

Speech Illusions in People at Clinical High Risk for Psychosis Linked to Clinical Outcome

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Background and hypothesis: Around 20% of people at clinical high risk (CHR) for psychosis later develop a psychotic disorder, but it is difficult to predict who this will be. We assessed the incidence of hearing speech (termed speech illusions [SIs]) in noise in CHR participants and examined whether this was associated with adverse clinical outcomes. **Study design:** At baseline, 344 CHR participants and 67 healthy controls were presented with a computerized white noise task and asked whether they heard speech, and whether speech was neutral, affective, or whether they were uncertain about its valence. After 2 years, we assessed whether participants transitioned to psychosis, or remitted from the CHR state, and their functioning. **Study results:** CHR participants had a lower sensitivity to the task. Logistic regression revealed that a bias towards hearing targets in stimuli was associated with remission status (OR = 0.21, $P = .042$). Conversely, hearing SIs with uncertain valence at baseline was associated with reduced likelihood of remission (OR = 7.72, $P = .007$). When we assessed only participants who did not take antipsychotic medication at baseline, the association between hearing SIs with uncertain valence at baseline and remission likelihood remained

(OR = 7.61, $P = .043$) and this variable was additionally associated with a greater likelihood of transition to psychosis (OR = 5.34, $P = .029$). **Conclusions:** In CHR individuals, a tendency to hear speech in noise, and uncertainty about the affective valence of this speech, is associated with adverse outcomes. This task could be used in a battery of cognitive markers to stratify CHR participants according to subsequent outcomes.

Key words: signal-detection/white noise task/uncertainty/remission/transition

Introduction

Psychosis is often preceded by a clinical high risk (CHR) stage, characterized by attenuated psychotic symptoms and a reduction in functioning. Although 40%–50% remit from the CHR state within 2 years,¹ more than half continue to experience symptoms and impairments in functioning^{2,3} and around 20% develop psychosis.^{4–6}

People with hallucinatory experiences are at increased risk of developing psychosis.^{7,8} One way to experimentally

assess proneness to psychotic experiences is to use the white noise task (WNT).⁹ In this computerized paradigm, participants are presented with white noise, with or without neutral speech, and asked whether they heard speech and if so, whether speech was neutral, positive, negative, or whether they were unsure about the valence of speech. The incidence of speech illusions (SIs)—speech heard on white noise-only trials—is increased in people who report hearing voices,¹⁰ is related to the level of familial risk for psychosis,⁹ and is associated with schizotypy in some⁹ but not all¹¹ studies. However, to date, the frequency of SIs in CHR participants has not yet been compared to that in healthy controls (HC).

Data from the WNT can be analyzed within a signal detection theory (SDT) framework¹² which describes the probabilistic processes of decision-making under conditions of uncertainty. According to SDT, on a given trial in which a target stimulus or noise may be presented, participants respond according to the value of an inner decision variable. If this reaches a certain criterion, the participant responds that a target is present; otherwise, the participant responds that it is not. Responses are categorized into hits (correctly detecting speech), false alarms (hearing speech when there is none), sensitivity (d'), and a bias towards responding “yes” or “no” (c).^{13,14} Healthy participants who report more hallucinatory experiences experience more false alarms, accompanied by a bias towards responding “yes,”^{15–17} but results are mixed as to whether this is associated with altered sensitivity on the WNT.^{12,17} The first aim of this study was to compare the incidence of SIs and SDT parameters of performance in a large sample of CHR participants and controls. We hypothesized that CHR participants would report SIs more frequently than healthy volunteers and would show reduced sensitivity and greater response bias.

Within CHR participants, impaired performance across a range of different cognitive tasks has been associated with adverse outcomes, including transition to psychosis,^{18–21} persistence of CHR symptoms,²² and low functioning.²² Whilst the perceived length of SI²³ has been linked to transition to psychosis, the incidence of SIs, and associated SDT parameters, have not been associated with clinical outcome. The second aim of this study was to assess whether within a CHR cohort the incidence of SIs or associated SDT parameters at baseline is associated with transition to psychosis, persistence of symptoms, or decreased functioning, 2 years later.

Methods

Sample

Data were collected from 344 CHR participants and 67 HCs recruited as part of the EU-GEI high-risk study (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia) (<https://www.eu-gei.eu/>),²⁴ a naturalistic prospective

multicentre study. Eleven sites contributed and from these sites, HCs were recruited from the general population.

Inclusion criteria for CHR participants were: Meet at least 1 criterion in the Comprehensive Assessment of At Risk Mental State (CAARMS⁴): (1) attenuated psychotic symptoms (subthreshold positive psychotic symptoms for at least 1 month in the previous year), (2) brief limited intermittent psychotic symptoms (an episode of frank psychotic symptoms that resolved in less than 1 week without treatment), and (3) vulnerability (a first-degree relative with a psychotic disorder or schizotypal personality disorder and a drop in functioning for at least 1 month in the previous year). Exclusion criteria for CHR participants were: An IQ lower than 60, a current or past psychotic disorder, or that symptoms could be explained by a disease or substance dependency. For CHR participants, the CAARMS was used to determine whether individuals met at least one of CHR criteria: Attenuated Psychosis Group, Vulnerability Group, or Brief Limited Intermittent Psychotic Symptoms Group. Exclusion criteria for all participants were: (1) past/present diagnosis of psychotic disorder, determined by CAARMS, and Structural Clinical Interview for DSM Disorders, (2) relevant symptoms explained by neurological disorder or drug/alcohol dependency, (3) contraindications to MRI scanning or unwillingness to provide blood/saliva sample (for the measures collected within the larger EU-GEI study); and (4) IQ estimate <60. HC participants did not meet CHR criteria. Typical age of participants was 18–35 years but not restricted due to variation between sites in the age at which persons are accepted by clinical services (table 1).

Instruments

Clinical Measures. Clinical measures were assessed at baseline and follow-up by assessors trained in the use of the CAARMS and the Global Assessment of Functioning Scale (GAF^{4,25,26}). Participants undertook follow-up assessments at 24 months. Transition to psychosis was defined as the development of psychotic disorder using the CAARMS.⁴ Available clinical records were used to determine any diagnosis of a psychotic disorder when participants did not return for follow-up assessments. In CHR participants that could not be contacted at follow-up, the onset of psychosis was defined using information from clinical records. Remission was defined as a participant no longer meeting the criteria for the CHR state at follow-up. Those who transitioned at follow-up were classed as non-remitters. Level of functioning was assessed based on the GAF disability score, as in previous research.²²

White Noise Task. The WNT was used to assess the incidence of SIs heard in white noise^{9,11,27,28} (figure 1). Participants, wearing earphones, sat in a room with a trained experimenter and were presented with either: (1)

Table 1. Sociodemographic Variables of the Participants Who Completed the White Noise Task, Split By Participant Group, Transition Status, and Remission Status

Measure	Subject Group			Transition Status			Remission Status		
	HC (N = 51)	CHR (N = 308)	P	T (N = 55)	NT (N = 253)	P	NR (N = 88)	R (N = 52)	P
Age in years, M (SD)	23.35 (3.99) 0	22.66 (4.92) 0	.134	22.71 (4.95) 0	22.64 (4.92) 0	.959	23.39 (5.34) 0	22.83 (4.59) 0	.759
Female sex, no (%)	24 (47.05) 0	145 (47.08) 0	1.00	24 (43.63) 0	121 (47.83) 0	.655	41 (46.59) 0	26 (50) 0	.729
Years in education, M (SD)	16.35 (2.84) 0	14.48 (3.12) (29)	<.001	14.13 (3.49) 9	14.55 (3.04) 20	.306	14.89 (3.36) 8	15.37 (2.58) 1	.189
WAIS IQ, mean (SD)	110.25 (17.71) 0	98.65 (16.95) 20	<.001	96.98 (13.64) 3	99.02 (17.60) 17	.470	97.59 (14.92) 3	102.60 (14.22) 2	.040
Number of cigarettes per day, M (SD)	6.69 (8.38) 25	10.81 (11.49) 117	.030	2.58 (1.55) 17	11.14 (11.94) 94	.414	10.23 (10.97) 32	8.65 (6.87) 21	.817
No. of alcoholic drinks per week, M (SD)	6.21 (7.08) 8	7.7 (11.63) 99	.750	8.95 (11.03) 18	7.43 (11.76) 81	.281	8.38 (10.09) 25	5.97 (8.69) 14	.135
How often uses cannabis, M (SD)	3.26 (1.19) 16	2.8 (1.56) 90	.095	2.58 (1.55) 17	2.84 (1.56) 73	.416	2.55 (1.55) 24	2.97 (1.48) 14	.160
Uses antipsychotic medication, no (%)	N/A	23 (9.2) 57	N/A	9 (19.14) 6	14 (6.86) 49	.020	10 (12.82) 10	1 (2.43) 11	.095
Baseline CAARMS positive score, M (SD)	N/A	9.98 (4.05) 5	N/A	10.58 (3.56) 0	9.56 (4.14) 5	.253	9.82 (4.11) 0	9.50 (3.64) 0	.526
Baseline CAARMS negative score, M (SD)	N/A	7.01 (3.41) 9	N/A	7.45 (3.39) 0	6.91 (3.41) 9	.374	7.51 (3.10) 1	7.69 (3.20) 0	.956
Baseline CAARMS total score, M (SD)	N/A	49.15 (15.73) 62	N/A	52.43 (15.80) 8	48.38 (15.65) 54	.169	50.45 (14.11) 13	48.81 (12.94) 3	.548
Baseline GAF average score, M (SD)	87.14 (9.17) 1	55.5 (9.9) 26	<.001	53.99 (9.98) 5	55.83 (9.87) 21	.085	53.74 (9.61) 5	56.89 (8.08) 0	.015

Note: HC, healthy controls; CHR, participants at clinical high-risk of psychosis; T, transition; NT, non-transition; NR, non-remission; R, remission; P, significance; SD, standard deviation; how often use cannabis, 1 = every day, 2 = more than once per week, 3 = a few times per month, 4 = a few times per year, 5 = only once or twice; no, number; N/A, not applicable. Significant differences are in bold. Number of missing values for each variable is given in italics.

white noise only, (2) white noise plus clearly audible neutral speech, and (3) white noise plus barely audible neutral speech. The neutral speech fragments had content such as: “Sport is good for health,” Speech was adapted to each country’s native language. Each fragment had a duration of 4.3 s and sound fragments were binaurally presented through headphones. Participants were presented with 25 trials of each condition, in random order, and were required to verbally endorse one of five possible responses per trial: (1) no speech heard, (2) heard speech saying something neutral, (3) heard speech saying something positive, or (4) heard speech saying something negative, and (5) heard speech, but uncertain if it was positive, negative, or neutral. A response of 2,3,4, or 5 during condition 1 (white noise only) was defined as a SI.

IQ. A 15-minute version of the short-form Wechsler Adult Intelligence Scale, including Digit Symbol Coding, Block Design, Information, and Arithmetic subtests^{29,30} assessed intellectual function.

Groups for Analysis. Comparisons were made between the entire CHR sample and HC, and between CHR subgroups defined according to clinical outcomes: transition to psychosis (CHR-T vs CHR-NT) and remission from the CHR state (CHR-R vs CHR-NR).

Signal Detection Theory. The WNT was analyzed using a SDT framework.¹⁴ Conditions (2) and (3) (white noise with neutral speech) were treated as the target, and condition (1) (“white noise only”) was treated as the nontarget. Three parameters were calculated:

1. False alarms (F) (proportion of white-noise-only trials incorrectly identified as targets) (with a log-linear transformation to account for extreme values in the data³¹).
2. Sensitivity d' as a global measure of performance,³¹ calculated as the difference between the inverse normal distribution of the hit rate and the inverse normal distribution of the false alarm rate (NORMSINV(H)—NORMSINV(F) in excel).³¹
3. Response bias c , signifying a bias towards detecting a stimulus as a target (a lower value of c indicates a bias towards responding “yes”),³¹ calculated as the average of the inverse normal distribution of the hit rate and the inverse normal distribution of the false alarm rate ((NORMSINV(H) + NORMSINV(F))/2 in excel).³¹

Affective and Uncertain SIs. We assessed whether SIs were affectively salient, ie, when participants perceived speech as negative or positive, or whether there was uncertainty around SIs, ie, when participants were uncertain if the perceived speech was neutral or had either a negative or positive salience. SI scores were skewed, as expected, because participants expressed a low rate of false alarms. To address this, following previous work,^{9,27,28} performance was parameterized as 3 dichotomous variables according

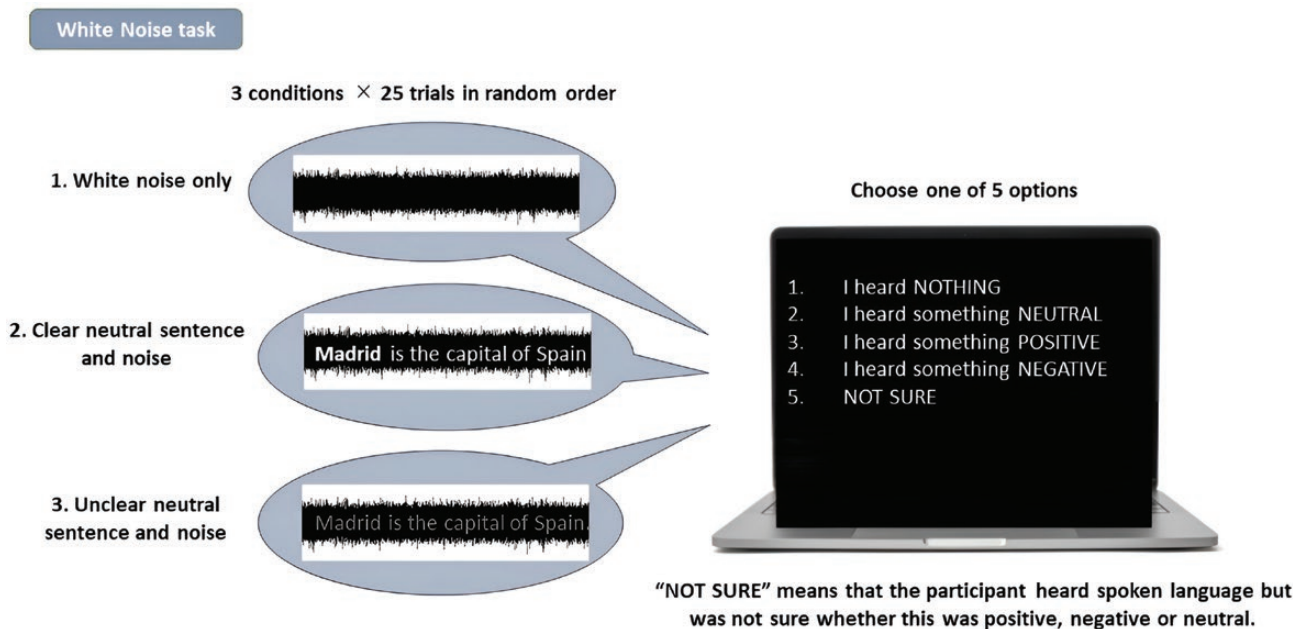


Fig. 1. The white noise task. Participants were presented with one of three conditions whilst wearing earphones: (1) white noise only, (2) white noise plus clearly audible neutral speech, (3) white noise plus barely audible neutral speech and required to verbally endorse one of five possible responses per trial: (1) no speech heard; (2) heard speech saying something neutral; (3) heard speech saying something positive; (4) heard speech saying something negative; (5) heard speech, but uncertain if it was positive, negative, or neutral. A response of 2,3,4, or 5 during condition 1 (white noise only) was defined as a speech illusion.

to responses during the white noise-only condition: Each participant was rated as 1 or 0 depending on whether they heard at least 2 SIs that they perceived as (1) neutral, (2) positive or negative, or (3) unsure whether they were neutral, positive, or negative. We included a threshold of at least 2 SIs per condition, to exclude possible erroneous attributions of SIs.²⁷

Group Differences. Group differences between participant group (CHR vs HC), transition status and remission status on the incidence of SIs were assessed using Fisher's exact tests, and on hit rate, false alarms, sensitivity (d'), and response bias (c'), using independent samples t tests. All tests used a significance threshold of $P < .05$ (two-tailed).

Association With Outcome

SDT Parameters. We applied a logistic regression model to each of the three SDT parameters (false alarm rate, sensitivity, or response bias) to assess whether each variable predicted transition or remission status in CHR participants. We also applied a linear regression model to each of the three SDT parameters to assess whether each variable predicted GAF disability score in CHR participants.

Dichotomous Variables. We applied a logistic regression model to each of the 3 dichotomous variables (heard 2 or more SIs, heard 2 or more positive/negative SIs, heard 2 or more SIs with uncertain valence) to assess whether

each variable predicted transition or remission status in CHR participants. We also applied a linear regression model to each of the 3 dichotomous variables to assess whether each variable predicted GAF disability score in CHR participants.

All models used a significance threshold of $P < .05$.

All regression models were adjusted for site, age, sex, cannabis and tobacco use, IQ (shortened WAIS), and years in education, based on the previous work^{9,28} and on which variables showed group differences between HC and CHR participants (table 1).

Attrition Analysis. Due to numerous attritions at follow-up, we assessed group differences between participants who did or did not drop out at follow-up, to confirm that attritions were random and did not influence the assessment of association with outcome, using independent samples t tests with a significance threshold of $P < .05$ (two-tailed).

Effect of Antipsychotic Medication. We repeated the analyses to include only CHR participants who were not on antipsychotic medication at the baseline assessment.

Results

Demographics

All sociodemographic, clinical, and medication data categorized by group, transition, and remission status are summarized in table 1. Two years from baseline, 55 CHR

participants (18% of the total sample) transitioned to psychosis (CHR-T) and 252 (82%) did not (CHR-NT), and 88 (63% of the remaining sample) had not remitted from the CHR state, and 52 (37%) had remitted. At baseline CHR participants had fewer years of education, lower IQ, smoked more cigarettes, and had a lower baseline GAF score than HC participants. Fewer CHR participants who transitioned to psychosis at 2 years were taking antipsychotic medication at baseline, and CHR participants who remitted from the CHR state had a higher IQ and a higher GAF average score at baseline. Of CHR participants who heard 2 or more SIs on the WNT, fewer were female, and participants who heard 2 or more affectively salient SIs at baseline had more years in education (supplementary table 4).

Group Differences on the WNT

Group differences on the WNT are summarized in table 2. HC participants ($N = 51$, $M = 3.58$) had a higher sensitivity d' than CHR participants ($N = 308$, $M = 3.26$) ($P = .018$). There were no other differences in the SDT parameters or the 3 dichotomous variables (heard 2 or more SIs, heard 2 or more affectively salient SIs, heard 2 or more SIs with uncertain valence) between HC and CHR participants, CHR-T ($N = 55$) and CHR-NT ($N = 253$) participants, or between CHR participants whose symptoms persisted at follow-up (CHR-NR) ($N = 88$) compared to CHR participants whose symptoms had resolved at follow-up (CHR-R) ($N = 52$) (table 2).

Performance on the WNT Associated With Outcome

All results of the outcome regression models are summarized in table 3. In CHR participants, a lower value of c (a higher likelihood of hearing targets in stimuli) ($OR = 0.21$, $P = .042$) and hearing 2 or more SIs with uncertain valence at baseline ($OR = 7.72$, $P = .007$), were associated with non-remission at 2-year follow-up. See figure 2A for a figure summarizing the significant results. There were no other associations between task parameters and outcome measures.

Attrition Analysis

All results of the attrition analysis are summarized in supplementary table 1. CHR participants with follow-up data ($N = 111$) were at baseline older, had more years in education, and had a lower CAARMS positive score and a higher CAARMS negative score and a low CAARMS positive score than CHR participants without follow-up data ($N = 197$), and fewer CHR participants with follow-up data were taking antipsychotic medication at baseline than CHR participants without follow-up data.

Table 2. Participant Group and Outcome Differences on Signal Detection Theory Parameters Hit Rate, False Alarm Rate, d' and c , and 3 Dichotomous Speech Illusion Variables “Heard 2 or More SI”, “Heard 2 or More Affective SI”, “Heard 2 or More Uncertain SI”. Significant differences are in bold. SI: Speech Illusion; no, Number

Measure	Participant Group			Transition Status			Remission Status		
	HC ($N = 51$)	CHR ($N = 308$)	P	T ($N = 55$)	NT ($N = 253$)	P	NR ($N = 88$)	R ($N = 52$)	P
False alarm rate mean (SD)	0.12 (0.16)	0.14 (0.17)	.368	0.12 (0.12)	0.14 (0.18)	.273	0.16 (0.17)	0.12 (0.16)	.171
d' mean (SD)	3.58 (0.84)	3.26 (1.01)	.018	3.29 (0.83)	3.26 (1.04)	.803	3.19 (0.89)	3.39 (0.87)	.200
c mean (SD)	-0.35 (0.39)	-0.28 (0.51)	.290	-0.27 (0.44)	-0.29 (0.53)	.743	-0.38 (0.44)	-0.23 (0.46)	.064
Heard SI, no (%)	6 (11.8)	39 (12.7)	1.0	10 (18.2)	29 (11.5)	.182	15 (17.0)	5 (9.6)	.318
Heard affective SI, no (%)	1 (1.9)	24 (7.8)	.229	6 (10.9)	18 (7.1)	.402	9 (10.2)	2 (3.8)	.212
Heard SI with uncertain valence, no (%)	18 (35.3)	120 (39.0)	.645	23 (41.8)	97 (38.3)	.649	42 (47.7)	16 (30.7)	.053

Table 3. Logistic Regression Models Assessing the Association Between Transition Status/Remission Status and Linear Regression Models Assessing the Association Between Functional Outcome, With Signal Detection Theory Parameters Hit Rate, False Alarm Rate, d' and c , and 3 Dichotomous Speech Illusion Variables “Heard 2 or More SI”, “Heard 2 or More Affective SI”, “Heard 2 or More Uncertain SI”. Each Row Signifies a Separate Model for Transition Status, Remission Status, and Functional Outcome. Significant Predictors are in Bold. All Models Were Adjusted for Age, Gender, Years in Education, IQ, Cigarettes Smoked Per Day, Site, and Cannabis Use, Replicating Previous Work^{9,29} and on Variables Showing Significant Differences at Baseline (table 1)

Measure	Transition Status ($N = 145$)		Remission Status ($N = 70$)		Functional Outcome ($N = 61$)			
	P	OR (95% CI)	P	OR (95% CI)	P	B	SE B	β
False alarm rate	.237	7.45 (0.27, 207.59)	.279	10.59 (0.15, 759.81)	.107	-19.84	12.08	-0.23
d'	.215	0.71 (0.42, 1.22)	.570	0.78 (0.34, 1.81)	.122	3.96	2.52	0.21
C	.431	0.61 (0.17, 2.09)	.042	0.21 (0.05, 0.94)	.386	3.94	4.5	0.12
Heard SI	.063	3.82 (0.93, 15.73)	.320	0.37 (0.05, 2.63)	.229	-6.60	5.41	-0.16
Heard affective SI	.582	1.72 (0.25, 11.89)	.711	0.59 (0.04, 9.67)	.251	-9.27	7.97	-0.17
Heard SI with uncertain valence	.059	2.87 (0.96, 8.58)	.007	7.72 (1.73, 34.49)	.099	-.88	4.09	-0.23

Note: OR, odds ratio.

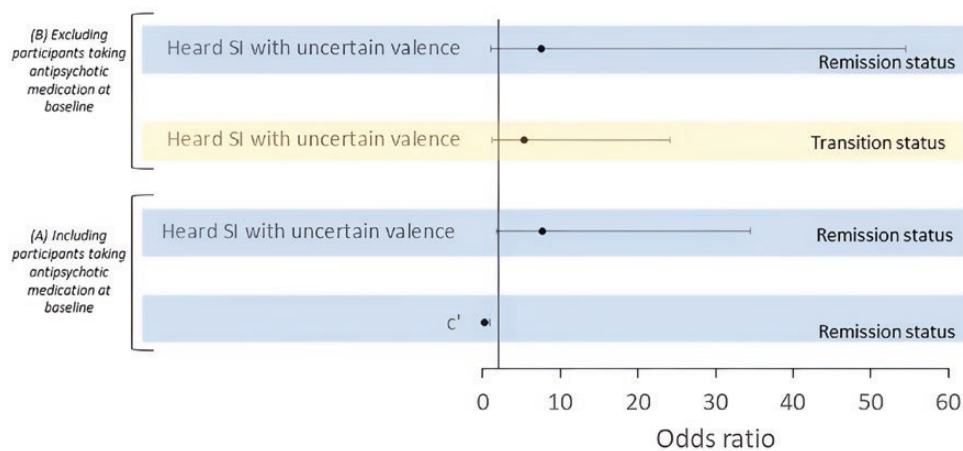


Fig. 2. Associations between performance on the white noise task and outcomes in CHR participants 2 years later, (A) including participants taking antipsychotic medication at baseline, and (B) excluding participants taking antipsychotic medication at baseline.

Effect of Antipsychotic Medication

All results of the analysis which included only CHR participants who were not on antipsychotic medication at the baseline assessment are summarized in [supplementary tables 2 and 3](#) ($N = 46$ HC and 228 CHR when excluding participants on antipsychotic medication [and participants whose data about antipsychotic medication was missing] compared to $N = 51$ HC and 308 CHR when including all participants). As in the analysis of all CHR participants ([table 2](#)), HC participants ($N = 46$, $M = 3.53$) had a higher sensitivity d' when compared to CHR participants who were taking antipsychotic medication ($N = 228$, $M = 3.24$) ($P = .048$), but there were no other group differences ([supplementary table 2](#)). As with the analysis in all CHR participants ([table 3](#)), in CHR participants who were not taking antipsychotic medication, hearing 2 or more SIs with uncertain valence at baseline was associated with non-remission from the CHR state at 2-year follow-up (OR = 7.61, $P = .043$). Unlike the analysis in

all CHR participants ([table 3](#)), the association between c and non-remission at 2-year follow-up was not significant in CHR participants who were taking antipsychotic medication ([supplementary table 3](#)) (OR = 0.38, $P = .277$). A new finding was that hearing 2 or more SIs with uncertain valence at baseline was associated with transition to psychosis in CHR participants who were taking antipsychotic medication ([supplementary table 3](#)) (OR = 7.61, $P = .029$). See [figure 2B](#) for a figure summarizing the significant results. There were no other associations between task parameters and outcome measures.

Discussion

The main findings of the study were that CHR participants had lower sensitivity (d'), and that CHR participants with a bias towards reporting hearing targets in stimuli, or who heard SIs with uncertain valence on the WNT at presentation, were less likely to be in remission at 2-year follow-up. This association between

hearing SIs with uncertain valence and non-remission remained significant when assessing only CHR participants who were not taking antipsychotic medication at baseline. Furthermore, in this cohort, SIs with uncertain valence were also associated with transition to psychosis at follow-up.

Cognitive models propose that perception represents a compromise between top-down beliefs and bottom-up sensory information,³² and that psychosis symptoms,³³ including hallucinations³⁴ may result from an imbalance between these parameters. The finding that CHR participants had lower sensitivity on the WNT, and the associations between performance on the task and adverse outcomes at follow-up, is in line with this account. Our approach to assessing uncertainty on the WNT is in contrast to previous studies using this task, which strictly focused on affective salience.^{9,27,28} We examined uncertainty because decision-making under conditions of uncertainty is suboptimal in CHR participants,³⁵⁻³⁷ and is associated with psychotic-like symptoms.³⁸ From a computational psychiatry perspective, this alteration can be attributed to the suboptimal precision-weighting of beliefs in the context of new information during perception.³⁹ Interestingly, we found that within the CHR sample, SDT measures of performance were associated with worse clinical outcomes. SDT describes the probabilistic processes of decision-making under conditions of uncertainty.¹⁴ We are the first to assess an association between SDT parameters on the WNT and clinical outcome in CHR participants. Our analysis revealed that across all CHR participants, sensitivity (d') is reduced, and in CHR participants whose symptoms persisted, a bias towards responding "yes" (c) predicted non-remission. This extends previous work showing that psychosis patients have worse general performance and make more false alarms than other psychiatric populations²⁸ and evidence of an association between psychotic experiences and response bias.¹³ Together, these results suggest that psychosis symptoms are associated with altered uncertainty processing.¹³ It is notable that this association did not survive when assessing only CHR participants who were not taking antipsychotic medication at baseline ([supplementary table 3](#)). This result could be explained by a decrease in statistical power, given that 23% of CHR participants were removed in this second analysis, either because they were taking antipsychotic medication at baseline or because data about their medication use was missing. Another interpretation is that the association between response bias and non-remission in the main analysis was caused by CHR participants who were taking antipsychotic medication. This is possible given that some studies have found that cognitive impairments in psychosis are influenced by antipsychotic use.^{40,41}

Feeling uncertain about the valence of SIs was linked to subsequent clinical outcomes in CHR participants. This link to uncertainty is potentially in line with evidence that

beliefs about volatility are associated with a hippocampal-cerebellar network on a perceptual conditioning task,⁴² and remission from the CHR state is associated with normalization in hippocampal perfusion,⁴³ which hints at a neural correlate for our behavioral results. Indeed, verbal memory in CHR participants is associated with hippocampal function,⁴⁴ and verbal recall performance is also associated with remission in CHR participants.^{22,45} Generally, CHR participants show altered uncertainty processing as measured by salience tasks³⁹ which are associated with transition to psychosis.⁴⁶

In CHR participants not taking antipsychotic medication at baseline, we replicated the association between hearing SIs with uncertain valence and non-remission, and we also observed an association between hearing SIs with uncertain valence and transition to psychosis. This latter result is in line with a previous study that reported that the perceived length of SIs in multispeaker babble was associated with transition to psychosis in CHR participants,²³ but only in medication-free participants. Similarly, our result was observed only in CHR participants not taking antipsychotic medication at baseline, suggesting that antipsychotic use confounded the association between SIs and transition to psychosis. Given replication of our results, the propensity to make uncertain responses on a cognitive task could offer a putative marker of clinical outcome in early psychosis, particularly in participants not taking antipsychotic medication, as would likely be the case at initial presentation. Future studies should investigate the association with outcomes using a battery of computational tasks which can offer individualized measures of uncertainty weighting, such as expected volatility, belief-updating,³⁸ and learning rate.^{47,48} Task bases indicators of this type are likely to be cheaper and more practical to administer compared to neuroimaging procedures that may also have the potential to predict outcomes.

We did not observe an association between SIs and functioning, in contrast with previous evidence linking with poorer functional outcomes in CHR participants with impaired performance on other cognitive tasks.^{22,49,50} This discrepancy could be because functional outcomes in the CHR participants in this study were associated with general cognitive functioning rather than probabilistic reasoning or uncertainty processing. Another explanation is that the rate of SIs on the WNT is low (only 13% of CHR participants reported hearing a SI in our task, similar to previous studies using this task^{27,28}) which may have generated a floor effect in our data. Also, we did not observe an association between affectively salient SIs and outcome, despite previous findings that psychosis patients are more likely to hear affectively salient SIs.^{9,27,28} This hints that alterations in affective salience processing develop after changes in uncertainty processing associated with outcomes in CHR individuals.

Strengths of the study include its prospective design and a large sample size of CHR individuals who were mostly medication-naïve. However, the correct hit rate on the WNT used was high (mean = 93%, SD = 15% across participants), suggesting that it may have been relatively easy for participants to detect true speech, and thus introduced a ceiling effect. We did not tailor detection thresholds for the task because, within a SDT analysis, it is assumed that all participants were exposed to the same stimuli. Although the hit rate was high, the false alarm rate (the variable of interest) was approximately the same as in other studies.⁵¹ Also, we only carried out a cross-sectional single assessment at baseline, and follow-up was only up to 2 years; it is possible that a more extensive longitudinal measure would provide a more sensitive insight into the association with outcome. Part of the CHR group were on antipsychotic medication. It should also be acknowledged that only 36% ($N = 111$) of the CHR participants had at least 1 outcome measure (remission vs non-remission, or functioning) at follow-up. Group comparisons showed that as well as being associated with CAARMS positive and negative scores, attrition was associated with a lower age, fewer years in education, and use of antipsychotic medication. We, therefore, repeated the analysis only assessing participants who were not using antipsychotic medication at baseline, and age and years in education were included as covariates in all analyses. It is also important to note that although we provided instructions that responding “not sure” on a trial indicates uncertainty about the valence of a SI, some participants may have misunderstood the task instructions, and their response “not sure” could indicate uncertainty as to whether speech was heard or not. Future studies should check that participants understand this instruction post-task. Furthermore, the WNT does not explicitly ask participants to employ top-down processing, rather relying on presentation of speech in some trials to induce an implicit expectation of speech. This type of expectation may differ from expectations induced explicitly, such as in tasks that show that hallucination-prone participants are more likely to hear SIs upon explicit instruction to employ auditory imagery.^{52,53} Finally, it is not clear whether susceptibility to SIs represents a novel marker for psychosis outcome, or whether it formalizes the link between hallucinatory experiences and psychosis risk which has already been observed in epidemiological studies in the general population.^{7,8}

In conclusion, we show that in CHR participants, hearing SIs with uncertain valence was associated with non-remission from the CHR state and transition to psychosis. Uncertainty processing is altered in CHR participants, and our results suggest that this is also associated with future outcomes. Our findings relate to computational perspectives of psychosis which explain the disorder as an alteration in the precision-weighting

of beliefs and new information. This could reflect a model in which early alterations in uncertainty processing are associated with prolonged subthreshold psychosis symptoms and a greater likelihood of developing psychosis or non-remission from the CHR state. Understanding these associations (and replication) could allow the incorporation of measures of uncertainty into predictive models to stratify individuals according to subsequent outcomes, and to tailor treatments to individuals.

Supplementary Material

Supplementary material is available at <https://academic.oup.com/schizophreniabulletin/advance-article/doi/10.1093/schbul/sbac163/6901995>.

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