



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

## Impaired theta-gamma coupling during working memory performance in schizophrenia

Mera S. Barr<sup>a,b,d</sup>, Tarek K. Rajji<sup>b,c</sup>, Reza Zomorodi<sup>b</sup>, Natasha Radhu<sup>b</sup>, Tony P. George<sup>a,d</sup>, Daniel M. Blumberger<sup>b,c</sup>, Zafiris J. Daskalakis<sup>b,d,\*</sup>

<sup>a</sup> Biobehavioural Addictions and Concurrent Disorders Laboratory (BACDRL), Addictions Division, Canada

<sup>b</sup> Temerty Centre for Therapeutic Brain Intervention, Mood and Anxiety Division, Canada

<sup>c</sup> Geriatric Psychiatry Division, Centre for Addiction and Mental Health, Canada

<sup>d</sup> Department of Psychiatry, Division of Brain and Therapeutics, University of Toronto, Toronto, Canada

### ARTICLE INFO

#### Article history:

Received 13 October 2016

Received in revised form 21 January 2017

Accepted 24 January 2017

Available online xxxx

#### Keywords:

DLPFC

Schizophrenia

Theta-gamma coupling

Working memory

### ABSTRACT

**Background:** Working memory deficits represent a core feature of schizophrenia. These deficits have been associated with dysfunctional dorsolateral prefrontal cortex (DLPFC) cortical oscillations. Theta-gamma coupling describes the modulation of gamma oscillations by theta phasic activity that has been directly associated with the ordering of information during working memory performance. Evaluating theta-gamma coupling may provide greater insight into the neural mechanisms mediating working memory deficits in this disorder.

**Methods:** Thirty-eight patients diagnosed with schizophrenia or schizoaffective disorder and 38 healthy controls performed the verbal N-Back task administered at 4 levels, while EEG was recorded. Theta (4–7 Hz)-gamma (30–50 Hz) coupling was calculated for target and non-target correct trials for each working memory load. The relationship between theta-gamma coupling and accuracy was determined.

**Results:** Theta-gamma coupling was significantly and selectively impaired during correct responses to target letters among schizophrenia patients compared to healthy controls. A significant and positive relationship was found between theta-gamma coupling and 3-Back accuracy in controls, while this relationship was not observed in patients.

**Conclusions:** These findings suggest that impaired theta-gamma coupling contribute to working memory dysfunction in schizophrenia. Future work is needed to evaluate the predictive utility of theta-gamma coupling as a neurophysiological marker for functional outcomes in this disorder.

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### 1. Introduction

Schizophrenia is a severe and debilitating disorder that affects approximately 1% of the population (Carpenter and Buchanan, 1994). Working memory (WM) dysfunction is considered a core feature of schizophrenia (Silver et al., 2003) that predicts relapse in the first year of psychosis (Rund et al., 2007) and is the strongest single predictor of functional capacity among first-episode (Vesterager et al., 2012). Despite this, mechanisms underlying WM dysfunction are not fully understood.

Disrupted oscillatory activity particularly in the theta (4–8 Hz) and gamma (30–50 Hz) frequency ranges has been associated with WM dysfunction in schizophrenia (Cho et al., 2006; Basar-Eroglu et al., 2007; Barr et al., 2010; Berger et al., 2016). However, these reports are

mixed and have yet to establish a relationship between this activity and task performance. It is therefore possible that other mechanisms may contribute to WM dysfunction in schizophrenia. Modulation of gamma oscillations by theta oscillations has been suggested as one mechanism through which to maintain multiple items active in order during WM performance (Lisman and Idiart, 1995). It is hypothesized that gamma oscillations encode items of information and modulation of gamma amplitude by theta phase (theta-gamma coupling) order these items providing a “neural code” for WM (Lisman and Idiart, 1995; Lisman and Jensen, 2013). Emerging lines of evidence from animal (Tort et al., 2009; Shirvalkar et al., 2010; Li et al., 2012), electrocorticography (Mormann et al., 2005; Canolty et al., 2006; Axmacher et al., 2010; Jacobs and Kahana, 2010; Khurshid et al., 2011), and electroencephalography (EEG) (Park et al., 2013; Rajji et al., 2016) have demonstrated the role of coupling with WM performance. Recently, coupling has been suggested to be important for the correct ordering of information during N-Back performance (Rajji et al., 2016) whereby coupling independently contributed to WM load on trials which required ordering of information (i.e., target correct trials) compared to trials in which

\* Corresponding author at: Therapeutic Brain Intervention, Research Training and Clinician Scientist Program, Centre for Addiction and Mental Health (CAMH), University of Toronto, 1001 Queen Street West, Unit 4, First Floor, Toronto, Ontario M6J 1H4, Canada.  
E-mail address: [Jeff.Daskalakis@camh.ca](mailto:Jeff.Daskalakis@camh.ca) (Z.J. Daskalakis).

the correct order was neither necessary nor advantageous in healthy participants (i.e., non-target correct trials; (Rajji et al., 2016)).

The objective of this study was to evaluate coupling during correct trials (target and non-target trials) on the N-Back performance among schizophrenia patients compared to controls. We hypothesized that coupling would be impaired among patients during target correct trials compared to non-target correct trials among compared to controls. Secondary objective was to determine the relationship between coupling and performance. Coupling and performance were hypothesized to be positively correlated.

## 2. Materials and methods

### 2.1. Participants

Thirty-eight patients with diagnosis of schizophrenia or schizoaffective disorder (Structured Clinical Interview for DSM-IV (SCID-IV) (Spitzer, 1994)), and 38 non-psychiatric healthy controls participated in this study. Patients were treated with antipsychotic medication and on stable dose for at least one month. Severity of psychopathology was evaluated using the positive and negative symptom scale (PANSS; (Kay et al., 1987)). Exclusion criteria were pregnancy or history of SCID-IV substance abuse or dependence in the last 6 months. Controls were excluded if they had a concomitant major and unstable medical, neurologic illness and/or the presence of psychopathology determined by the personality assessment screener (PAS; Psychological Assessment Resources, Inc.). Participants provided their written informed consent and the protocol was approved by the Centre for Addiction and Mental Health local Research Ethics Board in accordance with the declaration of Helsinki.

### 2.2. N-Back task

The verbal N-Back task was administered while their EEG was recorded (STIM2, Neuroscan, U.S.A.) according to our previously published protocols (Barr et al., 2009) (Fig. 1). Four WM loads were tested and number of targets was: 46 of 198 (23.2%) 1-Back, 31 of 197 trials (15.7%) 2-Back, and 59 of 400 trials (14.6%) 3-Back. Task was 1 h and 15 min, order of loads were randomized and counterbalanced.

### 2.3. EEG recording

EEG data were acquired using 64-electrode cap and Synamps2 DC-coupled EEG system (Compumedics, U.S.A.) recorded at 1000 Hz DC 0.3 to 200 Hz band pass hardware filter. Electrode impedances were lowered to <5 k $\Omega$  and referenced to electrodes PO7/PO8 on the mastoids.

### 2.4. EEG offline data processing

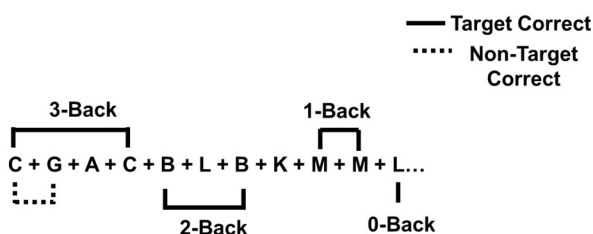
EEG data was processed offline using MATLAB 7.04 (The Mathworks, Inc. Natick, MA, USA) and the EEGLAB toolbox custom scripts developed by co-author RZ (Rajji et al., 2016). Oscillations were measured from electrodes (AF3/4, F1/2, F3/4, F5/6, F7/8) encompassing DLPFC for correct responses. Signals were filtered into theta (4–7 Hz) and gamma (30–50 Hz) frequencies with zero-phase shift and Hilbert transformed to separate phase and amplitude of the signal. Data was epoched – 1400 ms to +3100 ms relative to stimulus onset. Responses from stimulus onset until fixation cross (+3000 ms) were used for analysis. Epochs were baseline corrected with respect to the pre-stimulus interval of 1400 ms to 5 ms prior to stimulus onset and filtered using zero-phase shift of 1–120 Hz band pass filter. Sixty Hz power line artefact was removed from each trial across channels using Thomson F-test based on multi-taper spectral estimate techniques. Channels by trials matrix of all the ones was created and assigned value of zero if an epoch met the following criteria: (1) amplitudes larger than  $\pm 150 \mu\text{V}$ ; (2) power spectrum that violated the 1/f power law; (3) standard deviation, kurtosis or skewness 3 times greater than average of all trials; (4) if corresponding row had >60% of columns (trials) coded as zeros; (5) if corresponding column had >20% of row (channels) coded as zeros; or (6) anomalous irregularities determined through visual inspection. Independent Components Analysis was performed across WM load for each participant to remove eye blink or movement artefacts.

### 2.5. Measurement of theta-gamma coupling

Coupling was calculated using modulation index (MI) for both target-correct and non-target correct trials (Axmacher et al., 2010; Tort et al., 2010; Rajji et al., 2016). Raw EEG signal for theta (4–7 Hz) and gamma (30–50 Hz) was filtered using a zero-phase shift. Hilbert transformation was applied to time series for theta phase and gamma amplitude. Data was segmented into 5000 ms through the concatenation of random epochs for each participant, trial type and electrode representing the duration between the time of the stimulus onset and the response. Concatenated signal length of 5000 ms across loads controlled for the length of the window's effect (i.e., stimulus onset to response time) on the value of MI itself (Tort et al., 2010; Voytek et al., 2013; Aru et al., 2015; Rajji et al., 2016). Phase of theta was binned into 18 ( $20^\circ$  intervals) and mean gamma amplitude of each bin was calculated and normalized ( $MI = (\log(N) - H(P)) / (\log(N))$ ) where  $N$  is the number of phase bins,  $\log(N)$  represents the entropy of a uniform distribution,  $P$  is the relative amplitude distribution sorted according to phase bins, and  $H(P)$  is the entropy of the  $P$  distribution calculated as  $H(P) = -\sum_{j=1}^N P(j) \log[P(j)]$ . MI measures the divergence of the phase-amplitude distribution from the uniform distribution ( $MI = 0$ ). The greater MI away from 0, the lower the entropy  $H(P)$  and the greater the coupling (Tort et al., 2010).

### 2.6. Statistical data analysis

Analyses were performed using SPSS (SPSS 15.0, SPSS Inc., Chicago, Illinois, USA) on accepted trials for each target type and WM load. Mean percentage of trials  $\pm 1$  standard deviation for the 1-Back (target correct:  $69.22\% \pm 18.74$ ; non-target correct:  $75.82\% \pm 16.88$ ), 2-Back (target correct:  $64.28\% \pm 26.12$ ; non-target correct:  $76.98\% \pm 17.72$ ), and 3-Back (target correct:  $54.23\% \pm 25.83$ ; non-target correct:  $71.18\% \pm 18.54$ ). Five separate repeated measures ANOVA were performed on MI, theta power, gamma power, accuracy (percentage of correct responses) and reaction time with group (patients versus controls) as the between subject factor and load (0–3-Back) as within-subject factor, significance level set at  $p < 0.05$  for target-correct responses. If Mauchly's sphericity test was violated, Greenhouse-Geisser correction was employed. Subsequent planned comparisons were performed with the level of significance Bonferroni-adjusted. Multilinear



**Fig. 1.** Representation of the verbal N-Back task administered at the 0-, 1-, 2-, and 3-Back working memory loads. Number of target letters: 1-Back (46/198), 2-Back (31/197), 3-Back (59/400). In this task, letters appeared one at a time separated by a fixation cross on a computer monitor. Participants were instructed to push one button if the current letter on the screen was the same (target) letter as 'N' letters back otherwise (non-target) they would press a different button. Solid line represent target correct trial, while dashed line represent non-target correct trial. Theta-gamma coupling was determined for correct responses to target and non-target trials.

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