Auditory hallucinations: The perception of voices that do not exist

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Every mental phenomenon can be (and is) studied at different «levels of explanation», including auditory verbal hallucinations (AVHs)

- **Cultural/Social**
  - Norms, beliefs, attitudes

- **Clinical**
  - Symptoms, syndromes, diagnosis

- **Cognitive**
  - Perception, attention, executive, language

- **Brain imaging**
  - Neuronal systems and networks

- **Cellular**
  - Synapses and neurotransmitters

- **Molecular**
  - Genes, DNA, proteins
Schizophrenia

- Heterogenous disorder – multitude of sub-classifications and symptoms
- Diagnosis is descriptive and functional
- Underlying mechanism(s) for the disorder not known
- Problem predicting treatment effects - leads to a "trial-and-error" approach
ERC Advanced Grant Projects (I and II)
"Hearing Voices" - From cognition to brain systems

- Focus on the symptom rather than the diagnosis phenotype, «phenotype constraining approach»
- Auditory verbal hallucinations are the most characteristic symptom in schizophrenia, it "defines" a psychosis
- An hallucination is the experience of a perception in the absence of a corresponding sensory source

**Three characteristic dimensions:**
- Perceptual dimension ("hearing a voice")
- Cognitive dimension ("cannot control the voice")
- Emotional dimension ("the voice is evil")

**Two additional characteristics:**
- Spontaneously initiated
- Fluctuate across time, ‘come-and-go’

• heterogeneity in a symptom can be quantified, heterogeneity in a diagnosis cannot
• easier to focus research questions and hypotheses
• easier to translate between levels of explanation
• (easier to follow the literature)
The content of auditory verbal hallucinations (AVHs)

- «The voices not only speak to the patient, but they pass electricity through the body, beat him,paralyze him, take his thoughts away… »
- «Threats or curses form the main and most common content of the «voices».
- «Day and night they come from everywhere, from the walls, from above and below, from the cellar and the roof, from heaven and from hell, from near and far…»

Eugene Bleuler,
Dementia Praecox,
or The Group of Schizophrenia,
Monograph 1911
Why is it of interest to study an isolated symptom?

Hallucinations cross the borders between different psychiatric disorders

- Bipolar disorder
- Depression
- PTSD
- OCD
- Personality disorders
- Drug abuse

Hallucinations cross the border between psychiatric and neurological disorders

- Dementia
- PD
- Epilepsy

Hallucinations cross the border between pathological and normal states

- "Voice hearing" in the general population, could be a proxy for studies of the complexities of the mind, and states of consciousness
Perceptual dimension: Where to start looking…..

• If auditory hallucinations (AVH) are experienced as "someone speaking to the patient", it follows that they could have a neuronal origin in the same brain regions that encode normal speech perception.

• Normal speech perception is encoded in the posterior temporal lobe, primarily on the left side...

• ...thus, AVH are speech perceptual phenomena, mis-attributed to an external agent, caused by neuronal hyper-excitation in posterior temporal lobe regions.

• Such a definition can however not explain other aspects of AVH, such as failure of inhibition and attention focus, failure of cognitive control, ...

• ...thus, AVH may have an origin in temporal lobe abnormality, but are maintained through abnormal fronto-parieto-temporal network activity.

First prediction: Abnormal neuronal activity in the speech perception areas in the peri-Sylvian region.
Neuronal activation in healthy subjects in the *presence* of an external speech sound

Neuronal activation in hallucinating patients in the *absence* of an external speech sound

Perceptual dimension


Meta-analysis, Jardri et al, *Am J Psychiatry*, 2011, Fig 2
A "paradoxical" finding - the activation is reduced or disappears...

Auditory cortex activation in the absence of a speech signal in hallucinating patients

Auditory cortex activation in the presence of a speech signal in hallucinating patients

- The neurons seem to be "refractory" and the perceptual system is "shut down" during AHs...

- …or could be an attentional bias effect towards the «voice» which prevents the recognition of an external stimulus, the cognitive system is "shut down"...

- Neuronal interference, and competition for common neuronal resources have also been reported by Woodruff et al. 1997, Hubl et al., 2007

"Severity of AVHs was significantly associated with GMV reductions in the left and marginally with the right STG, including Heschl’s gyrus”.

/Meta-analysis by Modinos et al., Cortex, 2013, Abstract/

Replicated again in Mørch-Johnsen et al., (Schiz Bull, in press)

Caveat

«Functional and structural abnormality at the brain level of explanation must however be shown to have a correspondence at the behavioral level because perception is about behavior, or in other words, nothing in neuroscience makes sense without behavior»
Dichotic listening to probe speech perception

«Auditory hallucinations should interfere with the perception of an external speech sound»

Correlating dichotic listening performance and PANSS P3 symptom scores

Third prediction: Should be a negative correlation between dichotic listening right ear performance and PANSS
N = 160, data from Norway, Turkey, USA

Hugdahl, Løberg, Kompus et al. Schizophrenia Research (2012)
Patients report reduced attentional salience to external events. Could this be seen as reduced ability to shift attention in a modified version of the dichotic listening paradigm?

Cognitive dimension

Fourth prediction: If AVHs reduce attention span to external stimuli, then there should be a negative correlation between FR/RE performance and PANSS P3 score.

Additional prediction: If AVHs reduce cognitive control, then there should be a negative correlation between FL/LE performance and PANSS P3 score.

Three conditions.
- No instruction (NF) (perception)
- Forced-right (FR) (attention)
- Forced-left (FL) (executive function)
...which have neuronal correlates in the classic hypofrontality in schizophrenia in response to cognitive effort (working memory, executive, attention)

Emotional dimension

BAVQ-R (Chadwick et al., 2000)

Self-report scale

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(only first 14 questions listed on this slide)

We know from previously that the Malevolent (M) and Omnipotency (O) factors in the BAVQ questionnaire correlates positively with PANS P3 (AVH) scores.

We now ask the question, are there brain correlates of negative emotional «voice» content, and if so, where in the brain should we look?

M = Malevolent, B = Benevolent, O = Omnipotent
BAVQ scores and Amygdala volume

«Smaller volume leaves negative emotions to dominate over positive emotions, there is not «room» for both»

Fifth hypothesis: Brain activation in the limbic system/amygdala should be increased in patients with frequent AVHs

Preliminary data by Kristiina Kompus, and Liv Falkenberg, Bergen fMRI Group
Significant increase in functional connectivity between the right amygdala and thalamus, could be a driving factor behind the the negative emotional valence in AVH+ patients.

Preliminary data by Kristiina Kompus, Bergen fMRI Group
Neurochemistry of auditory hallucinations

- Cultural/Social
- Clinical
- Cognitive
- Brain imaging
- Cellular
  (transmitters, receptors, synapses)
- Molecular

Where do we go from here?

Pharmacological fMRI

Drug Memantine to block glutamate action at the receptor site. Significant reductions in BOLD activation in PFC in the memantine condition.

Wageningen, Jørgensen, Hugdahl et al., Cerebral Cortex, 2009

MR spectroscopy (MRS and fMRI)

The healthy individual

1. Cortical Glu is synthesized from astroglia Gln
2. Release of Glu is balanced by GABA release
3. Striatal DA release is controlled by Glu/GABA

The schizophrenia patient

1. Cortical Glu is not balanced because of GABA dysfunction
2. Glu hyper-activity initiates AH
3. AH not inhibited by DA-antagonistic antipsychotic medication, because AHs are Glu-mediated (Risperidone/Clozapine example)

The hallucinating patient

1. Glu hypo-activity in schizophrenia leaves DA-receptors uninhibited, causing positive symptoms
2. Antipsychotic medication reduces DA-levels

Sixth prediction:
Since AVHs are excitatory phenomena, we should search for an excitatory transmitter, i.e. glutamate concentrations should correlate positively with frequency of AVHs.
The «VOICE» Model

Clinical challenge: How could the temporal hyper-activation be inhibited or suppressed and at the same time excite or enhance the frontal hypo-activation?

iPhone/iPod app for training to shift attention/control the «voices»

Train the ability to switch attention away from the «voices» and towards the surrounding world, increase executive cognitive control.
Summary and conclusions

• We have a fairly good understanding of the neurobiological markers of the perceptual and cognitive aspects of auditory hallucinations, we have however just began getting data from the emotional dimension, and why the «voices» are predominantly negative.

• We have fairly well outlined the neuronal architecture at the cognitive and imaging levels of explanation, and also have emerging data at the receptor and transmitter level, but we lack good data from the molecular level, is there a genetic explanation «deep down»?

• We have a reasonably good understanding of the neurobiological markers of the onset, or initiation of a hallucinatory episode, but we almost totally lack data on what makes an episode spontaneously disappear, i.e. what are the neurobiological markers of the offset, of a hallucinatory episode, this is the focus of the ERC II project.