

Early auditory impairments as a candidate marker of attenuated sensory symptoms of psychosis

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ABSTRACT

Background and hypothesis: Deficits in early auditory processing (EAP), as indexed by tone-matching performance, have been consistently demonstrated in individuals with schizophrenia spectrum disorders. However, the ontogeny of tone-matching deficits in schizophrenia remains relatively unknown. The current study aims to determine the relationship between clinical high risk for psychosis and EAP.

Study design: We employed a web-based screening approach to identify CHR individuals. A sample of 892 community dwelling participants completed the 16-item version of the prodromal questionnaire (PQ16) for the assessment of attenuated psychotic symptoms, a 9-item questionnaire of perceptual and cognitive aberrations (PCA) for the assessment of basic symptoms and a tone-matching task.

Study results: 505 (43.4%) participants met cut-off criteria for attenuated psychotic symptoms ($PQ16 \geq 6$ endorsed items), 614 (68.3%) for basic symptoms ($PCA \geq 3$ endorsed items), 647 (72.0%) for either and 358 (40.1%) for both of them. No significant differences in tone-matching performance were observed between CHR and non-CHR subjects, using either attenuated psychotic symptoms, basic symptoms, either or both cutoffs. In the CHR group screened with attenuated psychotic symptoms, auditory and tactile sensory symptoms were significantly associated with tone-matching deficits.

Conclusion: Tone-matching may not serve as a reliable biomarker for CHR status but rather a risk marker for the emergence of early sensory manifestations.

Key-words: clinical high risk; tone-matching; early auditory processing

INTRODUCTION

Early auditory processing (EAP) differences consistently feature among central sensory changes in psychosis groups, such as schizophrenia (Donde et al., 2023b; Javitt and Sweet, 2015). A well-documented effect in the literature pertains to the pitch discrimination of non-verbal sounds, assessed through a behavioral tone-matching task (Donde et al., 2017), initially developed by Strous and colleagues based on “echoic memory” concepts (Strous et al., 1995). It has been repeatedly demonstrated that impaired EAP in patients has a direct impact on overall cognition, contributing significantly to functional outcomes in social and occupational domains (Donde et al., 2019b; Thomas et al., 2017). Sensory training programs based on tone-matching have proven efficacy in improving cognitive abilities and functional outcomes (Donde et al., 2019c) and can be used for personalizing treatment and informing the selection of cognitive remediation exercises (Medalia et al., 2023).

The experimental setup for tone-matching involves presenting subjects with pairs of non-verbal tones in series. In each pair, the tones are either identical or vary by a specified amount of pitch. Participants are required to indicate whether the tones are "same" or "different" through a 2-button press. Tone-matching deficits index wider markers such as impaired mismatch negativity (MMN) generation, reduced functional connectivity within both primary and associative auditory cortex, as well as glutamatergic and N-methyl-D-aspartate receptor (NMDAR) hypofunction in psychosis groups (Donde et al., 2023a; Donde et al., 2023b; Javitt and Freedman, 2015).

Despite the pathophysiological relevance and clinical utility, the ontogeny of tone-matching deficits in schizophrenia remains relatively unknown. The clinical high risk (CHR) for psychosis is a clinical construct that captures potentially prodromal manifestations of schizophrenia in young people and has proven useful in investigating neurodevelopmental and neurodegenerative mechanisms associated with schizophrenia (Donde et al., 2023b). However, investigations into tone-matching deficits within CHR groups have yielded mixed results, warranting further exploration and replication in larger cohorts. A pilot investigation in CHR participants found intact tone-matching abilities in the clinical group (Corcoran et al., 2015; Donde et al., 2019a). By contrast, deficits in related neurophysiological indices, such as MMN, have been shown in individuals with prodromal psychotic symptoms, and may predict functional disability, clinical remission and conversion to schizophrenia (Hamilton et al., 2021; Perez et al., 2014; Tada et al., 2019). Nevertheless, associations were not replicated by

others (Atkinson et al., 2017; Dheerendra et al., 2024; Erickson et al., 2016; Hamilton et al., 2022; Hirt et al., 2019; Nagai et al., 2013) and results are thought to be affected by factors such as medication status, duration or severity of illness and recruitment methods (Hamilton et al., 2022; Lepock et al., 2020).

CHR criteria instruments include a genetic risk plus functional deterioration syndrome, brief limited intermittent psychotic episodes as well as, in most cases, attenuated psychotic symptoms. In parallel, CHR criteria also have been based on the basic symptom concept. Attenuated psychotic symptoms are defined by the presence of hallucinations, delusions, or disorganized speech in attenuated form, while basic symptoms are subtle, subjectively experienced disturbances in mental processes (Schultze-Lutter et al., 2010; Schultze-Lutter and Theodoridou, 2017). Individuals at CHR can be screened in the general population or community across ages using brief self-report questionnaires such as the PQ16 (Prodromal Questionnaire) for attenuated psychotic symptoms and the PCA (Perceptual and Cognitive Aberrations) for basic symptoms. A large-scale online community study provided evidence for the possibility to identify and study large cohorts of CHR individuals with these screening tools through population-based web screening (McDonald et al., 2019).

Our primary aim, using an online community study approach, was to determine if CHR individuals exhibited EAP deficits (assessed with a tone-matching task) compared to non-CHR counterparts. Online research platforms facilitate global recruitment, automated data collection, and standardized procedures. These platforms offer flexibility in data collection and analysis, while ensuring participant privacy and informed consent (Newman, 2020). Given the pathophysiological continuum between CHR and full-blown psychotic disorders, we hypothesized that there would be significantly lower tone-matching scores in the CHR group. Additionally, we explored the link between EAP deficits and CHR symptom severity, expecting that lower tone-matching performance would predict higher PQ16 and PCA scores.

METHODS

1. Recruitment and Participants

The TONE-P cohort was a cross-sectional online study investigating EAP in non-help-seeking adults screened for CHR. Participants aged 18 to 35 years were recruited via French

and UK universities' undergraduate mailing lists and Amazon's Mechanical Turk. Informed consent was obtained online, followed by socio-demographic questions, CHR screening self-questionnaires (PQ16 and PCA scale), and the tone-matching task. The study received ethical approval from Durham University and University of Southampton, United Kingdom (UK), and the University Grenoble Alpes, France. The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki).

2. CHR screen questionnaires

The 16-item PQ16 questionnaire (Ising et al., 2012) was developed on the basis of the Prodromal Questionnaire, a 92-item self-report questionnaire that measures attenuated psychotic symptoms (Loewy et al., 2005). The PQ16 measures the degree of perceived distress associated with each item, rated on a 4-point Likert scale as “none”, “mild”, “moderate” or “severe”. The total score is the result of the sum of the scores obtained for each of the 16 items.

The PCA is a 9-item self-assessment screening questionnaire for basic symptoms. The scale was translated and validated in French in an adolescent population (Spillebout et al., 2023). The PCA questions the degree of perceived distress, rated as “none”, “mild”, “moderate” or “severe” on a 4-point Likert scale. The total score is the result of the sum of the scores obtained for each of the 9 items.

Cut-off criteria for CHR were 6 or more positively endorsed items on the PQ16, and/or a cut-off score of 3 or more positively endorsed items on the PCA (Ising et al., 2012; McDonald et al., 2019). These cut-offs were used to identify two groups (CHR vs. non-CHR) for a between-groups design.

3. Tone-matching task

The tone-matching task is a simple behavioral test that assesses discrimination of basic features of non-verbal sounds. The experiment consists of presenting to subjects pairs of non-verbal and not-too-distant short tones in series presented through headphones. Within each pair, tones are either identical or differ in pitch – the auditory percept associated with sound frequency – by specified amounts. Participants have to respond by pressing “same” or “different” on a 2-button press. In this study, the task consisted in 144 pairs of short 100 ms pure tones (i.e., "beeps") with a 500 ms intertone interval. Half of these pairs consisted of

tones that differed by one of five predetermined pitch differences ($\Delta 2.5\%$, $\Delta 5\%$, $\Delta 10\%$, $\Delta 20\%$, $\Delta 50\%$ Hz), while the other half consisted of identical tones (i.e., 50% chance performance). Tones were derived from three reference frequencies (500, 1000, and 2000 Hz) to avoid learning effects. The order of presentation of the tone pairs was randomized. The test is preceded by audiometric screening to ensure absence of hearing impairment, and by a series of practice pairs to ensure correct understanding of the task and comfortable sound level for each participant. Percent correct responses across all pairs was used as outcome.

4. Statistical analyses

The groups were compared using Student *t*-tests, Mann-Whitney tests in case of non-normal distributions for continuous variables, and using χ^2 tests for categorical data.

Relationship between tone-matching performance and symptoms was assessed using principal component analyses with varimax rotation separately applied to the questionnaires. This analysis converts a larger number of correlated variables into a smaller set of uncorrelated factors (components), which are linear combinations of the original variables. The number of factors (components) was chosen based on the Kaiser stopping criterion (i.e., all components with eigenvalues ≥ 1) and visual inspection of the scree plot. To explore the association between symptom factors and early auditory processing, multiple regression analyses were then conducted with tone-matching score as dependent variable and factors as independent, associated to potential socio-demographic confounders.

All statistical tests were two-tailed with pre-designated α -level of significance of $p < 0.05$. Data were analyzed with SPSS version 22.

RESULTS

1. Sample characteristics

A sample of 949 participants were enrolled in the TONE-P study. Participants with missing data ($N = 34$), mean reaction times above 5% and below 5%, tone-matching percent correct responses $< 50\%$ (i.e., chance performance) ($N = 22$) were excluded. In total, 892 participants' data were analysed, including 352 (39.2%) from France and 547 (60.8%) from the UK. The majority of subjects were female (71.5%) and the mean age was 21.4 ± 4.7 years. Mean education years was 4.8 ± 1.9 years. The majority were either employed or students

(94.4%).

505 (56.6%) participants met cut-off criteria for attenuated psychotic symptoms (PQ16 ≥ 6 endorsed items), 614 (68.3%) for basic symptoms (PCA ≥ 3 endorsed items), 647 (72.0%) for either and 358 (40.1%) for both of them. None of the socio-demographic variables were significantly associated with CHR status. There were no significant differences in age, gender, or level of education between the French and English participants (all $p > .05$, table 1).

2. Tone-matching performance symptoms

No significant differences in tone-matching performance were observed between CHR and non-CHR subjects, using either attenuated psychotic symptoms, basic symptoms, either or both cutoffs (Figure 1). A sensitivity analysis was conducted on the 22 excluded participants with outlying tone-matching data (9 CHR and 13 non-CHR, based on the three cutoffs). No significant differences were observed between the two groups ($z = 0.36$, $p = .72$).

As exploratory, we compared non-CHR subjects scoring below both attenuated psychotic symptoms and basic symptoms cutoffs with a “top-tier” CHR group including the tier of participants scoring above both attenuated psychotic symptoms and basic symptoms cutoffs and exhibiting the highest total attenuated psychotic symptoms and basic symptoms summed scores. No significant difference was observed ($t = -.431$, $p = .67$) (Figure 1). According to a previous study in which a bimodal distribution of tone-matching across individuals with schizophrenia was demonstrated, with one group showing intact tone-matching (score $\geq 77.7\%$ correct) (Donde et al., 2019a), we compared the proportion of CHR subjects between intact ($\geq 77.7\%$) and impaired ($< 77.7\%$) tone-matching groups (see histogram in Supplementary Figure 1). Screened CHR (PQ16 ≥ 6 and PCA ≥ 3), was significantly more prevalent in the impaired tone-matching group (59% vs. 38%, $\chi^2 = 14.5$, $p < .0001$).

3. Contribution to attenuated psychotic symptoms

In order to evaluate the relationship between tone-matching and attenuated psychotic symptoms, PQ16 questionnaire items were first entered into separate principal component analyses in the CHR respective groups. Then, factors (components) and socio-demographics were entered as independent variables and tone-matching as dependant into multiple regression analysis.

In the CHR group screened with attenuated psychotic symptoms (N= 387 with ≥ 6 endorsed items), four factors emerged from the principal component analysis and accounted for 47.21 % of the variance in scores (Table 2). In the regression analysis, only the Factor 4 (including PQ16-4 “I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears”, PQ16-12 “Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of.” and PQ16-16 “I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.”) emerged as a significant but weak contributor to tone-matching deficits ($\beta = -.12$, $p = .019$), whereas Factor 1–3 were not significantly associated with tone-matching (all p -values > 0.05 , Table 4). We reproduced this analysis on the “top-tier” CHR group including the tier of participants exhibiting the highest total attenuated psychotic symptoms scores. No factor was significantly associated with tone-matching (all p -values > 0.05).

4. Contribution to basic symptoms

The same procedure was conducted using PCA questionnaire items. In the CHR group screened with basic symptoms (N= 614 with ≥ 3 endorsed items), two factors emerged from the principal component analysis and accounted for 50.26% of the variance in scores (Table 3). In the regression analysis, no factor was significantly associated with tone-matching (all p -values > 0.05 , Table 4).

DISCUSSION

We investigated tone-matching performance in a large community sample of screened CHR individuals identified using PQ16 and PCA questionnaires (proxies), aiming to explore the relationship between EAP and CHR. Additionally, we examined whether tone-matching could predict symptoms in CHR participants. The CHR prevalence rates (43.4% met cut-off criteria for the attenuated psychotic symptoms and 68.3% met cut-off criteria for the basic symptoms) were consistent with those found in previous online study (McDonald et al., 2019). Our results revealed intact tone-matching performance; however, significant relationships between tone-matching and specific symptoms in the CHR group were observed, independently of sociodemographic variables.

1. Tone-matching is intact in screened CHR

Contrary to our main hypothesis, no significant differences in tone-matching performance were noted between groups, even when using a subgroup with higher levels of symptoms. This finding contrasts our expectation and aligns with a priori pilot report (Corcoran et al., 2015; Donde et al., 2019a) and the preserved MMN to pitch deviants in CHR participants (Atkinson et al., 2017; Erickson et al., 2016; Hamilton et al., 2022; Hirt et al., 2019; Nagai et al., 2013) [but see (Hamilton et al., 2021; Perez et al., 2014; Tada et al., 2019)].

This result may in part be explained by our CHR sample, as screening approaches, utilizing self-questionnaires like PQ16 and PCA, have been associated with a notable false positives rate, reaching approximately 2/3 (McDonald et al., 2019). Recent research suggests that questionnaire items endorsed by individuals not seeking help may capture more normative experience than symptoms related to psychosis risk (Capizzi et al., 2022). Our study did not verify CHR diagnosis through interviews for participants scoring above the PQ16 cut-off, potentially including false positives. Considering that CHR diagnosis converts to psychosis for about one quarter of individuals within 2–3 years (Caballero et al., 2023), it might be that reduced tone-matching is evident only in those later converters, supported by altered functional connectivity in auditory brain regions in CHR individuals who later convert (Anticevic et al., 2015; Colibazzi et al., 2017), and the relationship between this connectivity and tone-matching performance (Donde et al., 2019a). This hypothesis is in line with the observation of preserved tone-matching in a preliminary cohort of CHR individuals, but impaired in two individuals who did convert to psychosis within a two-year period (Corcoran et al., 2015). However, our cross-sectional study did not allow us to witness potential transition, and then compare tone-matching between psychosis converters and non-converters. Additionally, even increased EAP indicated by higher MMN amplitude and higher tone-matching performance relative to controls have been reported in CHR, as a potential consequence of hyperexcitability associated with excitation-inhibition imbalance early in the course of psychosis (Donde et al., 2019a; Krystal et al., 2017; Rivolta et al., 2014). Collectively, these findings imply that intact tone-matching observed in our CHR sample may reflect an average of ‘normal’ (in false positives), reduced (in converters) or even elevated performance levels. However, even CHR participants with highest scores on both attenuated psychotic symptoms and basic symptoms did not perform differently than their non-CHR

counterpart on tone-matching task, which reinforces the conception of preserved EAP in CHR.

The intact tone-matching in our CHR sample aligns with a meta-analysis suggesting no significant differences in auditory MMN deficits between CHR and first-episode psychosis participants (Erickson et al., 2016), indicating that significant impairments in EAP may only manifest at later illness stages (Salisbury et al., 2007). Another potential explanation for the preserved tone-matching ability could involve the engagement of extra-auditory processing mechanisms during the task. Tone-matching task necessitate precise discrimination between pure tones followed by binary perceptual decision-making (“same” or “different”). In other words, the task measures how information gathered from the auditory system is combined and used to influence the perceptual decision. While disturbances of preattentive processing and precision at the level of early auditory regions have been extensively documented in psychosis (Donde et al., 2023b; Donde et al., 2019e; Javitt and Sweet, 2015), it remains uncertain whether impaired tone-matching solely stems from early sensory dysfunction or if deficits in prefrontal-mediated ability to translate early processing into behavioral responses also play a role (Domenech and Dreher, 2010; Heekeren et al., 2008). Thus, it is plausible that our CHR group compensated early auditory dysfunction with increased functioning of higher-order brain regions during the task, akin to findings in reward processing paradigms in this population (Wotruba et al., 2014). This observation may indicate earlier dysfunction of auditory versus prefrontal brain regions over the course of psychosis.

In a previous study, a bimodal distribution of tone-matching across individuals with schizophrenia was demonstrated, with one group showing intact tone-matching (score \geq 77.7% correct). Those with the deficit have overall worse prognosis, including cognitive impairments, reduced functional capacity and less probability to have pursued education beyond high school (Donde et al., 2019a). Participants in our CHR sample were predominantly self-referenced and comprised a majority of high school student. While a significant proportion of CHR individuals scored less than 77.7% correct, it is plausible that our recruitment procedure has only captured a small subset of the CHR population with tone-matching deficits, particularly if such bimodality emerges at prodromic stages of psychosis.

2. Tone-matching dysfunction is associated with auditory symptoms of CHR

A novel aspect of our study is the investigation of the relationship between CHR symptoms and tone-matching abilities. As anticipated, we found that lower tone-matching

performance is associated with higher intensity of specific symptoms. Notably, two symptoms significantly associated with tone-matching in the regression analysis refer to “auditory” attenuated psychotic manifestations assessed by the PQ16 (i.e, hearing unusual sounds, and being abnormally salient to sounds), suggesting early auditory contributions to these manifestations at early-stage of psychosis. This result is in line with the demonstration that tone-matching deficits may contribute to incorrect sourcing of perceptual material, which in turn may lead to misattribution of internally-generated events to an external source and, in turn, to the pathogenesis of auditory hallucinations in schizophrenia (Donde et al., 2019d). Evidence suggests that basic sensory features such as pitch, as perceived during EAP, are key elements for optimal sourcing of a sensory event (Johnson et al., 1993; Sugimori and Tanno, 2010). In schizophrenia, this contribution has been put forward in the auditory domain by a previous study showing that contrary to healthy controls, participants with schizophrenia with prominent auditory hallucinations do not require the distortion of their feedback to misattribute their own speech to an external source, indicating EAP dysfunction in these patients (Johns et al., 2001). Similarly, poorer tone-matching performance has been reported in a group of patients with schizophrenia and auditory hallucinations compared with a non-hallucinating group (McLachlan et al., 2013). The association between PQ16-16 symptom (bodily illusions) and tone-matching is consistent with demonstration associations between auditory hallucinations and disturbances of the sense of body ownership in schizophrenia (He et al., 2022). Association between attenuated symptoms and tone-matching deficits suggests potential benefit of targeted interventions on EAP at a behavioral level in CHR. For instance, as previously demonstrated in schizophrenia (Kantrowitz et al., 2019), non-invasive brain stimulation targeting auditory hallucinations may have a specific role in modulating EAP related to higher-order clinical manifestations. However, it should be noted that these considerations should be approached cautiously, as the principal component analysis revealed a weak association between the factor grouping the three mentioned sensory PQ16 items and tone-matching performance in CHR. Moreover, this association was not significant in the CHR subgroup with more severe symptoms.

In contrast, no relationships were observed between tone-matching and basic symptoms, suggesting either that these symptoms are not related to auditory pathophysiological processes, or that EAP dysfunction in individuals with basic symptoms is not sufficient to translate into decreased tone-matching performance. The latter consideration

is in line with earlier development of neurobiological processes underlying basic symptoms vs. attenuated psychotic symptoms (Schultze-Lutter and Theodoridou, 2017).

The ubiquity of numerous non-specific attenuated psychotic manifestations in screening instruments for psychosis, including the Prodromal Questionnaire (Bernardin et al., 2023), has been recently refined by the demonstration of “hearing voices”, among other symptoms, as one of the most discriminating manifestations of CHR (Karcher *et al.*, 2020, Gauld *et al.*, 2024). Knowing that tone-matching deficits predict auditory attenuated symptoms intensity, it is a possibility that EAP deficits only emerge in a subgroup of individuals at CHR experiencing specific sensory attenuated psychotic symptoms. In other words, EAP deficits are not associated with CHR status, but are rather linked to sensory prodromal proneness. This supports a model where EAP deficits and sensory hallucination-proneness are discrete dimensions of CHR status and may imply sensory manifestations are more relevant to identify for CHR conversion.

3. Limitations

First, we recruited participants who were self-referred from the general population. There is evidence to suggest that recruitment of CHR participants outside clinical pathways is associated with a dilution of psychosis risk (Fusar-Poli et al., 2016) and may have led to the inclusion of false positives in our CHR sample. Research indicates that a significant number of questionnaire items endorsed by individuals who do not seek help may capture normative experiences rather than psychosis-related symptoms (Capizzi et al., 2022). Moreover, the absence of semi-structured interviews for CHR diagnosis in our study prevented the confirmation of CHR status among screened participants. Nevertheless, the persistence of non-significant differences in tone-matching performance between non-CHR and top-tier CHR subjects suggests that the results are not likely due solely to false positives.

Second, it was not within the scope of our study to follow-up with our CHR group, thus we were unable to compare converters to non-converters on tone-matching measure.

Third, our study did not include simultaneous measures of other early auditory measures exhibiting larger deficit effect sizes, such as MMN and tone-matching to duration deviants (Donde et al., 2020; Nagai et al., 2013; Todd et al., 2008). Recent analyses are currently under replication to identified the most indicative symptoms of CHR for increased screening specificity (Gauld et al., 2024a, b), warranting replications before clinical use. The present results collected online suggest the need for concurrent evaluations of symptoms,

tone-matching, and auditory neurophysiological measures in future longitudinal studies in order to limit the risk of false positives and further understand the early pathophysiological sensory mechanisms associated with at-risk symptoms and transition to psychosis.

5. CONCLUSION

Our findings indicate intact tone-matching among participants screened for CHR. In contrast, tone-matching deficits may predict specific symptoms of CHR associated with clinically significant auditory disturbances. Our data suggests that tone-matching may not serve as a reliable biomarker for CHR status but rather a risk marker for the emergence of early sensory manifestations.

Figure Caption

Figure 1. Tone-matching task performance across groups.

CHR = Clinical High Risk for psychosis. PCA = Perceptual Cognitive Abnormalities scal.

PQ16 = Prodromal Questionnaire 16-items. n.s. = not significant.

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CONFLICT OF INTEREST

Authors report no conflict of interest related to the present study.

AUTHOR CONTRIBUTION

CD designed the study and wrote the first draft of the manuscript. BAD supervised the study. CG contributed to the statistical analyses. MP and EPC contributed to participants' recruitment and provided relevant inputs to the manuscript. All authors reviewed and approved the manuscript in its final form.

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