40-Hz Auditory Steady-State Responses Characterize Circuit Dysfunctions and Predict Clinical Outcomes in Clinical-High-Risk Participants: A Magnetoencephalography Study

Supplemental Information

Follow-Up Assessments

Participants meeting CHR-P criteria were re-assessed at 3, 6, 9, 12, 18, 24, 30 and 36 months intervals to examine persistence of Ultra-High-Risk (UHR) criteria and transition to psychosis. Persistence of UHR-criteria was operationalized as the continued presence of APS on the CAARMS for up to 12 months. Criteria for transition to psychosis were defined on the basis of the CAARMS symptom scores of sufficient duration and frequency (symptoms minimally 1 hour/day, 3-6 times/week, > 1 week present), using symptom severity (5-6 out of 6) and frequency scores. When transition to psychosis was confirmed, a SCID Interview was conducted to establish the DSM-IV-category of the psychotic disorder. An overview of all follow-up data is presented below in supplementary Table S1.

Table S1. Follow-Up data

Baseline status	**Follow-up missing**	**status up to 12 Month**	**Transitioned cases**
SPI-A only (n=33)	n=2	**SPIA only** (n=25) 17 at 12 months 8 < 12 months **Meeting UHR/APS** (n=6) 4 at 12 months 2 < 12 months	18 Month (n=1) 26 Month (n=1) 36 Month (n=1)
Meeting UHR threshold for APS: (n=83)	n=4	**APS non-persistent** (n=39) 30 at 12 months 9 > 12 months **APS-persistent** (n=40) 30 at 12 months 10 < 12 months	36 Month (n=1) 24 Month (n=3) 12 Month (n=2) 9 Month (n=2) 6 Month (n=2)

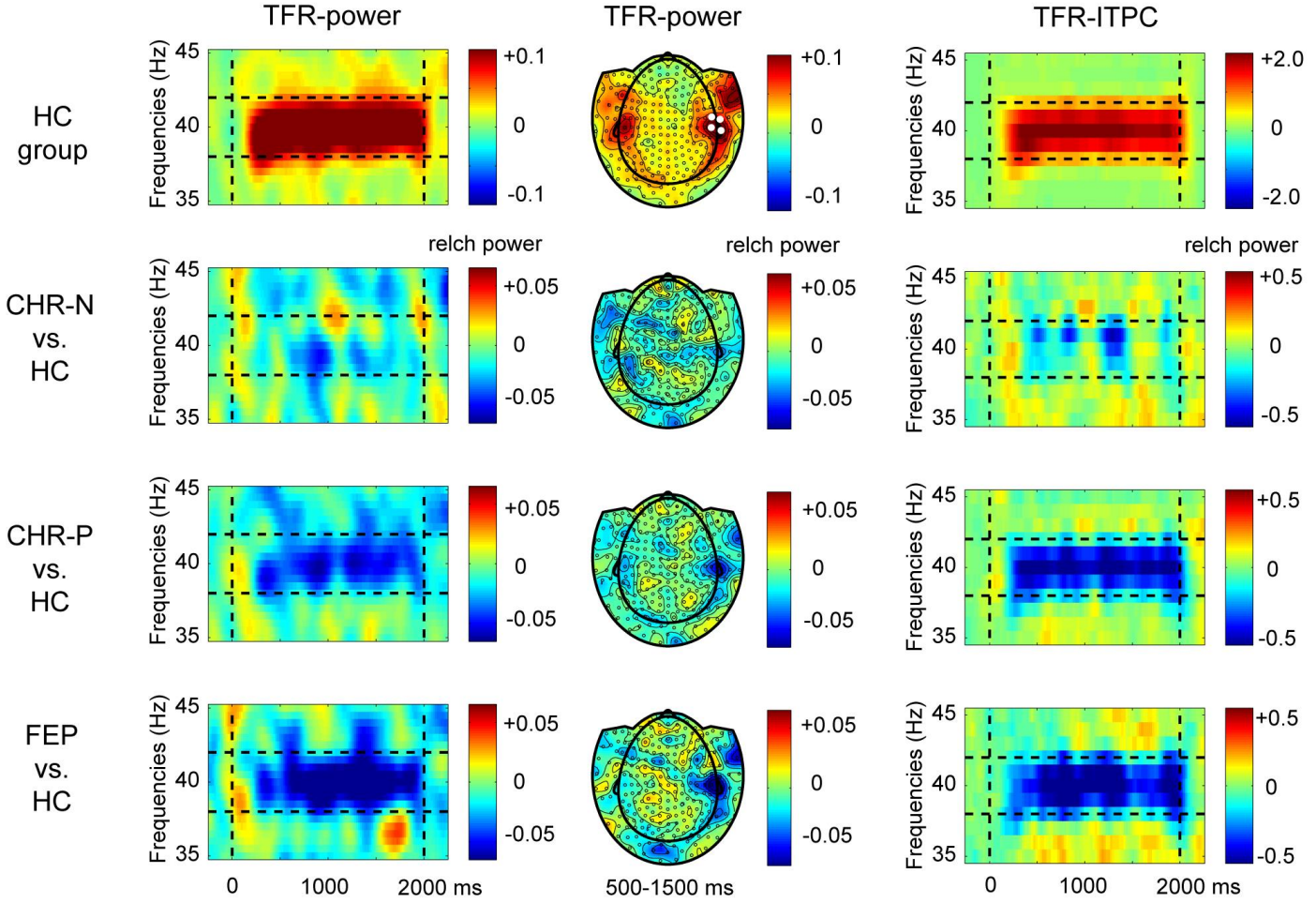
Abbrev.: FUP = Follow-up, UHR = Ultra High Risk, APS = attenuated psychotic symptoms, SPI-A = Schizophrenia Proneness Instrument, Adult Version (Basic symptom criteria).

SENSOR-LEVEL analysis of 40-Hz ASSR data

Our main analyses focused on data transformed into source space because regional specificity at each sensor is compromised by field-spread through inputs from multiple sources. Also, inter-individual differences in temporal cortex folding tend to create large variance in source projections to the scalp of auditory-cortex activity, which diminishes sensitivity to find group differences at sensor-level. Sensor-level TFR and ITPC data, however, was analysed and results are presented below.

Supplementary Figure S1 shows the main power (left column) and ITPC responses (right column) for the HC group (top row), with data averaged across a subset of four sensors over right frontal-temporal sites (white dots in top middle topographical distribution plot of planar-transformed data) covering the strongest entrainment response in the grand-average of the HC group. The three lower rows of the figure show the data for the main group contrasts between clinical groups and controls.

Figure S1. Main Group Differences in 40-Hz ASSR Signals at Sensor Level



Abbrev.: HC = healthy controls, CHR-N = clinical-high-risk negative, CHR-P = clinical-high-risk positive, FEP = First-Episode Psychosis, relch = relative change from baseline (-500-0 ms) activity

A reduction in 40-Hz power and 40-Hz ITPC can be seen over right frontal-central sensors for CHR-P and FEP groups, but not for the CHR-N group. To test for significant group differences, we first used non-parametric cluster-based permutation (n=1000), independent-sample F-tests (alpha = 0.05). No significant clusters of group differences were found. As the 40-Hz response was very localized, we followed up with non-parametric Kruskal-Wallis test for data averaged over 4 right-hemisphere sensors covering the maximum response in HCs (location indicated in middle top-row distribution plot). Again, no group differences were found in either TFR ($H(3) = 3.9$, $p = 0.27$) or ITPC data $H(3) = 4.8$, $p = 0.18$.

Table S2. Demographic and Clinical Characteristics for APS-persistent and APS-non-persistent CHR-P participants

	APS-P	APS-NP	statistical results [a]
Number of participants	34	39	
Age: years (SD)	23 (5.3)	22 (4.4)	
Sex: male/female (%male)	12/22 (35.3)	10/24 (29.4)	
Education: years (SD)	15 (3.6)	16 (3.2)	
BACS [b]: mean (SD)			
Verbal memory	-0.42 (1.1)	-0.25 (1.2)	
Digit sequencing	-0.43 (1.8)	-0.05 (1.5)	
Token motor	-1.15 (1.4)	-1.00 (1.1)	
Verbal fluency	0.00 (1.5)	0.06 (1.4)	
Symbol coding	-0.60 (0.9)	-0.56 (1.2)	
Tower of London	-0.20 (1.3)	-0.21 (1.6)	
Composite score	-0.74 (1.4)	-0.55 (1.5)	
CAARMS scores: mean (SD)			
Unusual Thought Content	2 (2.1)	1 (1.8)	
Non-bizarre Ideas	4 (1.4)	3 (1.8)	
Perceptual Abnormalities	3 (1.5)	3 (1.5)	
Disorganized Speech	2 (1.5)	1 (1.5)	
Total severity score	42 (16.1)	30 (14.4)	H(1) = 10.2, APS-P > APS-NT: p = 0.001
SPI-A severity: mean (SD)	13 (16.1)	9 (10.7)	
CHR-P categories: n (%)			
CAARMS only	7 (21)	19 (49)	
CAARMS + SPI-A (COGDIS / COPER/ both items)	27 (79) (3 / 13 /11)	20 (51) (4 / 8 /8)	
MINI categories [c]: n (%)			
Depressive/Mood disorders	21 (62)	25 (64)	
Anxiety disorders/PTSD/OCD	27 (79)	32 (82)	
Drug/alcohol abuse/dependence	11 (32)	13 (33)	
Eating Disorders	6 (18)	3 (8)	
GAF: mean (SD)	54 (13.3)	57 (14.3)	
GF-role: mean (SD)	7.1 (1.1)	7.5 (1.1)	
GF-social: mean (SD)	7.3 (1.4)	7.4 (1.1)	
Transitions (%)	4 (11.8%)	1 (2.6%)	
Medication [d]: n (%)			
None	18 (53)	19 (49)	
Anti-depressants	14 (41)	16 (41)	
Mood stabilizers	2 (6)	2 (5)	
Anti-Psychotics	1 (3)	1 (3)	
Other	5 (15)	7 (18)	
MEG Trials: total included (SD)	85 (6.7)	87 (5.1)	
Task Performance			
Hit rate (% correct, SD)	99.1 (2.9)	100.0 (0.0)	
False Alarms (% errors, SD)	0.35 (0.68)	0.28 (0.70)	
Mean RT (ms, SD)	499 (113.8)	502 (120.6)	

Abbreviations: APS, attenuated psychotic symptoms; APS-P = Persistent CAARMS group basis on the last assessment within a 12 months follow-up period; APS-NP = non-persistent CAARMS, remitted group; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; COGDIS, Cognitive Disturbances and COPER, Cognitive-Perceptive Basic Symptoms criteria; GAF, global assessment of functioning; GF, global functioning; MINI, Mini-International Neuropsychiatric Interview; SPI-A, Schizophrenia Proneness Instrument, Adult version, SD = standard deviation of the mean, ms = milliseconds, RT = reaction time

[a] All tests are based on non-parametric Kruskal-Wallis H-tests: alpha=0.05, 2-sided, adjusted for ties.
[b] BACS scores for clinical groups were standardized to control group data, controlled for sex.
[c] Multiple ratings possible for comorbidities.
[d] Multiple ratings possible.

Table S3. Demographic and Clinical Characteristics for Transitioned and Non-transitioned CHR-P participants

	CHR-P-NT	CHR-P-T	statistical results [a]
Number of participants	97	13	
Age: years (SD)	22 (4.4)	21 (4.7)	
Sex: male/female (%male)	29/68 (29.9)	3/10 (23.1)	
Education: years (SD)	15 (3.3)	15 (2.4)	
BACS [b]: mean (SD)			
Verbal memory	-0.30 (1.3)	-0.52 (0.9)	
Digit sequencing	-0.09 (1.5)	-0.73 (1.5)	
Token motor	-1.08 (1.3)	-0.79 (1.4)	
Verbal fluency	-0.01 (1.3)	-0.39 (0.8)	
Symbol coding	-0.52 (1.2)	-0.81 (0.6)	
Tower of London	-0.19 (1.5)	0.23 (1.1)	
Composite score	-0.59 (1.4)	-0.82 (0.8)	
CAARMS scores: mean (SD)			
Unusual Thought Content	2 (1.9)	3 (2.2)	
Non-bizarre Ideas	3 (1.8)	3 (1.7)	
Perceptual Abnormalities	3 (1.6)	3 (1.5)	
Disorganized Speech	1 (1.4)	2 (1.4)	
Total severity score	29 (18.0)	37 (17.9)	
SPI-A severity: mean (SD)	11 (11.9)	12 (10.3)	
CHR-P categories: n (%)			
SPI-A only (COGDIS/COPER/both items)	27 (28) (4 / 14 / 9)	1 (8) (0 / 0 / 1)	
CAARMS only	24 (25)	5 (38)	
CAARMS + SPI-A (COGDIS / COPER/ both items)	46 (47) (6 / 21 / 19)	7 (54) (2 / 2 / 3)	
MINI categories [c]: n (%)			
Depressive/Mood disorders	57 (59)	13 (100)	
Anxiety disorders/PTSD/OCD	70 (72)	12 (92)	
Drug/alcohol abuse/dependence	30 (31)	8 (62)	
Eating Disorders	7 (7)	2 (5)	
GAF: mean (SD)	58 (14.5)	51 (6.0)	H(1) = 4.5, CHR-P-T < CHR-P-NT: p = 0.034
GF-role: mean (SD)	7.5 (1.2)	7.0 (1.3)	
GF-social: mean (SD)	7.5 (1.3)	6.8 (1.0)	H(1) = 5.1, CHR-P-T < CHR-P-NT: p = 0.024
Medication [d]: n (%)			
None	52	7	
Anti-depressants	37	4	
Mood stabilizers	5	0	
Anti-Psychotics	2	0	
Other (Unknown)	15 (0)	2 (0)	
MEG Trials: total included (SD)	86 (5.6)	85 (6.4)	
Task Performance			
Hit rate (% correct, SD)	99.5 (2.2)	99.2 (2.8)	
False Alarms (% errors, SD)	0.28 (0.64)	0.61 (0.75)	H(1) = 4.0, CHR-P-T > CHR-P-NT: p = 0.046
Mean RT (ms, SD)	499 (128.0)	563 (139.6)	
SCID diagnosis for CHR-P-T	Schizophrenia (n = 1), Schizophrenia, Major Depressive Disorder (n = 1), Schizoaffective Disorder, Bipolar-I, Major Depressive Disorder (n = 2), Schizoaffective Disorder, Major Depressive Disorder (n = 2), Delusional Disorder (n = 1), Delusional Disorder, Major Depressive Disorder, Bipolar I (n = 1), Psychotic Disorder NOS (n = 2), Bipolar-II with psychotic features, Major Depressive Disorder with psychotic features (n = 2), and 1 case unknown (no SCID data available).		

Abbreviations: CHR-P-NT = non-transitioned CHR-Ps; CHR-P-T = transitioned CHR-Ps; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; COGDIS, Cognitive Disturbances and COPER, Cognitive-Perceptive Basic Symptoms criteria; GAF, global assessment of functioning; GF, global functioning; MINI, Mini-International, N/A, Not applicable Neuropsychiatric Interview; SPI-A, Schizophrenia Proneness Instrument, Adult version, SD = standard deviation of the mean, ms = milliseconds, RT = reaction time

[a] All tests are based on non-parametric Kruskal-Wallis H-tests: alpha=0.05, 2-sided, adjusted for ties.
[b] BACS scores for clinical groups were standardized to control group data, controlled for sex.
[c] Multiple ratings possible for comorbidities.
[d] Multiple ratings possible.

Table S4. Post-hoc Pairwise Comparisons of MEG 40-Hz ASSR data

Main Groups	RHES amplitude	RHES ITPC	RSTG amplitude	RTHA amplitude	RHIP amplitude
CHR-N versus HC	Not significant	Not significant	Not significant	Not significant	Not significant
CHR-P versus HC	[p = 0.082]	diff = -0.45 CI = [-0.95 -0.04] p = 0.043 d = 0.34	Not significant	diff = -3.28 CI = [-6.20 -1.20] p = 0.0028* d = 0.47	diff = -2.45 CI = [-4.98 -0.32] p = 0.019 d = 0.37
FEP versus HC	diff = -3.31 CI = [-6.32 -0.37] p = 0.044 d = 0.48	Not significant	Not significant	diff = -3.71 CI = [-6.76 -0.82] p = 0.028 d = 0.52	diff = -3.27 CI = [-6.14 -0.39] p = 0.037 d = 0.49
CHR-P subgroups	**RHES amplitude**	**RHES ITPC**	**RSTG amplitude**	**RTHA amplitude**	**RHIP amplitude**
APS-NP versus HC	Not significant	diff = -0.67 CI = [-1.21 -0.21] p = 0.012 d = 0.50	Not significant	Not significant	Not significant
APS-P versus HC	[p = 0.054]	Not significant	Not significant	diff = -3.86 CI = [-6.68 -1.13] p = 0.014 d = 0.57	diff = -4.20 CI = [-6.74 -1.97] p = 0.0024* d = 0.72
APS-P versus APS-NP	Not significant	diff = 0.63 CI = [0.09 1.31] p = 0.037 d = 0.52	Not significant	Not significant	diff = -3.06 CI = [-4.96 -1.05] p = 0.0034* d = 0.70
CHR-P-NT versus HC	[p = 0.058]	[p = 0.063]	Not significant	diff = -2.78 CI = [-5.85 -0.69] p = 0.018 d = 0.40	[p = 0.064]
CHR-P-T versus HC	Not significant	diff = -0.84 CI = [-1.32 -0.29] p = 0.039 d = 0.76	Not significant	diff = -6.25 CI = [-8.84 -3.47] p = 0.0078* d = 1.02	diff = -5.35 CI = [-7.83 -2.38] p = 0.014 d = 0.88
CHR-P-T versus CHR-P-NT	Not significant	Not significant	Not significant	diff = -3.38 CI = [-5.04 -1.17] p = 0.049 d = 0.72	[p = 0.057]

Notes: Result from Estimation statistics, online tool, (https://www.estimationstats.com/#/analyze/shared-control), and includes non-parametric bias and accelerated bootstrapping (n=5000), and confidence intervals (CI) obtained from the central 95% of resampling distribution. Cohen's d-values were computed afterwards from mean and standard deviation of the group being compared. In addition, p-values from all contrasts within either the main groups or CHR-P subgroups were FDR corrected for multiple comparisons (survival indicated by an asterisk). Abbreviations: HC, healthy controls (n=49); CHR-N, clinical risk-negative (n=38); CHR-P, clinical high-risk positive (n=116); FEP, first-episode psychosis (n=33); APS-P, attenuated psychotic symptoms positive (n=34); APS-NP, attenuated psychotic symptoms negative (n=39); CHR-P-NT, CHR-Ps who did not transition (n=97); CHR-P-T, CHR-Ps who transitioned to psychosis (n=13); RHES, Right Heschl's Gyrus; RSTG, Right Superior Temporal Gyrus; RTHA, Right Thalamus; RHIP, Right Hippocampus; ITPC, Inter-Trial-Phase Coherence; diff, difference between means of included groups; Not significant = p-values > 0.1, trend-level p-values between 0.05 and 0.1 are indicated between squared brackets.