Hemispheric differences over frontal theta-band power discriminate between stimulus- versus memory-driven saccadic eye movement

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ARTICLE INFO

ABSTRACT

Although several electrophysiological studies have demonstrated the role of theta band during the execution of different visuospatial attention tasks, this study is the first to directly investigate the role of theta power during the planning, execution and cognitive control of saccadic eye movements (SEMs). The current study aims at addressing this issue by investigating absolute theta power over the frontal cortex during the execution of random and fixed SEMs. Twelve healthy volunteers, performed two tasks involving different conditions in the planning, execution and cognitive control of SEMs while their brain activity pattern was recorded using quantitative electroencephalography. We found an interaction between SEM condition and electrode (F3, F4, Fz), and a main effect of time point and electrode. Our key finding revealed that the stimulus presentation induces different patterns over frontal theta power increase between the left and right hemisphere. We conclude that right and left frontal regions are an important factor to discriminate between memory- versus stimulus-driven SEMs, and speculate on their different contributions to visuospatial attention.

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Saccadic eye movements (SEMs) are directly related to attention processes by integrating visual information with specific oculomotor movements, which can therefore be considered the first stage of sensorimotor integration and information processing [18,30]. Sensorimotor integration is a complex process that allows for the generation of an internal plan, beginning with the input of sensory stimuli, in order to perform a motor task [31]. The planning of

SEM is comprised of a motor and a cognitive component [2,8,17] with the motor component mainly regulating the generation and oculomotor control of the saccades, and the cognitive component being involved in the selection of relevant stimulus features or the modulation of voluntary SEM [8,17]. Because of the crucial contribution of SEM to visual attention processes, SEM is often used as a behavioral parameter to measure and quantify the attention process during the selection of relevant stimuli [5,17,19].

Functional brain imaging studies have consistently revealed similar frontal brain regions (e.g., frontal-eye-fields) as being activated during the execution of tasks requiring SEM in which subjects were required to direct their attention to particular

stimuli or spatial locations [1,5,21,23]. These frontal brain regions which underlie the preparation and execution of SEM and at the same time represent core regions of the visual attention network in the brain critically include the frontal-eye-fields (FEF) of both hemispheres [19,24,27]. This relationship between selective visual attention and SEM is particularly strong during tasks in which a target-stimulus has to be spatially located [9,10,16].

Several electrophysiological studies indicate that increase in the theta band (4.5–7 Hz) represent the neural correlate for the integration of sensory information with a respective motor response and the generation of voluntary behavior [3,4,6,14]. Caplan et al. [4] demonstrated that theta oscillations underlie the coordination of sensory and motor brain activity. Other human studies have also shown an association between theta band activity and the execution of different spatial attention and spatial navigation tasks [4,7,28]. However, although the role of theta band activity for spatial attention and sensorimotor integration tasks has been demonstrated, no study hitherto has directly investigated the specific role of theta band power activity during the planning, execution and cognitive control of SEM.

The current study aims to directly address this issue by investigating absolute theta power over the frontal cortex during the execution of two different SEM paradigms. The "fixed" SEM paradigm requires subjects to perform repetitive, i.e., fixed SEMs to the same peripheral spatial location, while in the "random" SEM paradigm, subjects are asked to perform SEM driven by a pure random series of presented target-stimuli. Using these paradigms, we first wanted to investigate whether theta power increase over the frontal cortex plays a role for the planning, execution and cognitive control of SEM per se, and secondly, we aimed to reveal whether the role and/or lateralization of these theta increases may discriminate between fixed and random SEM.

Twelve healthy volunteers (3 males; mean age: 26.25 (SD 4.13)) were recruited for this study. All participants had normal or corrected-to normal vision and no sensory, motor, cognitive or attentional deficits that would affect saccadic eye movement. Inclusion criteria were: absence of mental or physical impairments and no history of psychoactive or psychotropic substance use (screened by a previous anamnesis and a clinical examination) and right handed [32]. Subjects signed a consent form which thoroughly described the experimental procedure. The experiment was approved by the Ethics Committee of the Psychiatric Institute of Federal University of Rio de Janeiro (IPUB/UFRJ) (number FR-233406).

Subjects were seated on a comfortable chair in a darkened and sound-protected room in order to minimize sensory interference. At the participants' eye level, a bar composed of 30 light emitting diodes (LEDs) was positioned with 15 of these LEDs located on the left side of fixation, and 15 on the right side. The bar had a length of 120 cm. The distance between participants' eyes and the LED bar was standardized to 100 cm. Computer software controlled the LED bar and determined the presentation of the stimulus. Participants were asked to keep their eyes fixed on the center of the bar, and to shift their eyes when they perceived one of the diodes lighting up. Participants were instructed to follow the LEDs with their eyes in such way that their heads remained static.

The SEM paradigm consisted of two different conditions: a fixed pattern and a random pattern. In the fixed pattern, the target-stimulus (target LED) always appeared at a pre-defined position, i.e. LED 12, of either the left or right side (alternating between left and right). This condition is characterized by the predictability of the appearance of the stimulus at a pre-defined spatial location in the periphery of the visual field, and was thus considered to be memory-driven. In contrast, the random pattern presented a fully randomized series of target LEDs at completely unpredictable spatial positions across the central and both peripheral visual fields

(the light could appear at any of the 30 LEDs). This experimental condition was considered purely stimulus-driven. In both conditions, each LEDs remained lit for 250 ms, with a inter-LED-time of 2 s. Each participant underwent 12 consecutive blocks, 6 blocks fixed SEM and 6 blocks random SEM, with 20 trials per block. The probability of a light to appear on the left or right side was counter-balanced within and across blocks, so were both SEM conditions.

The International 10/20 EEG electrode system [13] was used with a 20-channel EEG system (Braintech-3000, EMSAMedical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivations using the earlobes reference. Impedance of EEG and EOG electrodes was kept between 5 and 10 kΩ. The data recorded had a total amplitude of less than 70 μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between .01 Hz (high-pass) and 80 Hz (low-pass), and sampled at 200 Hz. The software *Data Acquisition* (Delphi 5.0) at the Brain Mapping and Sensory Motor Integration Lab, was employed with the following digital filter: notch (60 Hz).

Four additional electrodes of 9 mm in diameter mounted in a bipolar form were used to measure the electrooculogram (EOG). Electrodes were arranged horizontally from the outer canthi of both eyes to determine the horizontal EOG (hEOG) and vertically above both eyes to determine the vertical EOG (vEOG).

We applied a visual inspection and independent component analysis (ICA) to remove possible sources of artifacts produced by the task (i.e., blink, muscles and saccade-related artifacts). The data were collected using the bi-auricular reference and they were transformed (re-referenced) using the average reference after we conducted the artifact elimination using ICA. We removed those trials that clearly showed a blink and a saccade-related artifacts "influence" by visual inspection and we removed the components that showed blink and saccade-related artifacts "contamination'" using independent component analysis (ICA). A classic estimator was applied for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier transform), which was performed by MATLAB 5.3 (Matworks, Inc.). The number of samples was 800 (4 s × 200 Hz) with rectangular windowing. We extracted Quantitative EEG parameters within a time window between 500 ms before the stimulus presentation and 500 ms after the target stimulus (LEDs) (the selected epoch started 500 ms before and ended 500 ms after the trigger, i.e., moment 1 and moment 2, respectively). Thereafter, all raw EEG trials were visually controlled and trials contaminated with ocular or muscle artifacts were discarded. The Fourier transform resolution was 1/4 s to .25 Hz (FFT). To examine a stationary process, the "run-test" and "reverse-arrangement test" were applied. Specially, the stationary process was accepted for each 4 s (epoch's duration in this period). In this manner, based on artifact-free EEG epochs, the threshold was defined by the mean plus three standard deviations with epochs showing a total power higher than this threshold not being included into the analysis.

Absolute theta power (4.5–7 Hz) was the dependent variable of interest. The statistical analyses of the absolute theta power was performed using a three-way repeated measures ANOVA with the factors SEM condition (2 levels: fixed versus random SEM), electrode (3 levels: F3, F4 and FZ), and time point (2 levels: pre- versus post-stimulus epoch) as the three within-subject factors.

The three-way repeated measures ANOVA revealed a main effect for the factor "electrode" ($F = 362.431$, $p < .001$) with the Fz electrode showing the strongest absolute theta power increase, followed by F4 and F3 (Fig. 1). We also revealed a main effect of the factor "time point" ($F = 340.244$, $p < .001$) with the epoch 500 ms post target-stimulus showing stronger theta power increase as compared to the epoch 500 ms before the target-stimulus (Fig. 2). Most importantly, we also found a significant interaction between
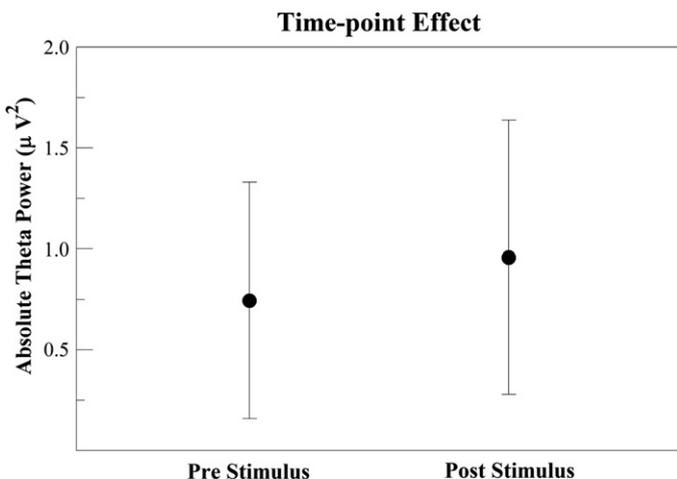
Frontal Sites
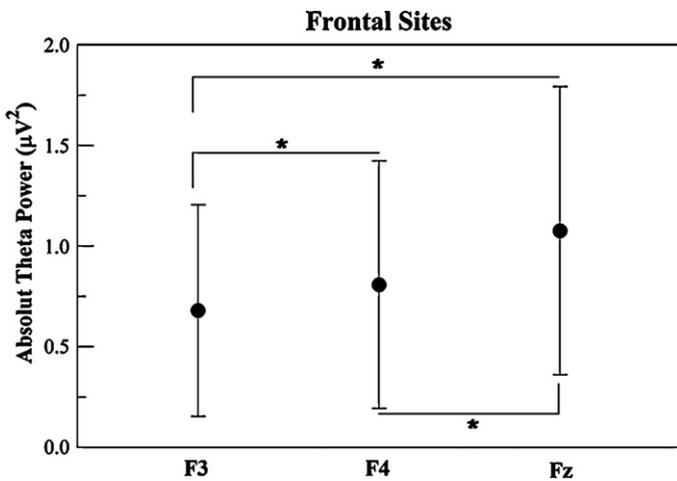
Fig. 1. Mean and standard deviation of absolute theta power at electrodes F3, F4 and Fz. The figure illustrates the difference among electrodes. The statistical analysis revealed a main effect of electrode ($p < .001$).

the factors "electrode" and "SEM condition" ($F = 6.071$, $p = .002$), indicating that the difference in absolute theta power between the fixed and random SEM paradigm is significantly different between the three frontal electrodes FZ, F3, and F4 (Fig. 3).

This study aimed at shedding light into the relationship between absolute theta power within frontal cortices and the planning, execution and voluntary control of SEMs. We hypothesized that absolute theta power over left and right frontal brain regions also act as a main neural mechanism underlying SEM. The experiment simulated different task conditions that involved a variety of attention patterns of SEM. The target-stimulus presented in the random condition could emerge in the central and peripheral areas of the LED bar. In contrast, the fixed condition had the target-stimulus always appear at the same peripheral location. We here aimed to investigate possible electrophysiological differences as measured by the strength of absolute theta power within frontal cortex during the planning and preparation of either stimulus- or memory-driven SEM.

The analysis of the absolute theta power within frontal cortex revealed a task-related increase in theta band activity at electrode sites FZ, F4, and F3 with FZ yielding the strongest absolute theta power increase, followed by F4 and F3 (significant main effect electrode site). Moreover, theta band power increase was

Time-point Effect

Fig. 2. Mean and standard deviation of absolute theta power at pre- and post-stimulus moment. The statistical analysis revealed a main effect of time point ($p < .001$).

Frontal Site x Condition
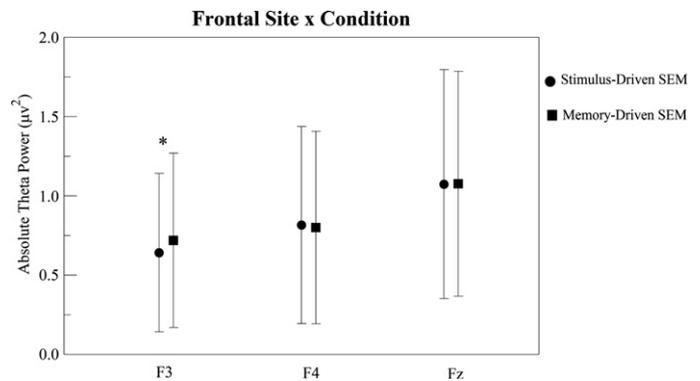
Fig. 3. Mean and standard deviation of absolute theta power shown separately for the three frontal electrodes (F3, Fz and F4) and the two SEM conditions (memory and stimulus-driven). The statistical analysis revealed an interaction between SEM condition and electrode ($p = .002$). Post hoc analyses revealed that this interaction was driven by a significant difference between both SEM conditions at electrode F3 ($p < .05$).

significantly stronger in the post-stimulus period as compared to the pre-stimulus period (significant main effect time point). Several previous studies have proposed that theta power increase coordinates the activity of multiple brain regions, especially sensory and motor areas, during behavior that requires the updating of motor plans according to incoming sensory information [3,4,14]. De Araujo et al. [6] observed that theta power increases are a predictor of the update or the recovery of a motor plan. In this context, the increase of absolute theta power in the post-stimulus period revealed in our study is likely associated with the end of the motor task and the preparation and planning for the next action. Regarding the main effect of the electrode factor, theta power increase appeared more significantly over the midline frontal cortex than over the right and left frontal cortex. Frontal midline theta has been widely studied in a variety of mental tasks [12,28], including those that require high levels of sustained attention. Frontal midline theta originates in the anterior cingulate cortex, and it is considered an important component of an anterior attentional network [22,26,29]. Our results can thus be indicating that frontal midline theta power participates in the attentional process responsible for visual search and later in the planning and sequencing of SEM. Previous studies have demonstrated that the increase of absolute theta power (peak between 6 and 7 Hz) over frontal sites is associated with high levels of concentrated attention demand [11,28]. This region is activated at the beginning of the eye movement during the voluntary saccade [19,20,23].

We also did reveal a significant two-way interaction between left and right frontal cortex (i.e. F3 versus F4) and SEM condition (i.e. fixed versus random SEM) (Fig. 4). We show that both SEM conditions were processed differently by the left and right frontal cortex, while at the midline frontal cortex no significant differences between the two SEM conditions were detected. This indicates that the random and fixed SEM conditions systematically modulate increase of absolute theta power at electrodes F3 and F4 in the following manner: while the right frontal cortex showed a higher magnitude of theta band power increase during the random as compared to the fixed SEM pattern, this relationship was reversed over the left frontal cortex, where the magnitude of theta was higher during the fixed as compared to the random SEM condition. We thus revealed a double dissociation between left versus right frontal cortex and fixed versus random SEM patterns with respect to the underlying increase in absolute theta band. Our data suggest that theta band activity within left frontal cortex modulates the planning and sequencing of memory-guided saccades. Specifically, theta activity over the left frontal cortex is an indicative of eye motor sequencing. This finding is in agreement
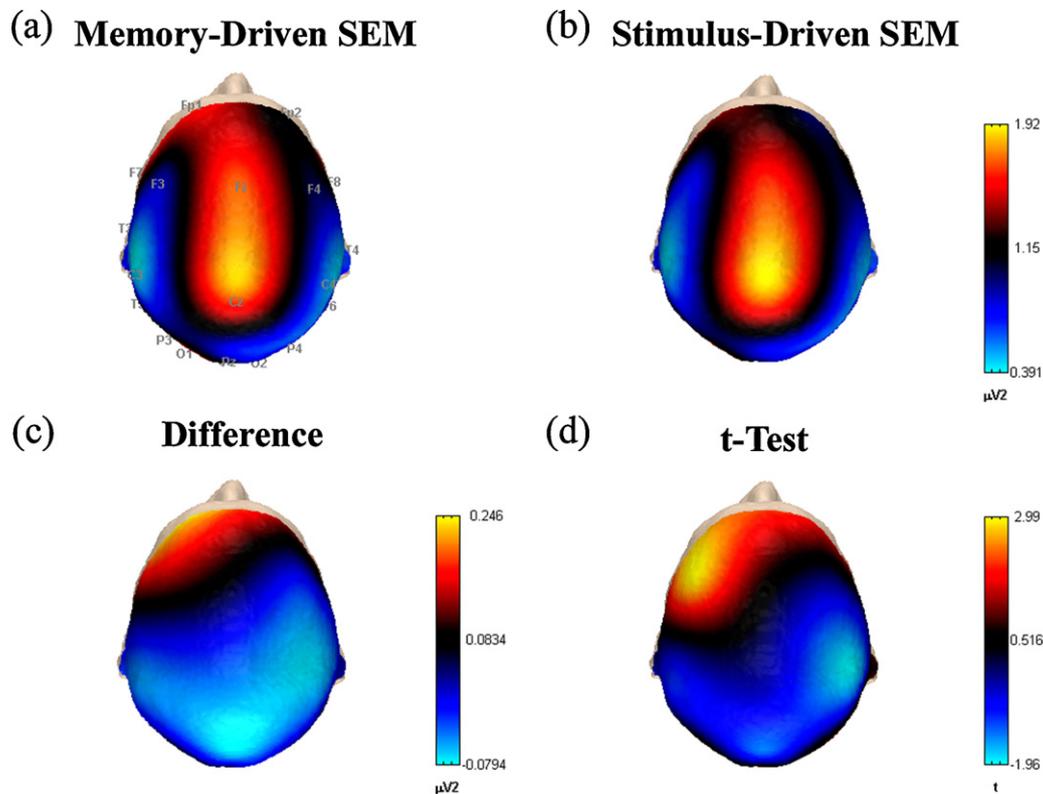
Fig. 4. Power activity of the cerebral cortex generated from the analysis of fast Fourier transform (FFT). The FFT was analyzed in the range of 500 ms following the presentation of the target stimulus (LED). (a) Memory-driven saccadic eye movement; (b) stimulus-driven saccadic eye movement; (c) difference between the two SEM conditions; (d) *t*-test value. Left frontal cortex showed significant power differences between SEM conditions.

with a study conducted by Gaymard et al. [9] investigating single versus sequential SEMs concluded that the supplementary motor area of the left hemisphere plays a role in motor sequencing [9,25], complementing the evidence for left hemispheric involvement in saccade motor control [15,27]. The proximity between the supplementary eye field and supplementary motor area also suggested the participation of the left frontal cortex in saccade control [9,19]. Our data thus further strengthen the evidence for a specific role of left frontal cortex in the motor sequencing of SEM, which in our case explains the increase of theta activity over this area. It may thus be speculated that the increase over F3 theta observed during the fixed SEM pattern represents the coordination and programming of motor sequencing with regard to peripheral vision. Since this condition is mainly memory-driven, the theta power increase over the left frontal area may also represent the neural mechanism underlying the update of information previously recorded and that contains importance for the planning of the next saccades.

In contrast, right frontal cortex showed greater theta magnitude in the random SEM as compared with the fixed SEM pattern. The random condition requires participants to actively search for the target-stimulus along the bar, thereby demanding more spatial processing. Previous studies pointed out that tasks involving spatial behavior mainly guided by external stimuli promotes brain activity in the right hemisphere [5,27]. In accordance with this, our results show an increase in theta power over the right frontal cortex during the random condition, suggesting that unpredictable spatial tasks that require subjects to perform a spatial search leads to greater involvement of the right hemisphere. In a previous fMRI study [27] on SEM, including predictive saccade (memory-driven) and visually guided saccade (stimulus-driven), the authors observed greater activity in the frontal eye field of the right hemisphere during stimulus-driven saccades, a result also in very good agreement with our lateralized theta band power increase data presented here.

In general, our results support the association of theta band with the planning and preparation of SEM, and the specific role of this frequency band in the attention network and for the coordination and integration of sensorial information with a motor response. Moreover, our findings strongly suggest that both types of SEM sequencing promoted a different, clearly lateralized, pattern of brain activity in terms of different increases of absolute theta band. We conclude that right and left frontal regions are an important factor to discriminate between memory- versus stimulus-driven SEMs.

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