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REVIEW

Auditory verbal hallucinations: imaging, analysis, and intervention

Philipp Homan · Jochen Kindler · Daniela Hubl · Thomas Dierks

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Abstract In this article, we will link neuroimaging, data analysis, and intervention methods in an important psychiatric condition: auditory verbal hallucinations (AVH). The clinical and phenomenological background as well as neurophysiological findings will be covered and discussed with respect to noninvasive brain stimulation. Additionally, methods of noninvasive brain stimulation will be presented as ways to intervene with AVH. Finally, preliminary conclusions and possible future perspectives will be proposed.

Keywords Schizophrenia · Auditory verbal hallucinations · Transcranial magnetic stimulation · Cerebral blood flow · Arterial spin labeling

Introduction

One theoretical model of the genesis of psychosis assumes a functional imbalance of higher-order brain systems that are linked to three different domains of psychopathology [23]: the limbic system (related to affectivity) [26], the motor system (related to motor behavior) [3, 25], and the language system (related to the perception and production of speech) [22]. In the language domain, AVH are a key feature of a dysbalanced system. To an observer, they appear as a perception without an adequate stimulus. To a patient, however, they are serious and often horrifying experiences. Often they are resistant to medication, and frequently their persistence is responsible for a low quality of life in schizophrenia [20] or even suicide attempts [8]. Thus, it is obvious that therapeutic options are highly relevant. Besides conventional drug therapy, currently discussed therapeutic options are noninvasive physical interventions: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

P. Homan · J. Kindler · D. Hubl · T. Dierks (✉)
Department of Psychiatric Neurophysiology,
University Hospital of Psychiatry, University of Bern,
Bolligenstrasse 111, 3000 Bern 60, Switzerland
e-mail: dierks@puk.unibe.ch

Neuroimaging and electroencephalography (EEG) of AVH

Noninvasive therapeutic interventions of brain function require hypotheses on the mechanism of the brain's involvement in AVH. In 1999, we showed that normal hearing and AVH involve the same region in the brain: the primary auditory cortex [5]. This finding has been replicated in several imaging studies as described in a recent meta-analysis [16], although it is still a matter of debate whether the involvement of the primary auditory cortex is obligate or facultative for the experience of AVH. However, the main difference to normal hearing is that AVH apparently only involve the dominant hemisphere. That is in line with the assumption that not only the auditory cortex is activated but also regions that belong to the neuronal language production and perception system, which is located in the dominant hemisphere. However, one common problem in the research of AVH is their fleeting nature, that is, AVH are dynamic on a minutes or subminutes time scale. This dynamic has been studied in fMRI [5, 11, 21] and electroencephalography (EEG) studies [13] to investigate neurophysiological changes even at the subsecond level [14].

In addition to the functional disturbance in AVH, structural changes have been described [12, 24]. AVH are associated with altered brain fibers connecting the cortical

language regions like the arcuate fasciculus and the corpus callosum [12]. Thus, AVH arise from a disorder of inner speech and its monitoring [17]. Altered activation in speech production areas (i.e., inferior frontal gyrus) and altered coupling with monitoring areas (anterior cingulate) and language reception areas (Wernicke's area) have been proposed in a model of bottom-up dysfunction through over-activation in secondary (and occasionally primary) sensory cortices that lead to the experience of vivid perceptions in the absence of sensory stimuli [12, 13]. On the phenomenological level, the consequence of all this is the patient's unability to differentiate self-generated thoughts from external stimulation.

Arterial spin labeling (ASL) imaging and analysis: introducing aslm, an SPM8 toolbox

It is obvious that neuroimaging plays an important role in the elucidation of such an intriguing psychopathological phenomenon like hallucinations. An interesting approach in studying AVH is the measurement of resting brain perfusion with arterial spin labeling (ASL), a relatively new magnetic resonance imaging (MRI) technique to quantitatively measure the cerebral blood flow (CBF). The main difference to techniques like positron emission tomography (PET) is that no contrast agents are required. In ASL, blood flowing into the brain is magnetically labeled. The labeled blood exchanges with tissue water, altering the tissue magnetization, which can then be measured by MRI slice by slice. A perfusion-weighted image can be generated by the subtraction of an image in which inflowing spins have been labeled from an image in which spin labeling has not been performed [6, 9, 27]. To provide means of analyzing ASL images as well as other MRI data in a semi-automatic way, we developed an extension to the analysis package SPM8 (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm8), a toolbox called "a slightly modified asl-module" or "aslm" (downloadable at http://www.fil.ion.ucl.ac.uk/spm/ext/). The idea of the toolbox is to use an object-oriented approach that allows pipelining and intuitive operations like subtraction, addition, multiplication between objects (Fig. 1). That way, regions of interests (ROI) derived from functional MRI measurements can be used as input for a regional CBF calculation of these ROI.

Noninvasive brain stimulation

Besides using neuroimaging to elucidate neural mechanisms of AVH, an additional approach is to disrupt those mechanisms in question. One such intervention that is based on results derived from neuroimaging is noninvasive brain stimulation.

Transcranial magnetic stimulation (TMS)

In TMS, electrical stimuli are applied to the brain through the intact scalp by induced magnetic fields. Depending on the stimulation parameters, TMS is able to excite or inhibit the brain. Repetitive TMS is able to change and modulate activity even beyond the stimulation period, which is why it is sometimes referred to as offline TMS. Therefore, TMS

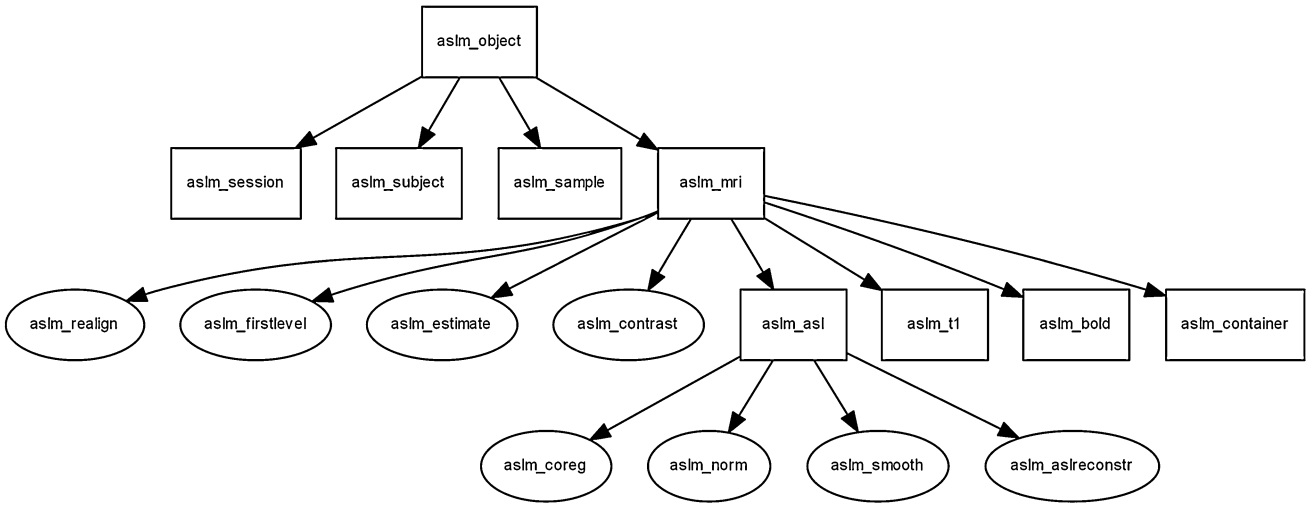

Fig. 1 Objects and routines involved in aslm, a data analysis toolbox for SPM8. The simplified dependency graph shows objects (*box shape*) and routines (*ellipse shape*) involved in the module, illustrating how code redundancy can be reduced by using an object-oriented approach where common functionality is defined in base classes. In addition, objects in aslm provide a command line interface (that is not present in SPM8 itself), which is useful in the automated analysis of large datasets

has therapeutic potential in patients with neurological and psychiatric disorders. It is, however, unclear by which mechanism TMS induces these lasting effects on the brain. A common hypothesis is that TMS affects the brain by changes in synaptic plasticity, i.e., mechanisms like long-term potentiation and long-term depression. Plasticity is the ability of the brain to reorganize itself, enabling short- and long-term remodeling of neural communication that outlasts an experimental manipulation or period of training. A new TMS protocol that has recently been introduced into clinical research is theta burst stimulation (TBS) [10, 15]. Compared with the often used 1 Hz stimulation protocol, TBS has the advantage that the application duration is very short, making the treatment more convenient for the patient. TMS has been studied as a method in treating psychosis, especially in AVH. In 2007, the first meta-analysis on 212 patients revealed a promising effect size of 0.76 [1]. However, the effectiveness of TMS in reducing AVH has recently been questioned. The largest study so far ($n = 62$) found no difference between verum and placebo TMS on the severity of AVH [21]. Notably, the authors used functional MRI to define their TMS target area individually (an approach called neuronavigation), which was supposed to increase the efficacy of TMS. The authors concluded that there is no difference in TMS and placebo (sham) applied to the left temporal cortex or to the site of maximal hallucinatory activation in medication-resistant AVH. However, an interesting extension in the combined TMS and neuroimaging approach is to include measurements of resting perfusion with ASL before and after TMS. Being noninvasive and relatively easy to employ, ASL measurements might be a clinically relevant way to monitor treatment success in patients with schizophrenia and AVH. By combining TMS and ASL in a basic clinical study, we have previously shown that TMS to the primary motor cortex caused a significant increase in CBF compared to sham, suggesting that inhibitory TMS induced a "virtual lesion" which then led to the mobilization of additional neuronal resources. As we did not find a specific modulation in motor behavior, we concluded that acute changes caused in the brain by TMS are probably compensated immediately and that this compensation is observable on a metabolic but not on a motoric level [19].

Transcranial direct current stimulation (tDCS)

Another stimulation approach is transcranial direct current stimulation (tDCS). In tDCS, weak direct currents are applied to the brain for several minutes noninvasively. Depending on the electrode, this leads to shifts in membrane potentials without causing neuronal firing like in TMS. Cathodal (negative) tDCS decreases, whereas anodal (positive) tDCS increases cortical excitability (Fig. 2). To rule out any placebo effect, it is common to compare verum

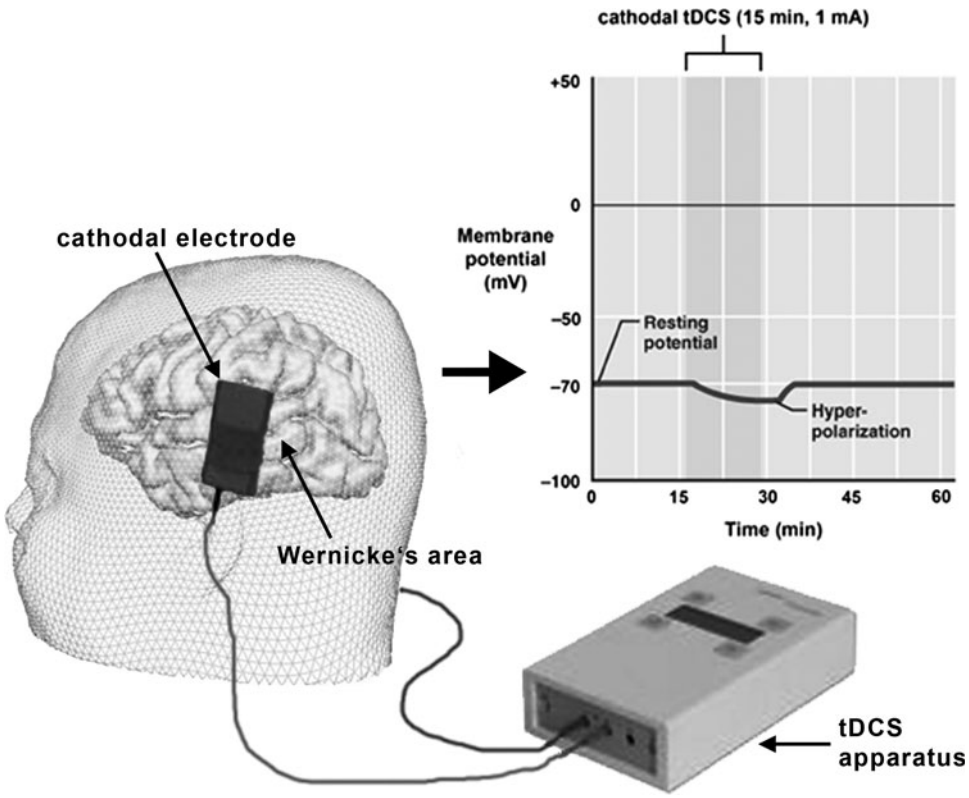

Fig. 2 Cathodal (negative) transcranial direct current stimulation (tDCS) supposedly causes hyperpolarization at Wernicke's area. Wernicke's area and other language regions are hyperperfused (hyperactive) in auditory verbal hallucinations in schizophrenia [5, 7]. The reference electrode (anode) is placed at the contralateral frontal area (not shown)

to pseudo-stimulation in tDCS. In pseudo-stimulation, the device is turned off after 1/30 of the normal stimulation time, and the device does not show which mode it is using. By applying in-house developed software (BlindTDCS.exe, downloadable at http://blindtdcs.sourceforge.net) that calculates numeric stimulation codes at random, even the investigator can remain blinded to the intervention. Thus, double-blind study designs can easily be employed in tDCS [18]. Interestingly, tDCS has effects not only at the motoric level, but also on brain metabolism [28]. The monitoring of intervention efficacy with ASL seems thus to be an obvious approach. Presently, we are conducting a randomized, double-blind, sham-controlled study in 10 patients with schizophrenia and persistent AVH. Before and after 10 days of cathodal tDCS over Wernicke's area and the anode placed on the right frontal area, we measure perfusion MRI with ASL. In our first patient, we found that a decrease in regional CBF in Wernicke's area and Broca'a area was associated with a promising symptom reduction [7]. This result has just recently been confirmed in a larger study ($n = 30$), where effects until 3 months after treatment have been reported [4]. Thus, tDCS seems to be a promising treatment approach.

Conclusion

It was shown that AVH are associated with a dysbalance in auditory- and speech-related networks mainly in the left temporal and frontal lobe. This altered activity can possibly be disrupted by means of noninvasive brain stimulation. To further investigate the effectiveness of tDCS and TMS, both will be compared with respect to clinical and neurophysiological efficacy in chronic hallucinations. In addition, it might be interesting to apply concurrent tDCS and MRI, i.e., measuring the subject in the scanner during stimulation with tDCS. Technically this is possible, and first studies on the motor cortex have recently been published [2]. Another approach could be to investigate whether there are alternative brain regions in nonresponders to TMS that could be considered as possible target regions. These current approaches and further development of noninvasive treatment of AVH show promise to be an important option.

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Conflict of interest The authors declare that they have no conflict of interest.

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