Vestibular neuromodulation: stimulating the neural crossroads of psychiatric illness

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In a recent provocative Opinion article in Trends in Cognitive Sciences, Downar et al.1 (see also Goodkind et al.2) draw from quantitative meta-analyses of repositories of structural neuroimaging studies to propose a "common core" of brain regions whose function is disturbed in a wide variety of psychiatric disorders. Central to this core is the (dorsal) anterior cingulate cortex (ACC) and (anterior) insular cortex (IC). These regions map closely onto a functional anterior cingulo-insular network (aCIN), or "salience" network, that has also been identified with meta-analyses of thousands of neuroimaging studies. The psychiatric common core/aCIN is argued to stand at a crossroads position in the network architecture of the brain, being active during behavioural self-control, emotion regulation, and social cognition, and acting as a switch to deploy other major functional networks mediating cognition and emotion. Dysfunction in this "hub" role can thus predispose to multiple psychiatric illnesses such as bipolar disorder, major depressive disorder, schizophrenia, obsessive compulsive disorder, anxiety disorders, post-traumatic stress disorder, attention deficit hyperactivity disorder, autism spectrum disorders, eating disorders and substance dependence disorders.

Downar et al.1 also discuss prospects for precisely targeting key nodes of the common core for therapeutic effect, potentially with broad-spectrum benefits across psychiatric disorders. They review various brain stimulation methods, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), epidural cortical stimulation, and deep brain stimulation (DBS), and point out that the non-invasive techniques in particular require further development before being able to successfully target deeply-situated and relatively focal common core nodes like dorsal ACC and anterior IC, as well as relevant subcortical regions such as the putamen (PN) in the basal ganglia. It is suggested that targeting the common core/aCIN with brain stimulation could lead to improved treatments for many psychiatric illnesses, and in turn align psychiatry with neurology as psychiatric illness pathology becomes better defined.

1 Stimulating the Common Core/aCIN with Caloric Vestibular Stimulation

With this line of reasoning, it needs to be commented that there already exists a simple, non-invasive brain stimulation technique that is known to reliably activate key nodes of the psychiatric common core/aCIN. Nearly a decade ago, it was proposed3 that caloric vestibular stimulation (CVS) could potentially treat a wide variety of psychiatric and neurological conditions, with examples including mania, depression, insight, insula, mania, neuroimaging, neuromodulation.
Table 1  Reported modulations with CVS and additional modulations with GVS

Postlesional disorders
- Attentional, intentional, and representational neglect
- Anosognosia
- Somatoparaphrenia
- Macrosomatognosia
- Hemianesthesia
- Aphasic syndrome
- Prosopagnosia (GVS)
- Figure copying deficit (GVS)
- Disturbed arm position sense (GVS)
- Postural control
- Minimally conscious state

Other neurological disorders
- Cervical dystonia (GVS)
- Autonomic/motor responsiveness in Parkinson’s disease and multisystem atrophy (GVS)

Psychiatric disorders
- Mania in bipolar disorder and schizoaffective disorder
- Insight in mania and schizophrenia
- Conversion disorder with involuntary movements

Pain disorders
- Phantom limb pain and sensations
- Complex regional pain syndrome
- Spinal cord injury pain
- Thalamic pain syndrome (central pain)
- Allodynia
- Migraine

Normal brain functions
- Spatial perception and localization
- Auditory space perception
- Spatial and verbal memory
- Visual recall (GVS)
- Visual and mental imagery
- Binocular rivalry/ambiguous figure perception
- Tactile perception
- Pain thresholds
- Bodily misperception
- Positively biased beliefs
- Purchase decision-making
- Positive and negative mood
- Affective control
- Sleep and dreams (GVS)

CVS, caloric vestibular stimulation; GVS, galvanic vestibular stimulation.

As cited in Miller and Ngo and Grabherr et al., and in the text. Other reported effects of vestibular stimulation, particularly motion-induced stimulation in neurodevelopmental disorders, are not listed here but can be found in Grabherr et al.

attempting to treat psychiatric illness with vestibular stimulation (usually motion-induced stimulation) is far less known. In the mid-late 20th century, reports also emerged of the remarkable ability of cold left-ear CVS - which predominantly activates right-sided structures - to temporarily reverse unilateral attentional neglect and anosognosia (denial of illness) associated with right-hemisphere stroke. Subsequently, a model of bipolar disorder - the ‘Sticky Interhemispheric Switch’ model - was proposed based on new findings of slow binocular rivalry in bipolar disorder (see below) and CVS modulation of binocular rivalry, as well as existing evidence for hemispheric lateralization of cognitive style, mood and mood disorders. This model specifically predicted that left-ear CVS would reduce the signs and symptoms of mania (restoring toward normal the ‘stuck’ left greater than right imbalance) while right-ear CVS would do the same for depression (restoring toward normal the ‘stuck’ right greater than left imbalance).

2  VESTIBULAR NEUROMODULATION OF MANIA AND INSIGHT

The first empirical evidence to support these CVS psychiatric therapeutic predictions was a report that left-ear CVS induced a striking reduction in Young Mania Rating Scale score (from 32 to 10), with a concomitant improvement in insight, in an inpatient in the manic phase of bipolar disorder. This patient had become intolerant of pharmacotherapy and refractory to five ECT treatments (despite ECT having been effective for previous episodes) and had been manic for two months. Left-ear CVS caused immediate slowing of thoughts and speech (subjectively and objectively observed), a reduction in spontaneous laughter and movement, calming of behaviour, and embarrassment regarding recent behaviour. This effect of CVS remained evident 24 hours later and had fully diminished by 72 hours. It was able to be repeated with a second stimulation with a longer duration of effect (although longer-term outcomes were not reported). A second confirmation of CVS psychiatric therapeutic predictions came in a report that a patient with schizoaffective disorder exhibited a response to left-ear, but not right-ear, CVS, with reduced mania, including reduced psychomotor agitation, increased insight, and calmer, more cooperative behaviour. In this case, the effect lasted 20 minutes, had diminished by 60 minutes, and was repeatable.

Consistent with these case studies, it has also been shown that CVS modulates both affective control and mood in healthy subjects. In that study, drawing on lateralized CVS mood modulation predictions, 16 participants received left-ear CVS and sham CVS while another 16 received right-ear CVS and sham CVS. An affective Go/NoGo task was employed, utilizing pictures from the International Affective Picture System. Affective control in response to target pictures improved following right-ear CVS when viewing positive stimuli but decreased following left-ear CVS, relative to sham stimulation. In addition, positive mood ratings on the Positive and Negative Affect Schedule decreased following left-ear CVS, again relative to sham stimulation (although with no effect on mood ratings following right-ear CVS). Also in healthy subjects, CVS has been shown to modulate binocular rivalry. Binocular rivalry is a visual switching phenomenon that has been repeatedly shown to be anomalous in bipolar disorder, to have substantial genetic basis, and to be a candidate endophenotype for bipolar disorder.

Furthermore, following suggestion that CVS be applied in decision-making contexts, it was recently shown that left-ear CVS relative to sham stimulation in healthy subjects reduces purchase probability and the desirability of products. Extrapolated to a clinical context,
this finding is consistent with the excessive spending and risky financial decision-making observed in mania. Vestibular stimulation also has (complex) effects on sleep in healthy subjects, and interestingly in the context of mania, historical records refer to the sedating and sleep-promoting effects of rotation apparatuses.5,19

The immediate post-CVS restoration of insight in mania in the case studies described earlier resembles the immediacy of responses observed in right-sided stroke patients who deny their left hemiplegia (anosognosia) or confabulate to explain it.20,21 Following left-ear CVS, such patients rapidly accept and acknowledge their hemiplegia, and dispense with confabulation, with the effect usually diminishing around 20 minutes following stimulation. These similarities between insight improvements following left-ear CVS in mania and in right-hemisphere stroke, along with existing comparisons between anosognosia and a lack of insight in schizophrenia, led to prediction that left-ear CVS might also improve insight in schizophrenia.3 This too has since been demonstrated in two such cases.3 In addition, consistent with predictions regarding CVS modulation of belief,3 a study in which 31 participants received simultaneous left- and then right-ear CVS successively, showed only left-ear CVS attenuated unrealistically optimistic thoughts regarding the likelihood of future illness.22 Those authors concluded, on the basis of CVS neuromodulation findings, that a unitary mechanism underlies both anosognosia in stroke patients and unrealistic optimism in healthy subjects (see also Gerretsen et al.23). An excess of unrealistic optimism is also, of course, characteristic of mania, and many of the psychiatric and behavioural disorders discussed by Downar et al.,1 and even general medical disorders,24 involve reduced insight.

3 | EXAMINING THE THERAPEUTIC EFFICACY OF VESTIBULAR NEUROMODULATION

While not escaping the attention of cognitive neuroscientists, the remarkable reports described above of CVS neuromodulation of psychiatric illness, and supporting studies in healthy subjects, have not attracted the attention of clinical psychiatrists, research psychiatrists, and psychiatric brain stimulation researchers. This may be due to a general unawareness of such reports, or perhaps even to incredulity that a simple, inexpensive, non-technological, and nonspecialized brain stimulation technique – indeed, a bedside neuromodulation technique – could possibly modulate conditions such as mania and schizophrenia. However, with the recent proposal of common core/aCIN nodes of dorsal ACC and anterior IC (with PN as a relevant subcortical region as well),1,2 and existing meta-analytical evidence for activation by CVS of dorsal (caudal) ACC, anterior IC, and PN,4 the case for examination of CVS psychiatric neuromodulation is now strong. Indeed, given the wide-ranging phenomenological modulations known to occur following CVS (Table 1), particularly clinical psychiatric modulations, the technique itself provides further evidence in support of the common core/aCIN proposal. It may also shed light on other commonalities between psychiatric symptoms and the vestibular system.25

It is worth pointing out though, that CVS additionally activates regions outside of the common core/aCIN.34 However, the ability of CVS to activate from the periphery, vestibular subcortical and cortical targets linked to balance, orienting behavior, movement, spatial attention, vision, insight, social cognition, decision-making, motivation, impulse control, salience and reward processing, error detection, interception, bodily representation, homeostasis, autonomic function, pain, affect, and mood, may represent a key advantage over other stimulation techniques which attempt to intervene only at particular points along this ancient neural pathway.3 Nonetheless, further research is needed to fully understand lateralization of both CVS activations5 and mood disorder modulation,26 a full discussion of which is beyond the scope of this commentary. These issues for further investigation need not delay examination of CVS as a readily accessible neuromodulation procedure in clinical psychiatry. The next step is for CVS studies to employ larger sample sizes, repeated stimulation protocols, placebo/sham controls (particularly controlling for the cold arousal component of CVS), and adequate longer-term follow-up.

This is beginning to occur in neurological contexts, such as daily right-ear CVS for four weeks improving aphasic syndrome in left-hemisphere stroke27 and disturbed arm position sense in poststroke neglect improving with galvanic vestibular stimulation (GVS)28 relative to sham stimulation29 (note that GVS does not appear to activate ACC).4 There are also reports of GVS relative to sham GVS improving autonomic, motor and other functions in Parkinson’s Disease and other central neurodegenerative disorders,30–33 and early evidence that repeated CVS for several weeks can induce behavioural improvement in the minimally conscious state.34 Moreover, following reports of persistent pain and allodynia modulation by CVS in case studies and small case series (discussed in Miller and Ngo5; see also McGeoch et al.35), a recent study36 examined 34 subjects with persistent (mostly neuropathic) pain and found that (i) a single session of right-ear CVS induced small but statistically significant short term modulations of pain relative to a forehead icepack cold-arousal control condition, (ii) three of nine subjects with allodynia had large, clinically significant CVS modulations, and (iii) CVS was well tolerated, with only one subject experiencing vomiting.

The gold standard for assessing therapeutic efficacy however is the double-blind randomized placebo-controlled trial (RCT). RCTs of repeated CVS (rCVS) are needed for mania, depression (both bipolar and unipolar depression), persistent pain, postlesional conditions, and other psychiatric and neurological disorders.3,5 RCTs of repeated GVS (rGVS) in hemispatial neglect have commenced, with enduring therapeutic benefits reported37 (see also Schindler et al.38, though see Ruet et al.39 for a negative study). The call for RCTs of rCVS (and rGVS) in psychiatry should ring particularly loudly, given issues with current therapeutic brain stimulation options,40–45 including: (i) complexity of administration variables, (ii) modest therapeutic effects with rTMS and controversial effects with tDCS, (iii) invasiveness and expense of DBS, with disappointing efficacy for depression, and (iv) inconvenience and potential side-effects of anaesthesia-requiring ECT. CVS, however, is noninvasive, safe (with guidelines regarding medical contraindications36), inexpensive, easy to administer (outlined in Miller and Ngo5), and uncomplicated by administration variables (just left- vs right-ear; although with emerging opportunities for CVS technological developments).27,34 These features should
make for relatively straightforward examination of CVS as a therapeutic option in clinical psychiatry and application of CVS as a research tool in cognitive neuroscience and biological psychiatry. Indeed, confirmation of mood improvement in mania and depression with left- and right-ear CVS, respectively, would provide strong support for the Sticky Switch model of bipolar disorder from which such therapeutic predictions arose. Moreover, such confirmation may help explain recent findings of corpus callosum and (lateralized) ACC white matter deficits in bipolar disorder. Finally, it should be noted that the model does, however, imply that induction of mania or depression from repeated right- or left-ear CVS, respectively, needs to be considered and monitored for, particularly for psychiatric but also for neurological treatment indications.

4 | CONCLUSIONS

While well known as a neurological diagnostic technique, vestibular stimulation has also historically been examined for psychiatric symptom modulation. Only recently, however, has there been clear documentation of the potentially therapeutic psychiatric effects of activating the vestibular system. CVS is a simple, safe, and inexpensive neuromodulation technique, now with ample evidence to suggest that it should be carefully examined for therapeutic efficacy in a variety of psychiatric and neurological conditions. With the common core/ aCIN proposal, and known activations of nodes in this network by CVS, evaluating the therapeutic efficacy of CVS becomes an even more urgent priority. The urgency lies not just in illustrative cases of initial candidates, but also in the field’s obligation to openly examine potential clinical translation of findings from psychiatric neuroimaging studies that have involved tens of thousands of patients and to examine noninvasive ahead of invasive potential therapies. The range of psychiatric disorders that may respond to CVS is large, given many such disorders exhibit structural or functional abnormalities in common core nodes; however, mania, depression and disorders with reduced insight stand out as promising initial candidates. If therapeutic efficacy of CVS is proven, a final common pathway of vestibular neuromodulation for psychiatric and neurological illnesses would indeed align these clinical disciplines.

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DISCLOSURE

The author of this paper does not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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