Computerised cognitive training during early-stage psychosis improves cognitive deficits and gamma-band oscillations: A pilot study

Kate Haining, MSc[1]; Tineke Grent-'t-Jong, Ph.D.[2]; Ben Chetcuti, MD, MRCPsych, MBA[3]; Ruchika Gajwani, Ph.D.[4]; Joachim Gross, Ph.D.[1,5]; Conail Kearns, MD, MRCPsych[6]; Rajeev Krishnadas, MBBS, MD, Ph.D., FRCPsych[6]; Stephen M. Lawrie M.D.[7]; Siamak Molavi, MD, MRCPsych[6]; Cristina Paton, MRCPsych[8]; Filippo Queirazza, MD, MRCPsych, MSC, Ph.D.[1]; Elspeth Richardson, MBChB, MSc, MRCPsych[6]; Frauke Schultze-Lutter, Ph.D.[9,10,11]; Matthias Schwannauer, Ph.D.[12] & Peter J. Uhlhaas, Ph.D.[1,2]

1. School of Psychology and Neuroscience, University of Glasgow, Glasgow, UK
2. Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany
3. NHS Ayrshire and Arran, Scotland
4. Institute of Health and Wellbeing, , University of Glasgow, Glasgow, UK
5. Institute for Biomagnetism and Biosignalanalysis, University of Münster, Münster, Germany
6. NHS Greater Glasgow and Clyde, Scotland
7. Department of Psychiatry, University of Edinburgh, Edinburgh, UK
8. NHS Lanarkshire, Scotland
9. Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
10. Department of Psychology, Faculty of Psychology, Airlangga University, Surabaya, Indonesia
11. University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland
12. Department of Clinical Psychology, University of Edinburgh, Edinburgh, UK

Corresponding Author:

Dr. Peter J. Uhlhaas

Department of Child and Adolescent Psychiatry

Charité Universitätsmedizin

Berlin, Germany

Email: peter.uhlhaas@charite.de

Tel: 0049 30 450 516 193

Main text: words

Figures: 1

Keywords: cognitive remediation; clinical high-risk; first-episode psychosis; early intervention; neural oscillations; magnetoencephalography

Neural oscillations are a fundamental mechanism for enabling cognitive and perceptual processes (Uhlhaas et al., 2008). In schizophrenia, gamma-band oscillations (> 30 Hz) are reduced during perceptual tasks (Uhlhaas and Singer, 2013), and deficits are already present in the early stages of psychosis, including in first-episode psychosis (FEP) patients and in participants meeting clinical high-risk for psychosis (CHR-P) criteria (Grent-'t-Jong et al., 2020). Interestingly, neuroplasticity-based computerised cognitive training (CCT), which aims to improve higher level cognitive functions through training of basic auditory and visual-perceptual processes, has been shown to improve cognitive function and enhance task-related gamma-band activity in schizophrenia patients (Popov et al., 2012). However, there is only preliminary evidence for the effectiveness of CCT on cognitive performance during the early-stages of psychosis (Fisher et al., 2015; Glenthøj et al., 2017), and the impact on oscillatory activity is currently unknown. Therefore, we sought to assess whether 10 hours of neuroplasticity-based CCT could improve cognitive performance and enhance gamma-band activity in a sample of participants meeting CHR-P or FEP criteria.

CHR-P participants and FEP patients were recruited as part of the Youth Mental Health Risk and Resilience (YouR) study (Uhlhaas et al., 2017) or via referral from the ESTEEM First Episode Psychosis Service in Glasgow. Eligibility for the CHR-P group was established using the Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al. 2005) and the Schizophrenia Proneness Instrument, Adult version (SPI-A, Schultze-Lutter et al., 2007). Eligibility for the FEP group was established using the Structured Clinical Interview for DSM-IV.

Participants completed 10 sessions of CCT using the BrainHQ software (Posit Science, San Francisco; www.brainhq.com), Each session was 60 minutes in duration, over approximately 3 weeks. Training was completed at home using a computer, mobile phone or laptop. Each session was comprised of eight different visual processing exercises, each repeated three times. Training activity was monitored via an online system and participants received regular reminders by email or text.

Before and after the CCT, participants completed the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) and magnetoencephalographical (MEG) data were obtained during a visual grating task (Figure 1A). In order to minimise practice effects, we

utilised different versions of the BACS verbal memory and executive function tests at the post-training assessment.

MEG data were acquired using a whole-head, 248-channel magnetometer system (Magnes 3600 WH, 4D Neuroimaging, San Diego, CA) at a sampling rate of 1017.25 Hz with a low-pass filter at 400 Hz. At sensor-level, oscillatory activity was examined in the 30-80 Hz frequency range, averaged across 250-750 ms. Significant effects were followed up with source-level analyses. For statistics, we used Monte-Carlo permutation-based dependent samples t-tests (2000 permutations), with correction for multiple comparisons. Power was expressed as relative change from baseline activity (−500 to 0 ms). Statistical significance was set at $p<.05$ (two-tailed).

Overall, 16 participants were recruited (n=6 CHR-P; n=10 FEP) and 13 participants (n=5 CHR-P; n=8 FEP) completed the study. The mean training duration was 22.15 days (SD=14.55).
CHR-P and FEP study-completers were similar in age [CHR-P: mean=24.4 (SD=4.22); FEP: mean=23.9 (SD=3.80) years] and sex [CHR-P: 3F/2M; FEP: 3F/5M]. We found significant improvements in verbal memory ($p<.001$; $d=1.43$), motor speed ($p=.030$, $d=0.68$), attention and processing speed ($p=.015$, $d=0.79$) and BACS composite score ($p=.008$, $d=0.88$) as well as a significant reduction in executive function ($p=.044$, $d=0.62$) from pre- to post-training (Supplementary Table 1). There were also significant improvements on all 8 BrainHQ exercises over time ($p<.01$), with large effect sizes (Supplementary Table 2; Supplementary Figure 1).

Cluster-based permutation tests revealed a significant increase in gamma-band activity (~40-44 Hz) pre- to post-training over central-frontal sensors between 250-750 ms (cluster $t(12)=145.01$; $p=.013$, $d=1.41$, 95% CI [0.008 to 0.018]) (Figure 1B). In addition, we performed whole-head source estimation of 40-44 Hz power between 250-750 ms and found a significant increase pre- to post-training in frontal, motor and cingulate regions ($t(12)=3.90$, $d=1.08$) (Figure 1C, D).

Our findings suggest that 10 hours of CCT can improve cognitive performance in early-stage psychosis, especially in the domain of verbal memory. Importantly, we also found a significant increase in gamma-band activity in areas associated with attentional and motor-

related processes, suggesting that CCT improved task preparation and top-down attentional control, and resulted in a switch from reactive to proactive cognitive control strategies. Limitations of the study include the small sample size and the lack of an active control group. Furthermore, it is unclear whether symptoms and/or functioning improved at post-training and whether effects were durable over time. Nevertheless, our findings suggest the potential utility of CCT to improve cognitive deficits and the underlying circuit deficits in early-stage psychosis.

REFERENCES

Dale, C.L., Brown, E.G., Fisher, M., Herman, A.B., Dowling, A.F., Hinkley, L.B., Subramaniam, K., Nagarajan, S.S., Vinogradov, S., 2016. Auditory cortical plasticity drives training-induced cognitive changes in schizophrenia. Schizophr. Bull. 42, 220–228. https://doi.org/10.1093/schbul/sbv087

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID - I/P). Biometrics Research, New York State Psychiatric Institute, New York.

Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, J.D., Niendam, T., Schlosser, D., Pham, L., Miskovich, T., Vinogradov, S., 2015. Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. Schizophr. Bull. 41, 250–258. https://doi.org/10.1093/schbul/sbt232

Glenthøj, L.B., Hjorthøj, C., Kristensen, T.D., Davidson, C.A., Nordentoft, M., 2017. The effect of cognitive remediation in individuals at ultra-high risk for psychosis: A systematic review. npj Schizophr. 3, 1–8. https://doi.org/10.1038/s41537-017-0021-9

Grent-’t-Jong, T., Gajwani, R., Gross, J., Gumley, A.I., Krishnadas, R., Lawrie, S.M., Schwannauer, M., Schultze-Lutter, F., Uhlhaas, P.J., 2020. Association of magnetoencephalographically measured high-frequency oscillations in visual cortex with circuit dysfunctions in local and large-scale networks during emerging psychosis. JAMA psychiatry 77, 852–862. https://doi.org/10.1001/jamapsychiatry.2020.0284

Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68, 283–297. https://doi.org/10.1016/j.schres.2003.09.011

Popov, T., Rockstroh, B., Weisz, N., Elbert, T., Miller, G.A., 2012. Adjusting brain dynamics in schizophrenia by means of perceptual and cognitive training. PLoS One 7, e39051.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., Klosterkötter, J., 2007. Schizophrenia Proneness Instrument-Adult version (SPI-A). Giovanni Fioriti Editore, Rome, Italy.

Uhlhaas, P.J., Gajwani, R., Gross, J., Gumley, A.I., Lawrie, S.M., Schwannauer, M., 2017. The Youth Mental Health Risk and Resilience Study (YouR-Study). BMC Psychiatry 17, 1–8. https://doi.org/10.1186/s12888-017-1206-5

Uhlhaas, P.J., Haenschel, C., Nikolić, D., Singer, W., 2008. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. Schizophr. Bull. 34, 927–943. https://doi.org/10.1093/schbul/sbn062

Uhlhaas, P.J., Singer, W., 2013. High-frequency oscillations and the neurobiology of schizophrenia. Dialogues Clin. Neurosci. 15, 301–313. https://doi.org/10.31887/DCNS.2013.15.3/puhlhaas

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust. N. Z. J. Psychiatry 39, 964–971. https://doi.org/10.1080/j.1440-1614.2005.01714.x

Figure 1. Sensor and Source-level Magnetoencephalography (MEG) Data

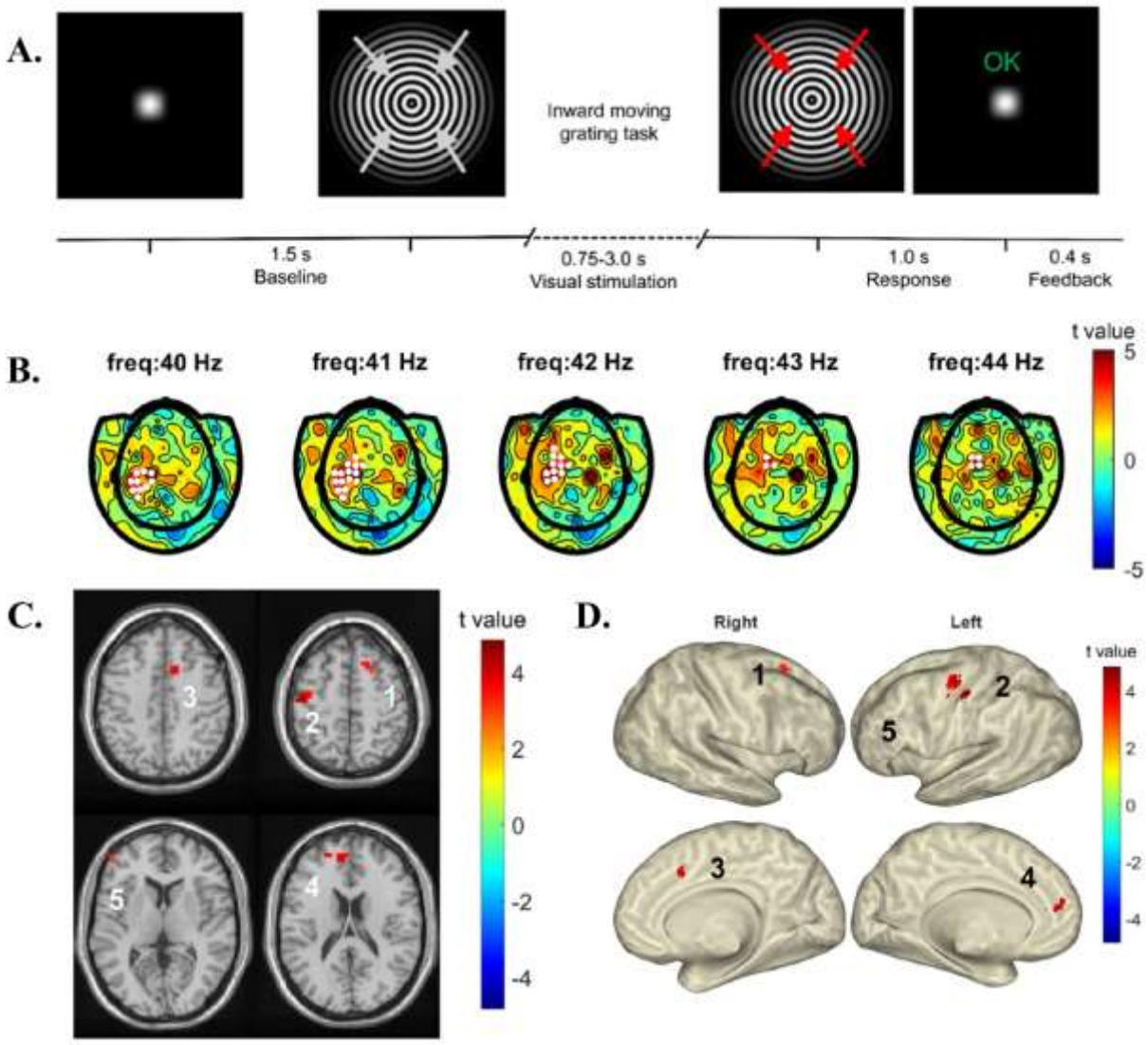

Figure 1. (A) Participants had to press a button when a speed change was detected in a concentric inward moving visual grating stimulus. Speed changes randomly occurred between 0.75-3.0 s post-stimulus onset (B) Topography of the change in gamma power from pre- to post-training. White dots indicate sensors significant after cluster correction. Slice (C) and surface (D) plot representations of gamma source-power differences pre- to post-training (FDR corrected). Colour bars indicate the distribution of t values, with red colours (positive t-values) indicating an increase in power. ROI 1: Right supplementary motor area (RSMA), right dorsal superior frontal gyrus (RdSFG) and right middle frontal gyrus (RMFG); ROI 2: Left precentral gyrus (PreCG) and left postcentral gyrus (LPoCG); ROI 3: Right median cingulate and paracingulate gyri (RDCG); ROI 4: Left anterior cingulate and paracingulate gyri (LACG), left medial superior frontal gyrus (LmSFG) and left dorsal superior frontal gyrus (LdSFG); ROI 5: Left middle frontal gyrus (LMFG) and left inferior frontal gyrus, triangular part (IFGtriang)