Schizophrenia Research 212 (2019) 1–3

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Auditory hallucinations in schizophrenia: Where are we now and where do we go from here? A personal commentary

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ARTICLE INFO

Article history:
Received 28 November 2017
Received in revised form 5 June 2019
Accepted 11 July 2019
Available online 2 August 2019

Keywords:
Auditory hallucinations
Schizophrenia
tDCS
fMRI
EEG

Auditory verbal hallucinations (AVH) are typically claimed to be present in about 60–80% of the patients with schizophrenia (Andreasen and Flaum, 1991). For research purposes, our group is always eager to engage patients without a lifetime history of hallucinations, as they would make a good comparison group in studying patients suffering from this distressing symptom. In our experience, however, most patients who are referred to us by their clinicians as *not* having experienced hallucinations, often admit to having experienced this symptom at least once during their illness during a systematic interview. For this interview, we use a detailed questionnaire (Questionnaire for Psychotic Experiences, QPE), developed by the International Consortium for Hallucinations Research (ICHR) (Sommer et al., 2018; Rossell et al., 2019). When interviewed this way, hallucinations appear to be a mainstay finding in people with schizophrenia. Therefore, we would like to propose that the actual percentage of lifetime hallucinations may well be much higher than the usually stated 60–80%.

Hallucinations may not necessarily lead to disturbed daily functioning, as some patients excel in knowing how to disguise their voices, and can still engage in a conversation or complete their work, even though they regularly hear negative emotional voices. Regrettably, other people face chronic hallucinations who severely decrease their potential and quality of life (Breier and Berg, 1999). Thus, coping techniques, insight and individual existential aspects are of utmost importance for the way hallucinations may or may not lead to dysfunction and distress. An extended interview for either clinical or research purposes should therefore include questions about the meaning of hallucinations for the individual person, potential coping skills and quantification of stress and dysfunction associated with hallucinations. The impressively high prevalence and at times high rate of associated distress of hallucinations among patients schizophrenia, have motivated the scientific community in recent years to better understand this symptom in order to improve treatment and relieve also those with intractable hallucinations.

To date, considerable progress has been made in the field to better understand and treat hallucinations. This editorial commentary is an invitation to provide a personal commentary in relation to the special issue in Schizophrenia Research. Research presented in this issue provide further evidence on the neural basis of hallucinations, providing new angles for focal stimulation and/or investigating the effect of focal stimulation. We will also discuss strong and weak points of current research and provide future directions to steer the field to more fruitful and practical outcomes in terms of enhanced knowledge about the underlying mechanisms, leading to patient-benefits.

Having read these recent papers on hallucinations, what do we learn from them and how does this further the field? Firstly, they show us that the auditory circuit including insula, superior temporal cortex, temporo-parietal cortex and cingular areas is probably more active and highly connected in hallucinating than in non-hallucinating patients. The introduction to the field of functional and structural connectivity has added a new dimension to theoretical interpretations and theories, which goes beyond a traditional view of impairments of function in specific brain areas. These areas may not be malfunctioning or atrophic, but may rather be 'too busy' with the generation of hallucinations, which prevent simultaneous use of the circuit for other jobs (as observed with MMN or sensory gating paradigms, see this issue). We can use such information to improve treatment for patients with hallucinations. For example, patients can actually use this rivalry for brain resources to cope with their voices; if they engage in demanding auditory/language tasks (reading aloud, singing, having a discussion), resources for generating voices run low, and the hallucination tend to become less severe.

Other papers in the current issue also show us that in addition to existing treatment options (such as coping protocols, cognitive behavioral therapy (CBT), and antipsychotic medication), repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) may be valid, easy and safe options for treatment of hallucinations. We need to remain creative and resourceful to provide better treatment to help patients decrease severity and stressfulness of their voices. Recent meta analyses (see e.g. Lee et al., 2017) have reported effect-sizes for tDCS well above what is seen for clozapine treatment, and where tDCS is effective in situations with little or no effect of antipsychotics. A critical point in such meta

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https://doi.org/10.1016/j.schres.2019.07.017

analyses is however the mixing data from randomized clinical trial and open label designs. Open-label designs do not control for nonspecific placebo effects, such as improvement of symptoms due to attention from a clinical research team, more knowledge about distressing symptoms and good hopes (both from patients and researchers) for improvement. These factors are controlled for in a double-blind random controlled trial (RCT) design, as patients in the sham condition (if well blinded) will show a similar improvement due to these factors as the treatment group. Therefore, we recommend to exclude the open label studies and only investigate double blind RCTs, as this will give a much more accurate picture and probably a much lower effect size. So far, we are not convinced by this review that tDCS is indeed the solution needed and more high quality RCTs are needed. In addition, it should perhaps be noted that tDCS has so far never been linked to any functional or structural brain change, with scant evidence in animals (Rohan et al., 2015; Kronberg et al., 2017), and there have been questions whether tDCS can stimulate neuroplasticity (Antal et al., 2015; Horvath et al., 2015; Chrysikou et al., 2017), or even reach the brain at all (Underwood, 2016). If tDCS is indeed able to improve sensory gating, demonstrated in a double-blind design, it would greatly help to establish this method as a valid treatment option.

1. fMRI functional connectivity studies

Another hot topic in hallucinations research, also reflected in the current issue, is functional connectivity studies based on resting-state fMRI. Functional connectivity assessed with fMRI reflects a state of the brain during no specific tasks or instructions, a kind of "mind-wandering". Although important results have emerged from such studies (see e.g. Chang et al., 2017), they are also vulnerable to many influences. Examples of such unwanted influences are: anxiety in the scanner, general anxiety or preoccupation with specific thoughts, but also to sedative effects of medication or sleep deprivation and to motor artifacts caused by increased anxiety, extrapyramidal side-effects or decreased cooperativeness. Given all these potential influences that are generally present in comparing patients to controls, functional connectivity studies are easily biased by many factors that are not under study. Another general comment regarding resting-state fMRI is that it in principle studies the functioning of the brain in non-task situations, i.e., in situations when no specific stimuli or instructions linked to specific cognitive processes are presented. It is therefore not obvious how to interpret findings of the existence of so called task-positive networks, such as e.g. the salience network, central executive network, dorsal attention network, during a resting-state situation (see Lee et al., 2012 for review). As the name implies, a task-positive network is a network associated with a particular cognitive task or process. On the other hand a task-negative network, like the Default Mode Network (DMN) (Raichle et al., 2001), appears in the absence of a task, i.e. during a resting-situation. If the same network appears during both rest and active processing it is unclear what it reflects in terms of underlying cognitive processes, including hallucinations.

2. Looking ahead: Open issues and questions

Now looking forward to the years to come, we see two important questions regarding hallucinations, which still remain to be answered. We will address them both briefly, with suggestions for future research in order to advance our knowledge in this research area, having both a clinical and more general research importance.

3. Why are hallucinations fluctuating over time?

With the introduction of functional imaging techniques, like PET and in particular fMRI, it was suddenly possible to start asking questions about the neuronal mechanisms underlying hallucinatory behavior (Silbersweig et al., 1995; Sommer et al., 2008). Although these techniques have moved the borders of our knowledge about auditory hallucinations (AH), see for example Jardri et al. (2011) and Kompus et al. (2011), there is also an obvious limitation with this line of research, since it has almost exclusively been preoccupied with the changes in brain activity that accompanies the *initiation and onset* of a hallucinatory episode. An equally important question is to understand the *termination and offset* of an episode. A common characteristic of auditory hallucinations is that they fluctuate over time. It is quite rare to find patients that experience continuous hallucinations, although there are great individual variations regarding frequency, and duration. The bottom-line is nevertheless that hallucinatory episodes fluctuate over time, i.e. they come and go on a daily basis. We would like to direct the attention to the importance of studying the offsets, and not only the onsets. As suggested by Hugdahl and Sommer (2018) in their analysis of auditory hallucinations across "levels of explanation", the observed fluctuations at the behavioral level, may have its counterpart of transmitter fluctuations at the synapse and receptor level. This suggestion was based on recent findings of increased levels of excitatory neurotransmitters in the language areas of the brain (Ćurčić-Blake et al., 2017; Hugdahl et al., 2015) in hallucinating patients. This could act as triggers for a hallucinatory episode, which in turn would change neuronal firing and metabolism in these areas, with a corresponding change in blood flow and activation, as observed by fMRI, at the systems level of explanation. Following the suggestions by Jardri et al. (2016) that auditory hallucinations may represent an imbalance of excitatory and inhibitory neuronal influences (the E/I-imbalance model), we now advance the hypothesis that on- and off-fluctuations of hallucinatory episodes may reflect corresponding fluctuations of excitatory/inhibitory neurotransmitter influences, where transmitters either are in or out of balance over time. As we pointed out above, such a view emphasizes that the brain areas involved in generating auditory hallucinations may not necessarily be malfunctioning, or atrophic, but that they are "too busy" or hyper-excited, which is normalized during periods when the "voices" are silent. The paper by Thoma et al. (present issue) nicely shows how the neural circuitry regulating inhibitory processes is altered during hallucinatory periods compared to periods when the voices are absent. Another paper addressing a similar topic is the paper by Alonso-Solís et al. (present issue), who used a novel analysis approach to analyze fMRI imaging data based on amplitude of low frequency fluctuations. These slow fluctuations indirectly reflect subtle changes in neuronal excitation and inhibition, i.e. changes in neuronal activity, which in turn can explain why hallucinatory episodes fluctuate over time. An unanswered question is however what causes these alterations in inhibition and excitation at lower levels of explanation, and are they related to corresponding alterations in excitatory/inhibitory transmitters? There is surprisingly little research devoted to the neurochemistry of hallucinations. This is the more surprising with the availability of modern MR techniques, like MR spectroscopy (De Graaf, 2019), which makes it possible to record small changes in transmitter concentrations in selected brain regions (see e.g. Ćurčić-Blake et al., 2017; Hugdahl et al., 2015).

4. What causes a hallucinatory episode?

Another unanswered question is what causes, or triggers, a hallucinatory episode on a daily basis. This is not to say that we lack knowledge of eliciting factors for the onset of hallucinations in the first place. There is ample evidence that childhood trauma is a risk-factor and in that sense a trigger for later hallucinations (Dvir et al., 2013). The question we ask here is not what may be predisposing factors for psychosis and psychotic symptoms, but rather what environmental or internal factors may act as acute triggering events for a hallucinatory episode. This is an important question for several reasons. First, there are great individual differences when episodes occur. Some patients report being overwhelmed by their "voices" in situations of calm and

tranquility, like when being alone at home, others report that the "voices" typically occur in noisy and stressful situations, while still others do not report any environmental events or circumstances as being linked to the occurrence of a hallucinatory episode. Bless et al. (2017) found that about half of their sample of 130 non-clinical individuals who experienced hallucinations could not identify a specific event as a trigger of the first time they experienced a hallucinatory episode. Those that did identify a specific triggering event on the other hand experienced emotionally more negative hallucinations, and they also had been in contact with mental health services over the years. These examples show that whether a hallucinatory episode occur as a spontaneous, almost random, experience, or can be related to specific internal states and external events, is an important issue for advancing knowledge about the underlying neurobiological causes of hallucinations, not in the least for the understanding of the underlying neurochemistry of hallucinations. It would not be unreasonable to hypothesize that spontaneous, random, episodes could be more driven by alterations in excitatory/inhibitory neurotransmitter balances, while event-elicited episodes could more be driven by psychological and mental factors. The findings that repeatedly occurring hallucinatory episodes not always seem to have clear triggers in the environment is an intriguing observation. It should be pointed out however that there is not much known about day-to-day fluctuations of emotional and arousal states in relation to hallucinatory episodes. This has been partly hindered by inaccessibility of monitoring hallucinatory episodes on an hourly basis during an ordinary day, not possible to monitor through retrospective interview questionnaires like PANSS, PsyRats, or the more recent QPE (Rossell et al., 2019). The introduction of smartphone technologies into mental health services and research has changed this, where it is now possible to use an app to collect data on episodes throughout a day (Smelror et al., 2019). The answers to questions like these are not only of theoretical interest, it could also pave the way for new personalized treatment and intervention approaches, targeting both pharmacological treatments and other therapy interventions, depending on the individual profile of the occurrence of hallucinatory episodes.

Contributors

Author Iris Sommer conceptualized and wrote the first draft of the manuscript. Author Kenneth Hugdahl wrote the concluding part and provided feedback and revised the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to thank all the contributors to the special issue and all the reviewers who have helped improve the submissions with constructive feedback. Funding: Dutch research organisation ZonMW "stratified research and Treatment for Hallucinations (STAR-H)" funded to Iris Sommer, project nr 63631 001 0 and European Research council Advances grant to Kenneth Hugdahl "Voices" project nr 693124

Funding body agreements and policies

The funding source had no further role in the current study with regard to data collection, data analysis and interpretation of findings or in manuscript preparation and the submission decision.

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