Schizophrenia Bulletin Advance Access published February 9, 2012

Schizophrenia Bulletin
doi:10.1093/schbul/sbs006

Taking Back the Brain: Could Neurofeedback Training Be Effective for Relieving Distressing Auditory Verbal Hallucinations in Patients With Schizophrenia?

Simon McCarthy-Jones*

Macquarie Centre for Cognitive Science, Institute of Human Cognition and Brain Science, Macquarie University, Balaclava Road, North Ryde, Sydney, New South Wales 2109, Australia

*To whom correspondence should be addressed; tel: +61-2-9850-8669, fax: +61-2-9850-6059, e-mail: s.mccarthyjones@gmail.com

Progress in identifying the neural correlates of auditory verbal hallucinations (AVHs) experienced by patients with schizophrenia has not fulfilled its promise to lead to new methods of treatments. Given the existence of a large number of such patients who have AVHs that are refractory to traditional treatments, there is the urgent need for the development of new effective interventions. This article proposes that the technique of neurofeedback may be an appropriate method to allow the translation of pure research findings from AVH-research into a clinical intervention. Neurofeedback is a method through which individuals can self-regulate their neural activity in specific neural regions/frequencies, following operant conditioning of their intentional manipulation of visually presented real-time feedback of their neural activity. Four empirically testable hypotheses are proposed as to how neurofeedback may be employed to therapeutic effect in patients with AVHs.

Key words: psychosis/brain-computer interface/hearing voices

Auditory verbal hallucinations (AVHs), the experience of hearing a voice in the absence of an appropriate external stimulus, are often associated with severe distress and social and occupational impairment. Approximately, 3 in 4 patients with schizophrenia will experience AVHs[1] (henceforth termed SZ:AVH+). While the past decade has seen significant progress in identifying the neural activity underpinning AVHs, researchers now face the challenge of translating this improved understanding into therapeutic interventions. The urgency of this arises from the limitations of existing treatments. Although the exact percentage is unclear,[1] a consensus exists that a significant minority of SZ:AVH+, possibly as high as 25%–30%, have antipsychotic medication-resistant AVHs.[2] Furthermore, the evidence base for cognitive-behavioral therapy for AVHs is weak, (S.M.-J. et al, unpublished data, 2011) and despite a recent meta-analysis finding transcranial magnetic stimulation (TMS) over the left temporoparietal junction to be effective for AVHs,[3] a recent large randomized controlled trial (RCT) of TMS for AVHs has reported negative results.[4] There is hence a pressing need for novel therapeutic developments for SZ:AVH+, grounded in and guided by pure research findings. This article will argue that one such promising option is neurofeedback.

Neurofeedback

Neurofeedback involves individuals using a brain-computer interface to manipulate their own neural activity. This is achieved by feeding back real-time information of an individual's brain activity to them, allowing them to undertake endogenous control of neural activity in vivo.[5] In electroencephalography-based (EEG) neurofeedback studies, the power of participants' neural oscillations in a given frequency (eg, alpha, gamma) are visually displayed to them, typically in the form of a bar graph whose height is proportional to the real-time EEG amplitude and which fluctuates accordingly.[5] Participants try to learn to manipulate this visual feedback, increasing/decreasing it to a predefined threshold level, with an operant conditioning paradigm employed involving a reward when amplification/suppression to this threshold is achieved.[5,6] Participants are not typically given explicit instructions or mental strategies as to how to achieve control over their EEG but are told to be guided by the visual feedback process.[6]

The ability of healthy individuals to manipulate their own EEG amplitudes using neurofeedback has been repeatedly demonstrated.[5–7] For example, Keizer and colleagues[7] found that eight 30-minute EEG neurofeedback sessions spread over 10 days, resulted in participants being able to intentionally increase the power of their gamma frequency signal (at the Oz electrode). Of interest for the application of neurofeedback to clinical conditions is what has been termed the "transfer effect."

This is where, after neurofeedback training, participants are able to employ the strategies they have learned to control their neural activity to successfully reduce/increase activity in a specific area in the absence of neurofeedback (eg,[8]).

Neurofeedback may also be undertaken using real-time fMRI (rtfRMI), which allows the presentation (albeit with the delay of the hemodynamic response of around 6 s) of images of neural activity to the participant while still in the scanner.[9] Compared with EEG neurofeedback, rtfMRI is more expensive and technically demanding, potentially impacted by the inherent delay of the hemodynamic response, and less comfortable for participants.

The ability to self-regulate neural activity through neurofeedback has been found to have potential cognitive/affective effects, including improving working memory,[6] intelligence,[7] and identification of emotional prosody.[10] This has led to its clinical application to a range of psychiatric disorders. Although meta-analyses have found neurofeedback to be effective for attention deficit hyperactivity disorder (ADHD)[11] and epilepsy,[12] evidence meeting this high standard of proof has yet to be provided for other disorders (eg, depression, autism).

Could Neurofeedback Be Applied to AVHs?

Although it may be queried whether the cognitive impairments found in patients with schizophrenia[13] affect their ability to successfully undertake neurofeedback training, all 4 studies to date employing neurofeedback with this population[14–17] have found patients able to self-regulate their own neural activity. However, the group analyses typically reported do not indicate what percentage of patients can achieve this. The best neurofeedback study to-date performed with patients with schizophrenia ($N = 9$) reported the results of 12 sessions of rtfMRI neurofeedback targeting the bilateral anterior insula.[17] After these 12 training sessions, blood oxygen level dependent (BOLD) signal in this area, compared with a control region, significantly increased. However, when patients were asked able to perform self-regulation in the scanner without any form of neurofeedback, only a trend toward a transfer effect was found. Thus, while neurofeedback training is feasible in patients with schizophrenia, evidence for a transfer effect has yet to be clearly documented.

In order to undertake neurofeedback in SZ:AVH+, there must be clearly documented neural areas known to be associated with AVHs that can be targeted. An extensive body of neuroimaging work has employed a symptom-capture design (typically involving participants indicating the onset/offset of AVHs they experience, while being imaged, via a button press) to identify the neural activity associated with AVHs. A recent meta-analysis of fMRI symptom-capture studies of AVHs[18] found neural activity to occur in the bilateral anterior insula, frontal operculum, inferior parietal lobule, and in the left inferior frontal gyrus (IFG), precentral gyrus, middle temporal gyrus (MTG), superior temporal gyrus (STG), and hippocampus/parahippocampal region. Other work has found that the single area most commonly found to be activated during AVHs (found by 69% of fMRI studies) is the STG, with the only other areas to have been found $\geq$50% of fMRI studies being the IFG, cingulate regions and the MTG.[1] Consistent with these findings, in the past decade, the single EEG symptom-capture study[19] and 3 of the 4 magnetoencephalography (MEG) symptom-capture studies of AVHs, all found significant electrophysiological activity in the left STG specific to the occurrence of AVHs.[20–22] Yet such studies cannot discriminate between the areas involved in the generation and perception of AVHs. The largest fMRI study to-date designed to isolate the neural activity immediately preceding the onset of AVHs found them to be most prominently preceded by deactivation in the left parahippocampal gyrus and also by deactivation in the left STG, right IFG (Broca's area), left middle frontal gyrus, right insula and left cerebellum, suggesting a causal role for these areas.[23]

Going beyond dysfunction in isolated neural regions, both MEG[21,24] and EEG[25] studies have suggested the involvement of a frontotemporal circuit specific to AVHs, possibly involving the arcuate fasciculus.[26] Although the evidence is from diffusion tensor imaging studies is somewhat mixed, these also suggest that some form of altered connectivity in the arcuate fasciculus is specifically associated with AVHs (eg,[27,28]). This has led to the proposal that AVHs reflect a form of disconnection (or delayed connection) between frontal speech production and temporal speech perception regions.[29]

In conclusion, although a wide range of neural areas are associated with AVHs, the most consistently documented are the STG, IFG, and the arcuate fasciculus tract connecting them. This clearly defined neural geography makes targeted neurofeedback feasible.

How Should Neurofeedback Be Applied to AVHs? 4 Hypotheses

Initial neurofeedback studies for SZ:AVH+ should target neural areas that have been reliably found to be associated with AVHs and which have been previously demonstrated to be amenable to neurofeedback. As the STG is the area most reliably associated with AVHs, and (healthy) individuals are able to use neurofeedback to regulate STG activity,[30] this is the most promising target. Although the STG is activated during AVHs, it appears to be deactivated immediately preceding them. This raises the question as to whether learned upregulation or downregulation of the STG may be beneficial. It appears plausible that both may be. While during AVHs, the application of strategies to

downregulate the activity of the STG may be beneficial, during the seconds immediately preceding AVHs, the application of strategies to upregulate the activity of the STG may be fruitful. The latter suggestion draws on a neurofeedback study[31] which found that strategies to control cortical slow potentials leant by epileptic patients during EEG neurofeedback could be used by such patients when they felt a fit coming on in the real world, to prevent it. Although it may be queried how SZ:AVH+ could know when pre-AVH–related neural activity was occurring, many patients report sensing their AVHs coming on, or knowing triggers for their experiences (eg,[32]). Another reason to suggest STG-upregulation before AVH-onset may be beneficial comes from studies showing less AVHs occurring in periods when SZ:AVH+ are humming,[33] a task which has been shown to activate the STG (and IFG).[34] Indeed, in addition to the STG, the IFG was also noted above as being reliably associated with AVHs (also being deactivated immediately before them but activated during them) and has been shown to be amenable to intentional modulation through neurofeedback.[10] This leads to hypothesis 1:

> Neurofeedback training will enable patients to learn to individually both upregulate and downregulate activity in their STG or IFG. Through the transfer effect, patients will then be able to apply the cognitive strategies that they have learnt to alter STG or IFG activation, during real-life occurrences of AVHs. Upregulating the STG or IFG when voices are experienced as about to begin should prevent their onset, and downregulating the STG or IFG when AVHs are already occurring, should reduce their severity.

A further hypothesis may be developed from TMS studies. Ros and colleagues[5] found neurofeedback effect sizes comparable to excitability increases found using repetitive magnetic stimulation, suggesting that "whether endogenous or exogenous techniques are used, they appear to appeal to a common neural substrate"(p777). Neurofeedback may hence be an alternative way of achieving TMS, but "from the inside." Indeed, neurofeedback could potentially be more effective than TMS. Whereas patients cannot practically have multiple TMS sessions each day, they could employ strategies learned from neurofeedback throughout their day. Furthermore, given TMS's artificial method of externally altering neural activity, internally induced changes created using strategies learned from neurofeedback may be able to utilize more natural methods, which the brain may be more receptive to. Hypothesis 2 is thus:

> Neurofeedback training will enable patients with schizophrenia with AVHs to learn to modulate activity over their temporoparietal junction (TPJ). Employing the strategies that they learn to be effective for modulating TPJ activity, will result in a reduction of the severity of their AVHs.

Could neurofeedback also be used to therapeutically address the neural connectivity issues reliably associated with AVHs? Although one study[17] has found that neurofeedback training to increase insula activation in patients with schizophrenia led to connections between the insula cortex, amygdala and medial prefrontal cortex increasing, and new connections appearing between areas including the insula and anterior cingulate cortex (ACC), at present it has not been established whether neurofeedback can specifically increase connectivity in the arcuate fasciculus. A speculative hypothesis 3 is hence:

> Carefully engineered neurofeedback can be used to repair connectivity abnormalities in patients with AVHs, across a range of neural circuits, reducing the severity of such patients' AVHs.

Finally, and also speculatively, it may be hypothesized that neurofeedback's demonstrated ability to cause affective/cognitive changes may be used to "repair" malfunctioning affective/cognitive mechanisms linked to AVHs. For example, given that impairments to both context memory, ie, the binding of events into memory, and the control of retrieval from memory are thought to play a causal role in the etiology of AVHs,[35] it is possible that using neurofeedback to remedy this may help AVHs. As increasing power and synchrony in the gamma band through neurofeedback has been found to be associated with improved feature binding and control of memory retrieval,[7,36] hypothesis 4 is:

> EEG neurofeedback training aiming to increase power and synchrony in the gamma band will reduce the severity of AVHs

While the above hypotheses offer a promising research direction, there are some pertinent concerns. First, it is unclear how robust the transfer effect is, both in healthy individuals and in patients with schizophrenia.[17] In one study, only half of ADHD patients who successfully undertook neurofeedback training could later achieve this in the scanner without any direct feedback.[37] One way to mitigate this may be to screen SZ:AVH+, selecting only those who can perform a simple EEG neurofeedback task (such as modulating alpha frequency amplitudes) to go on to full neurofeedback training. Second, given the interindividual differences in neural activity associated with AVHs,[38] as well as the potential for subtypes of AVHs to be associated with different neural signatures,[39] optimal results may only be achieved by fMRI-guided neurofeedback (paralleling fMRI-guided TMS). Pilot work may wish to begin with relatively cheap, simple, and comfortable EEG neurofeedback and then build to individually designed fMRI-guided neurofeedback if such initial attempts prove unsuccessful. Alternatively, near-infrared spectroscopy neurofeedback may be a simpler method to begin piloting studies. Third, as most SZ:AVH+ spontaneously attempt to develop coping strategies for AVHs[40] with only limited effectiveness, it may be asked why techniques learned from neurofeedback should be any more effective. Here, a neurofeedback study of chronic pain

patients is informative.[41] This study's chronic pain patients had attempted to find their own ways to cope with their pain but had not managed to do so. However, learning to directly control ACC activity using neurofeedback was effective in reducing their pain. Neurofeedback may therefore succeed where previous self-learned strategies have failed. A final caution is that if patients' AVHs have their roots in earlier traumatic events, there may be ethical implications for treating these in a solely neurological manner, without psychological (or even sociological) interventions.[1]

If neurofeedback were to be effective for AVHs, a number of benefits would materialize. First, it would be preferable to TMS, which can be an unpleasant experience for some participants due to inadvertent motor activations. Second, following the rationale of cognitive behavioral therapy (CBT), it would allow patients to have a technique that they can take away and use themselves, which may be potentially empowering. Indeed, whereas TMS is a passive treatment which does not allow patients to experience the feeling that they themselves have overcome their AVHs, neurofeedback is an active process which, if effective, would allow patients to gain control over their AVH by their own efforts. Third, some patients report wanting to eliminate negative abusive AVHs yet to retain their friendly benevolent AVHs.[42] Neurofeedback would allow patients to apply their eliminative strategies only during the occurrence of their negative voices and hence to retain their valued AVHs.

In conclusion, neurofeedback appears to be a promising potential way in which pure research into the neural underpinnings of AVHs may be translated into therapeutic interventions. The promise of this technique to give SZ:AVH+ some measure of control over their brains, and hence their lives, justifies the investment of money and resources into a serious investigation of this technique's potential.

Funding

This work was supported by a Macquarie University Research Fellowship.

Acknowledgment

The author has declared that there are no conflicts of interest in relation to the subject of this study.

References

1. McCarthy-Jones S. *Hearing Voices: The Histories, Causes and Meanings of Auditory Verbal Hallucinations.* Cambridge, UK: Cambridge University Press; 2012.
2. Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophr Res*. 1998;32:137–150.
3. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *J Clin Psychiatry*. 2007;68:416–421.
4. Slotema CW, Blom JD, de Weijer AD, et al. Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biol Psychiatry*. 2011;9:450–456.
5. Ros T, Munneke MAM, Ruge D, Gruzelier JH, Rothwell JC. Endogenous control of waking brain rhythms induces neuroplasticity in humans. *Eur J Neurosci*. 2010;31:770–778.
6. Vernon D, Egner T, Cooper N, et al. The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *Int J Psychophysiol*. 2003;47:75–85.
7. Keizer AW, Verschoor M, Verment RS, Hommel B. The effect of gamma enhancing neurofeedback on the control of feature bindings and intelligence measures. *Int J Psychophysiol*. 2010;75:25–32.
8. Zotev V, Krueger F, Phillips R, et al. Self-regulation of amygdala activation using real-time fMRI neurofeedback. *PLoS ONE*. 2011;6:e24522.
9. Weiskopf N. Real-time fMRI and its application to neurofeedback. *Neuroimage*. October 14, 2011; doi: 10.1016/j.neuroimage.2011.10.009.
10. Rota G, Sitaram R, Viet R, et al. Self-regulation of regional cortical activity using real-time fMRI: the right inferior frontal gyrus and linguistic processing. *Hum Brain Mapp*. 2009;30:1605–1614.
11. Arns M, De Ridder S, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clin EEG Neurosci*. 2009;40:180–189.
12. Tan G, Thornby J, Hammond DC, et al. Meta-analysis of EEG biofeedback in treating epilepsy. *Clin EEG Neurosci*. 2009;40:173–179.
13. Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychol Rev*. 2005;15:73–95.
14. Gruzelier J, Hardman E, Wild J, Zaman R. Learned control of slow potential interhemispheric asymmetry in schizophrenia. *Int J Psychophysiol*. 1999;34:341–348.
15. Bolea AS. Neurofeedback treatment of chronic inpatient schizophrenia. *J Neurother*. 2010;14:47–54.
16. Surmeli T, Ertem A, Eralp E, Kos IH. Schizophrenia and the efficacy of qEEG-guided neurofeedback treatment: a clinical case series. *Neurosci Lett*. 2011;500S:e16.
17. Ruiz S, Lee S, Soekadar S, et al. Acquired self-control of insula cortex modulates emotion recognition and brain network connectivity in schizophrenia. *Hum Brain Mapp*. October 22, 2011; doi: 10.1002/hbm.21427.
18. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry*. 2011; 168:73–81.
19. Sritharan A, Line P, Sergejew A, Silberhei R, Egan G, Copolov D. EEG coherence measures during auditory hallucinations in schizophrenia. *Psychiatry Res*. 2005;136:189–200.
20. Ishii R, Shinosaki K, Ikejiri Y, et al. Theta rhythm increases in left superior temporal cortex during auditory hallucinations in schizophrenia: a case report. *Neuroreport*. 2000;11:3283–3287.
21. Reulbach U, Bleich S, Maihofner C, Kornhuber J, Sperling W. Specific and unspecific auditory hallucinations in patients

with schizophrenia: a magnetoencephalographic study. *Neuropsychobiology*. 2007;55:89–95.

22. Ropohl A, Sperling W, Elstner S, et al. Cortical activity associated with auditory hallucinations. *Neuroreport*. 2004;15: 523–526.
23. Diederen KMJ, Neggers SFW, Daalman K, et al. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry*. 2010;167:427–435.
24. Van Lutterveld R, Hillebrand A, Stam CJ. Auditory verbal hallucinations are related to decreased beta-band power in the anterior superior frontal gyrus—an MEG study. *Schizophr Res*. 2010;117:475.
25. Heinks-Maldonado TH, Mathalon DH, Houde JF, et al. Relationship of imprecise corollary discharge in schizophrenia to auditory hallucinations. *Arch Gen Psychiatry*. 2007;64:286–296.
26. Whitford TJ, Mathalon DH, Shenton ME, et al. Electrophysiological and diffusion tensor imaging evidence of delayed corollary discharges in patients with schizophrenia. *Psychol Med*. 2011;41:959–969.
27. Seok JH, Park HJ, Chun HW, et al. White matter abnormalities associated with auditory hallucinations in schizophrenia: a combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. *Psychiatry Res*. 2007;156:93–104.
28. de Weijer AD, Mandl RCW, Diederen KMJ, et al. Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. *Schizophr Res*. 2011;130:68–77.
29. Allen P, Larøi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev*. 2008;32:175–191.
30. Yoo S-S, Lee J-H, O'Leary H, Lee V, Choo S-E, Jolesz FA. Functional magnetic resonance imaging-mediated learning of increased activity in auditory areas. *Neuroreport*. 2007;18: 1915–1920.
31. Birbaumer N, Elbert T, Rockstroh B, Daum I, Woolf P, Canavan A. Clinical-psychological treatment of epileptic seizures: a controlled study. In: Ehlers A, Fiegenbaum E, Margraf J, Florin I, eds. *Perspectives and Promises of Clinical Psychology.* New York, NY: Plenum Press; 1991.
32. Escher SA, Romme M, Buiks A, Delespaul P, Van Os J. Independent course of childhood auditory hallucinations: a 10 sequential 3-year follow-up study. *Br J Psychiatry*. 2002;181(suppl 43):s10–s18.
33. Green MF, Kinsbourne M. Subvocal activity and auditory hallucinations: clues for behavioural treatments. *SchizophrBull*. 1990;16:617–625.
34. Özdemir E, Norton A, Schlaug G. Shared and distinct neural correlates of singing and speaking. *Neuroimage*. 2006;33: 628–635.
35. Waters FAV, Badcock JC, Michie PT, Maybery MT. Auditory hallucinations in schizophrenia: intrusive thoughts and forgotton memories. *Cognit Neuropsychiatry*. 2006;11:65–83.
36. Keizer AW, Verment RS, Hommel B. Enhancing cognitive control through neurofeedback: a role of gamma-band activity in managing episodic retrieval. *Neuroimage*. 2010;49:3404–3413.
37. Dresler R, Straub M, Doehnert M, Heinrich H, Steinhausen H-C, Brandeis D. Controlled evaluation of a neurofeedback training of slow cortical potentials in children with Attention Deficit/Hyperactivity Disorder (ADHD). *Behav Brain Funct*. 2007;3:35.
38. Shergill SS, Brammer MJ, Williams SCR, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiat*. 2000;57:1033–1038.
39. Jones SR. Do we need multiple models of auditory verbal hallucinations? Examining the phenomenological fit of cognitive and neurological models. *Schizophr Bull*. 2010;36:566–575.
40. Farhall J, Greenwood KM, Jackson HJ. Coping with hallucinated voices in schizophrenia: a review of self-initiated strategies and therapeutic interventions. *Clin Psy Rev*. 2007; 27:476–493.
41. deCharms RC, Maeda F, Glover GH, et al. Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci U S A*. 2005;102:18626–18631.
42. Jenner JA, Rutten S, Beuckens J, Boonstra N, Sytema S. Positive and useful auditory vocal hallucinations: prevalence, characteristics, attributions, and implications for treatment. *Acta Psychiatr Scand*. 2008;118:238–245.