

# Studi Psikopatologi Spasiotemporal: Abnormalitas Aktivitas Otak Keadaan Istirahat pada Gejala Halusinasi Auditorik Verbal Skizofrenia = Spasiotemporal Psychopathology Study: Abnormalities of Brain Resting Activity in Verbal Auditory Hallucinations of Schizophrenia

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## Abstrak

**Latar belakang:** Halusinasi auditorik verbal (HAV) dialami 70% dari 23 juta penderita gangguan skizofrenia di seluruh dunia. Data pasien skizofrenia di rawat jalan Departemen Psikiatri RSCM/FKUI periode tahun 2016-2017 kasus HAV resisten pengobatan berkisar 25-30%. Tujuan penelitian ini mengetahui abnormalitas spasiotemporal aktivitas neural otak kondisi istirahat yang berhubungan dengan HAV pada orang dengan skizofrenia (ODS) dan peran rTMS dalam memodulasi abnormalitas tersebut.

**Metode:** Penelitian ini dilakukan di Departemen Psikiatri dan Departemen Neurologi FKUI/RSCM selama Maret 2017 sampai Maret 2019 dengan desain uji klinis acak plasebo tersamar ganda. Studi mengikutsertakan 120 orang yaitu 40 ODS dengan halusinasi, 40 ODS tanpa halusinasi, 20 subjek saudara kandung dan 20 subjek sehat. Kriteria kelompok intervensi rTMS pasien skizofrenia HAV resisten pengobatan usia dewasa 18-59 tahun. Pemeriksaan dimensi temporal dan spasial aktivitas otak keadaan istirahat menggunakan perekaman elektroensefalografi (EEG). Pemeriksaan simtom halusinasi menggunakan instrumen PSYRATS dan uji kemampuan pemantauan-sumber. Dilakukan rTMS 1 Hz 90% AM 1000 pulse di titik T3P3 selama 10 hari berturut-turut. Data klinis pasien diperoleh dari wawancara atau catatan medis. *Informed consent* diperoleh dari pasien dan orang tua atau pasangan pasien.

**Hasil:** Ditemukan perbedaan kekuatan amplitudo gelombang theta di prefrontal kiri dan kanan (skizofrenia =  $15.19 \pm 4.54$  mV, sehat =  $7.37 \pm 2.49$  mV,  $p = 0.004$ ), frontal kiri dan kanan (skizofrenia =  $18.62 \pm 17.55$  mV, sehat =  $9.90 \pm 3.77$  mV  $p = 0.007$ ), temporal kiri dan kanan (skizofrenia =  $6.97 \pm 7.26$  mV, sehat =  $3.59 \pm 1.34$  mV,  $p = 0.010$ ). Kelompok skizofrenia ditemukan penurunan gandeng-fase amplitudo theta/gamma di frontal-parietal kiri F3-P3 (sehat = 28.06, skizofrenia = 24.06), frontal-temporal kiri F3-T3 (sehat = 30.89, skizofrenia = 22.47) dan frontal sentral kanan FP2-C4 (sehat = 25.78, skizofrenia = 25.00). Didapatkan peningkatan konektivitas fungsional di jejaring mode-standar yang berkaitan dengan kemampuan ODS memantau sumber stimulus. Antara jejaring mode-standar dengan sentral-eksekutif didapatkan korelasi positif di BA 8L-39L ( $r = 0.792$ ,  $p = 0.000$ ), BA 29L-40L ( $r = 0.522$ ,  $p = 0.032$ ) dan BA 8R-39R ( $r = 0.480$ ,  $p = 0.004$ ). Korelasi positif abnormal antara jejaring mode-standar dan eksekutif-pusat berhubungan dengan kesulitan ODS membedakan sumber stimulus. Pemberian rTMS 1 Hz menurunkan konektivitas jejaring mode-standar dan menurunkan gandeng theta-gamma yang menghasilkan perbaikan gejala HAV dan kemampuan pemantauan sumber.

**Simpulan:** Pada ODS keseimbangan aktivitas otak istirahat bergeser ke kekuatan frekuensi rendah, demikian juga peningkatan koherensi kortikal. Didapatkan hiperkonektivitas jejaring mode standar, korelasi abnormal antara DMN dan CEN, serta gandeng theta-beta DMN yang berhubungan dengan halusinasi auditorik verbal. Pemberian rTMS bisa memodulasi abnormalitas spasiotemporal tersebut mendekati kondisi normal dan berakibat perbaikan gejala halusinasi. EEG concordance alfa prefrontal frontal otak berpotensi menjadi kandidat penanda biologi respon terhadap terapi rTMS.

**Background:** Auditory Verbal Hallucinations (AVH) occur in 70% of 23 million people with schizophrenia worldwide. According to the 2016-2017 data on schizophrenia patients in the Outpatient Clinic of the Department of Psychiatry RSCM / FKUI, AVH treatment-resistant cases reach about 25-30%. The aim of this study was to determine the spatiotemporal properties of resting brain neural activities that cause changes in perceptions and abnormal space-time experience in people with schizophrenia, which then manifest as auditory verbal hallucinations, and also to determine the role of transcranial magnetic repetitive stimulation (rTMS) on modulating spatiotemporal abnormalities.

**Method:** This study was a double-blind placebo-controlled clinical trial conducted in the Department of Psychiatry and the Department of Neurology of FMUI/RSCM from March 2017 to March 2019. The study included 120 subjects consisting of 40 schizophrenia patients with hallucinations, 40 schizophrenia patients without hallucinations, 20 siblings of the patients, and 20 healthy subjects. The criteria for the rTMS intervention group were treatment-resistant schizophrenia with AVH of 18-59 years of age. Electroencephalography (EEG) was used to examine temporal and spatial dimensions of resting brain activities. The PSYRATS instrument and source-monitoring ability test were used to assess symptoms of hallucinations. Patients clinical data were collected from interviews or medical records. Informed consents were obtained from patients and their parents or spouses.

**Results:** Differences in amplitude strength of theta frequency were found at the left and right prefrontal cortices (schizophrenia =  $15.19 \pm 4.54$  mV, healthy =  $7.37 \pm 2.49$  mV,  $p = 0.004$ ), left and right frontal cortices (schizophrenia =  $18.62 \pm 17.55$  mV, healthy =  $9.90 \pm 3.77$  mV  $p = 0.007$ ), left and right temporal cortices (schizophrenia =  $6.97 \pm 7.26$  mV, healthy =  $3.59 \pm 1.34$  mV,  $p = 0.010$ ). Temporal cortical activities were shifted to low frequency fluctuations, and there were also decreasing relationships between various brain frequencies. The increase of functional connectivity in default-mode networks was found, which relates to schizophrenics ability to monitor sources of stimuli. This abnormal positive correlation between the default mode and the central executives network might disturb schizophrenics ability to distinguish internal stimuli from external stimuli. The administration of 1Hz of rTMS decreases connectivity in default-mode networks and theta-gamma coupling resulting in improved symptoms of HAV and source monitoring capabilities.

**Conclusion:** In people with schizophrenia, the balance of resting activity shift to low frequency power, as well as increase in its cortical coherence. It also found functional hyperconnectivity in default mode network among schizophrenia patients with HAV and abnormal positive correlation between DMN-CEN. The resting state theta-gamma coupling was increased in patient with schizophrenia that might underlie HAV. The administration of rTMS modulate spatiotemporal abnormalities to near-normal conditions, resulting in the improvement in hallucinatory symptoms. The alpha EEG cordances of prefrontal and frontal cortices has the potential to become a biological marker of response to rTMS therapy.