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From Speech Illusions to Onset of Psychotic Disorder: Applying Network Analysis to an Experimental Measure of Aberrant Experiences

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Aberrant perceptual experiences are a potential early marker of psychosis development. Earlier studies have found experimentally assessed speech illusions to be associated with positive symptoms in patients with psychotic disorders, but findings for attenuated symptoms in individuals without psychotic disorders have been inconsistent. Also, the role of affect is unclear. The aim of this study was to use the network approach to investigate how speech illusions relate to individual symptoms and onset of a psychotic disorder. We estimated a network model based on data from 289 Clinical High-Risk (CHR) subjects, participating in the EU-GEI project. The network structure depicts statistical

associations between (affective and all) speech illusions, cross-sectional individual attenuated positive and affective symptoms, and transition to psychotic disorder after conditioning on all other variables in the network. Speech illusions were assessed with the White Noise Task, symptoms with the BPRS and transition during 24-month follow-up with the CAARMS. Affective, not all, speech illusions were found to be directly, albeit weakly, associated with hallucinatory experiences. Hallucinatory experiences, in turn, were associated with delusional ideation. Bizarre behavior was the only symptom in the network steadily predictive of transition. Affective symptoms were highly interrelated,

with depression showing the highest overall strength of connections to and predictability by other symptoms. Both speech illusions and transition showed low overall predictability by symptoms. Our findings suggest that experimentally assessed speech illusions are not a mere consequence of psychotic symptoms or disorder, but that their single assessment is likely not useful for assessing transition risk.

Key words: network approach/hallucinatory experiences/hallucinations/psychosis/transition/high risk

Introduction

One of the oldest theories of delusion formation states that delusions often arise in a secondary fashion, in an attempt to explain unusual experiences, which may consist of an external event, such as a social encounter or an internal experience, such as a sensory perception.^{1–3} According to the aberrant salience theory,⁴ these experiences are filled with an augmented sense of significance—ie, are perceived as *unusual*—due to a dysregulated hyperdopaminergic state. Kapur⁴ conceptualizes hallucinations as a direct experience of the aberrant salience of internal representations and delusions as a cognitive effort to make sense of one's experiences. Findings from large epidemiological studies in non-clinical samples support the view that hallucinatory experiences (subthreshold hallucinations) often precede delusional ideation (subthreshold delusions), and that their co-occurrence enhances the risk of transition to psychotic disorder,^{5–7} possibly particularly in the context of affective dysregulation,^{8,9} although findings for the latter are mixed.^{10–12} In an interview study of patients with psychotic disorders, about 80% of the participants reported an onset of current delusions based on aberrant perceptual experiences, including hallucinatory experiences.¹³

Aberrant perceptual experiences can exist in all sensory modalities and in the context of an external stimulus (referred to as an illusion) or without an external stimulus (a hallucinatory experience, pseudo-hallucination, or hallucination). A potential cognitive mechanism of aberrant perceptual experiences is that they are driven by a disproportionate influence of sensory expectations, ie, “top-down processing,” on sensory input, ie, “bottom-up” processing.^{14,15} Empirical findings for this mechanism are inconsistent.^{16,17} There is some empirical support that experimentally assessed auditory illusions of speech (hereafter referred to as speech illusions) are a marker of psychosis liability: Hoffman et al¹⁸ found that the degree of speech illusions, here operationalized as the number of words falsely perceived in the external stimulus of incoherent multi-speaker “babble,” predicted transition to psychotic disorder in individuals at high risk for psychosis. As far as we are aware, there have been no studies aimed to replicate this finding.

Galdos et al,¹⁹ however, extended the aforementioned research and theories in their development of the *White Noise Task*: an experimental task to assess speech illusions, that intensifies the potential influence of top-down processing by priming subjects that speech might be expected while presenting different volume levels of speech on a white noise background. In order to study affectively salient meaning, the task includes assessment of perceived affective content. Two studies to date have demonstrated that speech illusions assessed with the White Noise Task are associated with positive (and not negative) symptoms in patients with psychotic disorders.^{19,20} Patients had higher rates of speech illusions compared to their siblings and healthy controls, particularly for speech illusions with affective content (hereafter referred to as affective speech illusions).^{19,21} Galdos et al¹⁹ also found an association between speech illusions and attenuated positive (and not negative) symptoms in a non-clinical sample. Other studies in non-clinical samples, however, have not found an association between attenuated positive symptoms and speech illusions,^{20–22} a negative association,²³ or only associations between speech illusions and some symptoms: hallucinatory experiences and overall negative affect and not delusional ideation.²⁴ In a recent study, the data of Catalan et al²⁰ was combined with more participants and re-analyzed. The authors found an association between speech illusions and attenuated positive symptoms in healthy controls, but this was not statistically significant after correcting for age, gender and cognitive ability.²⁵

The inconsistent findings with regard to clinical and non-clinical samples and for attenuated positive symptoms indicate that further research is required to examine whether White Noise Task speech illusions are indicative of psychosis proneness, as opposed to, for instance, resulting from consequences of psychotic illness. For this purpose, it is desirable to use a similar design to Hoffman et al¹⁸ and to include onset of a psychotic disorder as a main outcome of interest. Since the vast majority of psychotic experiences in the general population are transitory,²⁶ it is beneficial to study transition in individuals at high risk for psychosis. The Ultra-/Clinical High-Risk (UHR/CHR) and At-Risk Mental State (ARMS) constructs have been developed for this purpose.²⁷

Further, apart from Rimvall et al,²⁴ who examined hallucinatory experiences and delusional ideation separately, previous studies have all used composite measures of symptoms. According to the network theory of psychopathology, disorders may arise from individual symptom interactions, which can be encoded in a network structure.^{28,29} Within the network framework, symptoms are no longer regarded as mere indicators of a latent disorder, but rather interactions among symptoms become of central interest. In addition, to allow for the visual representation of these interactions, network models rely on advanced statistical techniques, such as model selection

routines (employed to find the best fitting model underlying the data^{30–32}), and regularization routines (employed to estimate interpretable and sparse models^{31,33}). These routines allow for highlighting many interactions simultaneously while controlling for spurious associations that may result from sampling error. For further details of the network framework in the context of psychotic symptomatology, please see ref.³⁴ The network approach could thus provide new insights into how speech illusions relate to individual symptoms and shed light on the complicated interplay between individual symptoms preceding the onset of psychotic disorder.

Consequently, the current study aimed to use the network approach to examine how experimentally assessed (affective and all) speech illusions relate to individual attenuated positive and affective symptoms, their interrelations, and onset of a psychotic disorder in a CHR sample. The hypothesis that speech illusions are indicative of psychosis proneness led us to expect a direct and strong relation between speech illusions and hallucinatory experiences. We expected delusional ideation to be intermediate in the relation between hallucinatory experiences and transition to psychotic disorder. Relations with other attenuated positive and affective symptoms were examined in an exploratory manner.

Methods

Participants and Procedure

Data pertain to the CHR sample participating in the “GxE Prodrome study” of the European network of national networks studying gene-environment interactions in schizophrenia (EU-GEI project)³⁵ (www.eu-gei.eu). The EU-GEI project aimed to identify the interactive genetic, clinical, and environmental determinants involved in the development, severity, and outcome of schizophrenia. EU-GEI Prodrome partners include the United Kingdom, the Netherlands, Denmark, Austria, Switzerland, Germany, France, and Spain, as well as partnerships outside Europe with Australia and Brazil. All participating sites obtained approval from their associated Medical Ethical Committees. The EU-GEI project was conducted in accordance with the Declaration of Helsinki for ethical conduct in research.

Instruments

Clinical Symptomatology. CHR status and transition to psychotic disorder were assessed with the Comprehensive Assessment of At-Risk Mental State (CAARMS).³⁶ The CAARMS is a valid and reliable instrument for assessing possible psychotic prodromes and their course.³⁶ CHR status is defined as presence of attenuated positive symptoms or brief, self-limited psychotic symptoms (BLIPS), genetic vulnerability for psychosis and persistent low or recently declined functioning.³⁷ Transition

to clinical psychosis was prospectively assessed as absent/present during 24-month follow-up. Transition was defined as threshold-level positive symptoms (hallucinations, delusions or thought disorder) occurring several times a week for a duration of at least 1 week.³⁸ The CAARMS symptom score levels are based on the level of severity (which may include level of conviction, distress, and impact on behavior), frequency, duration, and recency.

Baseline positive and affective symptoms were assessed with the extended version of the Brief Psychiatric Rating Scale (BPRS),^{39,40} a commonly used interview for the assessment of psychotic symptom severity. Positive and affective symptoms were selected for the current analysis based on the 5-factor framework solution reported in the meta-analysis conducted by Dazzi and colleagues.⁴¹ Positive symptoms within this framework are *grandiosity, suspiciousness, hallucinations, unusual thought content, and bizarre behavior*. Affective symptoms are *somatic concern, anxiety, depression, suicidality, and guilt*. The BPRS items were scored on a 1 (absent) to 7 (extremely severe) scale by trained assessors.

Speech Illusions. The White Noise Task¹⁹ is an experimental task for the illusion of speech in white noise. Participants, who are positioned behind a laptop and wear headphones, are presented with 75 sound fragments in random order consisting of 3 types of stimuli composed of 25 sound fragments each: white noise only, white noise, and clearly audible neutral speech, white noise and barely audible neutral speech. Subjects are asked to choose from 5 options: (1) hearing a positive voice, (2) hearing a negative voice, (3) hearing a neutral voice, (4) no speech heard, (5) heard speech but unsure whether the voice was positive, negative or neutral. The rate of hearing a voice in the white noise only condition is the variable of interest. Following the White Noise Task developers, Galdos et al,¹⁹ dichotomous variables (present or absent) for speech illusions with all and with affective content were created. Presence of “all” speech illusions, according to Galdos et al¹⁹ indicated a positive response to option 1, 2, or 3. Catalan et al²⁰ used an alternative operationalization for “all” speech illusions, indicating at least 2 positive responses to option 1, 2, 3, or 5. Presence of affective speech illusions indicated a positive response to option 1 or 2 in both methods (operationalizations confirmed through personal communication with one of the Catalan et al²⁰ authors, JvO).

Statistical Analyses

All analyses were performed using the R-statistical software, version 3.6.1.⁴² The network structure was constructed using the R-package *mgm*, version 1.2.6.⁴³ and visualized using the R-package *qgraph*, version 1.6.4.⁴⁴ The used R-code is provided as a [supplementary material](#).

We constructed 2 network models consisting of (1) all speech illusions (Galdos method¹⁹) and (2) affective speech illusions, baseline attenuated positive and affective symptoms as described above and prospective transition to psychotic disorder. Given that variables in a network can be interpreted in a predictive manner,⁴⁵ it is possible to see which baseline variable(s) is/are likely to predict which subjects transition to clinical psychosis at a later stage (ie, inter-individual prediction). All items were represented as *nodes*. An *edge* between any 2 nodes indicates that these 2 variables are statistically dependent on each other after conditioning on all other variables in the network structure. The wider and more saturated the edge, the stronger the association. Blue edges represent positive associations, red edges represent negative associations.

In order to account for the mixed type of data used in this study (ie, both continuous and binary), we fitted a Mixed Graphical Model⁴⁶ to our data. As the *mgm* software cannot currently handle missing data, we only used cases with complete data. In addition, as the current data were not univariate normally distributed, a nonparanormal transformation⁴⁷ to relax the normality assumption was applied to the continuous variables prior to constructing the networks. To obtain a sparse estimate, we used an algorithm that includes an L1-penalty; we selected the regularization parameter lambda using cross validation (CV). Because CV relies on the random seed and may be less conservative than other estimation techniques for regularized networks, we chose a more conservative estimation approach. Specifically, we estimated the network structure 1000 times using different seeds for the lambda parameter and only retained the edges that were non-zero in 95% of the cases. Given that we aimed to investigate between-domain links, this estimation approach is likely to ensure that the number of false-positives is reduced, hence ensuing more robust results.

While the employed methodology does not allow for the investigation of the network stability using traditional techniques,⁴⁸ the method in itself could be thought of being based on bootstrapping. Nonetheless, to further ensure this, we carried out an additional stability analysis using nonparametric bootstrap techniques, as described by Epskamp and colleagues,⁴⁸ but designed for the method described above. Details on this analysis are provided in the [supplementary appendix S1](#). In addition, we employed several more robustness checks, including constructing (1) an extended network structure including, in addition to the above symptoms, also cognitive symptoms, (2) a network plot displaying edge variability across the estimation of the 1000 network structures using different seeds for the lambda parameter, and (3) a network structure of *all speech illusions*, positive and affective symptoms and transition to clinical psychosis,

according to the operationalization of Catalan and colleagues.²⁰ Details on these additional checks are available in the [supplementary material](#).

The layout used when computing the network was the Fruchterman and Reingold layout,⁴⁹ which places nodes with stronger connections in the center. The estimated network was further analyzed by exploring the *strength* centrality measure of each node. Node strength is a measure of the number and the strength of connections within a network structure⁵⁰ and is generally identified as the most robust centrality measure.⁴⁸ Finally, to explore how much influence one can have on one node when intervening on all its neighbors, we computed *predictability measures*. Predictability can be defined as the shared variance of each node with all of its neighbors,⁵¹ and it is represented by the outer circle in each node: as predictability increases, the circle fills up with color.

Results

The overall sample consisted of $N = 345$ individuals meeting CHR criteria, of which $N = 289$ (83.9%) had complete data on all variables and were included in network analysis. [Table 1](#) shows the sociodemographic and [table 2](#) shows the clinical characteristics of the overall and the network samples. Missing data were found to be unevenly distributed among participants' age, education levels, and site locations. No differences were found for gender, rates of speech illusions, symptom levels, and rates of transition to clinical psychotic disorder. Three hundred eight individuals had data on both speech illusions and transition to psychotic disorder. Individuals with all speech illusions, according to Galdos et al¹⁹ ($N = 64$, 22.1%), transitioned in 25.0% ($N = 16$) of the cases and individuals without speech illusions ($N = 225$) in 16.0% ($N = 36$) of the cases. Individuals with affective speech illusions ($N = 35$, 12.1%) transitioned in 25.7% ($N = 9$) of the cases and individuals without ($N = 254$) in 16.9% ($N = 43$) of the cases. Individuals with all speech illusions, according to Catalan et al²⁰ ($N = 137$, 47.1%) transitioned in 18.2% ($N = 25$) of the cases and individuals without ($N = 152$) in 17.8% ($N = 27$) of the cases. A-posteriori conducted Chi-square tests showed no statistically significant association between the occurrence of speech illusions and transition for all 3 operationalizations (resp. $P = .098$, $P = .205$, $P = .915$).

Network Analysis

[Figure 1](#) displays the network structure of all associations between *Panel A*. affective speech illusions, *Panel B*. all speech illusions, attenuated positive and affective symptoms and *transition to clinical psychosis*, as well as the associations between the symptoms themselves, when conditioning on all other variables in the network structure. *Affective speech illusions* were found to be directly associated with *hallucinations*, but not *all speech illusions*. *Hallucinations*,

Table 1. Sociodemographic Characteristics of Clinical High Risk (CHR) Subjects

	Overall Sample N = 303–345	Network Sample N = 289
Gender		
%, N males	53.6% (N = 185)	52.9% (N = 153)
Age		
M years, SD	22.4 (4.9)	22.6 (4.9)
Site		
Amsterdam, The Netherlands	4.3% (N = 15)	4.8% (N = 14)
Barcelona, Spain	6.7% (N = 23)	8.0% (N = 23)
Basel, Switzerland	7.0% (N = 24)	7.3% (N = 21)
Cologne, Germany	4.3% (N = 15)	4.8% (N = 14)
Copenhagen, Denmark	5.5% (N = 19)	6.6% (N = 19)
London, UK	28.4% (N = 98)	27.7% (N = 80)
Melbourne, Australia	10.4% (N = 36)	4.8% (N = 14)
Paris, France	5.8% (N = 20)	6.9% (N = 20)
Sao Paulo, Brazil	5.8% (N = 20)	4.8% (N = 14)
The Hague, The Netherlands	18.3% (N = 63)	21.5% (N = 62)
Vienna, Austria	3.5% (N = 12)	2.8% (N = 8)
Highest level of education	N = 303	N = 262
Compulsory education, no qualification	9.2% (N = 28)	6.5% (N = 17)
Compulsory education, with qualification	32.7% (N = 99)	34.0% (N = 89)
Tertiary, first level non-compulsory education	29.7% (N = 90)	29.4% (N = 77)
Vocational education, completed	14.2% (N = 43)	14.9% (N = 39)
Higher education, undergraduate	11.9% (N = 36)	12.6% (N = 33)
Higher education, postgraduate	2.3% (N = 7)	2.7% (N = 7)

in turn, were positively associated with *suspiciousness*, *unusual thought content*, *depression*, and *suicidality* and negatively with *grandiosity* and *guilt*. The affective symptoms were highly interrelated in both network structures and the overall connections were almost identical, with the exception of the link to hallucinations. Prospective *transition to clinical psychosis* was associated with *bizarre behavior*.

When exploring centrality measures for both networks (presented in [figure 2](#)), the items with the highest overall number and strength of connections to the other variables were (in decreasing order) *depression*, *hallucinations* (second highest for the affective speech illusions network, third highest for the all speech illusions network), *unusual thought content* (second highest for the all speech illusions network, third highest for the affective speech illusions network) and *suicidality*. [Supplementary table S1](#) includes the raw and standardized centrality values for both networks. Given that closeness and betweenness are generally less stable centrality measures⁴⁸ and the current study is limited in power, we chose not to interpret closeness and betweenness measures in the current paper. Nonetheless, [supplementary appendix S2](#), [figure S1](#), and

[table S2](#) display the closeness and betweenness of both network structures, alongside raw and standardized centrality values for interested readers.

When exploring predictability measures, *speech illusions* and *transition to clinical psychosis* displayed low predictability: none of the neighboring nodes explained a high amount of shared variance. The items with highest predictability by their neighboring nodes were (in decreasing order) *depression* (48%), *suicidality* (36%), *anxiety* (32%), *unusual thought content* (31%), and *hallucinations* (26% for the all speech illusions network, 27% for the affective speech illusions network).

Supplementary Online Content

In the [supplementary appendix S1](#) we present the results of the stability analysis. These indicate that some caution is necessary when interpreting current results, some of the bootstrapped intervals being fairly wide. The edge between affective speech illusions and hallucinations, which is of central interest here, is steadily identified, though the bootstrapped interval is wide and the edge sometime switched sign. Nonetheless, the bootstrap mean is positive and very close to the value identified in the paper. In addition, it should be noted that the relation between a binary and a continuous variable is on a different scale than the relation between continuous variables themselves, and therefore the finding that these bootstrap intervals may be wider is not surprising.

Further, in the [supplementary appendix S3](#), we present an extended network structure which also includes 4 additional cognitive symptoms, as described in the meta-analysis by Dazzi and colleagues.⁴¹ Within the [supplementary appendix S4](#), we included 2 networks displaying the edge variability across our chosen estimation procedure for the affective speech illusions network structure and the affective speech illusions extended network structure. Markedly, within the extended network structure, the link between speech illusions and hallucinations did not pass the pre-defined threshold (ie, non-zero in 95% of the estimated networks), but it was nonetheless consistently identified as a link (ie, in 77.9% of the cases). Overall, the original and extended networks were well-aligned; the same edges were found, although not all meeting the threshold. Of note, an additional link between *affective speech illusions* and *mannerism and posturing* was identified in the extended network structure. Adding more nodes seems to result in an increase in negative associations, reduced power and a likely more unstable structure, due to the small sample size in relation to the number of nodes. Therefore, apparent differences in the extended network structure should be interpreted with caution.

Finally, in the [supplementary appendix S5](#) we present the network structure of *all speech illusions* and attenuated positive and affective symptoms and transition to clinical

Table 2. Clinical Characteristics of Clinical High Risk (CHR) Subjects

	Overall Sample N = 303–345	Network Sample N = 289
White Noise Task speech illusions	N = 308	N = 289
All speech illusion (Galdos method) %, N present	21.4% (N = 66)	22.1% (N = 64)
Affective speech illusion %, N present	12.0% (N = 37)	12.1% (N = 35)
All speech illusion (Catalan method) %, N present	47.1% (N = 145)	47.1% (N = 137)
BPRS symptoms ^a M, SD	N = 323-325	N = 289
Somatic concern	2.00 (1.38)	1.98 (1.37)
Anxiety	3.45 (1.53)	3.42 (1.53)
Depression	3.64 (1.46)	3.62 (1.43)
Suicidality	2.20 (1.26)	2.18 (1.26)
Guilt	2.01 (1.29)	2.06 (1.29)
Grandiosity	1.38 (0.92)	1.38 (0.90)
Suspiciousness	2.53 (1.43)	2.48 (1.42)
Hallucinations	2.32 (1.39)	2.29 (1.38)
Unusual thought content	2.62 (1.48)	2.62 (1.47)
Bizarre behavior	1.39 (0.87)	1.39 (0.88)
Self-neglect	1.34 (0.74)	1.36 (0.76)
Disorientation	1.18 (0.59)	1.18 (0.61)
Conceptual Disorganization	1.29 (0.67)	1.28 (0.66)
Mannerisms and Posturing	1.05 (0.30)	1.06 (0.31)
Transition to clinical psychosis %, N transition present	18.8% (N = 65)	18.0% (N = 52)

Note: ^aBrief Psychiatric Rating Scale (BPRS) scores 1: absent, 2: very mild, 3: mild, 4: moderate, 5: moderate severe, 6: severe, 7: extremely severe.

psychosis, according to the operationalization of Catalan et al²⁰, and discuss differences between the network structures of *all speech illusions* constructed according to the 2 different operationalizations (ie, the Galdos¹⁹ operationalization and the Catalan²⁰ operationalization). While the results are generally well-aligned for symptomatology, when using the operationalization of Catalan and colleagues, a negative association emerges between *speech illusions* and *grandiosity*, while when using the Galdos operationalization, no association between *speech illusions* and other symptoms is identified. This indicates that the way the speech illusions are operationalized is essential and can lead to different results and network structures.

All correlation matrices and R code are further available in the [supplementary material](#).

Discussion

The current study is the first to use a network approach to examine how experimentally assessed speech illusions relate to individual attenuated positive symptoms and transition to psychotic disorder. We found support for our first hypothesis, a link between the experimentally assessed speech illusions and attenuated positive symptoms that is specific to hallucinatory experiences, as would be expected and in line with the findings of Rimvall et al.²⁴ However, an association was only found for speech illusions with affective content, and not all content according to the Galdos or Catalan method.^{19,20} The modest strength of the association, the specificity for hallucinatory experiences when mostly composite symptom measures are used, along with low rates of speech illusions and attenuated symptoms in some non-clinical samples (discussed below) may explain why negative findings in non-clinical samples have been observed.^{20–23} It might also be that for some individuals hearing a voice in white noise is not a sign of hallucinatory proneness, but indicative of a broader trait such as suggestibility or fantasy proneness.⁵² However, the current combined findings of low predictability of speech illusions by symptoms and transition to psychosis suggest that speech illusions are not a mere artifact of positive or affective symptom severity or presence of a psychotic disorder.

As expected, delusional ideation (specifically unusual thought content and suspiciousness) were found to be intermediate between hallucinatory experiences and transition. This is in line with longstanding clinical observations^{1–3} and empirical findings^{5–7} and thus reflects imitable symptomatic interplay between perceptual aberrations and transition to psychotic disorder. However, we found the overall predictability of transition during 2-year follow-up by baseline assessment of speech illusions and all symptoms combined to be strikingly low. A-posteriori analysis showed that none of the operationalizations of speech illusions were associated with transition during 2-year follow-up. These findings suggest that a single assessment of speech illusions may not be useful as a risk factor for psychosis. Of note, although the participants in the current study were selected based on high-risk criteria, the transition rate in our sample (around 18%) was found to be lower than the average reported for 2-year follow-up of individuals meeting CHR status in meta-analytical data (29%).⁵³ In their meta-analysis, Fusar-Poli et al⁵³ reported that transition risk varied with the age of the subject, the provided treatment and the operationalization of the high-risk syndrome and transition constructs. Our findings suggest that there are important predictors not included in the current network, which likely include risk and protective factors that may alter symptomatic course, such as environmental exposure and treatment variables.

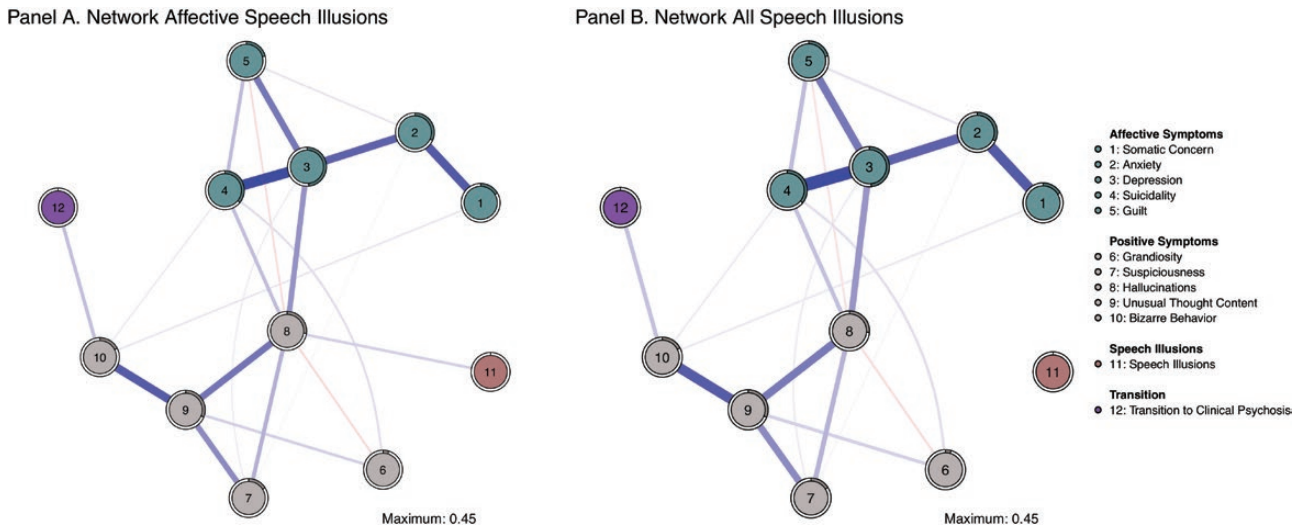


Fig. 1. (A) Network of affective speech illusions, positive and affective symptoms and transition to psychotic disorder. (B) Network of all speech illusions (Galdos method), positive and affective symptoms and transition to psychotic disorder. Symptom groups are differentiated by color and the maximum value is set to be the same in both networks for comparison purpose.

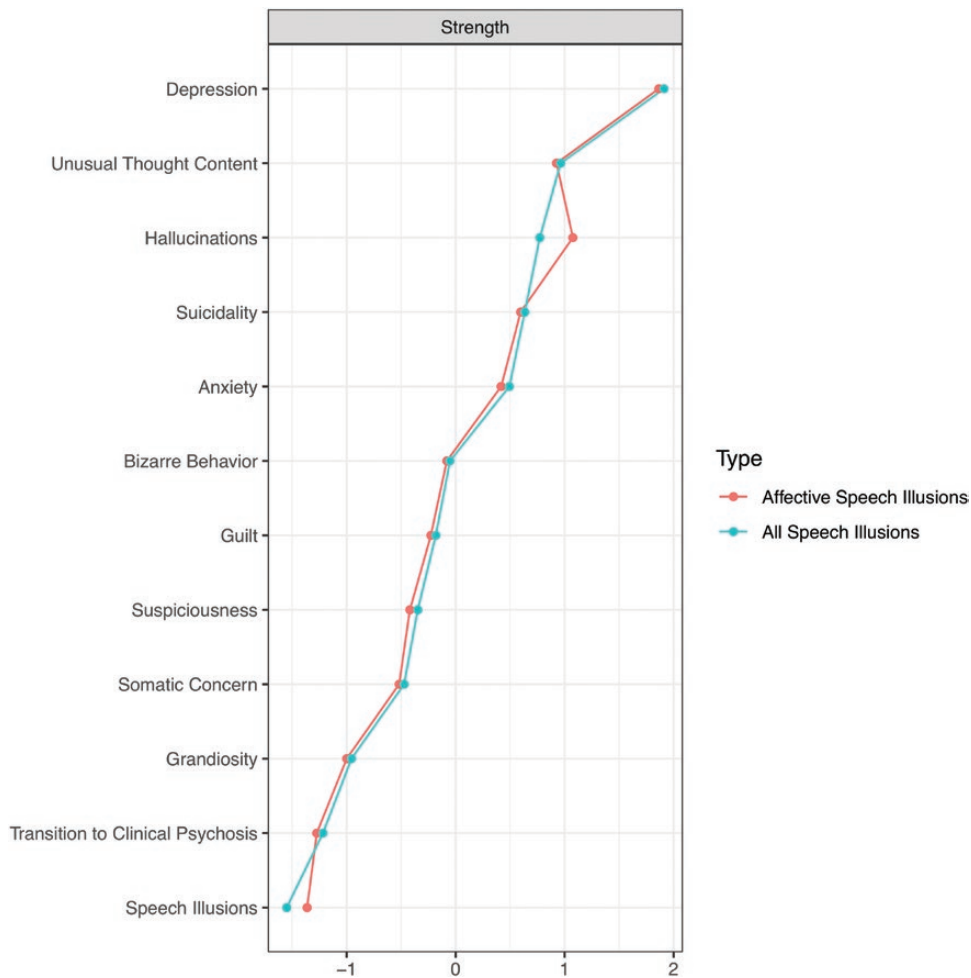


Fig. 2. Centrality Plot displaying the *strength* centrality for both the affective speech illusions and all speech illusions networks. Centrality measures are shown as standardized z-scores and are ordered by strength. Raw and standardized centrality scores are included in [supplementary table S1](#).

Galdos et al¹⁹ reported app. 30% speech illusions in patients with psychotic disorders, app. 14% in siblings of patients and 9% in healthy controls. The app. 22% prevalence rate of all speech illusions according to the Galdos method¹⁹ in the present sample of individuals with CHR status seems in line with these findings. Rates of affective speech illusions (app. 12% prevalence in the current study) vary widely between studies, ranging from app. 9% to 18% in patients with psychotic disorders^{20,21} and app. 0.4%–15% in healthy controls and individuals from the general population.^{20–22,24} Also, prevalence rates of studies claiming to use the Catalan method²⁰ (app. 47% in the current study) vary considerably: app. 33%–47% in patients with psychotic disorders^{20,21} and app. 9%–42% in healthy controls and individuals from the general population.^{20–22,24,25} Part of the variation may be explained by differences in sample characteristics, such as age and cognitive ability. Schepers et al²¹ indeed suggested that speech illusions may be a trait-dependent risk marker of psychosis and found support for this. To a lesser extent, part of the variation in prevalence may be explained by the operationalization of speech illusions. Close inspection of the operationalization of speech illusions revealed some differences across studies,^{21,24} with not all studies providing sufficient details for comparison. Research on the optimal operationalization of speech illusions, including divergent and convergent validity with other measures, is therefore warranted.

Given that there is some indication that cognitive ability may impact the relation between speech illusions and positive symptoms,^{21,25} within the [supplementary material](#), we presented an extended network structure, also including cognitive symptoms. This analysis suggested a possible additional relation between speech illusions and mannerisms and posturing. Exploration of the network's properties suggested that the variability between the original and extended network structures is likely due to lower power when more variables are included.

Further exploratory investigation suggested that *bizarre behavior* is a “gateway symptom” to psychotic disorder; it is the only individual symptom in our network model steadily predictive of whether a subject will transition to clinical psychosis or not. In the BPRS,^{39,40} the current measure of baseline symptoms, this item reflects behavior affected by hallucinations or delusions. Severely impacted behavior can also be an indicator of threshold severity of delusions in the CAARMS, the current measure of transition. Formal definition of a psychotic *disorder*, however, includes a minimum duration of consistent positive symptoms over at least a week, which could explain how one could have high levels of symptoms without meeting criteria for transition. (Note, this would be transition to psychotic disorder according to the CAARMS, which again varies from classification criteria for psychotic disorders as defined in the DSM or ICD.) One could argue that the distinction between

subthreshold psychosis and psychotic disorder is arbitrary, and that the latter is in need of validation from biomarkers or other validators of course and outcome, particularly given that these constructs do not adequately differentiate levels of functioning or need for care.⁵⁴ Other outcome measures may also be considered. In the current study, for instance, depression and suicidality are found to have relatively high levels of predictability and strength of connections to other symptoms, including hallucinatory experiences.

Explorative investigation of the affective symptoms shows that they are highly interconnected. Interestingly, speech illusions with affective content are currently not found to be directly connected to affective symptoms, only through attenuated positive symptoms. The current data on affective symptoms does not allow for interpretation on what type of affect is represented; scores might, for instance, represent a mood state, a comorbid affective disorder or the emotional appraisal of psychotic experiences. Additionally, Fusar-Poli et al¹² point to the problematic aspects of assuming a neat distinction between the constructs of affect and psychosis, ie, as readily distinguishable entities that might interact or causally influence each other. Early observation-based theoretical models of psychosis development describe a complex intertwinement between psychotic experiences and affect in early symptom development. In Conrad's classic 1958 stage model of psychosis development, the first stage, known as “delusional mood” or “trema,” describes a build-up of a not yet specified, anticipatory sense, during which first certain salient aspects and later the whole environment feel notably changed and affectively charged. Conrad describes that in this phase patients can experience a wide range of accompanying affect, such as excitement, fear, guilt, and depression, or any combination.⁵⁵ A large retrospective study of Conrad's stage model found support for this first “delusional mood” stage (although limited support for the latter stages).⁵⁶

Several limitations of the current study should be considered. Firstly, the analyses carried out here were mostly based on a single, cross-sectional assessment. Direction of effects are implied, but cross-sectional networks may not necessarily reflect how symptoms or states trigger each other over time.⁵⁷ Second, the estimation technique that we chose was designed to retain high specificity, and therefore, weaker connections between variables may not have been detected. Thus, absent connections should be viewed with some caution. Online presented supplementary exploration suggested possible additional relations between speech illusions and mannerisms and posturing. Third, stability analyses show some caution is necessary when interpreting the results and future research replicating these results in larger samples is warranted. Fourth, mixed graphical models do not have good means of handling missing data. As such, we included only the complete cases in our analysis. Fifth, some negative associations emerged

in the networks. These may be real effects, but they can also be false-positive effects or due to the presence of colliders in the data.⁵⁸ Further, we identified different associations between *all speech illusions* and symptomatology when using distinct operationalizations of speech illusions (ie, the Catalan operationalization versus the Galdos operationalization^{19,20}), with the Galdos method identifying no associations between *all speech illusions* and symptomatology and the Catalan method identifying a negative association between *all speech illusions* and *grandiosity*. This may result from low power and stability issues, but may also be an indication that the way speech illusions are operationalized is substantial and may affect results, including the network structure. Sixth, not all cases had full 2-year follow-up data. This means that we might have missed some cases who did make transition to psychotic disorder. Finally, due to sample size and power, we could not include all symptoms in the analysis. Also, other variables may be of interest as well, such as measures of cognitive functioning and reasoning, and potential modifiers of course, such as treatment variables. This, however, would have required an even larger dataset or more assessment points.

Conclusions

Negative findings in non-clinical samples^{20–24} might lead to abandonment of new research on experimentally speech illusions as a potential marker of psychosis proneness. Findings of the current study show that although single assessment of speech illusions may not be useful as a risk factor for psychosis, there is support for a specific and modest relation with hallucinatory experiences. The current findings also show imitable symptomatic interplay between aberrant perceptions and transition to psychotic disorder. While warranting replication in larger samples, our findings argue against speech illusions being a mere artifact of psychotic symptom severity or psychotic disorder. We, therefore, believe that abandonment of speech illusions as a marker of psychosis liability would be premature. Instead, we advocate for moving from studying associations with composite symptom measures to individual symptom interactions. Future studies may benefit from studying detailed trajectories of prospective symptom development in individuals at risk for psychosis, with the use of multiple, frequent assessment periods, inclusion of potential modifiers of course and a variety of clinical outcomes.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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References

- James W. *The Principles of Psychology*, Vol. 2. New York, NY: Henry Holt and Co; 1890.
- Reed G. *The Psychology of Anomalous Experience: A Cognitive Approach*. Oxford, UK: Hutchinson and Co London; 1972.
- Maher BA. Anomalous experience and delusional thinking: the logic of explanations. In: Oltmanns TF and Maher BA, ed. *Delusional Beliefs*. John Wiley; 1988:15–33.
- Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160(1):13–23.
- Krabbendam L, Myin-Germeys I, Hanssen M, et al. Hallucinatory experiences and onset of psychotic disorder: evidence that the risk is mediated by delusion formation. *Acta Psychiatr Scand*. 2004;110(4):264–272.
- Smeets F, Lataster T, van Winkel R, de Graaf R, Ten Have M, van Os J. Testing the hypothesis that psychotic illness begins when subthreshold hallucinations combine with delusional ideation. *Acta Psychiatr Scand*. 2013;127(1):34–47.
- Smeets F, Lataster T, Dominguez MD, et al. Evidence that onset of psychosis in the population reflects early hallucinatory experiences that through environmental risks and affective dysregulation become complicated by delusions. *Schizophr Bull*. 2012;38(3):531–542.
- Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J. The incidence and outcome of subclinical psychotic experiences in the general population. *Br J Clin Psychol*. 2005;44(Pt 2):181–191.
- Krabbendam L, Myin-Germeys I, Bak M, van Os J. Explaining transitions over the hypothesized psychosis continuum. *Aust N Z J Psychiatry*. 2005;39(3):180–186.
- Addington J, Piskulic D, Liu L, et al. Comorbid diagnoses for youth at clinical high risk of psychosis. *Schizophr Res*. 2017;190:90–95.
- Lim J, Rekh G, Rapisarda A, et al. Impact of psychiatric comorbidity in individuals at Ultra High Risk of psychosis - Findings from the Longitudinal Youth at Risk Study (LYRIKS). *Schizophr Res*. 2015;164(1-3):8–14.
- Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr Bull*. 2014;40(1):120–131.
- Freeman D, Garety PA, Fowler D, Kuipers E, Bebbington PE, Dunn G. Why do people with delusions fail to choose more realistic explanations for their experiences? An empirical investigation. *J Consult Clin Psychol*. 2004;72(4):671–680.
- Aleman A, Böcker KBE, Hijman R, De Haan EHF, Kahn RS. Cognitive basis of hallucinations in schizophrenia: role of top-down information processing. *Schizophr Res*. 2003;64(2–3):175–185.
- Hugdahl K. “Hearing voices”: auditory hallucinations as failure of top-down control of bottom-up perceptual processes. *Scand J Psychol*. 2009;50(6):553–560.
- Daalman K, Verkooijen S, Derks EM, Aleman A, Sommer IE. The influence of semantic top-down processing in auditory verbal hallucinations. *Schizophr Res*. 2012;139(1-3):82–86.
- Vercammen A, Aleman A. Semantic expectations can induce false perceptions in hallucination-prone individuals. *Schizophr Bull*. 2010;36(1):151–156.
- Hoffman RE, Woods SW, Hawkins KA, et al. Extracting spurious messages from noise and risk of schizophrenia-spectrum disorders in a prodromal population. *Br J Psychiatry*. 2007;191:355–356.
- Galdos M, Simons C, Fernandez-Rivas A, et al. Affectively salient meaning in random noise: a task sensitive to psychosis liability. *Schizophr Bull*. 2011;37(6):1179–1186.
- Catalan A, Simons CJ, Bustamante S, et al. Novel evidence that attributing affectively salient signal to random noise is associated with psychosis. *PLoS One*. 2014;9(7):e102520.

21. Schepers E, Lousberg R, Guloksuz S, *et al*. White noise speech illusions : a trait- dependent risk marker for psychotic disorder? *Front Psychiatry* 2019;10(September):1–10.
22. Schepers E, van Os J, Lousberg R. White noise speech illusions in the general population: the association with psychosis expression and risk factors for psychosis. *PLoS One*. 2019;14(2):e0211914.
23. Pries LK, Guloksuz S, Menne-Lothmann C, *et al*. White noise speech illusion and psychosis expression: an experimental investigation of psychosis liability. *PLoS One*. 2017;12(8):e0183695.
24. Rimvall MK, Clemmensen L, Munkholm A, *et al*. Introducing the White Noise task in childhood: associations between speech illusions and psychosis vulnerability. *Psychol Med*. 2016;46(13):2731–2740.
25. Gonzalez de Artaza M, Catalan A, Angosto V, *et al*. Can an experimental white noise task assess psychosis vulnerability in adult healthy controls? *PLoS One*. 2018;13(2):e0192373.
26. Kaymaz N, Drukker M, Lieb R, *et al*. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychol Med*. 2012;42(11):2239–2253.
27. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996;22(2):283–303.
28. Borsboom D. A network theory of mental disorders. *World Psychiatry*. 2017;16(1):5–13.
29. Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol*. 2013;9:91–121.
30. Haslbeck JMB, Waldorp LJ. Structure estimation for mixed graphical models in high-dimensional data. 2015. <http://arxiv.org/abs/1510.05677>. Accessed October 19, 2015.
31. Epskamp S, Fried EI. A tutorial on regularized partial correlation networks. *Psychol Methods*. 2018;23(4):617–634.
32. Williams DR, Rhemtulla M, Wysocki AC, Rast P. On nonregularized estimation of psychological networks. *Multivariate Behav Res*. 2019;54(5):719–750.
33. van Borkulo CD, Borsboom D, Epskamp S, *et al*. A new method for constructing networks from binary data. *Sci Rep*. 2014;4:5918.
34. Isvoranu AM, Boyette LL, Guloksuz S, Borsboom D. Network Models of Psychosis. In: *Dimensions of Psychosis: Comprehensive Conceptualization and Treatments*. New York, NY: Oxford University Press; 2020. In Press.
35. Van Os J, Rutten BP, Myin-Germeys I, *et al*. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. *Schizophr Bull*. 2014;40(4):729–736.
36. Yung AR, Yuen HP, McGorry PD, *et al*. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry*. 2005;39(11-12):964–971.
37. Yung AR, Yuen HP, Phillips LJ, Francey S, McGorry PD. Mapping the onset of psychosis: the comprehensive assessment of at risk mental states (CAARMS). *Schizophr Res*. 2003;60(1):30–31.
38. Yung AR, Stanford C, Cosgrave E, *et al*. Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophr Res*. 2006;84(1):57–66.
39. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 2011;10(3):799–812.
40. Ventura J, Nuechterlein KH, Subotnik K, Gilbert E. Symptom dimensions in recent-onset schizophrenia: the 24-item expanded BPRS. *Schizophr Res*. 1995;15(1):22.
41. Dazzi F, Shafer A, Lauriola M. Meta-analysis of the Brief Psychiatric Rating Scale - Expanded (BPRS-E) structure and arguments for a new version. *J Psychiatr Res*. 2016;81:140–151.
42. R Development Core Team R. *R: a Language and Environment for Statistical Computing*. 2014. <https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing>
43. Haslbeck JMB, Waldorp LJ. Structure estimation for mixed graphical models in high-dimensional data. *J Stat Softw*. 2015;VV(Ii):1–27. <http://arxiv.org/abs/1510.05677>.
44. Epskamp S, Cramer AOJ, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph : network visualizations of relationships in psychometric data. *J Stat Softw*. 2012;48(4):1–18.
45. Epskamp S, Waldorp LJ, Möttus R, Borsboom D. The Gaussian Graphical Model in cross-sectional and time-series data. *Multivariate Behav Res*. 2018;53(4):453–480.
46. Haslbeck JMB, Waldorp LJ. MGM: estimating Time-Varying Mixed Graphical Models in High-Dimensional Data. 2015;VV(Ii):1–49. <http://arxiv.org/abs/1510.06871>.
47. Liu H, Lafferty J, Wasserman L. The nonparanormal: semiparametric estimation of high dimensional undirected graphs. *J Mach Learn Res*. 2009;10:2295–2328.
48. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: a tutorial paper. *Behav Res Methods*. 2018;50(1):195–212.
49. Fruchterman TMJ, Reingold EM. Graph drawing by force-directed placement. *Software Pract Exper*. 1991;21:1129–1164.
50. Opsahl T, Agneessens F, Skvoretz J. Node centrality in weighted networks: generalizing degree and shortest paths. *Soc Networks*. 2010;32(3):245–251.
51. Haslbeck JMB, Fried EI. How predictable are symptoms in psychopathological networks? A reanalysis of 18 published datasets. *Psychol Med*. 2017;47(16):2767–2776.
52. Merckelbach H, van de Ven V. Another White Christmas: fantasy proneness and reports of ‘hallucinatory experiences’ in undergraduate students. *J Behav Ther Exp Psychiatry*. 2001;32(3):137–144.
53. Fusar-Poli P, Bonoldi I, Yung AR, *et al*. Predicting Psychosis: Meta-Analysis of Transition Outcomes in Individuals at High Clinical Risk. *Arch Gen Psychiatry*. 2012; 69(3):220–229.
54. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophr Res*. 2010;120(1–3):1–6.
55. Mishara AL. Klaus Conrad (1905–1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophr Bull*. 2010;36(1):9–13.
56. Hambrecht M, Häfner H. Trama, Apophänie, Apokalypse-Ist Conrads Phasenmodell empirisch begründbar? *Fortschr Neurol Psychiatr*. 1993;61(12):418–423.
57. Bos FM, Snippe E, de Vos S, *et al*. Can we jump from cross-sectional to dynamic interpretations of networks? Implications for the network perspective in psychiatry. *Psychother Psychosom*. 2017;86(3):175–177.
58. Pearl J. *Causality: Models, Reasoning and Inference*. Cambridge, MA: Cambridge University Press; 2000.