ARTICLE

Neuroplasticity and outcome in schizophrenia: the role of psychological interventions

Ravi Philip Rajkumar

Assistant Professor, Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

Abstract

Perhaps the best way to consider schizophrenia is as a progressive neurodevelopmental disorder, in which events at various stages in life, from the antenatal period to adolescence, have their effects on the brain. There is already substantial evidence for the notion that the abnormal brain connectivity in schizophrenia may be related to synaptic plasticity. Various forms of psychological intervention, including cognitive-behaviour therapy (CBT), can positively alter not just the symptoms of schizophrenia, but its long-term course. Though medications form an integral part of most treatment guidelines, there is a growing realisation that psychological therapies do "work", at least for certain specific symptoms. Firm recommendations are also made regarding five kinds of specific psychological intervention for schizophrenia *per se*: supported employment, skills training, CBT, token economy-based interventions and family-based interventions. In future guidelines, cognitive remediation may join these five approaches. Since schizophrenia is a disorder that affects several aspects of functioning, it is logical to expect that targeting more than one domain could lead to a better outcome. While it is too early to speak of "preventing schizophrenia" through psychological interventions that target neuroplasticity, it is too early to write off this possibility either. Perhaps we need to stop thinking of "schizophrenia" as a monolithic entity. Instead, we should study it in terms of its constituent syndromes and dimensions.

Rajkumar RP. Neuroplasticity and outcome in schizophrenia: the role of psychological interventions. Dysphrenia. 2013;4:89-96

Keywords: Duration of untreated psychosis. Progressive neurodevelopmental disorder. Negative expressed emotion. Cognitive remediation. Neuropil. Prevention. Neuroprotection.

Correspondence: ravi.psych@gmail.com

Received on 27 November 2012. Accepted on 7 December 2012.

Introduction

Schizophrenia is a major mental disorder, characterised by widespread disturbances in cognition, emotion and behaviour. It affects about 0.5% of the world's population.[1] Though there are wide variations across countries, studies have shown that around 42-79% of patients with this disorder have an unfavourable outcome, regardless of treatment.[2,3] At a clinical level, two sets of symptoms have been shown to correlate strongly with outcome in this illness: *negative symptoms*, such as impaired motivation and socialisation,[4] and *cognitive symptoms*, such as impaired motor speed, attention and executive functions.[5,6] There is some evidence that the initial phase of schizophrenia (the first three to ten years) is associated with a period of deterioration in these aspects of functioning.[7,8]

More recent research has found a fairly strong negative association between the duration of untreated psychosis (DUP) and the outcome of schizophrenia,[9-11] even in patients who were diagnosed and treated late.[9] A shorter DUP was associated with a better overall response to drug treatment.[11] Various explanations have been sought for these findings. For example, it has been suggested that the association with DUP could be due to confounding factors, such as an insidious onset or poor social support, which themselves predict a poor outcome.[12] Another possibility is that schizophrenia is associated with accelerated ageing.[13,14] Others have suggested that these findings are mediated by the neuroendocrine effects of stress, particularly distal stressors such as childhood abuse.[15] All these theories, though speculative, point to one basic fact: the findings on DUP are hard to reconcile with the most widely accepted contemporary model of schizophrenia, the neurodevelopmental model, which relates the illness to early genetic and environmental insults affecting brain development.[16,17]

This difficulty has led some authors to postulate that there are neurodegenerative processes, as well as developmental ones, involved in the pathogenesis of schizophrenia. According to this view, prolonged psychosis can lead to neuronal loss in the adult brains, through such mechanisms as excitotoxicity and apoptosis.[18] This viewpoint explains many of the puzzling findings related to DUP in schizophrenia, but is

not entirely consistent with evidence from brain imaging and neuropsychological studies.[19,20] Perhaps the best way to explain all these findings is to consider schizophrenia a progressive neurodevelopmental disorder,[21] in which events at various stages in life, from the antenatal period to adolescence, have their effects on the brain.[21,22] The apparent "degenerative" changes seen in patients can then be understood as the result of dynamic, and potentially reversible, changes in brain structure and function.[20,22]

Neuroplasticity as the explanation for apparent "degeneration"

A key idea in making the link between "neurodevelopmental" and apparently "neurodegenerative" processes in schizophrenia is the concept of synaptic plasticity or neuroplasticity.[20] In broad terms, "synaptic plasticity" refers to changes in the strength of connectivity between neurons, which are mediated by current and past activity.[23] The earliest systematic view of synaptic plasticity is Hebb's rule: "when an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as one of the cells firing B, is increased."[24] Hebb's rule has been proved by subsequent elegant work in the laboratory,[25] and has profound implications, not just in neurological or mental disorders, but in understanding the normal processes of learning and memory.[26,27] At a structural level, changes in synaptic plasticity can alter the level of synaptic syncytium or neuropil, between neurons[20,28] which could account for some of the findings of volume loss in the brains of adult patients with schizophrenia.[20,21] As McGlashan[20] suggests, persistent psychotic phenomena – such as a delusional belief that a patient is intensely preoccupied with, to the exclusion of other experiences – could, in the long run, lead to "content-driven alterations" in synaptic strength and in the structure and functioning of particular brain circuits.

It is true that the general concept of "impaired synaptic plasticity" is probably too broad to have any specificity for a particular disorder, such as schizophrenia. Indeed, such concepts have been applied to a variety of psychiatric disorders, including major depression[29] and bipolar disorder.[30] However, there is already substantial evidence for the notion that the abnormal brain connectivity in schizophrenia may be related to synaptic plasticity.[31] What I am proposing here is not a "synaptic plasticity model of schizophrenia", but a model through which the normal process of synaptic plasticity can be used to shed light on many of the unanswered questions related to this disorder. Thus, early neurodevelopmental processes retain their rightful place, but the concept of plasticity can be invoked at various stages in the course of the illness, to explain the impact that various events have on the symptoms, course and outcome of schizophrenia. As a starting point, we can address two of the issues raised above:

A. The relationship between DUP and treatment response can be understood as a measure of how far psychotic symptoms, such as delusions and hallucinations, have had a chance to alter neuronal connectivity. Thus, as already mentioned above, a persistent delusion may "crowd out" other important information[20] and reduce the opportunity for learning, leading to a vicious cycle in which delusional experiences, attributions and elaborations are "strengthened" at a neural level, at the expense of "real-world" experience. This would explain why, in an illness with short DUP, symptoms are more amenable to treatment – in fact, one of the proposed mechanisms of action of antipsychotics is a "dampening of the salience" attached to particular aberrant experiences.[32] This would also explain how early treatment – by reducing the unwanted changes in neural plasticity caused by such symptoms – could lead to a better long-term outcome.

B. The association between schizophrenic symptoms and life events – both current stressors and distal events such as child abuse – could be understood in terms of the effect that these events have on brain plasticity. Chronic stressors are associated with abnormal activation of the hypothalamic-pituitary-adrenal (HPA) axis, which has potentially negative effects on neural plasticity, such as reduced long-term potentiation and decreased levels of neurotrophic factors.[33] This would lead to persistence or worsening of existing symptoms. Similarly, early childhood adversities could sensitise this system,[34] leading to a worse outcome when compared to patients who have not experienced them.

Clinical implications of altered neuroplasticity in schizophrenia

These examples suggest ways in which the concept of neuronal plasticity can be used to illuminate our existing theoretical and clinical knowledge of schizophrenia. However, these considerations also raise an exciting possibility: if some (or even all) of the "chronicity" of schizophrenia is related to alterations in synaptic plasticity, then it might be possible to arrest or even reverse these changes through appropriate interventions. We can already infer – from the DUP data outlined above – that the early initiation of appropriate pharmacotherapy is one such intervention. While antipsychotics do not "cure" schizophrenia, what they do achieve – according to van der Gaag's model[35] - is a "detachment" from aberrantly salient phenomena, which could lead to a restructuring or even a resolution of

delusions. At the level of the brain, such changes must be reflected in altered neural "wiring" – in other words, with a positive change in synaptic plasticity. van der Gaag, however, goes on to suggest that changes in neural wiring may also underlie the effects of psychological interventions, such as cognitive-behaviour therapy (CBT), in schizophrenia. This is a logical conclusion and it leads us to consider that various forms of psychological intervention, including CBT, can positively alter not just the symptoms of schizophrenia, but its long-term course. In the next part of this paper, I shall review converging lines of evidence from various fields of research, in order to support this hypothesis and develop some of its implications.

Psychotherapy as a learning process: the role of neuroplasticity

One of the remarkable discoveries of modern psychiatry has been the finding that psychological interventions, such as cognitive and behavioural therapies, produce well-defined changes in brain functioning. This effect has been documented in various disorders, including major depression[36] and anxiety disorders,[37] and is remarkably similar to the brain changes produced by medication in these conditions. This is not to imply that medications and psychotherapy have an identical or even a common mechanism of action. Instead, it is consistent with a model in which interventions at various levels can share beneficial effects. Indeed, medication can be thought of as a "bottom-up" intervention that changes behaviour through alterations in brain transmission, while psychological therapies are "top-down" interventions that relieve symptoms through higher-order learning processes.[35] Other physiological effects of psychotherapy, such as changes in neurotransmitter[38] and neuroendocrine[39] functioning, have also been documented. All these physical changes must be mediated, in some way or the other, through the brain, since the brain is the "point of contact" of psychotherapy with the body. Indeed, some authors have found structural brain changes in patients treated with psychotherapy,[40] which may again relate to increases in synaptic syncytium.

A simple way of understanding these processes is to view psychotherapy as a process of learning. Regardless of theoretical orientation, almost all psychotherapies involve interaction between a therapist and a patient, and a transfer and reappraisal of experience, information, attitudes and skills. All these are processed by the brain in the same way as "normal" experiences, and are stored as memories – a process that involves changes in synaptic strength and connectivity between neurons.[25,27] In other words, the changes associated with psychotherapy can be best understood as a special case of Hebb's rule as applied to the learning process. While the finer details may vary according to the type of therapy adopted (for example, psychodynamic versus cognitive-behavioural), the fundamental principle – that psychotherapy produces long-term changes in neuroplasticity – still stands. This explanation is consistent with both basic and clinical research[41] and provides what Kandel has termed "a new intellectual framework" in which the complexity of mind-brain, biological-psychological interactions can be truly appreciated and studied. Just as earlier learning or experience can leave its mark on the brain, new learning opportunities and approaches – which most psychotherapies provide – can reduce or even overcome pathological experiences and phenomena.[42] And if the "content-driven alterations" seen in schizophrenia can be understood as abnormal learned experiences, they should be amenable, at least in part, to correction through appropriate psychological interventions.

Efficacy of psychological interventions in schizophrenia

Let us now consider the current status of psychological interventions in schizophrenia, as a reasonable starting-point from which we can consider further advances. Though medications form an integral part of most treatment guidelines, there is a growing realisation that psychological therapies do "work", at least for certain specific symptoms. The most recent Patient Outcomes Research Team (PORT) guidelines for schizophrenia,[43] after reviewing the available evidence, have made eight recommendations for psychosocial intervention. Some of these relate to service delivery (such as "assertive community treatment") and others are related to the management of comorbid conditions, such as substance abuse or weight gain. However, firm recommendations are also made regarding five kinds of specific psychological intervention for schizophrenia *per se*: supported employment, skills training, CBT, token economy-based interventions and family-based interventions. These are summarised in the table next page.

What is interesting about these approaches is that all of them – particularly the first four, which are targeted at individuals – can all be understood as learning experiences that act through a mechanism of neural plasticity. The first two involve the teaching of skills and behaviours that enable a patient with chronic schizophrenia to function better and provide opportunities for rehearsal and practice. The third, CBT, is more specifically directed at the "content-driven alterations" and "abnormal salience" of psychotic experiences. And finally, token economy systems are based on principles of social learning and operant conditioning: They prevent the patient from "settling into" maladaptive patterns of behaviour in an institutional setting and encourage desired behaviours. Since these learning processes are likely to take time, they are best administered as medium- or long-term interventions.

Table. Recommended psychosocial interventions for schizophrenia (PORT guidelines, 2009)[43]

Intervention	Techniques involved	Intended patient group
Supported employment	Job development, job search, ongoing support, and integration with mental health services, all tailored to the needs of the individual patient.	All patients with schizophrenia for whom employment is a goal.
Skills training	Interpersonal skills training based on behavioural methods, such as instruction, modelling, rehearsal, feedback and positive reinforcement	All patients with schizophrenia who have deficits in "everyday skills"
Cognitive-behavioural therapy (CBT)	Four to nine months of CBT in combination with medication; individual or group setting; identification of target symptoms and development of specific CBT strategies	Patients with schizophrenia experiencing persistent psychotic symptoms despite adequate pharmacotherapy
Token economy	Behavioural intervention involving positive reinforcement, individualised treatment and avoidance of punishment; based on social learning principles	Patients with schizophrenia staying in long-term, in-patient residential facilities
Family-based services	Six to nine months of psychoeducation, crisis intervention, emotional support and learning to deal with symptoms	All patients with schizophrenia who have ongoing contact with their families

The fifth intervention in our table, family therapy, is also of key importance from this point of view. A large body of research work has now shown, beyond reasonable doubt, that family attitudes towards the patient can critically influence the course of schizophrenia. In particular, negative emotional attitudes such as criticality, hostility and overinvolvement – collectively called *negative expressed emotions (EE)* – have been linked with relapse in patients with schizophrenia, especially in those with a chronic illness.[44] These negative attitudes, which are perceived as stressful by patients,[45] can actually worsen psychotic symptoms, and this worsening is most marked in patients with impaired working memory[46] – an example of the way in which external stress and pre-existing cognitive deficits can interact in the real world. Effective family interventions, which reduce the negative emotional tone of interactions between the patient and his caregivers, can minimise this stress – a factor that is known to adversely affect neural plasticity[33] – and hasten the process of recovery. It may also be possible to improve cognitive functions in schizophrenia by a process of retraining, as discussed below, and such training could enhance a patient's ability to cope with the "stresses of everyday life" without experiencing a relapse.

It is clear – at least if we go by PORT's evaluation of the evidence – that all these treatments work, and that they all have a major role to play in the long-term treatment of schizophrenia. In recent years, evidence has also been accumulating in favour of *cognitive remediation*, a treatment method in which patients receive computer- or pencil-and-paper-based training in basic cognitive skills, such as memory, concentration and problem-solving. Since cognitive deficits are associated with poorer functioning,[5,6] it would be expected that such remediation would improve overall functioning. A meta-analysis of this treatment approach[47] has found that it had a moderate effect in improving both cognition and psychosocial functioning, and also brought about a slight improvement in psychotic symptoms. This suggests that, in future guidelines, cognitive remediation may join the five approaches discussed above. However, we must now look one level deeper, and ask: is there any evidence that these treatments (a) actually alter brain function or (b) modify brain structure, in patients with schizophrenia?

Psychological interventions and changes in brain function in schizophrenia

Results from two studies strongly support the first of these notions, and provide evidence for the possibility of enhancing neural plasticity in patients with schizophrenia through training. In the first of these,[48] patients with chronic schizophrenia (n=six) were given 40 sessions of cognitive training, on a variety of tasks related to cognitive flexibility and different subtypes of memory, over a period of 12 weeks. They were compared to a healthy control group (n=six) as well as a group of patients with schizophrenia who received "non-specific" interventions, such as keeping a diary and relaxation (n=six). At the end of this period, three of the patients in the study group showed significant improvements in

memory. Functional magnetic resonance imaging (fMRI) of the subjects during a memory task found increased activation of the right inferior frontal gyrus in those receiving cognitive training compared to controls. Those receiving "non-specific" interventions showed reduced activation of this area, a well-documented phenomenon in schizophrenia.

In the second study,[49] patients with chronic schizophrenia were divided into two groups. One group (n=ten) received cognitive remediation and another (n=11) received social skills training. A comparable group of healthy adults (n=nine) served as controls. All subjects were scanned twice, using fMRI at an interval of six to eight weeks. Patients receiving cognitive remediation showed significant increases in activation in various brain structures, including the dorsolateral prefrontal cortex, anterior cingulate gyrus and frontopolar cortex – all of which are involved in the processes of attention and memory. The degree of activation in these areas was strongly related with improved performance on memory tasks and these changes were not seen in the other two groups.

Both these studies involved small numbers of patients and we must be careful in generalising from them. However, they do suggest that repeated cognitive training can cause increased functioning of key brain areas, even in patients with chronic schizophrenia. These increases are best understood as resulting from a strengthening of synaptic connectivity due to repeated activity. While there is not enough data to correlate these brain changes with general improvements in symptoms or functioning, studies in larger samples of patients will provide an answer to this question, and could help to further clarify the factors associated with improved neural plasticity following cognitive training.

Psychological interventions and structural brain changes in schizophrenia

We have earlier looked at the possibility that the structural brain changes seen in adults with schizophrenia, including volume loss in various areas, may reflect a reduction in neural plasticity – a sort of neural "disuse atrophy" of particular structures[20] – rather than a degenerative process. If this were the case, then interventions aimed at enhancing neural plasticity could potentially arrest, or even reverse, the reduction in volume seen in various brain structures over time in these patients. While there are obvious methodological problems involved in testing this hypothesis, the results of a recent trial suggest that this can and does happen in some patients. In this study,[50] 53 patients with a relatively short duration of psychosis (mean 3.22 years) were randomised to receive either cognitive enhancement therapy (CET, n=30) or enriched supportive therapy (EST, n=23) and followed up over two years, with annual structural brain imaging. CET addressed attention, concentration and memory (60 weekly sessions of computer-based training) as well as social cognition (45 weekly sessions of training). EST focused on education about the illness and strengthening coping skills.

At the end of two years, patients receiving CET showed significantly less grey matter volume loss in several key brain areas compared to those receiving EST. These areas included the left parahippocampal gyrus (involved in memory), the left fusiform gyrus (involved in the perception of faces), both anterior cingulate cortices (involved in attention, memory and error monitoring) and the right insula. Patients receiving CET also showed increased volume of the left amygdala, a structure involved in emotion recognition and emotional response, while those receiving EST showed no such changes. The reduction in volume loss in the CET group was significantly correlated with improvements in cognitive functioning.

The authors have used the term "neuroprotection" to describe their findings, but – as discussed earlier – an equally valid way of interpreting these results is to view them as due to improved neural plasticity, leading to increased neuropil and the prevention of schizophrenia-related reductions in plasticity ("disuse atrophy"). This is supported by the elegant correspondence between the tasks that formed part of CET and the brain areas that showed the most positive changes. These results are of great importance to our hypothesis, because they suggest that training may actually reverse or attenuate the "progression" of schizophrenia at a neural level.

Multimodal interventions for neural plasticity

The studies mentioned above, though encouraging, are limited in that they all deal with cognitive retraining in its various forms; only the third study[50] specifically included social cognition as part of its training package. While cognitive retraining is a valuable approach to enhancing neural plasticity, it must be remembered that its effects on functioning and symptoms are modest,[47] and that it targets only one of the many symptom domains of schizophrenia.

The neural effects of other forms of psychological intervention, including the five mentioned in PORT but potentially extending to others as well, still await investigation. However, since schizophrenia is a disorder that affects several aspects of functioning, it is logical to expect that targeting more than one domain could lead to a better outcome. This is already implicit in the more positive findings of the third trial discussed above, which addressed both basic and social cognitive skills. Such an approach, in which various evidence-based psychological treatments are combined to produce an optimal outcome,

is already being practiced in some centres under the name of integrated psychological therapy (IPT).[51] Another fruitful line of investigation would be studying the optimal balance between pharmacological and psychological treatments for schizophrenia, and the interactions between them.[52]

Finally, it must be remembered that learning processes need not involve a formal "therapy" session. There is evidence from studies in healthy humans that several forms of activity – including playing a musical instrument[53] and certain forms of meditation[54] – can promote neural plasticity and connectivity between distinct brain regions. Consistent with this, a small single-blind trial[55] has shown that four months of yoga can improve negative and depressive symptoms and enhance psychological quality of life in patients with chronic schizophrenia. Similarly, a trial of occupational therapy[56] found evidence of benefit even in highly resistant patients who were receiving clozapine. It is not yet clear how these and other "plasticity-enhancing" activities, such as physical exercise or art, could be incorporated into the treatment of patients with schizophrenia. However, they do hold out the possibility that there is more to psychological interventions than "therapy" alone, and that a broad spectrum of "neural plasticity promoters", tailored to the needs of individual patients, may act synergistically and beneficially. Such approaches could be incorporated into an "integrated psychological treatment" model without too much difficulty.

Neuroplasticity and the prevention of schizophrenia

Can we go even further? We now know that psychological interventions can reduce positive,[57] negative[58] and cognitive[47] symptoms of schizophrenia – and that these improvements are all probably mediated through neuroplasticity-based effects. Is it possible that psychological interventions, administered at an early stage, can enhance neural plasticity and thereby prevent "high-risk" individuals from progressing to "full-blown" schizophrenia? Such "high-risk" individuals include those experiencing schizophrenic symptoms in attenuated form or first-degree relatives of patients with schizophrenia who experience a sudden decline in functioning.[59] A number of groups have investigated this possibility, making use of either medications, psychological interventions or both.[60,61] While results have been inconsistent and have resulted in criticism,[62] there is some evidence[63] that an integrated treatment approach – incorporating social skills training and family intervention – has advantages over "standard" treatment in patients with a first episode of psychosis. While it is too early to speak of "preventing schizophrenia" through psychological interventions that target neuroplasticity, it is too early to write off this possibility either.

Conclusions: looking forward

In an article on the likely future of psychotherapy for schizophrenia, Spaulding and Nolting[64] review various evidence-based psychotherapies, and consider how these could evolve over the next two decades. Among the key issues they raise are: the need to match psychological treatment with illness stage; the need for scientific validity, including quantitative and animal-based models; the need to look beyond "schizophrenia" as a unitary entity; the need for an integrative model that uses different techniques at different steps; and the use of psychodynamic and "non-specific" principles common to most therapies. All these are important, and will remain so as psychological treatments for this complex disorder continue to grow and develop. To these could be added the key concept of neural plasticity, its implications for the course and progression of schizophrenia, and its potential "modifiability" by various forms of psychological intervention. Perhaps we need to stop thinking of "schizophrenia" as a monolithic entity, since no two patients with "schizophrenia" are alike. Instead, we should study it in terms of its constituent syndromes and dimensions – as well as the patient's psychological and social background - and choose the right combination of cognitive, behavioural, skill-based, family-based, milieu-based and other approaches in tackling the problems faced by an individual patient. It is not unrealistic to speak of the need for a psychological formulation in these patients, akin to the "psychodynamic formulation" used by therapists,[65] which would take into account biological and psychosocial factors and would serve as the basis for an integrated treatment plan. "Neuroprotection refers to treatments that aim to prevent or slow disease progression and secondary injuries by halting or slowing the loss of neurons".[66] Further work linking the basic science of neuroplasticity to its role in schizophrenia and its implications for the success of therapy would ensure better long-term outcomes for patients – and would deepen our understanding of schizophrenia itself

References

1. Bhugra D. The global prevalence of schizophrenia. PLoS Med. 2005;2:e151.

2. Jobe TH, Harrow M. Long-term outcome of patients with schizophrenia: a review. Can J Psychiatry. 2005;50:892-900.

3. Hopper K, Wanderling J. Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: results from ISoS, the WHO collaborative followup project. International Study of Schizophrenia. Schizophr Bull. 2000;26:835-46.

4. Möller HJ, Bottlender R, Wegner U, Wittmann J, Strauss A. Long-term course of schizophrenic, affective and schizoaffective psychosis: focus on negative symptoms and

their impact on global indicators of outcome. Acta Psychiatr Scand Suppl. 2000;(407):54-7.

5. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. Am J Psychiatry. 2006;163:418-25.

6. Gråwe RW, Levander S. Neuropsychological impairments in patients with schizophrenia: stability and prediction of outcome. Acta Psychiatr Scand Suppl. 2001;(408):60-4.

7. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. Schizophr Bull. 1988;14:515-42.

8. McGlashan TH, Fenton WS. Subtype progression and pathophysiologic deterioration in early schizophrenia. Schizophr Bull. 1993;19:71-84.

9. Tirupati NS, Rangaswamy T, Raman P. Duration of untreated psychosis and treatment outcome in schizophrenia patients untreated for many years. Aust N Z J Psychiatry. 2004;38:339-43.

10. Oosthuizen P, Emsley RA, Keyter N, Niehaus DJ, Koen L. Duration of untreated psychosis and outcome in first-episode psychosis. Perspective from a developing country. Acta Psychiatr Scand. 2005;111:214-9.

11. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005;162:1785-804.

12. Owens DC, Johnstone EC, Miller P, Macmillan JF, Crow TJ. Duration of untreated illness and outcome in schizophrenia: test of predictions in relation to relapse risk. Br J Psychiatry. 2010;196:296-301.

13. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? Schizophr Bull. 2008;34:1024-32.

14. Fernandez-Egea E, García-Rizo C, Miller B, Parellada E, Justicia A, Bernardo M, *et al*. Testosterone in newly diagnosed, antipsychotic-naive men with nonaffective psychosis: a test of the accelerated aging hypothesis. Psychosom Med. 2011;73:643-7.

15. Read J, Perry BD, Moskowitz A, Connolly J. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry. 2001;64:319-45.

16. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2000;12:501-27.

17. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 2005;10:434-49.

18. Pérez-Neri I, Ramírez-Bermúdez J, Montes S, Ríos C. Possible mechanisms of neurodegeneration in schizophrenia. Neurochem Res. 2006;31:1279-94.

19. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? Arch Gen Psychiatry. 2002;59:553-8.

20. McGlashan TH. Is active psychosis neurotoxic? Schizophr Bull. 2006;32:609-13.

21. de Haan L, Bakker JM. Overview of neuropathological theories of schizophrenia: from degeneration to progressive developmental disorder. Psychopathology. 2004;37:1-7.

22. Pantelis C, Yücel M, Wood SJ, McGorry PD, Velakoulis D. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust N Z J Psychiatry. 2003;37:399-406.

23. Jeffery KJ, Reid IC. Modifiable neuronal connections: an overview for psychiatrists. Am J Psychiatry. 1997;154:156-64.

24. Hebb DO. The organization of behavior. New York: John Wiley and Sons; 1949.

25. Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. Science. 2001;294:1030-8.

26. Green CS, Bavelier D. Exercising your brain: a review of human brain plasticity and training-induced learning. Psychol Aging. 2008;23:692-701.

27. Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci U S A. 1994;91:7041-5.

28. Cline HT. Topographic maps: developing roles of synaptic plasticity. Curr Biol. 1998;8:R836-9.

29. Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol. 2009;12:561-78.

30. Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology. 2008;33:110-33.

31. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry. 2006;59:929-39.

32. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003;160:13-23.

33. Corcoran C, Walker E, Huot R, Mittal V, Tessner K, Kestler L, *et al*. The stress cascade and schizophrenia: etiology and onset. Schizophr Bull. 2003;29:671-92.

34. Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr Scand. 2005;112:330-50.

35. van der Gaag M. A neuropsychiatric model of biological and psychological processes in the remission of delusions and auditory hallucinations. Schizophr Bull. 2006;32 Suppl 1:S113-22.

36. 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. Arch Gen Psychiatry. 2001;58:631-40.

37. Furmark T, Tillfors M, Marteinsdottir I, Fischer H, Pissiota A, Långström B, Fredrikson M. Common changes in cerebral blood flow in patients with social phobia treated

with citalopram or cognitive-behavioral therapy. Arch Gen Psychiatry. 2002;59:425-33.

38. Lehto SM, Tolmunen T, Joensuu M, Saarinen PI, Valkonen-Korhonen M, Vanninen R, *et al*. Changes in midbrain serotonin transporter availability in atypically depressed subjects after one year of psychotherapy. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:229-37.

39. Olff M, de Vries GJ, Güzelcan Y, Assies J, Gersons BP. Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD. Psychoneuroendocrinology. 2007;32:619-26.

40. de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, *et al*. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. Brain. 2008;131:2172-80.

41. Liggan DY, Kay J. Some neurobiological aspects of psychotherapy. A review. J Psychother Pract Res. 1999;8:103-14.

42. Kandel ER. Biology and the future of psychoanalysis: a new intellectual framework for psychiatry revisited. Am J Psychiatry. 1999;156:505-24.

43. Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, *et al*.; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull. 2010;36:48-70.

44. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry. 1998;55:547-52.

45. Cutting LP, Docherty NM. Schizophrenia outpatients' perceptions of their parents: is expressed emotion a factor? J Abnorm Psychol. 2000;109:266-72.

46. Rosenfarb IS, Nuechterlein KH, Goldstein MJ, Subotnik KL. Neurocognitive vulnerability, interpersonal criticism, and the emergence of unusual thinking by schizophrenic patients during family transactions. Arch Gen Psychiatry. 2000;57:1174-9.

47. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry. 2007;164:1791-802.

48. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, *et al*. Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. Br J Psychiatry. 2002;181:144-52.

49. Haut KM, Lim KO, MacDonald A 3rd. Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: effects of practice, generalization, and specificity. Neuropsychopharmacology. 2010;35:1850-9.

50. Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, Hogarty SS, *et al*. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch Gen Psychiatry. 2010;67:674-82.

51. Mueller DR, Roder V. Integrated psychological therapy for schizophrenia patients. Expert Rev Neurother. 2007;7:1-3.

52. Lenroot R, Bustillo JR, Lauriello J, Keith SJ. Integrated treatment of schizophrenia. Psychiatr Serv. 2003;54:1499-507.

53. Wan CY, Schlaug G. Music making as a tool for promoting brain plasticity across the life span. Neuroscientist. 2010;16:566-77.

54. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, *et al*. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 2011;191:36-43.

55. Duraiswamy G, Thirthalli J, Nagendra HR, Gangadhar BN. Yoga therapy as an add-on treatment in the management of patients with schizophrenia--a randomized controlled trial. Acta Psychiatr Scand. 2007;116:226-32.

56. Buchain PC, Vizzotto AD, Henna Neto J, Elkis H. Randomized controlled trial of occupational therapy in patients with treatment-resistant schizophrenia. Rev Bras Psiquiatr. 2003;25:26-30.

57. Rathod S, Kingdon D, Weiden P, Turkington D. Cognitive-behavioral therapy for medication-resistant schizophrenia: a review. J Psychiatr Pract. 2008;14:22-33.

58. Sensky T, Turkington D, Kingdon D, Scott JL, Scott J, Siddle R, *et al*. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. Arch Gen Psychiatry. 2000;57:165-72.

59. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr Bull. 2003;29:633-51.

60. Clarke M, O'Callaghan E. Is earlier better? At the beginning of schizophrenia: timing and opportunities for early intervention. Psychiatr Clin North Am. 2003;26:65-83.

61. McGorry PD, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry. 2008;7:148-56.

62. Pelosi AJ, Birchwood M. Is early intervention for psychosis a waste of valuable resources? Br J Psychiatry. 2003;182:196-8.

63. Petersen L, Jeppesen P, Thorup A, Abel MB, Øhlenschlaeger J, Christensen TØ, *et al*. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. BMJ. 2005;331:602.

64. Spaulding W, Nolting J. Psychotherapy for schizophrenia in the year 2030: prognosis and prognostication. Schizophr Bull. 2006;32 Suppl 1:S94-105.

65. Summers RF. The psychodynamic formulation updated. Am J Psychother. 2003;57:39-51.

66. Sfera A. Schizophrenia report: making sense of the latest news in schizophrenia and neurodegenerative disorders. Dysphrenia. 2013;4:82-4.