2012. Moving from efficacy to effectiveness in cognitive behavioral therapy for psychosis: a randomized clinical practice trial. J. Consult. Clin. Psychol. 80, 674–686.
Luo, C., Xu, H.Y., Li, X.M., 2005. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. Brain Res. 1063, 32–39.
Luoni, A., Berry, A., Calabrese, F., Capoccia, S., Bellisario, V., Gass, P., Cirulli, F., Riva, M.A., 2014. Delayed BDNF alterations in the prefrontal cortex of rats exposed to prenatal stress: preventive effect of lurasidone treatment during adolescence. Eur. Neuropsychopharmacol. 24, 986–995.
Lyons, D.M., Buckmaster, P.S., Lee, A.G., Wu, C., Mitra, R., Duffey, L.M., Buckmaster, C.L., Her, S., Patel, P.D., Schatzberg, A.F., 2010. Stress coping stimulates hippocampal neurogenesis in adult monkeys. Proc. Natl. Acad. Sci. U.S.A. 107, 14823–14827.
Malberg, J.E., Duman, R.S., 2003. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. Neuropsychopharmacology 28, 1562–1571.
Malberg, J.E., Eisch, A.J., Nestler, E.J., Duman, R.S., 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J. Neurosci. 20, 9104–9110.
Maren, S., Phan, K.L., Liberzon, I., 2013. The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat. Rev. 14, 417–428.
Mayberg, H.S., Silva, J.A., Brannan, S.K., Tekell, J.L., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 2002. The functional neuroanatomy of the placebo effect. Am. J. Psychiatry 159, 728–737.
Melo, T.G., Izídio, G.S., Ferreira, L.S., Sousa, D.S., Macedo, P.T., Cabral, A., Ribeiro, A.M., Silva, R.H., 2012. Antidepressants differentially modify the extinction of an aversive memory task in female rats. Progress Neuro-Psychopharmacol. Biol. Psychiatry 37, 33–40.
Meyer-Lindenberg, A., Tost, H., 2012. Neural mechanisms of social risk for psychiatric disorders. Nat. Neurosci. 15, 663–668.
Meyer-Lindenberg, A., Tost, H., 2014. Neuroimaging and plasticity in schizophrenia. Restor. Neurol. Neurosci. 32, 119–127.
Moncrieff, J., Wessely, S., Hardy, R., 2004. Active placebos versus antidepressants for depression. Cochrane Database Systematic Rev. 1, http://dx.doi.org/10.1002/14651858.CD14003012.pub14651852.
Moritz, S., Veckenstedt, R., Andreou, C., Bohn, F., Hottenrott, B., Leighton, L., Kother, U., Woodward, T.S., Treszl, A., Menon, M., Schneider, B.C., Pfueller, U., Roesch-Ely, D., 2014. Sustained and "Sleeper" effects of group metacognitive training for schizophrenia a randomized clinical trial. J. Am. Med. Assoc. Psychiatry 71, 1103–1111.
Morris, S.E., Rumsey, J.M., Cuthbert, B.N., 2014. Rethinking mental disorders: the role of learning and brain plasticity. Restor. Neurol. Neurosci. 32, 5–23.
Murray, D., Stoessl, A.J., 2013. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. Pharmacol. Ther. 140 (3), 306–318, http://dx.doi.org/10.1016/j.pharmthera.2013.07.009.
Normann, C., Schmitz, D., Fürmaier, A., Döing, C., Bach, M., 2007. Long-term plasticity of visually evoked potentials in humans is altered in major depression. Biol. Psychiatry 62, 373–380.
Pang, T.Y.C., Hannan, A.J., 2013. Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity. Neuropharmacology 64, 515–528.
Peciña, M., Bohnert, A.B., Sikora, M.<ET-A>, 2015. Association between placebo-activated neural systems and antidepressant responses: neurochemistry of placebo effects in major depression. J. Am. Med. Assoc. Psychiatry 72, 1087–1094.
Peckham, A.D., McHugh, R.K., Otto, M.W., 2010. A meta-analysis of the magnitude of biased attention in depression. Depression Anxiety 27, 1135–1142.
Peters, J., Dieppa-Perea, L.M., Melendez, L.M., Quirk, G.J., 2010. Induction of fear extinction with hippocampal-infralimbic BDNF. Science 328, 1288–1290.
Petrik, D., Lagace, D.C., Eisch, A.J., 2012. The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? Neuropharmacology 62, 21–34.
Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., Ingvar, M., 2005. Placebo in emotional processing—induced expectations of anxiety relief activate a generalized modulatory network. Neuron 46, 957–969.
Player, M.J., Taylor, J.L., Weickert, C.S., Alonzo, A., Sachdev, P., Martin, D., Mitchell, P.B., Loo, C.K., 2013. Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacology 38, 2101–2108.
Pope, A., Adams, C., Paton, C., Weaver, T., Barnes, T.R.E., 2010. Assessment of adverse effects in clinical studies of antipsychotic medication: survey of methods used. Br. J. Psychiatry 197, 67.
Popova, D., Ágústsdóttir, A., Lindholm, J., Mazulis, U., Akamine, Y., Castrén, E., Karpova, N.N., 2014. Combination of fluoxetine and extinction treatments forms a unique synaptic protein profile that correlates with long-term fear reduction in adult mice. Eur. Neuropsychopharmacol. 24, 1162–1174.
Possamai, F., dos Santos, J., Walber, T., Marcon, J.C., dos Santos, T.S., Lino de Oliveira, C., 2015. Influence of enrichment on behavioral and neurogenic effects of antidepressants in Wistar rats submitted to repeated forced swim test. Prog. Neuropsychopharmacol. Biol. Psychiatry 58, 15–21.
Price, R., Salavati, B., Graff-Guerrero, A., Blumberger, D.M., Mulsant, B.H., Daskalakis, Z.J., Rajji, T.K., 2014. Effects of antipsychotic D2 antagonists on long-term potentiation in animals and implications for human studies. Prog. Neuropsychopharmacol. Biol. Psychiatry 54, 83–91.
Rabideau, D.J., Nierenberg, A.A., Sylvia, L.G., Friedman, E.S., Bowden, C.L., Thase, M.E., Ketter, T.A., Ostacher, M.J., Reilly-Harrington, N., Iosifescu, D.V., Calabrese, J.R., Leon, A.C., Schoenfeld, D.A., 2014. A novel application of the intent to attend assessment to reduce bias due to missing data in a randomized controlled clinical trial. Clin. Trials 11, 494–502.
Riedinger, K., Kulak, A., Schmidt, W.J., von Ameln-Mayerhofer, A., 2011. The role of NMDA and AMPA/Kainate receptors in the consolidation of catalepsy sensitization. Behav. Brain Res. 218, 194–199.
Rief, W., Bingel, U., Schedlowski, M., Enck, P., 2011. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin. Pharmacol. Ther. 90, 722–726.
Rief, W., Glombiewski, J.A., 2012. The hidden effects of blinded, placebo controlled randomized trials: an experimental investigation. Pain 153, 2473–2477.
Rief, W., Glombiewski, J.A., Gollwitzer, M., Schubö, A., Schwarting, R., Thorwart, A., 2015. Expectations as core features of mental disorders. Curr. Opin. Psychiatry 28, 378–385.
Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A.J., Hofmann, S.G., 2009a. Meta-analysis of the placebo response in antidepressant trials. J. Affect. Disord. 118, 1–8.
Rief, W., Lilienfeld-Toal, v., Nestoriuc, A., Hofmann, Y., Barsky, S.G., Avorn, A.J., 2009b. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials. A systematic review and meta-analysis. Drug Saf. 32, 1041–1056.

Ross, L.E., Grigoriadis, S., Mamisashvili, L., VonderPorten, E.H., Roerecke, M., Rehm, J., Dennis, C.L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., 2013. Selected pregnancy and delivery outcomes after exposure to antidepressant medication a systematic review and meta-analysis. J. Am. Med. Assoc. Psychiatry 70, 436–443.
Rutherford, B.R., Pott, E., Tandler, J.M., Wall, M.M., Roose, S.P., Lieberman, J.A., 2014. Placebo Response in Antipsychotic Clinical Trials: A Meta-analysis. J. Am. Med. Assoc. Psychiatry 71, 1409–1421.
Rutherford, B.R., Roose, S.P., 2013. A model of placebo response in antidepressant clinical trials. Am. J. Psychiatry 170, 723–733.
Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.
Sarpal, D.K., Robinson, D.G., Lencz, T., Argyelan, M., Ikuta, T., Karlsgodt, K., Gallego, J.A., Kane, J.M., Szeszko, P.R., Malhotra, A.K., 2015. Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. J. Am. Med. Assoc. Psychiatry 72, 5–13.
Schedlowski, M., Enck, P., Rief, W., Bingel, U., 2015. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. Pharmacol. Rev. 67, 697–730.
Schmidt, L., Braun, E.K., Wager, T.D., Shohamy, D., 2014. Mind matters: placebo enhances reward learning in Parkinson's disease. Nat. Neurosci. 17, 1793–1797.
Schmitt, A., Weber, S., Jatzko, A., Braus, D.F., Henn, F.A., 2004. Hippocampal volume and cell proliferation after acute and chronic clozapine or haloperidol treatment. J. Neural Transm. 111, 91–100.
Schneier, F.R., Neria, Y., Pavlicova, M., Hembree, E., Suh, E.J., Amsel, L., Marshall, R.D., 2012. Combined prolonged exposure therapy and paroxetine for ptsd related to the world trade center attack: a randomized controlled trial. Am. J. Psychiatry 169, 80–88.
Simpson, J., Bree, D., Kelly, J.P., 2012. Effect of early life housing manipulation on baseline and drug-induced behavioural responses on neurochemistry in the male rat. Prog Neuropsychopharmacol. Biol. Psychiatry 37, 252–263.
Simpson, J., Kelly, J.P., 2012. The effects of isolated and enriched housing conditions on baseline and drug-induced behavioural responses in the male rat. Behav. Brain Res. 234, 175–183.
Sinyor, M., Levitt, A.J., Cheung, A.H., Schaffer, A., Kiss, A., Dowlati, Y., Lonctot, K.L., 2010. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. J. Clin. Psychiatry 71, 270–279.
Sørensen, H.J., Jensen, S.O.W., Nielsen, J., 2013. Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. Eur. Neuropsychopharmacol. 23, 872–878.
Spielmans, G.I., Kirsch, I., 2014. Drug approval and drug effectiveness. Annu. Rev. Clin. Psychol. Vol10 (10), 741–766.
Steinert, C., Hofmann, M., Kruse, J., Leichsenring, F., 2014. The prospective long-term course of adult depression in general practice and the community. A systematic literature review. J. Affect. Disord. 152, 65–75.
Summerfield, C., de Lange, F.P., 2014. Expectation in perceptual decision making: neural and computational mechanisms. Nat. Rev. Neurosci. 15, 745–756.
Sumner, J.A., Griffith, J.W., Mineka, S., 2010. Overgeneral autobiographical memory as a predictor of the course of depression: a meta-analysis. Behav. Res. Ther. 48, 614–625.
Sun, T., Liu, X., Li, M., 2014. Effect of enviromental cues on the behavioral efficacy of haloperidol, olanzapine, and clozapine in rats. Behav. Pharmacol. 25, 277–286.
Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Sassa, Y., Kawashima, R., 2013. Effects of working memory training on functional connectivity and cerebral blood flow during rest. Cortex 49, 2106–2125.
Teixeira, A.M., Pase, C.S., Boufleur, N., Roversi, K., Barcelos, R.C.S., Benvegnu, D.M., Segat, H.J., Dias, V.T., Reckziegel, P., Trevizol, F., Dolci, G.S., Carvalho, N.R., Soares, F.A.A., Rocha, J.B.T., Emanuelli, T., Buerger, M.E., 2011. Exercise affects memory aquisition, anxiety-like symptoms and activity of membrane-bound enzyme in brain of rats fed with different dietary fats: impairments of trans fat. Neuroscience 195, 80–88.
Thomas, A., Burant, A., Bui, N., Graham, D., Yuva-Paylor, L., Paylor, a.R., 2009. Marble burying reflects a repetitive and perseverative behavior more than novelty-induced anxiety. Psychopharmacology 204, 361–373.
Turner, E.H., Matthews, A.M., Linardatos, E., Tell, R.A., Rosenthal, R., 2008. Selective publication of antidepressant trials and its influence on apparent efficacy. N. Engl. J. Med. 358, 252–260.
Uranova, N.A., Orlovskaya, D.D., Apel, K., Klintsova, A.J., Haselhorst, U., Schenk, H., 1991. Morphometric study of synaptic patterns in the rat caudate nucleus and hippocampus under haloperidol treatment. Synapse 7, 253–259.
Vernon, A.C., Natesan, S., Crum, W.R., Cooper, J.D., Modo, M., Williams, S.C.R., Kapur, S., 2012. Contrasting effects of haloperidol and lithium on rodent brain structure: a magnetic resonance imaging study with postmortem confirmation. Biol. Psychiatry 71, 855–863.
Vernon, A.C., Natesan, S., Modo, M., Kapur, S., 2011. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. Biol. Psychiatry 69, 936–944.
Vetencourt, J.F.M., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, F., Castrén, O., Maffei, E.L., 2008. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 320, 385–388.
Wakade, C.G., Mahadik, S.P., Waller, J.L., Chiu, F.C., 2002. Atypical neuroleptics stimulate neurogenesis in adult rat brain. J. Neurosci. Res. 69, 72–79.
Walker, D.L., Ressler, K.J., Lu, K.-T., Davis, M., 2002. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J. Neurosci.: Off. J. Soc. Neurosci. 22, 2343–2351.
Walsh, B.T., Seidman, S.N., Sysko, R., Gould, M., 2002. Placebo response in studies of major depression: variable, substantial, and growing. J. Am. Med. Assoc. 287, 1840–1847.
Waltz, J.A., Frank, M.J., Robinson, B.M., Gold, J.M., 2007. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. Biol. Psychiatry 62, 756–764.
Wang, H.D., Dunnavant, F.D., Jarman, T., Deutch, A.Y., 2004. Effects of antipsychotic drugs on neurogenesis in the forebrain of the adult rat. Neuropsychopharmacology 29, 1230–1238.
Weikum, W.M., Oberlander, T.F., Hensch, T.K., Werker, J.F., 2012. Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception. Proc. Natl. Acad. Sci. U.S.A. 109, 17221–17227.
Weimer, K., Colloca, L., Enck, P., 2015. Placebo effects in psychiatry: mediators and moderators. Lancet Psychiatry 2, 246–257.
Wernicke, J.F., Ossanna, M.J., 2010. The placebo response in pain and depression: in search of a common pathway. Front. Biosci. (Schol Ed.) 2, 106–111.
Wichers, M.C., Barge-Schaapveld, D.Q., Nicolson, N.A., Peeters, F., de Vries, M., Mengelers, R., van Os, J., 2009. Reduced stress-sensitivity or increased reward experience: the psychological mechanism of response to antidepressant medication. Neuropsychopharmacology 34, 923–931.
Wiecki, T.V., Riedinger, K., von Ameln-Mayerhofer, A., Schmidt, W.J., Frank, M.J., 2009. A neurocomputational account of catalepsy sensitization induced by D2 receptor blockade in rats: context dependency, extinction, and renewal. Psychopharmacology 204, 265–277.
Wöhr, M., Orduz, D., Gregory, P., Moreno, H., Khan, U., Vörckel, K.J., Wolfer, D.P., Welzl, H., Gall, D., Schiffmann, S.N., Schwaller, B., 2015. Lack of parvalbumin in mice leads to behavioral deficits relevant to all human autism core symptoms and related neural morphofunctional abnormalities. Transl. Psychiatry 5, e525.
Wu, C.S., Gau, S.S., Lai, M.S., 2014. Long-term antidepressant use and the risk of type 2 diabetes mellitus: a population-based, nested case-control study in Taiwan. J. Clin. Psychiatry 75, 31–38.
Yau, S.Y., Li, A., Hoo, R.L., Ching, Y.P., Christie, B.R., Lee, T.M., Xu, A., So, K.F., 2014. Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc. Natl. Acad. Sci. U.S.A. 111, 15810–15815.
Yildirim, E., Erol, K., Ulupinar, E., 2012. Effects of sertraline on behavioral alterations caused by environmental enrichment and social isolation. Pharmacol. Biochem. Behav. 101, 278–287.
Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15, 528–536.
Zhang, C., Li, M., 2012. Contextual and behavioral control of antipsychotic sensitization induced by haloperidol and olanzapine. Behav. Pharmacol. 23, 66–79.
Zhang, W., Qin, S., Guo, J., Luo, J., 2011. A follow-up fMRI study of a transferable placebo anxiolytic effect. Psychophysiology 48, 1119–1128.
Zoladz, J.A., Pilc, A., 2010. The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. J. Physiol. Pharmacol. 61, 533–541.
Zou, K., Deng, W., Li, T., Zhang, B., Jiang, L., Huang, C., Sun, X., Sun, X., 2010. Changes of brain morphometry in first-episode, drug-naive, non-late-life adult patients with major depression: an optimized voxel-based morphometry study. Biol. Psychiatry 67, 186–188.