

Iris Else Sommer – Selected references

de Weijer, A. D., Neggers, S. F., Diederer, K. M., Mandl, R. C., Kahn, R. S., Hulshoff Pol, H. E. et al. (2013). Aberrations in the arcuate fasciculus are associated with auditory verbal hallucinations in psychotic and in non-psychotic individuals. *Human Brain Mapping*, 34, 626-634.

Notes: The pathophysiology of auditory verbal hallucinations (AVH) is still unclear. Cognitive as well as electrophysiological studies indicate that a defect in sensory feedback (corollary discharge) may contribute to the experience of AVH. This could result from disruption of the arcuate fasciculus, the major tract connecting frontal and temporo-parietal language areas. Previous diffusion tensor imaging studies indeed demonstrated abnormalities of this tract in schizophrenia patients with AVH. It is, however, difficult to disentangle specific associations with AVH in this patient group as many other factors, such as other positive and negative symptoms, medication or halted education could likewise have affected tract integrity. We therefore investigated AVH in relative isolation and studied a group of non-psychotic individuals with AVH as well as patients with AVH and non-hallucinating matched controls. We compared tract integrity of the arcuate fasciculus and of three other control tracts, between 35 non-psychotic individuals with AVH, 35 schizophrenia patients with AVH, and 36 controls using diffusion tensor imaging and magnetization transfer imaging. Both groups with AVH showed an increase in magnetization transfer ratio (MTR) in the arcuate fasciculus, but not in the other control tracts. In addition, a general decrease in fractional anisotropy (FA) for almost all bundles was observed in the patient group, but not in the non-psychotic individuals with AVH. As increased MTR in the arcuate fasciculus was present in both hallucinating groups, a specific association with AVH seems plausible. Decreases in FA, on the other hand, seem to be related to other disease processes of schizophrenia

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Daalman, K., Verkooijen, S., Derks, E. M., Aleman, A., & Sommer, I. E. (2012). The influence of semantic top-down processing in auditory verbal hallucinations. *Schizophrenia Research*, 139, 82-86.

Notes: **BACKGROUND:** Auditory verbal hallucinations (AVH) are one of the most prominent symptoms of schizophrenia but have also been reported in the general population. Several cognitive models have tried to elucidate the mechanism behind auditory verbal hallucinations, among which a top-down model. According to this model, perception is biased towards top-down information (e.g., expectations), reducing the influence of bottom-up information coming from the sense organs. This bias predisposes to false perceptions, i.e., hallucinations. **METHODS:** The current study investigated this hypothesis in non-psychotic individuals with frequent AVH, psychotic patients with AVH and healthy control subjects by applying a semantic top-down task. In this task, top-down processes are manipulated through the semantic context of a sentence. In addition, the association between hallucination proneness and semantic top-down errors was investigated. **RESULTS:** Non-psychotic individuals with AVH made significantly more top-down errors compared to healthy controls, while overall accuracy was similar. The number of top-down errors, corrected for overall accuracy, in the patient group was

in between those of the other two groups and did not differ significantly from either the non-psychotic individuals with AVH or the healthy controls. The severity of hallucination proneness correlated with the number of top-down errors. **DISCUSSION:** These findings confirm that non-psychotic individuals with AVH are stronger influenced by top-down processing (i.e., perceptual expectations) than healthy controls. In contrast, our data suggest that in psychotic patients semantic expectations do not play a role in the etiology of AVH. This finding may point towards different cognitive mechanisms for pathological and nonpathological hallucinations

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Diederer, K. M., van Lutterveld, R., & Sommer, I. E. (2012). Neuroimaging of voice hearing in non-psychotic individuals: a mini review. *Frontiers in Human Neuroscience*, 6, 111.

Notes: Auditory verbal hallucinations (AVH) or "voices" are a characteristic symptom of schizophrenia, but can also be observed in healthy individuals in the general population. As these non-psychotic individuals experience AVH in the absence of other psychiatric symptoms and medication-use they provide an excellent model to study AVH in isolation. Indeed a number of studies used this approach and investigated brain structure and function in non-psychotic individuals with AVH. These studies showed that increased sensitivity of auditory areas to auditory stimulation and aberrant connectivity of language production and perception areas is associated with AVH. This is in concordance with investigations that observed prominent activation of these areas during the state of AVH. Moreover, while effortful attention appears not to be related to AVH, individuals prone to hallucinate seem to have an enhanced attention bias to auditory stimuli which may stem from aberrant activation of the anterior cingulate regions. Furthermore, it was observed that decreased cerebral dominance for language and dopamine dysfunction, which are consistently found in schizophrenia, are most likely not specifically related to AVH as these abnormalities were absent in healthy voice hearers. Finally, specific aspects of AVH such as voluntary control may be related to the timing of the supplementary motor area and language areas in the experience of AVH

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Diederer, K. M., Daalman, K., de Weijer, A. D., Neggers, S. F., van Gastel, W., Blom, J. D. et al. (2012). Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. *Schizophrenia Bulletin*, 38, 1074-1082.

Notes: While auditory verbal hallucinations (AVH) are most characteristic for schizophrenia, they also occur in nonpsychotic individuals in the absence of a psychiatric or neurological disorder and in the absence of substance abuse. At present, it is unclear if AVH in these nonpsychotic individuals constitute the same phenomenon as AVH in psychotic patients. Comparing brain activation during AVH between nonpsychotic and psychotic individuals could provide important clues regarding this question. 21 nonpsychotic subjects with AVH and 21 matched psychotic patients indicated the presence of AVH during 3T functional magnetic resonance imaging (fMRI) scanning. To identify common areas of activation during the experience of AVH in both groups, a

conjunction analysis was performed. In addition, a 2-sample t-test was employed to discover possible differences in AVH-related activation between the groups. Several common areas of activation were observed for the psychotic and nonpsychotic subjects during the experience of AVH, consisting of the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri and postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole, and right cerebellum. No significant differences in AVH-related brain activation were present between the groups. The presence of multiple common areas of AVH-related activation in psychotic and nonpsychotic individuals, in the absence of significant differences, implicates the involvement of the same cortical network in the experience of AVH in both groups
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Howes, O. D., Shotbolt, P., Bloomfield, M., Daalman, K., Demjaha, A., Diederer, K. M. et al. (2012). Dopaminergic Function in the Psychosis Spectrum: An [18F]-DOPA Imaging Study in Healthy Individuals With Auditory Hallucinations. *Schizophrenia Bulletin*.

Notes: Background: The psychosis phenotype appears to exist in the population as a continuum, but it is not clear if subclinical psychotic symptoms and psychotic disorders share the same neurobiology. We investigated whether the dopaminergic dysfunction seen in psychotic disorders is also present in healthy, well-functioning people with hallucinations. Methods: We compared dopamine synthesis capacity (using 6-[(18)F]fluoro-L-DOPA [(18)F]-DOPA) positron emission tomography imaging) in 16 healthy individuals with frequent persistent auditory verbal hallucinations (hallucinating group) with that in 16 matched controls. Results: There was no significant difference in dopamine synthesis capacity in the striatum, or its functional subdivisions, between groups and no relationship between subclinical psychotic symptom severity or schizotypal traits and dopamine synthesis capacity in the hallucinating group. Conclusions: Altered dopamine synthesis capacity is unlikely to underlie subclinical hallucinations, suggesting that although there may be a phenomenological psychosis continuum, there are distinctions at the neurobiological level
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Laroi, F., Sommer, I. E., Blom, J. D., Fernyhough, C., Ffytche, D. H., Hugdahl, K. et al. (2012). The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: state-of-the-art overview and future directions. *Schizophrenia Bulletin*, 38, 724-733.

Notes: Despite a growing interest in auditory verbal hallucinations (AVHs) in different clinical and nonclinical groups, the phenomenological characteristics of such experiences have not yet been reviewed and contrasted, limiting our understanding of these phenomena on multiple empirical, theoretical, and clinical levels. We look at some of the most prominent descriptive features of AVHs in schizophrenia (SZ). These are then examined in clinical conditions including substance abuse, Parkinson's disease, epilepsy, dementia, late-onset SZ, mood disorders, borderline personality disorder, hearing impairment, and dissociative disorders. The phenomenological changes linked to AVHs in prepsychotic stages are also outlined, together with a review of AVHs in healthy

persons. A discussion of key issues and future research directions concludes the review
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Sommer, I. E., Clos, M., Meijering, A. L., Diederens, K. M., & Eickhoff, S. B. (2012). Resting state functional connectivity in patients with chronic hallucinations. *PLoS ONE*, 7, e43516.

Notes: Auditory verbal hallucinations (AVH) are not only among the most common but also one of the most distressing symptoms of schizophrenia. Despite elaborate research, the underlying brain mechanisms are as yet elusive. Functional MRI studies have associated the experience of AVH with activation of bilateral language-related areas, in particular the right inferior frontal gyrus (rIFG) and the left superior temporal gyrus (ISTG). While these findings helped to understand the neural underpinnings of hearing voices, they provide little information about possible brain mechanisms that predispose a person to experience AVH, i.e. the traits to hallucinate. In this study, we compared resting state connectivity between 49 psychotic patients with chronic AVH and 49 matched controls using the rIFG and the ISTG as seed regions, to identify functional brain systems underlying the predisposition to hallucinate. The right parahippocampal gyrus showed increased connectivity with the rIFG in patients as compared to controls. Reduced connectivity with the rIFG in patients was found for the right dorsolateral prefrontal cortex. Reduced connectivity with the ISTG in patients was identified in the left frontal operculum as well as the parietal opercular area. Connectivity between the ISTG and the left hippocampus was also reduced in patients and showed a negative correlation with the severity of hallucinations. Concluding, we found aberrant connectivity between the seed regions and medial temporal lobe structures which have a prominent role in memory retrieval. Moreover, we found decreased connectivity between language-related areas, indicating aberrant integration in this system potentially including corollary discharge mechanisms

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Sommer, I. E., Slotema, C. W., Daskalakis, Z. J., Derks, E. M., Blom, J. D., & Van der, G. M. (2012). The treatment of hallucinations in schizophrenia spectrum disorders. *Schizophrenia Bulletin*, 38, 704-714.

Notes: This article reviews the treatment of hallucinations in schizophrenia. The first treatment option for hallucinations in schizophrenia is antipsychotic medication, which can induce a rapid decrease in severity. Only 8% of first-episode patients still experience mild to moderate hallucinations after continuing medication for 1 year. Olanzapine, amisulpride, ziprasidone, and quetiapine are equally effective against hallucinations, but haloperidol may be slightly inferior. If the drug of first choice provides inadequate improvement, it is probably best to switch medication after 2-4 weeks of treatment. Clozapine is the drug of choice for patients who are resistant to 2 antipsychotic agents. Blood levels should be above 350-450 mug/ml for maximal effect. For relapse prevention, medication should be continued in the same dose. Depot medication should be considered for all patients because nonadherence is high. Cognitive-behavioral therapy (CBT) can be applied as an augmentation to antipsychotic medication. The success of CBT depends on the reduction of catastrophic appraisals, thereby reducing the concurrent

anxiety and distress. CBT aims at reducing the emotional distress associated with auditory hallucinations and develops new coping strategies. Transcranial magnetic stimulation (TMS) is capable of reducing the frequency and severity of auditory hallucinations. Several meta-analyses found significantly better symptom reduction for low-frequency repetitive TMS as compared with placebo. Consequently, TMS currently has the status of a potentially useful treatment method for auditory hallucinations, but only in combination with state of the art antipsychotic treatment. Electroconvulsive therapy (ECT) is considered a last resort for treatment-resistant psychosis. Although several studies showed clinical improvement, a specific reduction in hallucination severity has never been demonstrated

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van Lutterveld, R., Hillebrand, A., Diederer, K. M., Daalman, K., Kahn, R. S., Stam, C. J. et al. (2012). Oscillatory cortical network involved in auditory verbal hallucinations in schizophrenia. *PLoS ONE*, 7, e41149.

Notes: BACKGROUND: Auditory verbal hallucinations (AVH), a prominent symptom of schizophrenia, are often highly distressing for patients. Better understanding of the pathogenesis of hallucinations could increase therapeutic options.

Magnetoencephalography (MEG) provides direct measures of neuronal activity and has an excellent temporal resolution, offering a unique opportunity to study AVH pathophysiology. METHODS: Twelve patients (10 paranoid schizophrenia, 2 psychosis not otherwise specified) indicated the presence of AVH by button-press while lying in a MEG scanner. As a control condition, patients performed a self-paced button-press task. AVH-state and non-AVH state were contrasted in a region-of-interest (ROI) approach. In addition, the two seconds before AVH onset were contrasted with the two seconds after AVH onset to elucidate a possible triggering mechanism. RESULTS: AVH correlated with a decrease in beta-band power in the left temporal cortex. A decrease in alpha-band power was observed in the right inferior frontal gyrus. AVH onset was related to a decrease in theta-band power in the right hippocampus. CONCLUSIONS: These results suggest that AVH are triggered by a short aberration in the theta band in a memory-related structure, followed by activity in language areas accompanying the experience of AVH itself

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Waters, F., Woodward, T., Allen, P., Aleman, A., & Sommer, I. (2012). Self-recognition deficits in schizophrenia patients with auditory hallucinations: a meta-analysis of the literature. *Schizophrenia Bulletin*, 38, 741-750.

Notes: Theories about auditory hallucinations in schizophrenia suggest that these experiences occur because patients fail to recognize thoughts and mental events as self-generated. Different theoretical models have been proposed about the cognitive mechanisms underlying auditory hallucinations. Regardless of the cognitive model being tested, however, experimental designs are almost identical in that they require a judgment regarding whether an action was self-originated or not. The aim of the current study was to integrate all available literature for a meta-analysis on this topic and reach conclusions

about self-recognition performance in (1) patients with schizophrenia compared with healthy controls and (2) patients with auditory hallucinations compared with patients without these symptoms. A comprehensive literature review identified 23 studies that contrasted the performance of schizophrenia patients with healthy controls (1370 participants) and 9 studies that directly compared patients with and without auditory hallucinations (315 participants). We found significantly reduced self-recognition performance in schizophrenia patients, which was more pronounced in patients with auditory hallucinations compared with patients without. In patients with hallucinations, this pattern of performance was specific to self-recognition processes and not to the recognition of new external information. A striking finding was the homogeneity in results across studies regardless of the action modality, timing delay, and design used to measure self-recognition. In summary, this review of studies from the last 30 years substantiates the view that self-recognition is impaired in patients with schizophrenia and particularly those with auditory hallucinations. This suggests an association, perhaps a causal one, between such deficit and hallucinatory experiences in schizophrenia Centre for Clinical Research in Neuropsychiatry, Graylands Hospital, Mail Bag No 1, Claremont, Perth, 6910, Australia. Flavie.Waters@health.wa.gov.au

Daalman, K., Boks, M. P., Diederens, K. M., de Weijer, A. D., Blom, J. D., Kahn, R. S. et al. (2011). The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *Journal of Clinical Psychiatry*, 72, 320-325.

Notes: OBJECTIVE: Whereas auditory verbal hallucinations (AVHs) are most characteristic of schizophrenia, their presence has frequently been described in a continuum, ranging from severely psychotic patients to schizotypal personality disorder patients to otherwise healthy participants. It remains unclear whether AVHs at the outer borders of this spectrum are indeed the same phenomenon. Furthermore, specific characteristics of AVHs may be important indicators of a psychotic disorder. METHOD: To investigate differences and similarities in AVHs in psychotic and nonpsychotic individuals, the phenomenology of AVHs in 118 psychotic outpatients was compared to that in 111 otherwise healthy individuals, both experiencing AVHs at least once a month. The study was performed between September 2007 and March 2010 at the University Medical Center, Utrecht, the Netherlands. Characteristics of AVHs were quantified using the Psychotic Symptoms Rating Scales Auditory Hallucinations subscale. RESULTS: The perceived location of voices (inside/outside the head), the number of voices, loudness, and personification did not differentiate between psychotic and healthy individuals. The most prominent differences between AVHs in healthy and psychotic individuals were the emotional valence of the content, the frequency of AVHs, and the control subjects had over their AVHs (all P values < .001). Age at onset of AVHs was at a significantly younger age in the healthy individuals (P < .001). In our sample, the negative emotional valence of the content of AVHs could accurately predict the presence of a psychotic disorder in 88% of the participants. CONCLUSIONS: We cannot ascertain whether AVHs at the outer borders of the spectrum should be considered the same phenomenon, as there are both similarities and differences. The much younger age at onset of AVHs in the healthy subjects compared to that in psychotic patients may suggest a different pathophysiology. The high predictive value of the emotional content of voices implies that inquiring after the emotional content of AVHs may be a crucial step in the

diagnosis of psychotic disorders in individuals hearing voices
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Daalman, K., van Zandvoort, M., Bootsman, F., Boks, M., Kahn, R., & Sommer, I. (2011). Auditory verbal hallucinations and cognitive functioning in healthy individuals. *Schizophrenia Research*, 132, 203-207.

Notes: Auditory verbal hallucinations (AVH) are a characteristic symptom in schizophrenia, and also occur in the general, non-clinical population. In schizophrenia patients, several specific cognitive deficits, such as in speech processing, working memory, source memory, attention, inhibition, episodic memory and self-monitoring have been associated with auditory verbal hallucinations. Such associations are interesting, as they may identify specific cognitive traits that constitute a predisposition for AVH. However, it is difficult to disentangle a specific relation with AVH in patients with schizophrenia, as so many other factors can affect the performance on cognitive tests. Examining the cognitive profile of healthy individuals experiencing AVH may reveal a more direct association between AVH and aberrant cognitive functioning in a specific domain. For the current study, performance in executive functioning, memory (both short- and long-term), processing speed, spatial ability, lexical access, abstract reasoning, language and intelligence performance was compared between 101 healthy individuals with AVH and 101 healthy controls, matched for gender, age, handedness and education. Although performance of both groups was within the normal range, not clinically impaired, significant differences between the groups were found in the verbal domain as well as in executive functioning. Performance on all other cognitive domains was similar in both groups. The predisposition to experience AVH is associated with lower performance in executive functioning and aberrant language performance. This association might be related to difficulties in the inhibition of irrelevant verbal information

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van Lutterveld, R., Sommer, I. E., & Ford, J. M. (2011). The neurophysiology of auditory hallucinations - a historical and contemporary review. *Front.Psychiatry*, 2, 28. Notes: Electroencephalography and magnetoencephalography are two techniques that distinguish themselves from other neuroimaging methodologies through their ability to directly measure brain-related activity and their high temporal resolution. A large body of research has applied these techniques to study auditory hallucinations. Across a variety of approaches, the left superior temporal cortex is consistently reported to be involved in this symptom. Moreover, there is increasing evidence that a failure in corollary discharge, i.e., a neural signal originating in frontal speech areas that indicates to sensory areas that forthcoming thought is self-generated, may underlie the experience of auditory hallucinations

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Sommer, I. E., Selten, J. P., Dieren, K. M., & Blom, J. D. (2010). Dissecting auditory verbal hallucinations into two components: audibility (Gedankenlautwerden) and alienation (thought insertion). *Psychopathology*, 43, 137-140.

Notes: This study proposes a theoretical framework which dissects auditory verbal hallucinations (AVH) into 2 essential components: audibility and alienation. Audibility, the perceptual aspect of AVH, may result from a disinhibition of the auditory cortex in response to self-generated speech. In isolation, this aspect leads to audible thoughts: Gedankenlautwerden. The second component is alienation, which is the failure to recognize the content of AVH as self-generated. This failure may be related to the fact that cerebral activity associated with AVH is predominantly present in the speech production area of the right hemisphere. Since normal inner speech is derived from the left speech area, an aberrant source may lead to confusion about the origin of the language fragments. When alienation is not accompanied by audibility, it will result in the experience of thought insertion. The 2 hypothesized components are illustrated using case vignettes
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Sommer, I. E., Daalman, K., Rietkerk, T., Diederens, K. M., Bakker, S., Wijkstra, J. et al. (2010). Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. *Schizophrenia Bulletin*, 36, 633-641.

Notes: Epidemiological studies suggest that auditory verbal hallucinations (AVH) occur in approximately 10%-15% of the general population, of whom only a small proportion has a clinically relevant psychotic disorder. It is unclear whether these hallucinations occur as an isolated phenomenon or if AVH in nonclinical individuals are part of a more general susceptibility to schizophrenia. For this study, 103 healthy individuals with frequent AVH were compared with 60 controls matched for sex, age, and education. All participants were examined by a psychiatrist using standardized diagnostic interviews and questionnaires. The individuals with AVH did not have clinically defined delusions, disorganization, or negative or catatonic symptoms, nor did they meet criteria for cluster A personality disorder. However, their global level of functioning was lower than in the controls and there was a pronounced increase on all subclusters of the Schizotypal Personality Questionnaire (SPQ) and the Peters Delusion Inventory, indicating a general increased schizotypal and delusional tendency in the hallucinating subjects. History of childhood trauma and family history of axis I disorders were also more prevalent in these individuals. We showed that higher SPQ scores, lower education, and higher family loading for psychiatric disorders, but not presence of AVH, were associated with lower global functioning. Our data suggest that AVH in otherwise healthy individuals are not an isolated phenomenon but part of a general vulnerability for schizophrenia
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Sommer, I. E., Derwort, A. M., Daalman, K., de Weijer, A. D., Liddle, P. F., & Boks, M. P. (2010). Formal thought disorder in non-clinical individuals with auditory verbal hallucinations. *Schizophrenia Research*, 118, 140-145.

Notes: BACKGROUND: Auditory verbal hallucinations (AVH) and formal thought disorder (FTD) may originate from the same aberration in the language system. The hypothesis of a shared neurobiological basis would be strengthened by the presence of FTD in individuals who frequently experience AVH, but do not meet DSM-IV criteria for

a psychotic disorder. **METHODS:** In this study, FTD was quantified in 40 non-clinical subjects with AVH, in 50 healthy subjects without AVH and in 40 schizophrenia patients with AVH. Recorded speech samples were analysed by one rater who was blind to the presence/absence of AVH and to diagnosis, using the Thought and Language Index. **RESULTS:** Negative FTD was barely present in non-clinical subjects with AVH and in healthy controls without AVH. Positive FTD, however, was significantly higher in both groups experiencing AVH than in controls without AVH. Severity of positive FTD did not differ significantly between non-clinical subjects with AVH and schizophrenia patients with AVH. **CONCLUSION:** Negative FTD (alogia) appears not to be associated with AVH. However, the fact that positive FTD (disorganised speech) in schizophrenia patients with AVH is equally high in non-clinical subjects with AVH indicates that these two symptoms tend to co-occur, which may be suggestive of a shared neurobiological substrate

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