J. Indian Inst. Sci.
A Multidisciplinary Reviews Journal
ISSN: 0970-4140 Coden-JIISAD

REVIEW ARTICLE

Neural Basis of Delusions in Schizophrenia: Translational Implications for Therapeutic Neuromodulation

*Rujuta Parlikar, Damodharan Dinakaran, Anushree Bose, Naren P. Rao and Ganesan Venkatasubramanian**

Abstract | Delusions are false, fixed beliefs which are held with incredible conviction, in spite of being substantiated to the contrary. These are present in a number of brain disorders, primarily representing one of the fundamental components of schizophrenia, presenting in about 70% of the patient population. Responsivity of delusions to antipsychotic medication, if present, is only partial, with absolutely no response in several other cases. Limited studies have engaged in exploring the neural substrates of delusion. The most extensive study conducted in this field has implicated the right dorsolateral prefrontal cortex (rDLPFC) disruption, to be clinically associated with the severity of delusions. Using a brain stimulation technique, high-definition transcranial direct current stimulation (HD-tDCS), targeting the rDLPFC, has a potential to induce neuroplasticity changes that are presumed to decrease the delusion score and severity. Using HD-tDCS, focalized neuromodulation of rDLPFC can be implemented. Alongside mainstream treatment such as antipsychotic medications and cognitive behavioral interventions, HD-tDCS to rDLPFC, holds the potential to be an effective treatment module for addressing refractory delusions in schizophrenia.

Keywords: *Delusion, Schizophrenia, Dorsolateral prefrontal cortex, Transcranial direct current stimulation (tDCS), Salience network, Prediction error*

1 Introduction

Schizophrenia is broadly conceptualized to comprise of positive, negative and cognitive domains. It has been quite a challenge to postulate various neurobiological mechanisms underlying these psychopathological domains. There are only a few experimental studies that have attempted to explore putative mechanisms underlying the delusions[1]. The picture gets complex because of the heterogeneous presentation of delusions, studies relying on global rating scales and antipsychotic medication-related changes in neural circuitry and processing[2]. This complexity also manifests in the varied response of delusions to available treatment options which are neither neurobiologically informed nor tailor made to suit that particular individual.

Recent studies have postulated hypotheses based on 'two-factor model' in the origin and maintenance of delusions[3] and prediction error bias model that draws from the corollary discharge phenomenon[4]. Aberrant activation of right prefrontal cortex has been shown to positively correlate with severity of delusions[5, 6]. Based on such neurobiological findings, this review attempts to establish a case for the neural basis of delusions and postulate an informed treatment mechanism for its amelioration. It is desirable to conduct further translational clinical research by guiding models of neuromodulatory treatments targeted at amelioration of persistent clinical symptoms such as delusions by systematically examining the available neurobiological findings explaining its pathophysiology.

Schizophrenia Clinic, Department of Psychiatry, WISER Program, National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore 560029, India
**venkat.nimhans@gmail.com*

Springer IISc Press

2 Genesis and Maintenance of Delusions: Neural Basis

Delusions, often defined as inappropriate and inflexible beliefs, held with supreme conviction are postulated to result from aberrant functioning of at least two important neural circuits: (1) prediction error pathway, and (2) the salience network[6]. The meso-cortico-limbic pathway is attributed an important role in the processing of reward prediction error. The purpose of the positive prediction error is to ascertain newer learning when the outcome of an event is unexpected with respect to past representations of desired goal[7]. Likewise, the purpose of negative prediction error is to terminate older learning when newer learning is established[8, 9]. Empirical studies postulate two possible outcomes in the event of an aberration in the functioning of meso-cortico-limbic pathway: (a) every outcome is considered new and unexpected, leading to newer incorrect learning. This faulty learning fuels a climate of confused and disoriented uncertainty which in turn triggers the processes of delusion formation. The delusions placate the sufferer by letting them identify with some predictability and meaningfulness to the situation. This effect is believed to be responsible for the genesis of delusions, explaining its erroneous, incomprehensible nature[6]; (b) Defect in the negative prediction error, which causes loss of extinction learning required for termination of goal representations from past. There is loss of dissolution of representations that are no longer relevant to the present[10]. This lack or absence of termination mechanism of odd belief systems explains the strong and fixed nature of these construed beliefs, which are maintained with undeterred conviction in the face of contradictory evidence. This effect is believed to be responsible for the maintenance of delusions.

Another theory explaining the genesis and maintenance of delusions is the aberrant functioning of salience network. Under normal circumstances, this network engages in identifying a particularly vital or novel signal, by assigning attentional resources to it on priority. The signal is then forwarded to the prefrontal cortex, the seat of causal learning, where causality between effect and outcome is established. Imprinting of salience to stimuli is regulated by the neurotransmitter dopamine, and the indiscriminate hyper-assignment of salience results from its over activity[11]. As there is no one signal, but a variety, a chaotic input is presented to the prefrontal cortex for assessment[12]. This jumble leads to establishment of inappropriate causality between events and outcomes yielding to the coagulation of unrelated ideas as delusions[11]. These thusly malformed beliefs impart some amount of plausibility to the confusion that the sufferers experiences. After some time, there is a shift of the neural circuit of dopamine from flexible ventral striatum to fixed dorsal striatum, causing the beliefs to get habituated and become fixed in nature[6]. This shift explains the maintenance of delusional beliefs, in spite of the questionable reliability of its foundation. These are the two models that attempt to explain the genesis of delusions and the manner in which these erroneous beliefs are maintained against proof to the contrary.

3 Tonic and phasic dopamine, prefrontal cortex and its association with delusions

In line with the dopamine hypothesis of schizophrenia, some interesting findings have been evidenced. Across studies, it has been identified that schizophrenia is associated with attenuated activity of frontal cortex, especially the prefrontal cortex[13–15]. The latter, which is postulated to be the seat of tonic dopamine release is based on NMDA receptor-based glutamate activity[16, 17]. This tonic dopamine is claimed to play a very important role in the homeostasis of extracellular dopamine[18] and modulate the activity of the dopamine receptors that are important recipients of phasic dopamine input. The other form of dopamine activity occurs in the form of phasic dopamine release. It is released instantly from the ventral tegmental area and has a rapid re-uptake[19–21]. Furthermore, on account of high collateral connections in the striatum[22, 23], it is released instantaneously in escalated volumes. This phasic activity is found to be released in response to behaviorally relevant stimuli. Or, it is said to be important for conditioning the responses to stimuli[24–28].

When there is decreased prefrontal activity and resultant decrease in tonic dopamine, there is an upregulation of dopamine receptors in the striatum and loss of inhibition of downregulation of the receptors[29–31]. Now, when there is a phasic dopamine release in response to relevant stimuli, there is more than usual or rather escalated dopamine response on account of increased receptors. As mentioned earlier from one of the studies, dopamine stamps salience to stimuli and under these circumstances, increased response would make a subject vulnerable to a variety of stimuli. These stimuli would then be sent to prefrontal cortex where in absence of single attentive signal, inappropriate causality would be drawn between

varied stimuli resulting in erroneous beliefs of delusional nature. Studies exploring the disruption of prediction error signaling have essentially found another implication for the activity of phasic dopamine release[5]. In the context of predictable outcome from a particular set of stimuli, there is no room for new learning to occur[6]. However, in the context of an unexpected outcome, there is a phasic dopamine release from the midbrain ventral tegmental area that essentially engages the prefrontal area for the processing of these unanticipated associations and facilitates newer learning. The previous goal representations from the past are thusly modified and newer representations are established[32–34]. Sometimes due to disruption in the signaling process, even the expected outcomes are perceived as unexpected, triggering the process of learning to generate newer representations when none are warranted. Increased dopamine affects the prefrontal cortex representations, and eventually leads to inappropriate goal-based representations; this in turn leads to the possibility of raising inappropriate conclusions. The functional role of prefrontal cortex in the cascade of thought conclusion process has been thusly established from evidences.

Anatomical components of the prefrontal cortex have also been explored for their contribution to the formation of delusional belief process. Research studies have tried to identify specific region whose disruption is more vigorously responsible for the formation or maintenance of delusions. Prefrontal cortex, other than its vital functions, executes an important role in the salience network circuit[6] and prediction error signaling process[35]. In the salience network circuit, prefrontal cortex is responsible for establishing causality between events. Salience network, which is normally engaged in effective thought process required for directing the subject's attention to a particular salient/vital signal, is believed to be disrupted in patients with delusions[36]. Salience circuit is comprised of midbrain dopaminergic nuclei, associative striatum and finally prefrontal cortex[37]. When increased dopamine in the midbrain adds hyper-salience to varied stimuli, the striatum presents the chaotic information to prefrontal cortex which establishes inappropriate causality among them leading to the formation of delusions.

Left hemisphere is primarily held accountable for organization of new information within old schemas, whereas right hemisphere is held responsible for keeping a validation check on the saved information[38, 39]. From this premise, it has been postulated that damage to left side of the hemisphere will interfere with the attribution of relevance to new information, whereas damage to right side, especially the right parietal lobe, will lead to inadequate validation of the causality association in context. The latter will hinder the reality check of the incongruent belief or reason, paving way for acceptance of erroneous ideas[38, 40]. The incomprehensible erroneous nature of delusion thus, may indirectly be contribution from damage incurred to the right parietal lobe and right prefrontal cortex including areas such as the right DLPFC and the ventromedial prefrontal cortex.

Several studies have evaluated the association between of right-sided lesions and delusional state. In one of the studies evaluating disinhibition syndromes, where among many others, prediction error signaling is also involved, found that the right hemisphere lesions are most often than not affected in such patients[41]. One of the factors that up holds the basis of delusions is the defect in the reasoning process behind a belief, that engages working memory functions and plays a vital role in the decision-making process[42]. Studies on schizophrenia patients reveal that, when subjected to working memory tasks (that are important for the process of belief system processing), schizophrenia patients do not show the expected activation in the right frontal cortex as observed in control group; specifically in the dorsolateral prefrontal cortex[43]. Studies examining the delusional features of patients with Alzheimer's disease have reported similar findings. A PET- and SPECT-based study, exploring the regional brain abnormalities among Alzheimer's patients with delusions, reported decreased perfusion in the right prefrontal cortex along with right anterior cingulate gyri, right medial temporal cortex, and right parietal cortex[44]. Another study with similar investigation methodology reported hypo-metabolism in the right superior DLPFC, the right inferior frontal pole and right lateral orbitofrontal region[45]. Taken together, these evidences enlist an imperative contribution of right-sided brain structures in pathophysiology of delusion that is not specifically restricted to the schizophrenia, as converging findings have been reported from studies on patient population with Alzheimer's disease as well.

4 Delusions and Right-Dorsolateral Prefrontal Cortex (rDLPFC)

Prefrontal cortex, perhaps particularly plays an important role in the delusional pathogenesis, this hypothesis has led many studies to examine

its components for their role in formation and maintenance of delusion [46, 47]. A fMRI study aimed at evaluation of the neural component of delusions, specifically implicated right prefrontal cortex in prediction error processing[48–50]. Further intensive studies have elucidated contribution of right dorsolateral prefrontal activation in enhancement of logical reasoning over belief-generated ideas. The ventromedial PFC activation has been related to increase in belief-generated idea over logic[38, 40, 51]. DLPFC has been implicated in working memory functions and crucially so in the blocking of distractions [46]. Right DLPFC functioning, that is responsible for causal learning, has been found to be negatively correlated with delusional severity in patients[5, 52]. That is, patients with preserved link between the prefrontal cortex and the prediction error signaling via the meso-cortico-limbic pathway showed lowest delusional scores. This study noted down the measure of the unusual thought content on Brief Psychiatric Rating Scale for grading of the delusional scores. The fMRI study specifically found a direct correlation of disruption in the meso-cortico-limbic pathway and the prediction error signaling with severity of delusions in the patients.

One of the studies evaluating delusions elucidated a model of two-step damage in two distinct functional areas: (1) the perceptual area, and (2) the belief evaluation area. The latter is the function of DLPFC as established from previous reports, and involves the prediction error signaling pathway[6]. Another study investigating the role of prediction error signaling and response inhibition depending upon the learned behavior found rDLPFC to be activated (as seen in the fMRI BOLD signal activation), whereas the left dorsolateral prefrontal cortex was found to be activated in the context of behavioral changes made in response to the learned errors[53]. This study has comprehensively elaborated the role of the rDLPFC in the process of elucidating appropriate inhibitions in prediction errors and associated behaviors on the basis of learned behaviors. This study indirectly suggests the effects of aberrant functioning of error signaling and response inhibition in rDLPFC disruption.

5 Transcranial Direct Current Stimulation (tDCS) for Treatment of Clinical Symptoms

Transcranial direct current stimulation (tDCS) is a very specific focused brain stimulation technique in which a targeted part of the brain is stimulated by placing electrodes on the corresponding part of the scalp of a patient. The operating principle of this techniques, that electrical stimulation may have therapeutic benefit, is an old idea[54] that came to be revived as having clinical benefit in psychiatric conditions such as schizophrenia in the recent times. tDCS is safe, easy to operate and relatively convenient to handle. This technique is based on the concept of using weak direct currents effecting changes in cortical excitability. The basic mechanism of action as proposed by one of the studies is by increasing the local glutamatergic activity and *N*-acetyl aspartate action[55]. The applied constant weak current modulates the cortical excitability in a polarity-dependent fashion. These localized changes are believed to be responsible for the cognitive and the learning effects of tDCS. Studies examining the efficacy of tDCS in treating persistent auditory hallucination, negative and cognitive symptoms among schizophrenia patients have reported positive findings[56–58]. Some studies also indicate that tDCS has clinical edge in decreasing the refractory symptoms such as auditory hallucination among schizophrenia patients that do not respond well to antipsychotic medications (see review for details[58]).

However, there are several limitations to using conventional tDCS. It employs large electrodes, invariably gives both excitatory and inhibitory stimulation to brain areas larger than the actual area of interest. As conventional tDCS involves the establishment of a complete anodal and cathodal circuit, inhibiting a brain area is accompanied by stimulating another brain area. This is believed to influence the result of the treatment procedure since it becomes unclear if the stimulation of an area or the inhibition of another area is responsible for the enhancement or in some cases, the lack of improvement. These limitations can be overcome by HD-tDCS which though operates on the same principle as conventional tDCS but has technical edge over it. Empirical evidences indicate that HD-tDCS leads to a focused and enhanced field of electrical stimulation as compared to conventional tDCS[59, 60]. Evidences from PET and fMRI indicate that the neurophysiological efficacy of HD-tDCS to be superior to that of conventional tDCS[59, 61, 62]. A study conducted to compare the efficacy of the two procedures found that the peak current was delayed for a much longer time after HD-tDCS (about 30 min) as compared to tDCS[63]. In addition, the after effects of HD-tDCS lasted for about 2 h longer than conventional tDCS. These studies compositely

indicate technical edge of HD-tDCS over conventional tDCS.

HD-tDCS is a safe and well-tolerated neuromodulatory treatment used in clinical setting. HD-tDCS procedure can be done using standard equipment (Soterix Medical MxN HD-tDCS stimulator) as per established guidelines[64]. Such devices are battery-powered current generator capable of delivering a weak and constant current stimulation to targeted circumscribed brain areas with a maximum output (of ± 2.5) in strength range of milli-amperes (mA). These devices operate on rechargeable batteries. Electrodes can deliver direct current (DC) of either polarity; the stimulation can be anodal (excitatory) or cathodal (inhibitory) depending on how they are plugged into the 4 × 1 configuration of the output cable. This montage yields flexibility in choice of stimulation polarity, that is, either anodal or cathodal stimulation can be given. It also allows achievement of much greater focality in the stimulation protocol than possible the conventional tDCS. Special gel-based sintered silver chloride electrodes are used to achieve higher specificity in current delivery.

6 A Case for Stimulation of rDLPFC for Treating Resistant Delusions

Theoretically, because of the technical rigor that yields better focality, specificity and choice of polarity in unipolar stimulation, neuromodulation with HD-tDCS holds remarkable potential for treatment of resistant delusions in schizophrenia. The prefrontal cortex which has been identified as a seat of causal learning (disrupted in the patients suffering from delusions in schizophrenia) can be considered as the broad region of interest, while the right dorsolateral prefrontal cortex can be the region of targeted anodal stimulation. The central electrode (giving anodal stimulating) can be placed at the rDLPFC, and the surrounding electrodes can be positioned around it in ring configuration as per the established guidelines[64]. As twice daily, HD-tDCS sessions with a current strength of 2 mA for 20 min has been found to be well tolerated and clinically effective (unpublished data from pilot studies from our lab), an add-on HD-tDCS therapy can be given to schizophrenia patients with persistent delusion for 5 days.

7 Summary

In conclusion, the pathophysiology of persistent delusions that are non-responsive to mainstream antipsychotic treatment in schizophrenia patients is evidenced to be associated with disruptive functioning of the right dorsolateral prefrontal cortex along with midbrain hyper-dopaminergic activity. Hence, alongside conventional treatment antipsychotic medications, add-on neuromodulatory therapy such as HD-tDCS addressing the hypo-activity rDLPFC would serve as a potential treatment module in the treatment of delusions. Such direct current stimulation enhances activity of targeted brain regions such as the r-DLPFC by modulating its local neuroplasticity. Together with medications, psychotherapy and other forms of treatment, HD-tDCS stimulation to the rDLPFC can serve as a potential tool in the treatment of persistent delusions in chronic schizophrenia.

Acknowledgements

This work is supported by the Department of Science and Technology [DST] (Government of India) SwarnaJayanti Fellowship Research Grant (DST/SJF/LSA-02/2014-15) to G.V.S. R.P & A.B are supported by the DST Grant (DST/SJF/LSA-02/2014-15).

Received: 22 September 2017 Accepted: 24 October 2017
Published online: 22 November 2017

References

1. Roberts G (1992) The origins of delusion. Br J Psychiatry 161:298
2. Kimhy D, Goetz R, Yale S, Corcoran C, Malaspina D (2005) Delusions in individuals with schizophrenia: factor structure, clinical correlates, and putative neurobiology. Psychopathology 38:338–344
3. Coltheart M (2010) The neuropsychology of delusions. Ann N Y Acad Sci 1191:16–26
4. Fletcher PC, Frith CD (2009) Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat Rev Neurosci 10:48–58
5. Corlett P, Honey G, Fletcher PC (2007) From prediction error to psychosis: ketamine as a pharmacological model of delusions. J Psychopharmacol 21:238–252
6. Corlett PR, Taylor JR, Wang XJ, Fletcher PC, Krystal JH (2010) Toward a neurobiology of delusions. Prog Neurobiol 92:345–369
7. Pearce JM, Hall G (1980) A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. Psychol Rev 87:532
8. Rescorla RA, Wagner AR (1972) A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. Classical conditioning II: Curr Res Theory 2:64–99

9. Clifford WK (1999) The ethics of belief and other essays. Prometheus Books, Amhers
10. Corlett PR, Krystal JH, Taylor JR, Fletcher PC (2009) Why do delusions persist? Front Hum Neurosci 3:12
11. Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23
12. Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev 28:309–369
13. Buchsbaum MS, Ingvar DH, Kessler R et al (1982) Cerebral glucography with positron tomography: use in normal subjects and in patients with schizophrenia. Arch Gen Psychiatry 39:251–259
14. Farkas T, Wolf AP, Jaeger J et al (1984) Regional brain glucose metabolism in chronic schizophrenia: a positron emission transaxial tomographic study. Arch Gen Psychiatry 41:293–300
15. Ingvar D, Franzen G (1974) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 50:425–462
16. Godukhin O, Zharikova A, Novoselov V (1980) The release of labeledl-glutamic acid from rat neostriatum in vivo following stimulation of frontal cortex. Neuroscience 5:2151–2154
17. Kim J-S, Hassler R, Haug P, Paik K-S (1977) Effect of frontal cortex ablation on striatal glutamic acid level in rat. Brain Res 132:370–374
18. Grace A (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24
19. Tassin J, Thierry A, Blanc G, Glowinski J (1974) Evidence for a specific uptake of dopamine by dopaminergic terminals of the rat cerebral cortex. Naunyn-Schmiedeberg's Arch Pharmacol 282:239–244
20. Iversen LL (1975) Uptake processes for biogenic amines. In: Biochemistry of biogenic amines. Springer, US, pp 381–442
21. Holz RW, Coyle JT (1974) The effects of various salts, temperature, and the alkaloids veratridine and batrachotoxin on the uptake of [3H] dopamine into synaptosomes from rat striatum. Mol Pharmacol 10:746–758
22. Andén NE, Fuxe K, Hamberoer B, Hökfelt T (1966) A quantitative study on the nigro-neostriatal dopamine neuron system in the rat. Acta Physiol 67:306–312
23. Doucet G, Descarries L, Garcia S (1986) Quantification of the dopamine innervation in adult rat neostriatum. Neuroscience 19:427–445
24. Schultz W (1986) Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J Neurophysiol 56:1439–1461
25. Romo R, Schultz W (1990) Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. J Neurophysiol 63:592–606
26. Miller JD, Sanghera MK, German DC (1981) Mesencephalic dopaminergic unit activity in the behaviorally conditioned rat. Life Sci 29:1255–1263
27. Kiaytkin EA (1988) Functional properties of presumed dopamine-containing and other ventral tegmental area neurons in conscious rats. Int J Neurosci 42:21–43
28. Fabre M, Rolls E, Ashton J, Williams G (1983) Activity of neurons in the ventral tegmental region of the behaving monkey. Behav Brain Res 9:213–235
29. McGeer P, McGeer E, Scherer U, Singh K (1977) A glutamatergic corticostriatal path? Brain Res 128:369–373
30. McGeorge A, Faull R (1989) The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 29:503–537
31. Spencer HJ (1976) Antagonism of cortical excitation of striatal neurons by glutamic acid diethyl ester: evidence for glutamic acid as an excitatory transmitter in the rat striatum. Brain Res 102:91–101
32. Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry 46:312–328
33. Cohen JD (1999) 11 A biologically based computational model of working memory. Models of working memory: mechanisms of active maintenance and executive control, p 375
34. Braver TS, Cohen JD (1999) Dopamine, cognitive control, and schizophrenia: the gating model. Prog Brain Res 121:327–349
35. Murray G (2011) The emerging biology of delusions. Psychol Med 41:7–13
36. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF (2011) Regional contraction of brain surface area involves three large-scale networks in schizophrenia. Schizophr Res 129:163–168
37. Corlett PR, Murray GK, Honey GD et al (2007) Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. Brain 130:2387–2400
38. Gilleen J, David AS (2005) The cognitive neuropsychiatry of delusions: from psychopathology to neuropsychology and back again. Psychol Med 35:5–12
39. Ragin C, Blakeslee S (1998) Phantoms in the brain: human nature and the architecture of the mind. Fourth Estate, London
40. Sanfey AG, Rilling JK, Aronson JA, Nystrom LE, Cohen JD (2003) The neural basis of economic decision-making in the ultimatum game. Science 300:1755–1758

41. Starkstein SE, Robinson RG (1997) Mechanism of disinhibition after brain lesions. J Nerv Ment Dis 185:108–114
42. Diamond A (2013) Executive functions. Annu Rev Psychol 64:135–168
43. Barch DM, Sheline YI, Csernansky JG, Snyder AZ (2003) Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol Psychiatry 53:376–384
44. Nakano S, Yamashita F, Matsuda H, Kodama C, Yamada T (2005) Relationship between delusions and regional cerebral blood flow in Alzheimer's disease. Dement Geriatr Cogn Disord 21:16–21
45. Sultzer DL, Brown CV, Mandelkern MA et al (2003) Delusional thoughts and regional frontal/temporal cortex metabolism in Alzheimer's disease. Am J Psychiatry 160:341–349
46. Kane MJ, Engle RW (2002) The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. Psychon Bull Rev 9:637–671
47. Bechara A, Tranel D, Damasio H (2000) Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 123:2189–2202
48. Fletcher P, Anderson J, Shanks D et al (2001) Responses of human frontal cortex to surprising events are predicted by formal associative learning theory. Nat Neurosci 4:1043–1048
49. Corlett PR, Aitken MR, Dickinson A et al (2004) Prediction error during retrospective revaluation of causal associations in humans: fMRI evidence in favor of an associative model of learning. Neuron 44:877–888
50. Turner DC, Aitken MR, Shanks DR et al (2004) The role of the lateral frontal cortex in causal associative learning: exploring preventative and super-learning. Cereb Cortex 14:872–880
51. Goel V, Dolan RJ (2001) Functional neuroanatomy of three-term relational reasoning. Neuropsychologia 39:901–909
52. Whitfield-Gabrieli S, Ford JM (2012) Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 8:49–76
53. Garavan H, Ross T, Murphy K, Roche R, Stein E (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 17:1820–1829
54. Nieuwdorp W, Koops S, Somers M, Sommer IE (2015) Transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy for medication-resistant psychosis of schizophrenia. Curr Opin Psychiatry 28:222–228
55. Clark VP, Coffman BA, Trumbo MC, Gasparovic C (2011) Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a 1 H magnetic resonance spectroscopy study. Neurosci Lett 500:67–71
56. Praharaj SK, Behere RV, Sharma PS (2015) Cathodal transcranial direct current stimulation over left temporoparietal area for treatment-refractory delusions and auditory hallucinations in schizophrenia: a case study. J ECT 31:277–278
57. Brunelin J, Mondino M, Gassab L et al (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry 169:719–724
58. Agarwal SM, Shivakumar V, Bose A et al (2013) Transcranial direct current stimulation in schizophrenia. Clin Psychopharmacol Neurosci 11:118–125
59. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M (2009) Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain stimulation 2:201–207.e201
60. Kuo H-I, Bikson M, Datta A et al (2013) Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study. Brain stimulation 6:644–648
61. Minhas P, Bansal V, Patel J et al (2010) Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. J Neurosci Methods 190:188–197
62. Hogeveen J, Grafman J, Aboseria M, David A, Bikson M, Hauner K (2016) Effects of high-definition and conventional tDCS on response inhibition. Brain stimulation 9:720–729
63. Kuo HI, Bikson M, Datta A et al (2013) Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimul 6:644–648. https://doi.org/10.1016/j.brs.2012.1009.1010
64. Villamar MF, Volz MS, Bikson M, Datta A, DaSilva AF, Fregni F (2013) Technique and considerations in the use of 4 × 1 ring high-definition transcranial direct current stimulation (HD-tDCS). J Vis Exp (77):e50309. https://doi.org/10.3791/50309

Rujuta Parlikar is an MBBS graduate. Her interest in clinical research led her to the Translational Psychiatry Lab, Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. Under the guidance of Dr. G. Venkatasubramanian, she is pursuing a Ph.D. in Psychiatry after a brief exposure to basic of psychiatric research including patient recruitment, clinical assessment, anonymous record keeping, review of literature, etcetera. In her thesis, she is examining neuromodulation with high-definition transcranial direct current stimulation (HD-tDCS) in schizophrenia patients and examining the neural changes post stimulation using brain imaging techniques. Other than neuromodulation, she is receiving training in techniques such as brain imaging using functional MRI (fMRI), Diffusor tensor imaging (DTI), functional near-infra-red spectroscopy (fNIRS) and event-related potential (ERP). She plans to pursue further research towards addressing treatment-resistant psychiatric symptoms particularly those of severe psychiatric illness such as schizophrenia spectrum disorders.

Dinakaran Damodaran did his MBBS (2011) from Govt. Stanley Medical college, Tamil Nadu and M.D. in Psychiatry (2016) from National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore and Post-doctoral fellowship in clinical neurosciences and therapeutics in Schizophrenia (2017) at NIMHANS, Bangalore. He is currently working as non-post graduate senior resident at National Institute of Mental Health and Neurosciences, Bangalore. He has received best outgoing MD resident award from NIMHANS for the year 2016. Research interests include application of transcranial direct current stimulation to understand the neurobiology and therapeutic uses in schizophrenia.

Anushree Bose is a clinical researcher at Translational Psychiatry Laboratory, Department of Psychiatry, National Institute of Mental Health And Neurosciences (NIMHANS). She did her Ph.D [2017] from here, in which she explored effect of transcranial direct current stimulation on neural underpinnings of auditory verbal hallucination in schizophrenia. She holds a Bachelor's degree in Applied Psychology (Hons.) (2006–2009) and Master's degree in Psychology (2009–2011) from University of Delhi. She has twenty-eight peer-reviewed journal articles to her name. Her research interest lies in clinical utility of transcranial electric current stimulation, neural underpinning of positive symptoms and neurocognition of schizophrenia. She wishes to continue translational clinical research towards integrated understanding of schizophrenia spectrum disorders.

Naren P. Rao did his MBBS (2004) from Sri Devaraj Urs Medical college, Karnataka and M.D. in Psychiatry (2008) from National Institute of Mental Health and Neurosciences, Bangalore, Post-doctoral fellow at Research Imaging Centre, Centre for Addiction and Mental health, University of Toronto, Canada (2011–2013). He worked at Centre for Neuroscience, Indian institute of science as Inspire faculty from 2013–2015 and currently working as Associate Professor of Psychiatry at National Institute of Mental Health and Neurosciences, Bangalore. He has authored 75 peer-reviewed publications, four book chapters and is recipient of awards from Society of biological psychiatry, Brain and Behavior research foundation and Canadian institutes of health research. Research interests include application of structural and functional magnetic resonance imaging and positron emission tomography to understand the neurobiology of neuropsychiatric disorders.

G. Venkatasubramanian did his MBBS (1998) from Stanley Medical College, (Chennai), M.D. in Psychiatry (2001) and PhD in Psychiatry (2013) from National Institute of Mental Health and Neurosciences. He is currently Professor of Psychiatry at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. He is the co-ordinator of the InSTAR Program for Schizophrenia at NIMHANS (http://www.instar-program.org). He heads the Translational Psychiatry Laboratory at the Neurobiology Research Centre, NIMHANS (http://www.transpsychlab.org). His areas of research interest include: Neurobiology of Schizophrenia, Neuroimaging in Psychiatry, Computational Neuroscience, Transcranial Direct Current Stimulation and Biology of Consciousness. He has more than 225 publications in National & International Journals (H-Index: 30; RG Score: 43.27). He has been the recipient of several awards such as DST SwarnaJayanti Fellowship 2016, Dr. Vidyasagar Award by the ICMR 2013, Wellcome Trust/DBT India Alliance Senior Fellowship in 2011, INSA Young Scientist Medal 2009, Young Psychiatrist Award by the Indian Psychiatric Society in 2009, NASI Platinum Jubilee Young Scientist Award 2008, Innovative Young Biotechnologist Award 2008 and many more. He is also the co-ordinating editor of the Asian Journal of Psychiatry (http://www.asian-journalofpsychiatry.com).