Universitetet i Bergen
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HELSE BERGEN

Neuroimaging in psychiatry: Focus on auditory hallucinations

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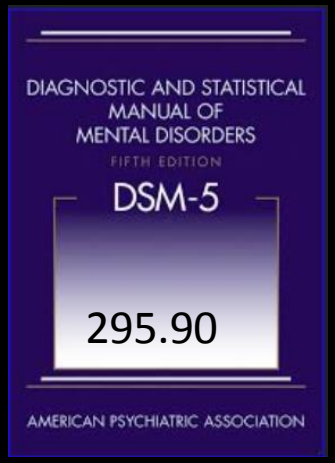
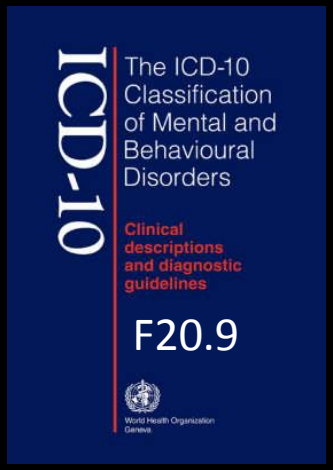
Schizophrenia

- **Heterogenous disorder – multitude of sub-classifications and symptoms**
- **Diagnosis is descriptive and functional**
- **Underlying mechanism(s) not known**
- **No biomarkers or predictive models identified**
- **Problem predicting treatment effects - leads to a "trial-and-error" approach**





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ERC Advanced Grant Project

"Hearing Voices" - From cognition to brain systems

- **Focus on the symptom phenotype rather than the diagnosis. phenotype, «Phenotype constraining approach»**
- **Auditory hallucinations are the most characteristic symptom in schizophrenia, it "defines" a psychosis**

- 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)

Three characteristic dimensions:

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

The content of hallucinations

- «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…»

Perceptual

Cognitive

Emotional

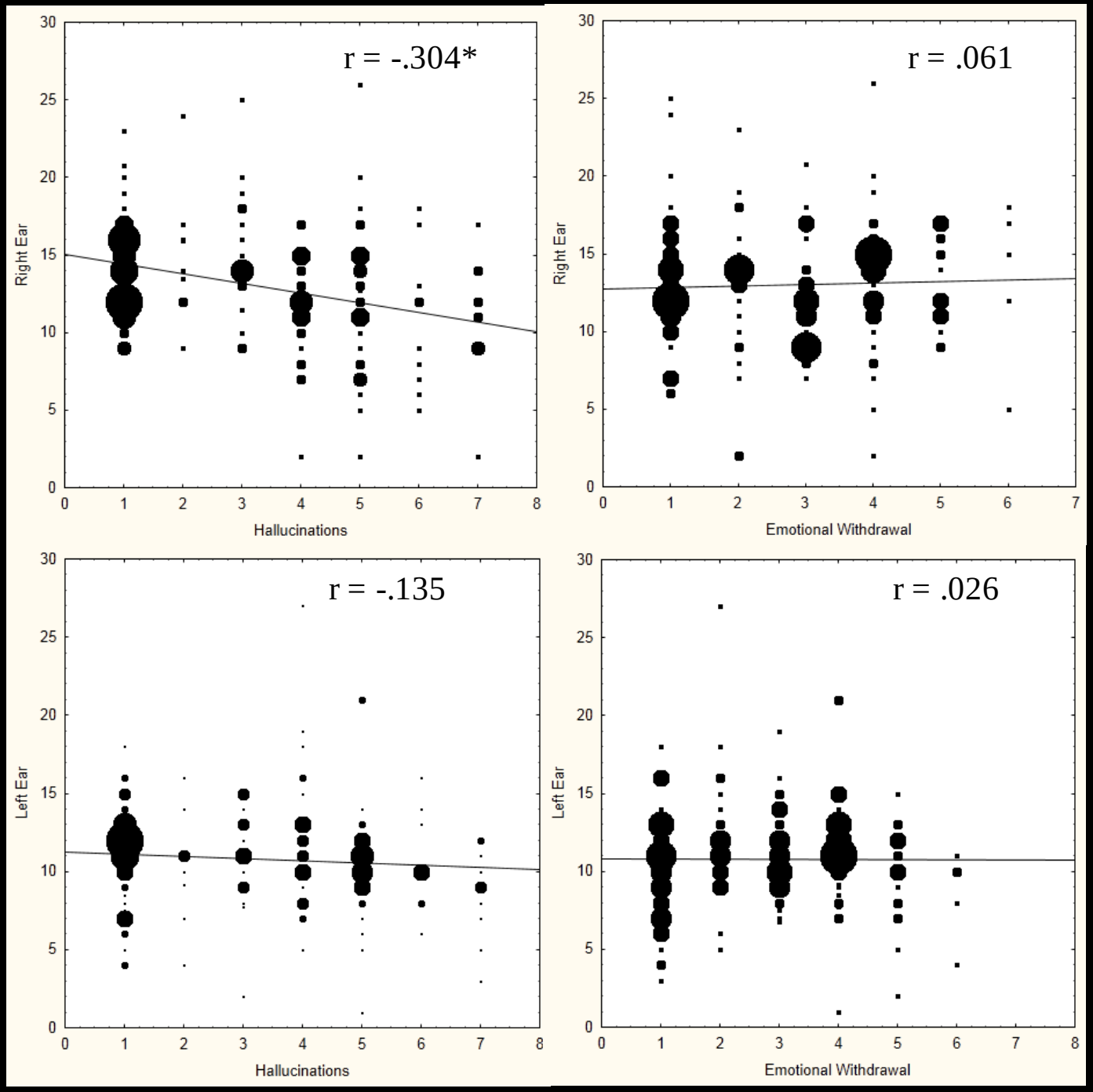
Eugene Bleuler, *Dementia Praecox, or The Group of Schizophrenia*, Monograph 1911

Perceptual dimension - Auditory hallucinations would interfere with the processing of an external sound

Correlating dichotic listening performance and PANSS P3 symptom scores

...should be a negative correlation between REA and PANSS

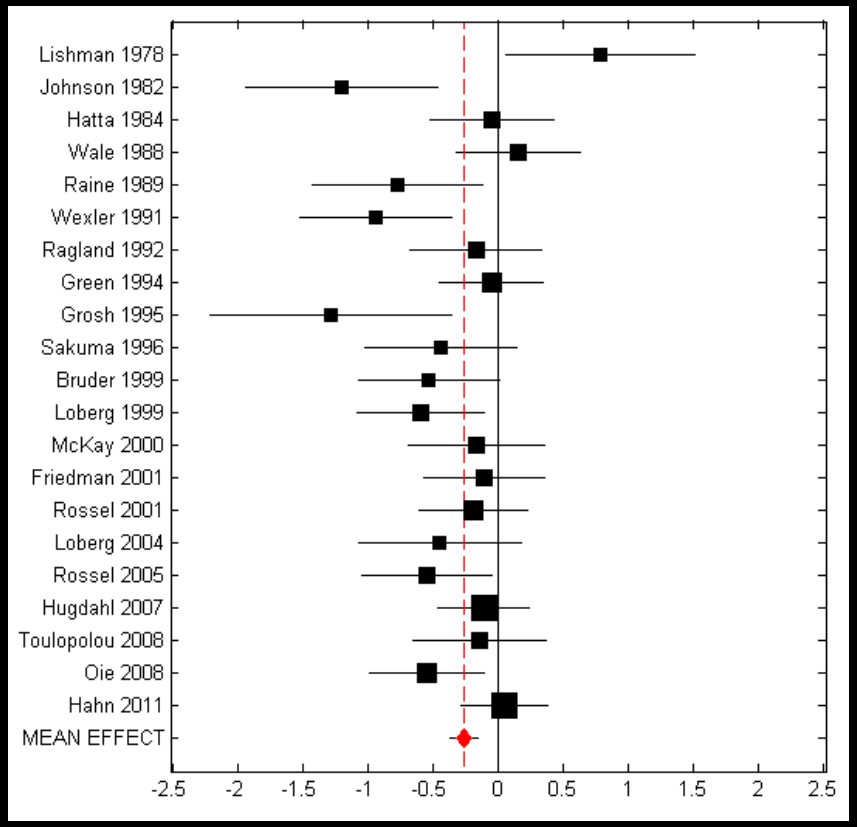
N = 160, data from Norway, Turkey, USA



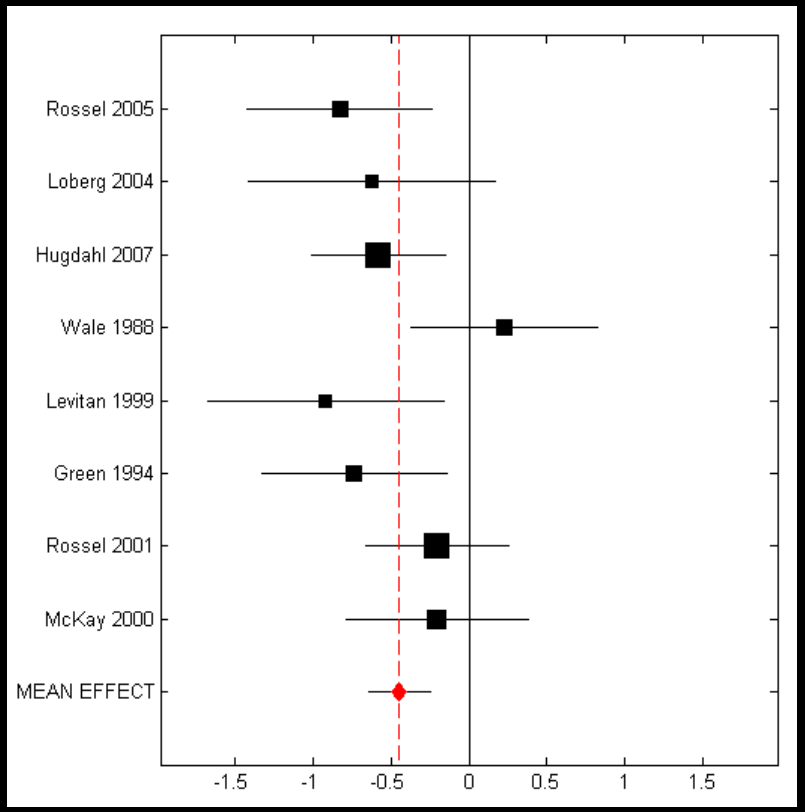
Hugdahl, Løberg, Kompus et al. *Schizophrenia Research* (2012)

Meta-analysis of difference in REA between Schizophrenia patients and Healthy controls
21 studies, N = 700 patients and 700 controls

Patients vs. Controls



Hallucinating patients. vs. Controls

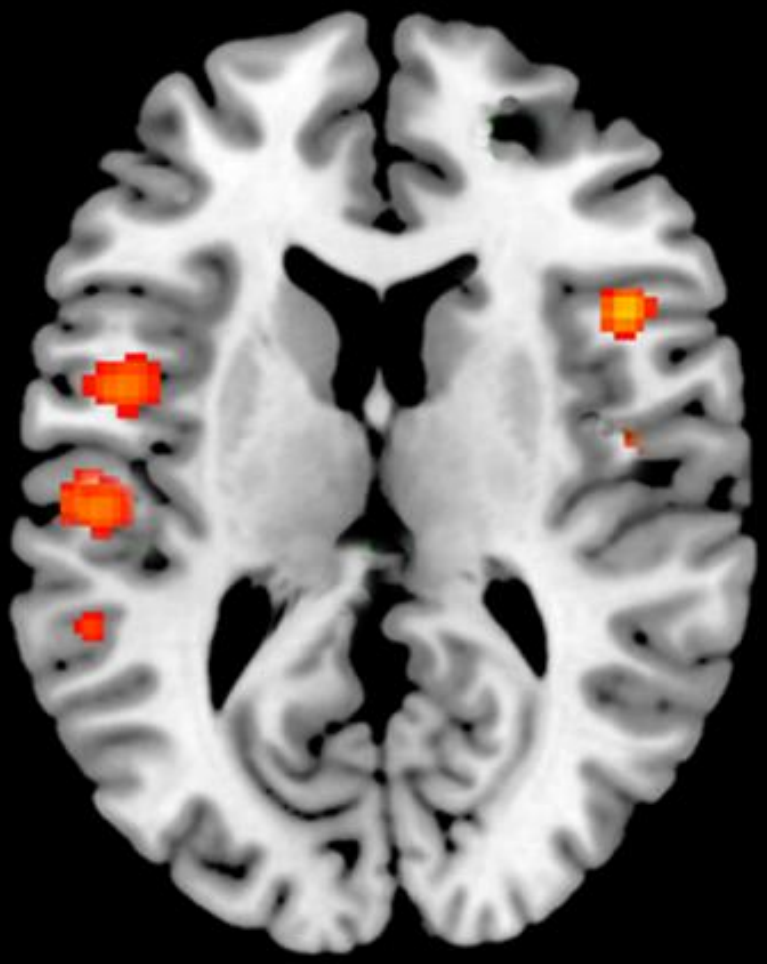


Ocklenburg, Westerhausen, Hirnstein et al., *JINS*, *2013*

Functional imaging data: State effects

Meta-analysis of PET and fMRI-studies

K. Kompus, R. Westerhausen, K. Hugdahl
Neuropsychologia (2011)



N = 103

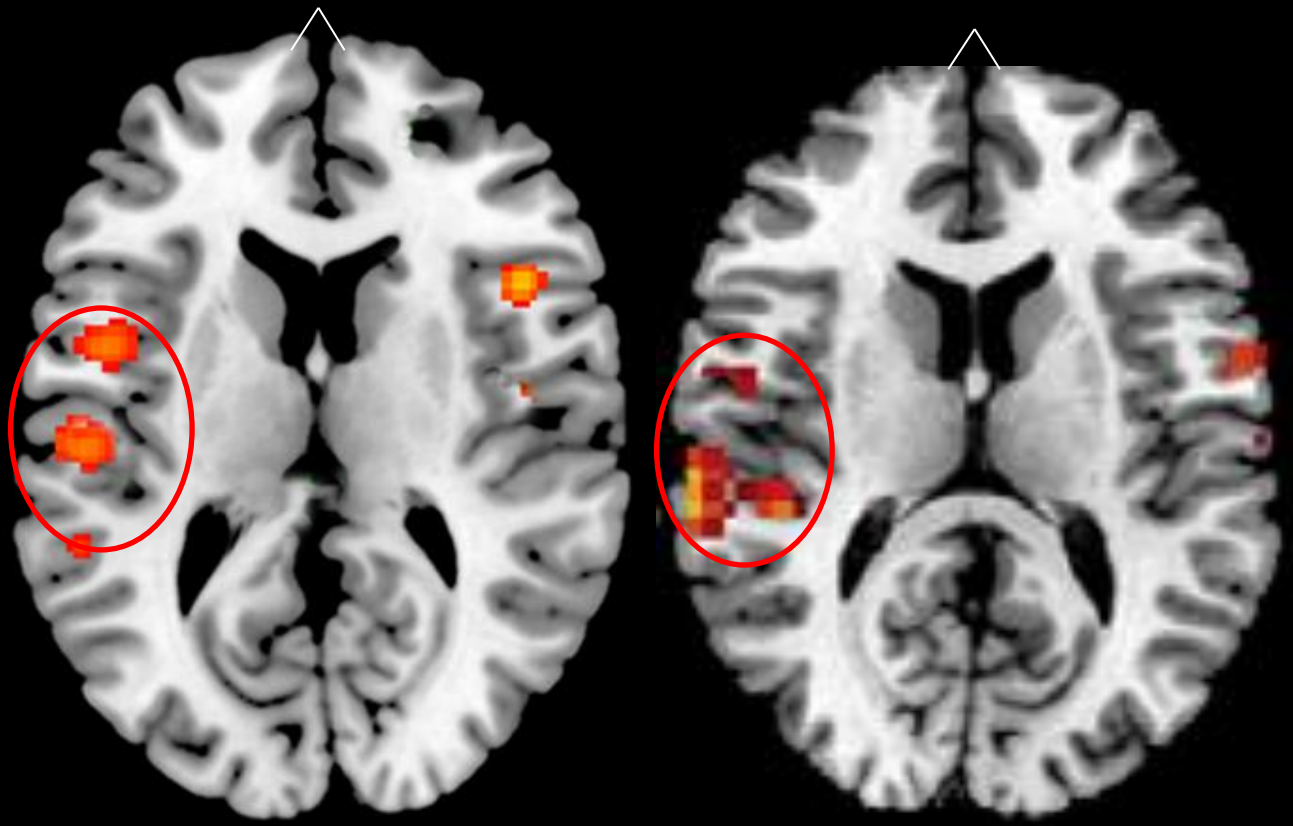
"...we were fortunate to be able to study the interesting and rare case of a woman with schizophrenia who experienced continuous AVH..."

"AVHs were associated with increased metabolic activity in the left primary auditory cortex ..." (Bentaleb et al., 2002, Abstract, p. 110)

...but is this the same area(s) that are activated in healthy individuals in the presence of an external spech sound?

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

Neuronal activation in healthy subjects in the ***presence*** of an external speech sound



N = 103

N = 12

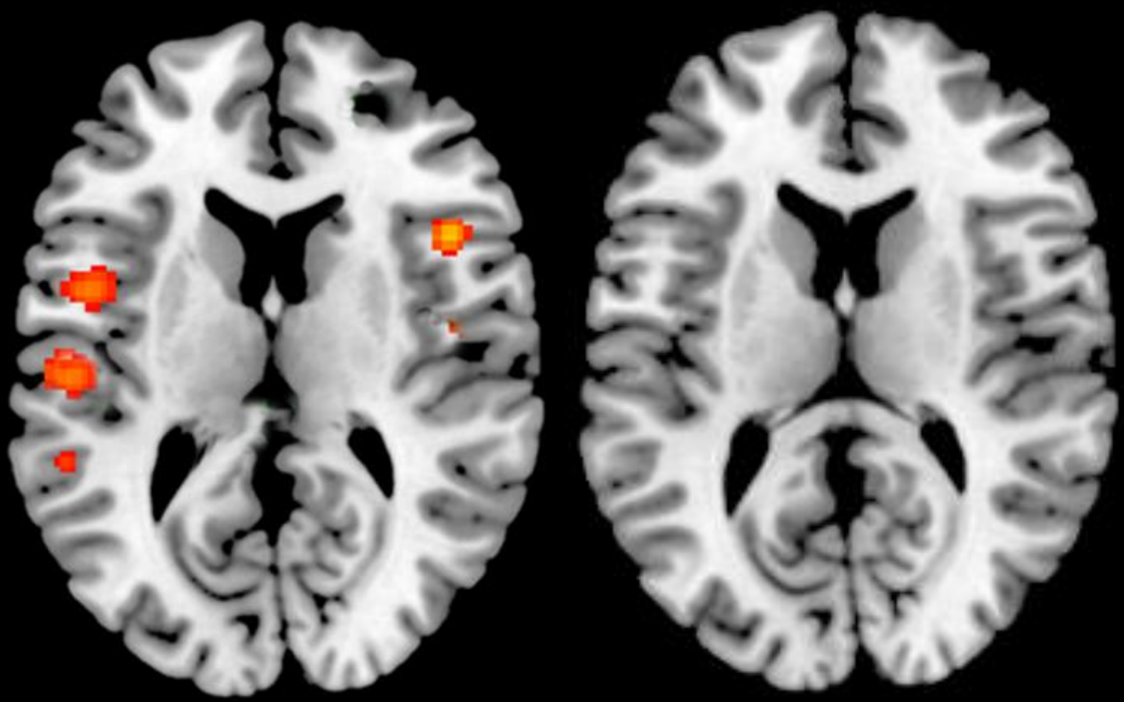
Kompus, Westerhausen, Hugdahl, *Neuropsychologia* (2011)

van den Noort, Specht, Rimol,, et al., *Neuroimage* (2008)

...that lead to a "paradoxical" finding - the activation is reduced or disappears...

Auditory cortex activation in the *absence* of a speech signal (state effect)

Auditory cortex activation in the *presence* of a speech signal (trait effect)



Kompus, Westerhausen, Hugdahl, *Neuropsychologia*, 2011

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

"Hallucinations lowered the N100 amplitudes, presumably due to a reduced left temporal responsivity to external stimulation between externally and internally generated physiological sources" (Hubl et al., 2007, Abstract, p. 87)

"The auditory hallucinatory state is associated with reduced responsivity in temporal cortical regions that normally process external speech, possibly because of competition for common neurophysiological resources" (Woodruff et al., 1997; Abstr. p. 1676)

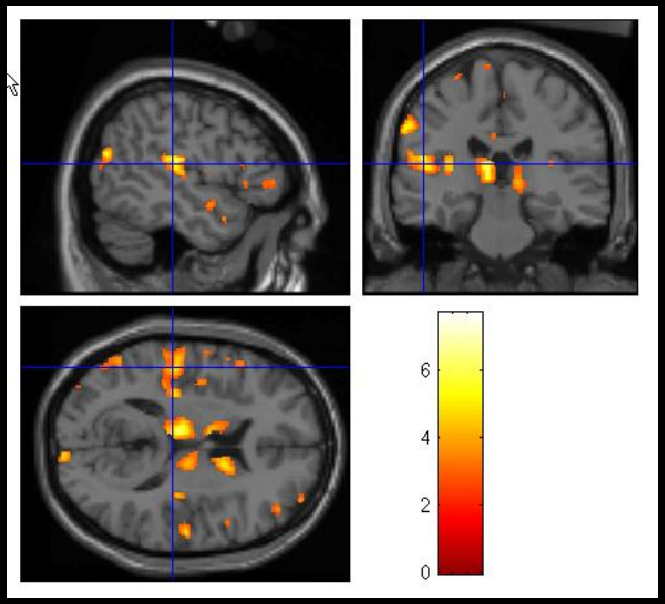
- **...or could be an attentional bias effect towards the «voice» which prevents the recognition of an external stimulus, the cognitive system is "shut down"...**
- **...or could be a signal-gating, rather than signal-processing effect, aberrant inhibition of noise, the sub-cortical system is "shut down"...**
- **In all instances, AHs *interfere* with processing of an external sound**

...but do patients really have problems with auditory and speech percption?

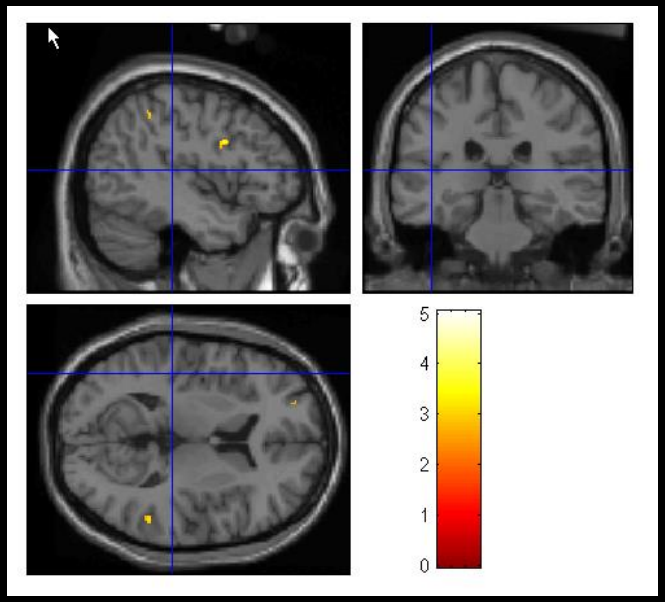
- Pitch perception deficits for basic auditory stimuli, failure of MMN change detection (Javitt et al., 2000; Ahveninen et al., 2006; Fischer et al., 2011)
- Impaired recognition of familiar voices (Zang et al., 2008)
- Impaired recall of previously presented voices (Waters & Badcock, 2009)
- Impaired ability to analyze speaker identity. (Chabra et al., 2012)
- Hallucinating patients are impaired in voice identity recognition (Alba-Ferrara et al., 2012)
- Hallucinators performed worse than non-hallucinators and controls for pitch discrimination of unmodulated tones and auditory streaming (MacLachlan et al., 2013)

Is there an underlying structural asymmetry that would strengthen the functional data?

Hallucinating patients



Non-Hallucinating patients

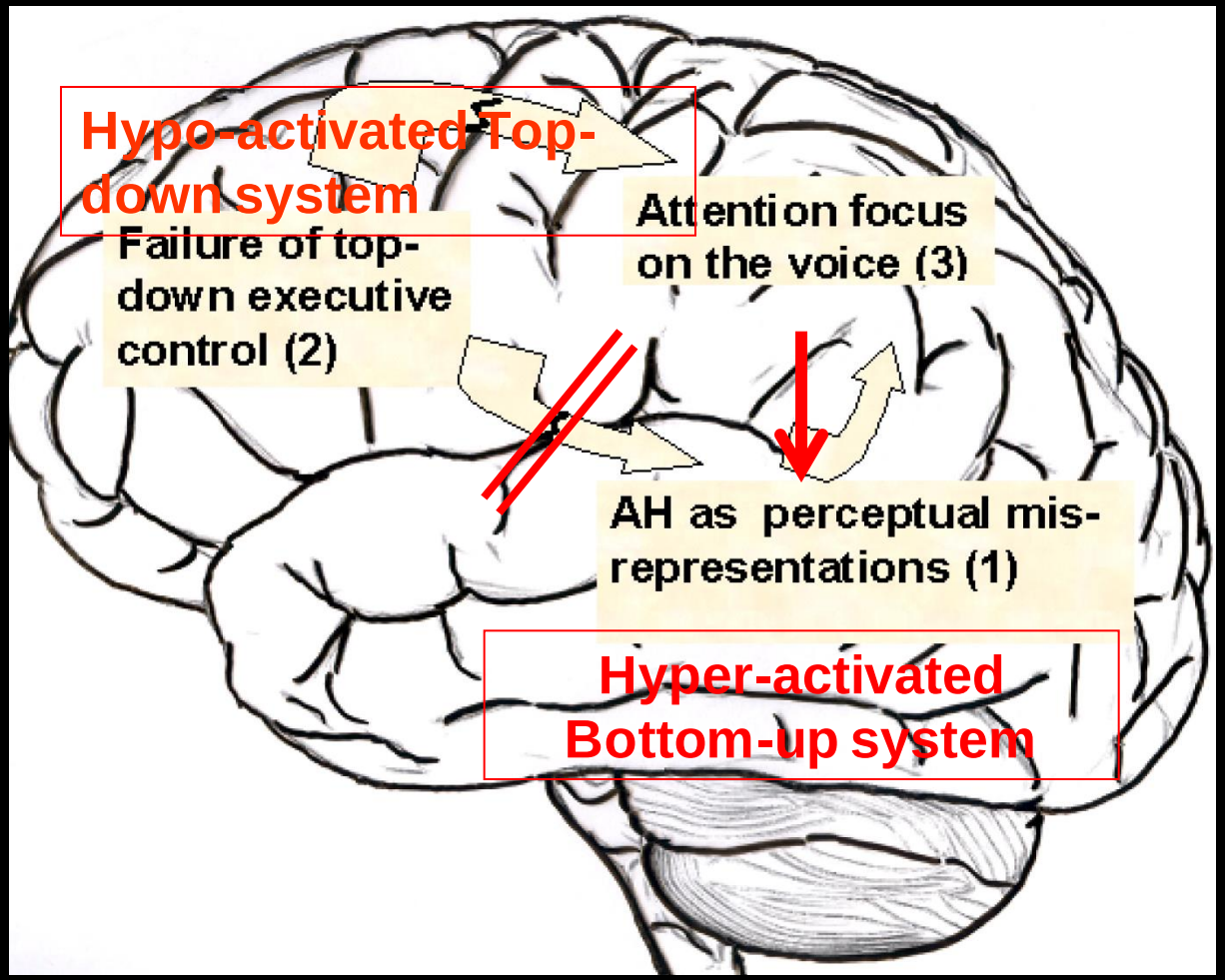


"Severity of AVHs was significantly associated with GMV reductions in the left and marginally with the right STG, including Heschl's gyrus"

/Meta-analysis by Modinos, Costafreda, van Tol,.McGuire, Aleman, Allen., Cortex, 2013, Abstract/ see also van Tol et al., 2013

G. Neckelmann, K. Specht, L. Ersland, K. Hugdahl et al. *Int J Neuroscience*, 2006

The Model



Clinical implication

Is it possible to selectively train attention focus away from the "voices" and towards the outer world, and at the same time increase cognitive control and executive function?

In other words, **hyper-excitate the top-down system!**

Hugdahl, Løberg, Nygård, *Frontiers in Neuroscience*, 2009

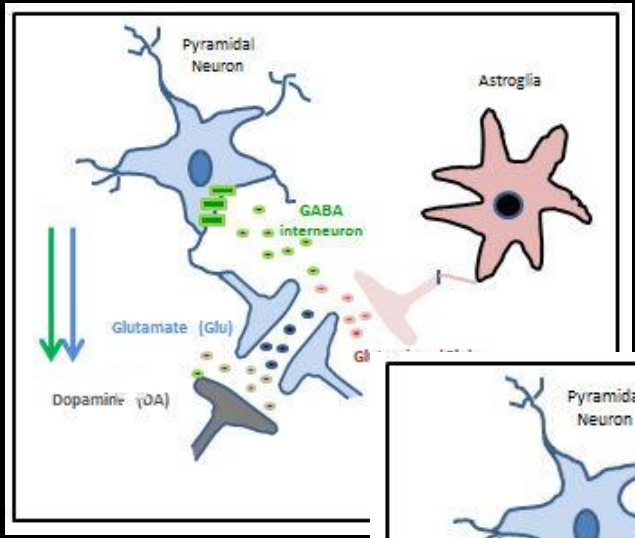
...if imaging data explains the cognitive data, what explains the imaging data? Levels of Explanation

- **Cultural/Social**
  Norms, beliefs, attitudes
- **Clinical**
  Symptoms/Syndromes/Diagnoses
- √ **Cognitive**
  Perception, Attention, Executive, Language
- √ **Brain imaging**
  Neuronal systems and networks
- √ **Cellular**
  Synapses and neurotransmitters
- **Molecular**
  Genes, DNA, proteins

AVHs seem to be excitatory phenomena, thus a first hint would be to search for an excitatory transmitter in the key regions in the brain

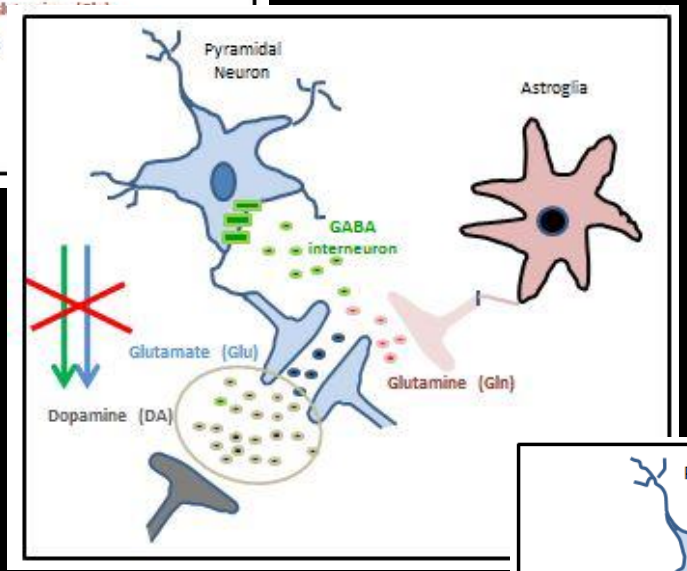
Neurochemistry of auditory hallucinations

The healthy indivdiual



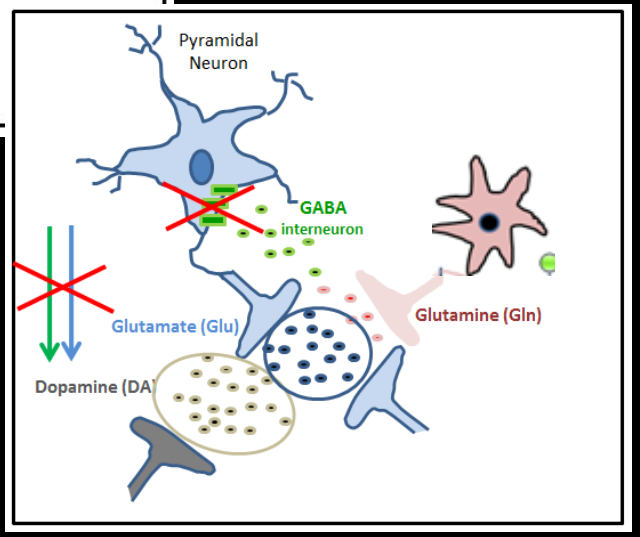
1. Cortical Glu is synthesized from astroglia Gln
2. Release of Glu is balanced by GABA release
3. Striatal DA release is controlled by Glu/GABA

The schizophrenia patient



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

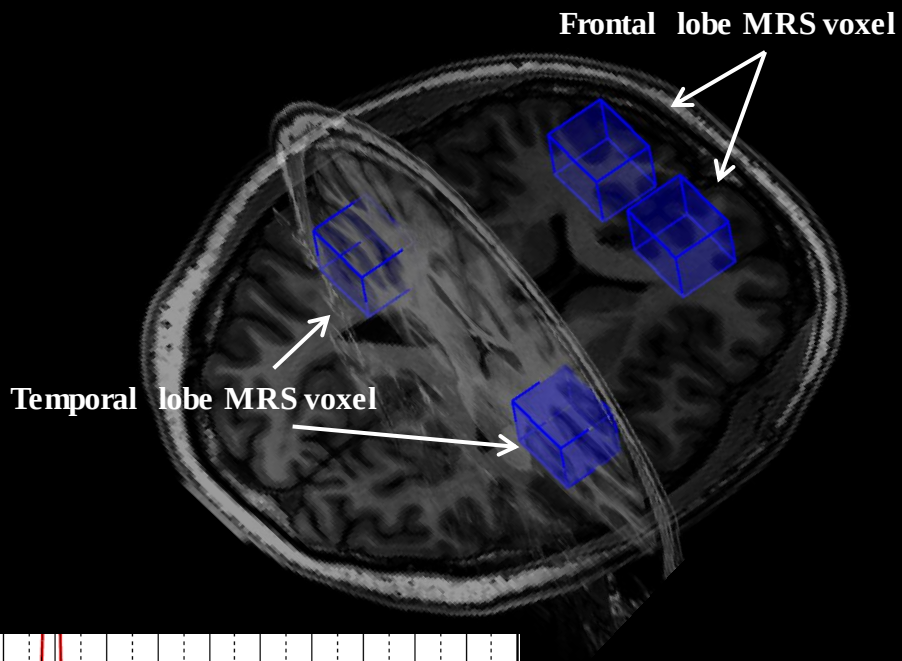
The hallucinating patient

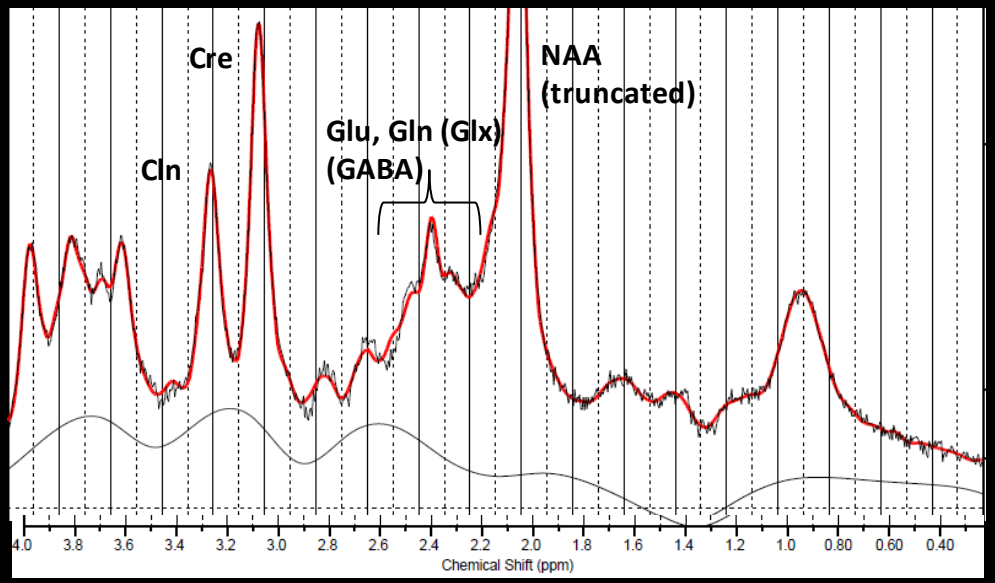


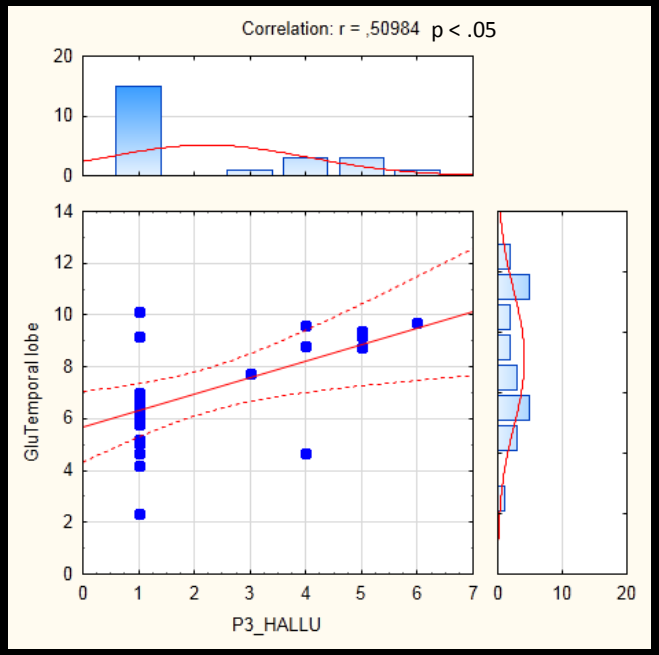
1. Cortical Glu is not balanced because of GABA dysfunction
2. Glu hyper-activity initiates AH
3. AH not inhibited by DA-antagonistic antipsychotic medication, beacuse AHs are Glu-mediated (Risperidone/Clozapine example)

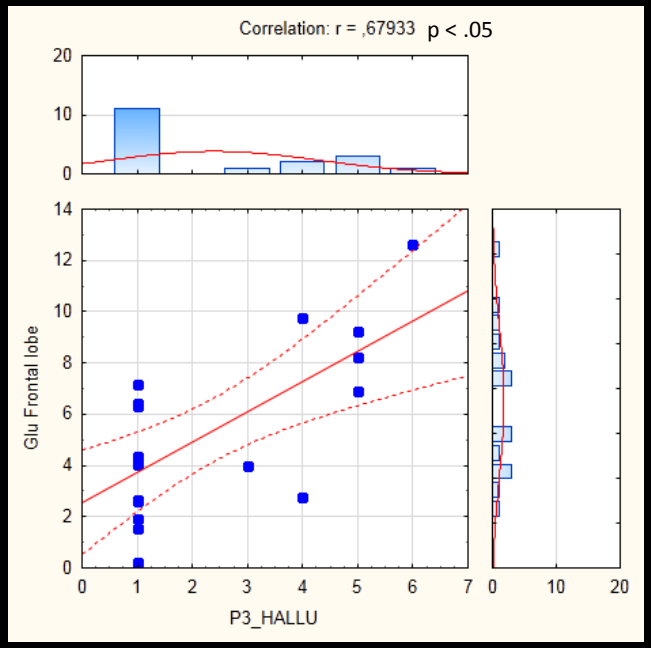
Thus, a first question is whether there is increased Glu levels in the hallucinating brain, and particularly in temporal (and frontal) areas?

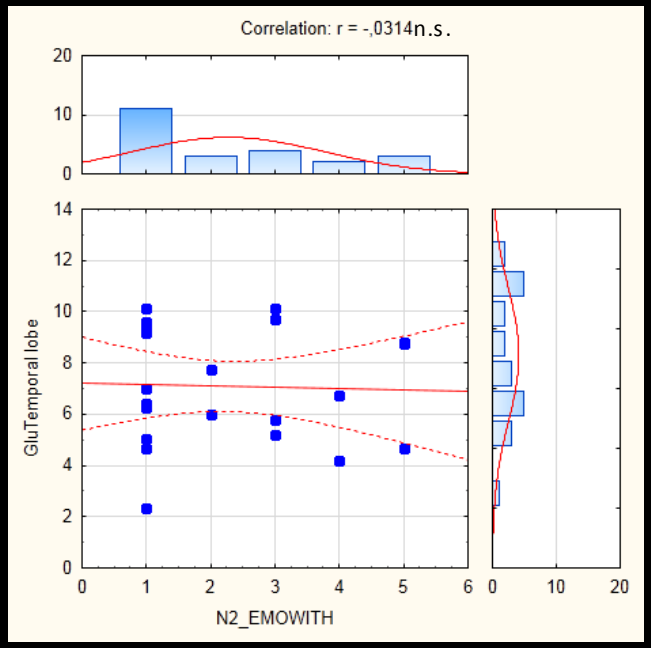
MR Spectroscopy (MRS)

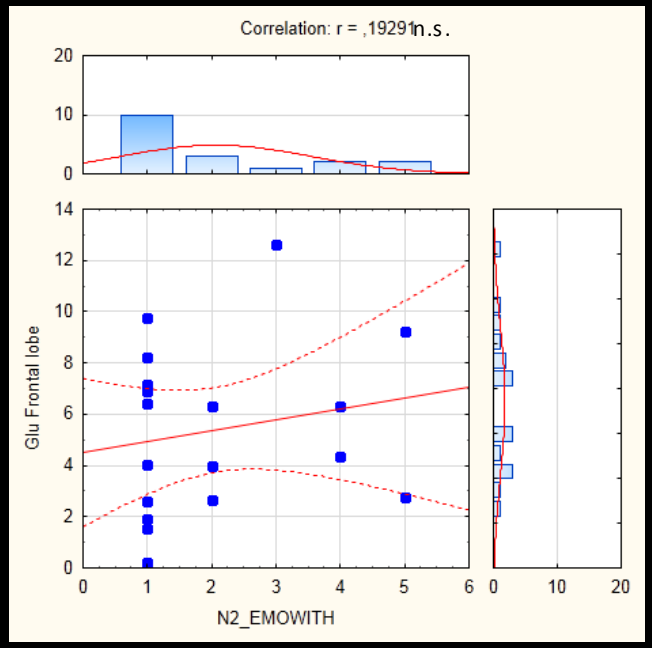












Hugdahl, Nygård, Løberg et al., in revision August 2014

How specific is the correlation with the AVH symptom and Glu across the range of PANSS symptoms?

Variable	GluTemporal lobe	Glu Frontal lobe
P1_DEL	0,455274	0,474314
P2_CON	0,238132	0,291792
P3_HAL	0,465845	0,640679
P4_EXC	0,228148	0,213766
P5_GRA	0,259896	0,397535
N1_BLU	-0,340804	-0,048366
N2_EMO	-0,031370	0,192913
N3_RAP	-0,101439	-0,012550
N4_PAS	-0,218014	0,019875
N5_ABS	0,212966	-0,046346
N6_SPO	-0,334065	-0,158890
G1_SOM	0,101679	0,076525
G2_ANX	0,050093	0,344407
G3_GUI	0,265660	0,129893
G4_TEN	-0,082463	-0,103093
G6_DEP	-0,248437	0,088020
G7_MOT	-0,076469	-0,137117
G9_THO	0,568660	0,538670
G10_DIS	-0,100623	-0,135750
G12_INS	0,422139	0,463303
G13_VOL	0,209462	0,057769
G16_AVO	-0,209722	0,244602

Red correlations are significant at $p < .05$, Spearman's r

Emotional dimension - attempt at quantification

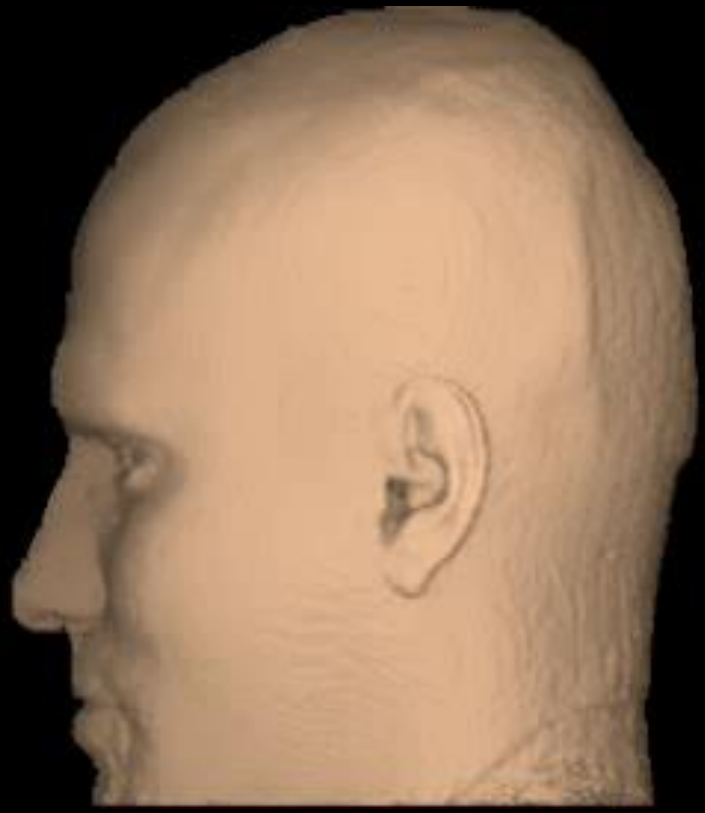
Use BAVQ scores to investigate if high PANSS score on P3 (AH) item goes together with negative or positive AH content (N = 54).

Is this specific for AH?

Variable	P3 HALLUCIN	POSTOT	N2 WITHDRAW	NEGTOT
1-PUNISH_M	0,274838	0,121820	0,123373	0,069036
2-HELP_B	0,058034	0,252693	0,008664	-0,038622
3-POWERFUL	0,414088	0,348763	0,156029	0,210688
4-PERSECUTE_M	0,277096	0,191334	0,151424	0,030268
5-PROTECT_B	0,139368	0,267693	-0,045175	-0,030294
6-TOKNOW	0,270248	0,077799	0,001390	-0,028161
7-EVIL_M	0,219607	0,104806	0,130189	0,162874
8-KEEPSANE_B	0,162179	0,225256	0,097013	0,017952
9-NOTWANTDO	0,397602	0,257474	0,115631	0,203970
10-HARMME_M	0,222105	0,088449	0,141370	0,102327
11-ABILITIES_B	0,148285	0,455472	-0,104422	-0,017671
12-CONTROL	0,248586	-0,054417	-0,000000	-0,029466
13-BADTHINGS_M	0,222683	-0,005041	0,228247	0,129434
14-GOALS_B	-0,011602	0,105479	-0,166058	-0,117758
15-KILLME	0,447455	0,471611	0,279768	0,238185
16-DESTROYME_M	0,319626	0,354744	0,163926	0,180273
17-GRATEFUL_B	0,125635	0,354186	-0,117614	-0,071674
18-RULESME	0,400083	0,298676	0,155235	0,197478
19-REASSURE_E	0,041169	0,066335	-0,095260	-0,214428
20-FRIGHTEN_R	0,172264	0,083696	-0,062911	-0,126874
21-HAPPY_E	0,128041	0,198385	-0,034174	-0,091409
22-FEELDOWN_R	0,132772	0,020760	-0,093022	-0,092998
23-FEELANGRY_R	0,275797	0,235114	-0,117864	-0,047925
24-FEELCALM_E	0,054394	0,298400	0,086643	0,011146
25-FEELANX_R	-0,066678	0,136742	-0,043273	-0,136234
26-FEELCONFID_E	0,037755	0,261319	0,262368	0,121993
27-LEAVEALONE_R	0,175265	0,146554	-0,089489	-0,202106
28-TAKEMINDOFF_R	-0,131640	-0,094491	0,001502	-0,049520
29-STOPIT_R	0,002893	-0,064693	-0,021661	-0,184768
30-PREVENTTALK_R	0,052504	-0,093887	-0,058856	-0,066055
31-NOTOBEY_R	0,036149	0,014499	0,209031	0,050628
32-WANTLISTEN_E	0,047782	0,159368	-0,021194	-0,006672
33-WILLFOLLOW_E	0,081756	0,129870	0,087621	0,145257
34-GETCONTACT_E	0,182100	0,236586	0,306197	0,233023
35-SEEKADVICE_E	0,043051	0,276203	0,148638	0,135893

Outstanding questions:

- **Why are the "voices" predominantly negative, where does the emotional aspect come from?**
- **What happens in the brain the last seconds before a patients wxpreineces "hearing a voice", the last seconds before the "voices" goes away?**
- **What is it with "voices" that makes them appear both in clinical and non-clinical contexts, where is the "bridge"?**
- **Is there a genetic predisposition "deep down"?**



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