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Treatment-Induced Brain Plasticity in Psychiatric Disorders

Maria Uscinska, Andrea Polla Mattiot and Silvio Bellino

Abstract

In tandem with a better-informed neurobiological model of mental illness, psychiatry has progressively been shaped into its current state of clinical neuroscience. The traditional dichotomy of organic versus endogenous mental disorders has been replaced by the growing recognition that all changes in mental processes are accompanied by changes in structures or functions of the brain. Thus, all psychiatric interventions are deemed to have a biopsychosocial nature, whereby drugs in addition to their effect on the brain have a psychological effect, and psychotherapies beyond their psychological effects may alter the brain. In this view, the ultimate goal of any psychiatric treatment is to induce neural plasticity in a manner that restores the full original function and potential of the injured brain. Herein present chapter gives an insight into how evidence-based treatments achieve their therapeutic effects on the level of cerebral reorganization across a host of psychiatric disorders. The main theme of this work is the posited mechanism of neuroplasticity on neural-systems level for each treatment modality.

Keywords: therapy, drugs, treatment, psychosis, schizophrenia, depression, disorder, antidepressant, antipsychotic, neuroimaging, fMRI, cognitive, plasticity, mood stabilizers, neural correlates

1. Neural parameters of therapeutic change

Mechanisms of neuroplasticity constitute fundamental processes behind learning and memory, that determine the ability of neuronal systems to incorporate novel environmental stimuli and to make appropriate adaptive response. Delineating cerebral processes of recovery from an insult to the brain holds promise for developing more refined and novel treatment modalities to target specific areas of pathology. Functional neuroimaging studies provide a mean to characterize changes in brain function related to psychiatric interventions. Well-established in indexing biomarkers of psychiatric disorders, novel neuroimaging techniques are now used to depict patterns of neural plasticity mediating post-treatment amelioration of symptoms. Various modalities provide indices of brain activity by measuring cerebral blood flow or glucose metabolism including functional magnetic resonance imaging (fMRI), 18fluorodeoxyglucose positron emission tomography (FDG-PET), and 99mtechnetium hexamethylpropyleneamineoxime single photon emission computed tomography (99mTc-HMPAO SPECT) [see ref. 1 for a detailed review] One powerful imaging modality that has significantly advanced our knowledge in this field is the task-based functional magnetic resonance imaging (t-fMRI).

It consists of a paradigm defined by a functional measurement including a stimulation adjusted to the brain area under investigation. The subject is required to perform a defined motor or sensorimotor, language or another cognitive or visual tasks in the MRI scanner while typically GRE T2*-weighed echo planner images (EDI) are rapidly acquired [for a more in-depth description of fMRI see ref. 1]. Local changes in cerebral blood flow (CBF) during task execution relative to resting state are used to infer brain regions/networks functionally involved in specific tasks. To ultimately determine the specificity and amount of therapy-induced neuroplasticity, multiple pre-, and post- therapy scans are compared against activity pattern changes in other active treatment groups and a no-treatment waiting-list group [2]. With this in mind, the next section follows with an overview of main findings associated with intervention-induced neuroplasticity and their interpretations.

2. Putative neuroplastic mechanisms of pharmacotherapy

Pharmacotherapy constitutes first-line treatment modality for majority of psychiatric disorders, and various theories exist as to how drug-induced neurochemical changes reverse different psychiatric symptoms. The posited purely neurotransmitter-based mechanism of action postulates either increased or reduced synaptic concentration of a target neurotransmitter that is implicated in a given disorder. This model is challenged by disjunction in the timescale of the onset of neurochemical versus therapeutic effects, wherein the potentiation or attenuation of neurotransmitter function often occurs within hours of administration and the clinical improvement is typically seen days or weeks after [3]. In quest of new rapid-acting agents, contemporary approaches to understanding of drug action focus on the role of adaptive neuroplastic processes that correlate in time with the onset of clinical improvement, hence are hypothesized to represent a more direct treatment target.

2.1 Antidepressant drugs and mechanisms of neuroplasticity

Current national and international guidelines recommend serotonin reuptake inhibitors (SSRIs) as first-line treatment for most patients with major depression, and the use of serotonin—norepinephrine reuptake inhibitors (SNRI) in patients resistant to the former [4, 5]. Although novel, better tolerated and more selective inhibitors of serotonin and norepinephrine reuptake are continuously being developed, the efficacy of tricyclic antidepressants such as amitriptyline for severe depression, has never been surpassed [6].

Most of currently licensed antidepressants act to enhance monoamine neurotransmission, where they are believed to achieve therapeutic effects by increasing availability of serotonin or/and norepinephrine, at least initially [7]. On the neural level, antidepressants normalize aberrant neural activity patterns underlying negative bias in affective information processing, posited to play central role in the etiology and maintenance of depressed state [8]. Thus, antidepressants were shown to attenuate hyperactivity in limbic areas of the brain (amygdala, insula, anterior cingulate), and enhance regulatory activity in the dorsolateral and medial prefrontal cortex as measured by functional magnetic resonance imaging [9, 10]. It was demonstrated that 7 days treatment with SSRI, citalopram, SNRI, and reboxetine reversed abnormal patterns of neural response to affective information, and induced a similar direction of change in healthy individuals [11, 12]. Noteworthy, short-term SSRI administration normalized amygdala hyperactivity in response to negative emotional stimuli prior to clinical changes in mood ratings in placebo-controlled

studies [13]. These findings allow to speculate that treatment-induced early reversal of negative emotional bias sets the scene for therapeutic recovery over time by reducing the influence of this key maintaining factor [14].

2.2 Antipsychotic drugs and mechanisms of neuroplasticity

Antipsychotic medication is the mainstay of effective management of psychosis where schizophrenia is the most prevalent among psychotic disorders. Most of what we know about antipsychotic drugs action is at the receptor level, where abnormalities in neurotransmission constitute either an excess or a deficiency of neurotransmitters, including dopamine, serotonin, and glutamate. Therein first-generation drugs act as antagonists of dopamine D2 receptors and target most positive symptoms such as hallucinations and delusions. The receptor-binding profile of second-generation drugs extends beyond D2 affinity antagonism to other neuroreceptors including serotonin 5-HT2A in the frontal lobe, thus accounting for superior efficacy of these drugs in the pathophysiology of negative symptoms and cognitive disorganization [15, 16]. Overall, treatment response has been shown to be associated to the level of D2 occupancy, which is the target of all currently licensed antipsychotics [17]. To delineate therapeutic mechanism of clinically effective drugs beyond receptor level, research has focused on neural systems effects before and after pharmacotherapy in medication-naïve patients with first-episode psychosis. Functional MRI studies revealed pre-treatment functional alterations within frontostriatal circuitry, marked by patterns of hypoactivity within the dorsolateral/medial prefrontal cortex coupled with hyperactivity in the hippocampus and striatum [18–20]. Thus, aberrant frontostriatal circuitry might represent a potential system- level mechanism of psychosis and a candidate for treatment target with antipsychotics. Post-treatment findings lend some evidence to validate this model, showing increases in task-related frontal cortical activation in patients who underwent 12 weeks of quetiapine fumarate treatment compared to a drug-naive group [21, 22], and in a small group of patients with schizophrenia medicated with risperidone [23]. A similar study on cortical structure and function alterations within 1 year of psychosis onset in unmedicated schizophrenia patients versus patients under short-term therapy with atypical antipsychotics revealed a more complex relationship [20]. Although the treatment was associated with enhanced cognitive control and increased prefrontal, middle temporal, parietal, and occipital activity, it also revealed post-treatment prefrontal cortical thinning in the treatment group. The mechanism by which antipsychotics are associated with the loss of gray matter remains unclear, however neuroinflammatory models posit elevations in proinflammatory cytokine levels [24], microglia activation [25], and increased extracellular volume in white and gray matter [26]. Thus, the study adds to the growing literature on therapeutic mechanisms of antipsychotics, mediated by normalization of aberrant frontal cortical function, and suggests that caution must be exercised in interpreting neuroanatomical changes as being potentially deleterious to brain function.

2.3 Mood stabilizers and mechanisms of neuroplasticity

Lithium and anticonvulsants with mood-stabilizing properties (lamotrigine, valproate) constitute first-line drug treatment for episodes of depression and mania with variable inter-episode remission [27–29]. Whilst different compounds may differentially target specific facets of bipolar disorders, lithium is effective for all phases including acute depression [30]. On the neural level, functional imaging studies consistently point to pre-treatment frontolimbic dysfunction during

cognitive control and emotion-paradigms in bipolar disorder patients [31–33]. Thus, abnormal emotion regulation and impaired cognition might be attributed to interference in cognitive control within medial prefrontal cortex though overactivity in subcortical structures (amygdala, ACC, insula), involved in emotion generation and appraisal. Findings of mood stabilizers-induced neural plasticity yield less consistent results due to methodological limitations that make it difficult to draw firm conclusions. Whilst some studies find no significant effects of pharmacotherapy upon functional measures of cerebral reorganization in bipolar patients [34–41] others reported increased task-related prefrontal cortical activity coupled with normalized subcortical limbic activity during emotional processing [38, 39, 42, 43]. Typically, individuals recruited in these studies are able to tolerate medication withdrawal and washout, and therefore are likely to have a milder form of the disorder. Given that it is not clinically feasible to withdraw all patients with bipolar disorder from medication, individuals with a more severe form of the disorder are likely to be underrepresented in many studies and therefore findings might not be generalizable to the most at-need of new treatments group.

3. Putative neuroplastic mechanisms of psychotherapy

Although studies of neural parameters of therapeutic change under psychotherapy are under-represented relative to analogous studies of medications, emerging literature support the thesis that changes in affect, cognition and behavior mediated by psychotherapy have demonstrable neuroplastic underpinnings. Since the call for more neuroscientifically informed approaches to psychotherapy [44], studies have elucidated neural mechanism of psychotherapy-induced changes in brain activity profiles across a range of psychiatric disorders.

3.1 Cognitive behavioral therapy and mood disorders

Psychotherapy processes appear to target maladaptive cognitive and emotional patterns by engaging their biological analogues that are responsive to a discrete mode of treatment [45]. One salient example involves re-appraisal technique under cognitive behavioral therapy (CBT) for depression, where patients are invited to re-interpret their negative perceptions of unpleasant occurrences in a more positive light. Mood ratings before and after re-thinking negative events revealed improved positive affect, mediated by elevated activity in dorsolateral and dorsomedial PFC coupled with decreased activity in the amygdala and orbitofrontal cortex [46]. To delineate CBT- induced mechanism of neuroplasticity in depression, FDG-PET scans before and after psychotherapy relative to paroxetine treatment were acquired from patients instructed to 'avoid ruminating on any one topic' during scanning [47]. Although efficacy of both treatments was comparable, differential activity patterns emerged in frontal and limbic regions, implying that medication and psychotherapy might achieve their therapeutic effects in different ways. Whilst CBT was associated with decreased metabolism in multiple frontal regions including the dorsolateral PFC together with increased activity in the hippocampus, parahippocampal gyrus, and dorsal cingulate gyrus, paroxetine- induced increased PFC metabolism, and decrease in hippocampal, parahippocampal, posterior cingulate and ventral subgenual cingulate activity. This modality-specific mechanism of neuroplasticity posits that CBT exerts 'top- down' changes in cognitive processing in favor of engaging ventral and limbic regions, which mediate attention to personally salient stimuli, whereas antidepressant drugs prompt 'bottom-up' disengagement of ventral, frontal and limbic regions. Although this model runs counter the

aforementioned emotion regulation model, divergent findings might result from using healthy subjects in the former study and patients with depression in the latter, invoking the notion that brain activation results from the interaction between underlying brain state and treatment modality [48].

In efforts to elucidate CBT- induced neural mechanism of anxiety disorders functional neuroimaging study examined pre-and-post CBT brain activity patterns in non-medicated patients with spider phobia and healthy subjects [49]. The former exhibited elevated activation in the parahippocampal gyrus and right dorsolateral PFC prior to the treatment, which was normalized with successful group CBT sessions focused on exposure therapy. Given that parahippocampal gyrus mediates contextual memory, authors suggested that after CBT less demand was placed on the dorsolateral PFC to construct a cognitive defense to the perceived threat. Moreover, a therapy- induced shift of activity to the ventral PFC was indexed, which might play a role in down-regulation of limbic activity and thereby dampening fear reaction. Collectively, these studies depict a neuroplastic model of cognitive behavioral therapy which posits altered engagement of dorsal prefrontal circuitry to down-regulate limbic and ventral prefrontal structures thereby improving affect in response to emotionally significant contexts.

3.2 Dialectic behavioral therapy and borderline personality disorder

Given that psychotherapy is the gold standard treatment modality for borderline personality disorder [50], extensive research efforts focused on measuring brain changes induced by specific modes of therapy. To date, dialectic behavioral therapy is the most researched, refined and evidenced-based therapy informed by a deficit model in self-regulation, distress tolerance and interpersonal skills, deemed to arise from transaction between highly sensitive individuals and invalidating environments [51, 52]. DBT purports to render individuals more mindful and able to manage relationships effectively by incorporating the concept of dialectics and strategy of validation into approach focused on skills acquisition and behavioral shaping.

Consistent with the skills deficit model of BPD, neuroimaging evidence supports that acquisition of affective control strategies under DBT balances neural substrates of emotion regulation. One salient example indexed neural activity alterations under re-appraisal and reported dampened insula and ACC activity, together with an enhanced connectivity of the latter to medial and superior frontal gyrus, superior temporal gyrus, and inferior parietal cortices [53]. Notably, treatment-induced increase in dorsal ACC activity during exposure to negative stimuli was associated with improvement self-reported BPD symptoms, suggesting a possible biomarker of improved affect regulation. In a similar study Winter et al. [54] set out to establish whether neural correlates of distraction might be amenable to a successful DBT. In this view, 31 BPD patients under constant medication were scanned before and after a 12- week residential DBT-based treatment while performing a distraction task. When compared to 15 BPD control patients under non-DBT-based treatment or no treatment at all, and 22 healthy participants, 16 DBT responders exhibited attenuated activity in the right inferior parietal lobe/supramarginal gyrus. Notably, this pattern of brain activity was correlated with improvement in self-reported borderline symptom severity (ZAN-BPD). Furthermore, treatment was associated with a reduction in the right perigenual ACC activity and increased activity in these regions during distraction in the context of aversive stimuli. These findings might reflect a shift from emotional to more cognitive processing in the context of aversive stimuli, thereby suggesting an improvement in emotional susceptibility under DBT.

Taken together aforementioned studies support that DBT processes target maladaptive emotional patterns by altering their biological analogues that are responsive to discrete cognitive strategies. DBT normalizes frontolimbic imbalances as part of the disturbed circuitry, which appear to mediate amelioration of BPD symptomatology. Caution must be exercised however, while interpreting results as medications may attenuate emotional responses in BPD patients [55], and giving combinations of drug subtypes makes it impossible to isolate the effect of a single agent.

3.3 IPT and depression

IPT is a short-term treatment that typically consists of 12–16 one-hour weekly sessions focused on improving interpersonal relationships. Drawing directly on identifiable issues between patients and therapists, it purports to instil the ability to make the necessary adjustments in interpersonal situations that will help to reduce symptoms of depression. Several imaging studies have examined biomarkers of cerebral reorganization induced by IPT relative to pharmacotherapy. One of them compared the effects of the former and venlafaxine (37.5 mg daily) on regional CBF using 99mTc-HMPAO SPECT in 28 drug-naive or drug-free patients with MDD [56]. Whilst comparative clinical improvements were mediated by elevated activity in the right basal ganglia in both treatment groups, patients in the IPT group also exhibited an increase in the right posterior cingulate activity. However, drawing firm conclusion from these findings is hampered by methodological issues as four patients with a strong preference for venlafaxine could choose the treatment, while one preferred IPT. Moreover, subjects in the latter evidenced greater striatal perfusion, potentially reflecting design limitation. Brief duration of IPT and relatively low dose of venlafaxine give rise to the possibility that both treatments were suboptimal, thereby underscoring the engagement of limbic and paralimbic recruitment in psychotherapy-induced changes reported in parallel research [56].

A similar study on the effects of IPT and paroxetine relative to healthy controls [57] reported results analogous to CBT effects described by Goldapple et al. [47]. Whilst treatment response in both groups was associated with an increase in metabolism in limbic and paralimbic regions (the right insula and left inferior temporal lobe) relative to controls, unlike CBT the effects of IPT were mediated by a decrease in dorsal and ventral prefrontal cortical metabolism. A follow-up study was set out to correlate treatment-mediated changes in brain activity patterns with amelioration in mood symptoms measured by the Hamilton Depression Rating Scale and the tension/anxiety and fatigue clusters of the Profile of Mood States [58]. A cohort of 39 patients under either paroxetine or IPT for MDD exhibited post-treatment reductions in ventral and dorsal frontal lobe metabolism, which was associated with improvements in the anxiety/somatization and psychomotor retardation symptom clusters. Unlike previous findings of negative correlation between activity in the dorsolateral PFC and improvement on global depression scores under CBT, in the present study alterations in dorsolateral PFC activity positively correlated with improvement in cognitive disturbance. These suggest that each treatment modality engages dorsolateral PFC function differently to achieve a specific therapeutic effect. While CBT appears to engage this region to attenuate 'over-thinking' in depression, IPT might induce it to improve general cognitive abilities.

3.4 Psychoeducation and euthymic bipolar disorder

Given that pharmacotherapy is often ineffective for treatment of residual depressive, dysthymic and dysphoric symptoms [59], researchers have shown

interest in psychoeducation in targeting emotional and cognitive processes [60–63]. Psychoeducation is a treatment option for bipolar disorder focused on improving coping strategies to manage symptoms in everyday life, compliance with medication to prevent thymic relapses, quality of life and social functioning [64, 65]. Whilst wealth of research exists to support its efficacy in clinical symptoms improvement, less is known how therapeutic change is achieved on the level of neural functioning.

Favre and collaborates [66] set out to index neural processes before and after psychoeducation therapy in 16 euthymic bipolar patients (EBP) matched against 16 healthy subjects. Pre-treatment fMRI scans revealed reduced activity of cognitive control regions (bilateral inferior and left superior frontal gyri, right insula, right fusiform gyrus and bilateral occipital gyri) and elevated activity of emotion-related processing regions (bilateral hippocampus, parahippocampal gyri and the left middle temporal gyrus) in the treatment group. Thus, aberrant cognitive and emotion processing that characterize acute episodes in bipolar disorder appear to persist during euthymic phase. Post-treatment clinical improvement was mediated by increased activity of inferior frontal gyri and a pattern of decreased activity of right hippocampus and parahippocampal gyrus. These findings suggest that psychoeducation improves cognitive control by engaging prefrontal networks and normalizes generation of emotional responses by quieting activity within limbic networks.

3.5 Cognitive remediation therapy and schizophrenia

Cognitive remediation therapy (CRT) is an evidence-based treatment for neuropsychological deficits in memory, attention, executive function, social cognition or metacognition across a host of neuropsychiatric disorders [67–69]. There is a growing literature focused on neurobiological changes that mediate cognitive recovery under this type of intervention in patients with schizophrenia [70–73], mood disorders [74], mild cognitive impairment [75] and in healthy adults [76]. Majority of studies examined the effects of cognitive remediation on brain functioning in patients with schizophrenia and have amounted to several systematic reviews and meta-analyses [76–78]. Findings lend support to the frontal hypoactivation mechanism of cognitive impairment and suggest that cognitive remediation improves these networks efficiency. Most commonly reported areas of post-treatment amelioration in efficiency involved prefrontal and thalamic regions. Meusel and collaborates [73] set out to describe functional correlates of cognitive remediation in patients with bipolar disorder or depression versus healthy controls. Thirty eight subjects completed 10 weeks of treatment and were scanned (fMRI) during an n-back working memory task and a recollection memory task to investigate the potential for change within these networks. PRE-POST improvements correlated with functional activation in lateral and medial prefrontal, superior temporal, and lateral parietal regions, suggesting neural correlates improved working memory under cognitive remediation.

4. Discussion

The predominant paradigm of modern psychiatry posits that advances in neurosciences can unravel the mysteries of mental illness. Since the 1990s were declared the decade of the brain, imaging evidence has taught us a great deal about neural correlates of symptoms expression and recovery from an insult to the brain [79]. Despite remarkable neuroscientific advances, specific mechanisms behind major mental illnesses, thus far, have not been identified [80]. Moreover, whilst neurotransmitters are known to mediate synaptic pathways, research has not yet

been able to explain any psychiatric disorder in terms of chemical imbalances [81]. Various reasons exist as to why neuroscience is unlikely to provide a definite understanding of the disordered mind. First and foremost, what is preventing the scientific strategy to reduce psychiatry to neuroscience is the fact that diagnoses listed in the Diagnostic and Statistical Manual of Mental Disorders' are not diseases but merely syndromes without a precise endophenotype [82]. Moreover, the pathways from temperamental vulnerabilities to illness cannot be understood without taking into account psychosocial adversities [83]. In this view, associations between biomarkers of pathological and treatment processes are unlikely to be strong or linear. Pharmacotherapy, whilst useful in severe mental disorders, it is not in any way curative, and psychosocial interventions continue to play an important role in psychiatric treatment, evoking multiple risk factors and complex interactive pathways to the disordered mind [84].

Research efforts in tandem with more powerful imaging techniques will further unravel the intricacy of cerebral organization behind pathological and treatment processes. Nonetheless, the scientific strategy to reduce psychiatry to neurosciences is hindered by a discrepancy between a clinical phenomenon and its neural substrate, which is rooted in a conceptual mind and brain gap.

5. Conclusion

Long before the era of functional neuroimaging it was suggested that intervention-driven changes in affect, cognition and behavior appear to have measurable biological analogues [85]. To date, the potential to characterize neural mechanisms of recovery processes have amassed vast neuroimaging data on treatment-induced brain plasticity. Pharmacotherapy and psychotherapy appear to engage neural circuits that are responsive to a discrete treatment modality. Although both have similar effects on brain activity patterns in patients who share the same diagnosis, their neural systems profile is not identical. While the former appears to act in a bottom- up manner on a subcortical level to regulate higher cortical structures, the latter acts top-down on cortical activity to subsequently impact subcortical regions. Although neuroimaging techniques have revolutionized our biological insight into recovery processes, little can be concluded about the precise neurobiological mechanism of these changes. The remaining question is whether these changes elucidate a neural mechanism of treatment action or simply reflect correlates of symptom amelioration. Despite methodological and theoretical limitations neuro-imaging literature holds promise to strengthen the credibility and utility of mainstay in psychiatric treatment, and to improve clinical decision-making.

Conflict of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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References

[1] Dougherty DD, Rauch SL, Rosenbaum JF. Essentials of Neuroimaging for Clinical Practice. Washington: American Psychiatric Association; 2004

[2] Fridriksson J, Morrow-Odom L, Moser D, Fridriksson A, Baylis G. Neural recruitment associated with anomia treatment in aphasia. NeuroImage. 2006;**32**(3):1403-1412

[3] Vetulani J, Sulser F. Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. Nature. 1975;**257**(5526):495-496. DOI: 10.1038/257495a0

[4] Cleare A, Pariante CM, Young AH. Evidence-based guidelinesfor treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology. 2015;**29**:459-525

[5] Bauer M, Bschor T, Pfennig A. For the WFSBP task force on unipolar depressive disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. The World Journal of Biological Psychiatry. 2007;**8**:67-104

[6] Cipriani A, Furukawa TA, Salanti G. Comparative efficacy and acceptability of 12 newgeneration antidepressants: A multiple-treatments meta-analysis. Lancet. 2009;**373**:746-758

[7] Ross SB, Renyi AL. Inhibition of the uptake of tritiated 5-hydroxytryptamine in brain tissue. European Journal of Pharmacology. 1969;**7**:270-277

[8] Beck AT. The evolution of the cognitive model of depression and its neurobiological correlates. American Journal of Psychiatry. 2008;**165**:969-977

[9] Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biological Psychiatry. 2003;**54**:515-528

[10] Ma Y. Neuropsychological mechanism underlying antidepressant effect: A systematic metaanalysis. Molecular Psychiatry. 2015;**20**:311-319

[11] Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. Increased positive versus affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. The American Journal of Psychiatry. 2004;**161**:1256-1263

[12] Norbury R, Mackay CE, Cowen PJ, Goodwin GM, Harmer CJ. Short-term antidepressant treatment and facial processing, Functional magnetic resonance imaging study. The British Journal of Psychiatry. 2007;**90**:531-532

[13] Godlewska BR, Norbury R, Selvaraj S, Cowen PJ, Harmer CJ. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychological Medicine. 2012;**42**:2609-2617

[14] Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. International Journal of Geriatric Psychiatry. 2014;**29**:1132-1139

[15] Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head to head comparisons of second-generation antipsychotics in the treatment of schizophrenia. The American Journal of Psychiatry. 2009;**166**:152-163

[16] Kendall T. The rise and fall of the atypical antipsychotics. The British Journal of Psychiatry. 2011;**199**:266-268

[17] Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D$_2$ occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. The American Journal of Psychiatry. 2000;**157**:514-520

[18] Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Archives of General Psychiatry. 2009;**66**(8):811-822

[19] Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: Mechanisms and meaning. Neuropsychopharmacology. 2011;**36**(1):316-338

[20] Lesh TA, Tanase C, Geib BR, et al. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. JAMA Psychiatry. 2015;**72**:226-234

[21] Meisenzahl EM, Scheuerecker J, Zipse M, et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: A functional MRI follow-up investigation. European Archives of Psychiatry and Clinical Neuroscience. 2006;**256**(8):522-531

[22] Jones HM, Brammer MJ, O'Toole M, et al. Cortical effects of quetiapine in first-episode schizophrenia: A preliminary functional magnetic resonance imaging study. Biological Psychiatry. 2004;**56**(12):938-942

[23] Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**(23):13432-13437

[24] Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. Biological Psychiatry. 2011;**70**(7):663-671

[25] van Berckel BN, Bossong MG, Boellaard R, et al. Microglia activation in recent-onset schizophrenia: A quantitative (R)-[11C]PK11195 positron emission tomography study. Biological Psychiatry. 2008;**64**(9):820-822

[26] Pasternak O, Westin CF, Bouix S, et al. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. The Journal of Neuroscience. 2012;**32**(48):17365-17372

[27] Goodwin GM. Evidence-based guidelines for treating bipolar disorder: Revised second edition—recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2009;**23**:346-388

[28] Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2009. Bipolar Disorders. 2009;**11**:225-255

[29] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. The World Journal of Biological Psychiatry. 2010;**11**:81-109

[30] Chisholm D, van Ommeren M, Ayuso-Mateos JL, Saxena S. Cost-effectiveness of clinical interventions for reducing the global burden of bipolar disorder. The British Journal of Psychiatry. 2005;**187**:559-567

[31] Green MJ, Cahill CM, Malhi GS. The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. Journal of Affective Disorders. 2007;**103**:29-42

[32] Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. The American Journal of Psychiatry. 2005;**162**:1697-1705

[33] Gabrieli S, Makris N, Laviolette P. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics. 2010;**153B**:120-131

[34] Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. The American Journal of Psychiatry. 2007;**164**:52-60

[35] Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, et al. Limbic hyper-activation during processing of neutral facial expressions in children with bipolar disorder. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:8900-8905

[36] Kronhaus DM, Lawrence NS, Williams AM, Frangou S, Brammer MJ, Williams SCR, et al. Stroop performance in bipolar disorder: Further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disorders. 2006;**8**:28-39

[37] Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, et al. Blunted activation in orbitofrontal cortex during mania: A functional magnetic resonance imaging study. Biological Psychiatry. 2005;**58**:763-769

[38] Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, et al. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biological Psychiatry. 2004;**55**:578-587

[39] Gruber SA, Rogowska J, Yurgelun-Todd DA. Decreased activation of the anterior cingulate in bipolar patients: An fMRI study. Journal of Affective Disorders. 2004;**82**:191-201

[40] Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, Strakowski SM. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disorders. 2004;**6**:540-549

[41] Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, et al. A functional magnetic resonance imaging study of bipolar disorder: State- and trait-related dysfunction in ventral prefrontal cortices. Archives of General Psychiatry. 2003;**60**:601-609

[42] Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology. 2005;**183**:308-313

[43] Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disorders. 2000;**2**:237-248

[44] Kandel ER. A new intellectual framework for psychiatry. American Journal of Psychiatry. 1998;**155**:457-469

[45] Beutel ME, Stern E, Silbersweig DA. The emerging dialogue between psychoanalysis and neuroscience: Neuroimaging perspectives. Journal of the American Psychoanalytic Association. 2003;**51**:773-801

[46] Ochsner K, Bunge SA, Gross JJ, Gabrieli JDE. Rethinking feelings: An fMRI study of the cognitive regulation of emotion. Journal of Cognitive Neuroscience. 2012;**14**:1215-1229

[47] Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical-limbic pathways in major depression: Treatment specific effects of cognitive behav ioral therapy. Archives of General Psychiatry. 2004;**61**:34-41

[48] Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple KK, Kennedy S, Segal Z, et al. Limbic-frontal circuitry in major depression: A path modeling metanalysis. NeuroImage. 2004;**22**:409-418

[49] Paquette V, Levesque J, Mensour B, Leroux JM, Beaudoin G, Bourgouin P, et al. 'Change the mind and you change the brain': Effects of cognitive-behavioral therapy on the neural correlates of spider phobia. NeuroImage. 2003;**18**:401-409

[50] Oldham JM. Borderline personality disorder and suicidality. The American Journal of Psychiatry. 2006;**163**(1):20-26

[51] Linehan MM, Comtois KA, Murray AM. Two year randomised controlled trial and follow-up versus treatment by experts for suicidal behaviours and borderline personality disorder. Archives of General Psychiatry. 2006;**63**(7):757-766

[52] Lynch WT, Trost N, Salsman N, Linehan MM. Dialectical behavior therapy for borderline personality disorder. Annual Review of Clinical Psychology. 2007;**3**(1):181-205

[53] Schmitt R, Winter D, Niedtfeld I, Herpertz SC, Schmahl C. Effects of psychotherapy on neuronal correlates of reappraisal in female patients with borderline personality disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2016;**1**(6):548-557

[54] Winter D, Niedtfeld I, Schmitt R, Bohus M, Schmahl C, Herpertz SC. Neural correlates of distraction in borderline personality disorder before and after dialectical behavior therapy. European Archives of Psychiatry and Clinical Neuroscience. 2016;**267**(1):51-62

[55] Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. Biological Psychiatry. 2016;**79**(2):97-106

[56] Martin SD, Martin RMN, Rai SS, Richardson MA, Royall R, Eng IEE. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: Preliminary findings. Archives of General Psychiatry. 2001;**58**:641-648

[57] Brody AL, Saxena S, Stoessel P, Gillies LA, Fairbanks LA, Alborzian S, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: Preliminary findings. Archives of General Psychiatry. 2001a;**58**:631-640

[58] Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biological Psychiatry. 2001b;**50**:171-178

[59] Tohen M, Hennen J, Zarate CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. American Journal of Psychiatry. 2000;**157**:220-228

[60] Swartz HA, Frank E. Psychotherapy for bipolar depression: A phase-specific treatment strategy? Bipolar Disorders. 2001;**3**:11-22

[61] Zaretsky A. Targeted psychosocial interventions for bipolar disorder. Bipolar Disorders. 2003;**5**:80-87

[62] Colom F, Vieta E. A perspective on the use of psychoeducation, cognitive behavioral therapy and interpersonal therapy for bipolar patients. Bipolar Disorders. 2004;**6**:480-486

[63] Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: State of the evidence. The American Journal of Psychiatry. 2008;**165**:1408

[64] Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. British Medical Journal. 1999;**318**:149-153

[65] Colom F, Vieta E, Reinares M, Martínez-Arán A, Torrent C, Goikolea JM, et al. Psychoeducation efficacy in bipolar disorders: Beyond compliance enhancement. Journal of Clinical Psychiatry. 2003b;**64**:1101

[66] Favre S, Aubry JM, Gex-Fabry M, Ragama-Pardos E, McQuillan A, Bertschy G. Translation and validation of a french version of the young mania rating scale. L'Encéphale. 2003;**29**:499

[67] Grynszpan O, Perbal S, Pelissolo A, Fossati P, Jouvent R, Dubal S, et al. 2011. Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: A meta-analytical study. Psychological Medicine. 2011;**41**:163-173

[68] Naismith SL, Redoblado-Hodge MA, Lewis SJG, Scott EM, Hickie IB. Cognitive training in affective disorders improves memory: A preliminary study using the NEAR approach. Journal of Affective Disorders. 2010;**121**:258-262

[69] McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A metaanalysis of cognitive remediation in schizophrenia. American Journal of Psychiatry. 2007;**164**:1791-1802

[70] Penadés R, Pujol N, Catalán R, Massana G, Rametti G, García-Rizo C, et al. Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. Biological Psychiatry. 2013;**73**(10): 1015-1023

[71] Bor J, Brunelin J, d'Amato T, Costes N, Suaud-Chagny MF, Saoud M, et al. How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. Psychiatry Research. 2011;**192**(3):160-166. DOI: 10.1016/j. pscychresns. 2010. 12. 004

[72] Wexler BE, Anderson M, Fulbright RK, Gore J. Preliminary evidence of improved verbal working memory performance and normalization of taskrelated frontal lobe activation in schizophrenia following cognitive exercises. The American Journal of Psychiatry. 2000;**157**:1694-1697

[73] Meusel LA, Hall GB, Fougere P, McKinnon MC, MacQueen GM. Neural correlates of cognitive remediation in patients with mood disorders. Psychiatry Research. 2013;**214**(2):142-152. DOI: 10.1016/j. pscychresns.2013.06.007

[74] Rosen AC, Sugiura L, Kramer JH, Whitfield-Gabrieli S, Gabrieli JD. Cognitive training changes hippocampal function in mild cognitive impairment:

A pilot study. Journal of Alzheimer's Disease. 2011;**26**(Suppl. 3):349-357

[75] Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the emotional brain: Improving affective control through emotional working memory training. Journal of Neuroscience. 2013;**33**:5301-5311

[76] Thorsen A, Johansson K, Løberg EM. Neurobiology of cognitive remediation therapy for schizophrenia: A systematic review. Frontiers in Psychiatry. 2014;**5**:103. DOI: 10.3389/fpsyt.2014.00103

[77] Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: A systematic review of randomized trials. Socioaffective Neuroscience & Psychology. 2016;**6**:30054

[78] Kurtz MM, Gerraty R. A meta-analytic investigation of neurocognitive deficits in bipolar illness: Profile and effects of clinical state. Neuropsychology. 2009;**23**:551-562

[79] Compston A. Decade of the brain. Brain. 2005;**128**:1741-1742

[80] Nemeroff CB, Kilts CD, Berns GS. Functional brain imaging: Twenty-first century phrenology or psychobiological advance for the millennium? The American Journal of Psychiatry. 1999;**15**:671-673

[81] Valenstein E. Blaming the Brain: The Truth About Drugs and Mental Health. New York (NY): Free Press; 1998

[82] Kendler KS, Prescott CA. Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders. New York (NY): Guilford Press; 2006

[83] Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science. 2003;**301**:386-389

[84] Paris J. Prescriptions for the Mind: A Critical View of Contemporary Psychiatry. New York (NY): Oxford University Press; 2008

[85] Freud S. Project for a Scientific Psychology. The Standard Edition of the Complete Psychological Works of Sigmund Freud. London: Hogarth Press; 1895. pp. 283-397