Sustained Negative Slow Wave and Mid-Frontal Theta Oscillations as Measures of Attention and Cognitive Control During Auditory Working Memory (WM): Dissociation of Ignore vs Suppress vs Remember Tasks

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Abstract

Background: We developed auditory analogs of visual Ignore/Suppress tasks to dissect the role of perceptual "bottom-up" and "top-down" attention or inhibitory control processes in WM that may underlie cognitive dysfunction in schizophrenia. **Methods:** ERPs (72 sites) were recorded from 31 healthy adults during encoding, maintenance, and item retrieval in 3 tasks (I: Ignore; S: Suppress; R: Remember) consisting of listening to a series of 4 letters alternately presented to each ear (0.6-s SOA), followed by a 3-s maintenance interval and a probe. Subjects selectively attended to letters presented to one ear and ignored those in the other ear (I), suppressed letters presented to one ear (S), or remembered all letters (R). The critical cue was provided either before (I) or after (S) the encoding series, or with the probe (R). **Results:** Here we focus on ERPs and event-related oscillations (EROs) over the entire 10-s trial interval after reference-free scalp current source density (CSD) transformation. A broad sustained negative slow wave (NSW) was greater for I than S and R during encoding but greater for S than I and R during maintenance. A time-frequency analysis of these data revealed distinct task-specific modulations of prominent mid-frontal theta (MFT) paralleling the NSW effects. Most importantly, MFT was selectively enhanced for S compared to I and R during maintenance (i.e., not due to task difficulty or source memory requirements). **Conclusions:** These findings, which were effectively replicated after 1-wk retest, strongly implicate MFT as an electrophysiological correlate of inhibition of information stored in WM.

Introduction

- ***Proactive control***, the ability to actively represent and manipulate goal information in WM to guide behavior, may be a common mechanism that drives cognitive deficits in schizophrenia (SZ)[1]
- Functional deficits in SZ, including hallucinations, are more common and severe for the auditory than visual modality[2-4], but most WM studies in SZ have focused on visual tasks[5]
- Auditory hallucinations may result from a deficit in cognitive control[6]
- Thus, we developed a new auditory working memory (WM) paradigm (**Fig. 1**) to dissect the role of perceptual *"bottom-up"* and *"top-down"* attention or inhibitory control processes in WM that would be of particular value in studies of cognitive function in schizophrenia[1]
- Each task consisted of listening to a series of 4 letters alternately presented to ***left ear*** (**LE**) and ***right ear*** (**RE**; 600 ms SOA), followed by a maintenance interval and a probe
- Participants selectively attended to letters presented to one ear and ignored those in the other ear (**I**: ***Ignore***), suppressed letters presented to one ear (**S: *Suppress***), or remembered all letters (**R: *Remember***)
- The critical cue was provided either *before* (**I**) or *after* (**S**) the encoding series, or *with the probe* (**R**)
- Here, we evaluate long-lasting ***event-related potentials*** (**ERPs**) and ***oscillations*** (**EROs**) unfolding across the trial timeline as a function of task (**I**, **S**, **R**)
- The a priori focus was on sustained ***negative slow wave*** (**NSW**), which has been related to maintenance of WM representations[7], and ***midline frontal theta*** (**MFT**; 4-8 Hz) oscillations, which serves a crucial function for WM and cognition[8]

Objective: Examine how NSW and MFT are modulated by cognitive control processes (*top-down*) of auditory WM in HC

Participants

Variable	Mean	SD	Range
	Healthy Participants (*n* = 31; 17 female, 54.8%)		
Age (years)	30.9	10.2	18 - 55
EHI LQ [a]	80.3	24.8	20 - 100
Education (years)	15.1	2.0	12 - 19
NART [b]	34.3	9.3	16 - 55
Parental SES [c]	42.0	17.2	7.5 - 66

Note. [a] *Edinburgh Handedness Inventory* (EHI)[9] laterality quotient (LQ) can vary between −100.0 (completely left-handed) and +100.0 (completely right-handed). [b] *National Adult Reading Test* (NART) scores[10] used for an estimate for premorbid intelligence. [c] Parental Socioeconomic Status (SES)[11], *n* = 27. Race and ethnicity were Native American (1), Asian (5), Black/African American (10), White/Caucasian (11), and more than one race (4).

Auditory WM Paradigm

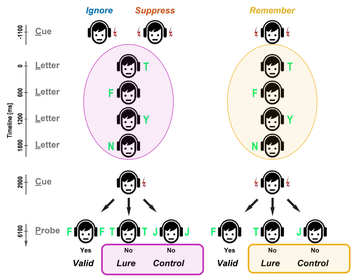


Fig. 1. Schematic for ***Ignore***, ***Suppress*** and ***Remember*** tasks.

Behavioral Performance

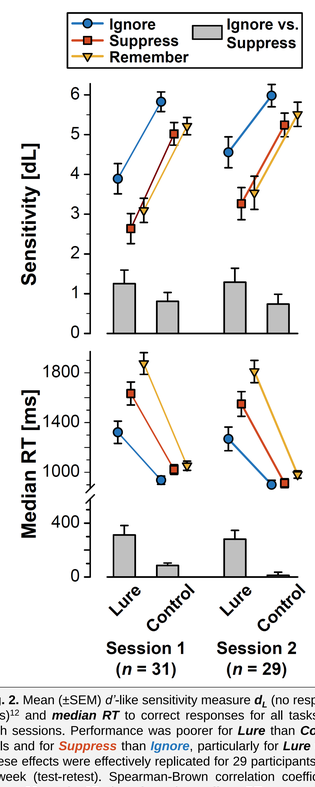
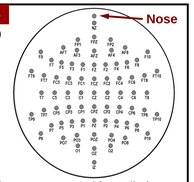


Fig. 2. Mean (±SEM) *d'*-like sensitivity measure d_L (no response bias)[12] and ***median RT*** to correct responses for all tasks and both sessions. Performance was poorer for ***Lure*** than ***Control*** trials and for ***Suppress*** than ***Ignore***, particularly for ***Lure*** trials. These effects were effectively replicated for 29 participants after 1 week (test-retest). Spearman-Brown correlation coefficients were .89 and .97 for d_L and ***median RT***, respectively. Cronbach's α values for each session and each measure ranged from .86 to .92. This suggests that these behavioral measures are both stable and internally consistent.

Ignore/Suppress/Remember Auditory WM Tasks

- Auditory analogs of visual *Ignore/Suppress* tests[13-14], which manipulate interference control during WM[15-16], were supplemented by a Sternberg-like *Remember* tests designed as a *Suppress* control condition (**Fig. 1**)
- WM tests combine advantages of serial position[7] and dichotic listening tasks[17]
- Encoding, maintenance and retrieval phases (item/cue sequence) are virtually identical for *Ignore*, *Suppress*, and *Remember* tasks
- Design prevents information from entering into WM (*Ignore*), removes encoded information from WM (*Suppress*), or keeps all information in WM (*Remember*)
- Comparison of accuracy and RT for negative responses to *Lure* and *Control* (each 30% of all trials) provides a behavioral index of cognitive control (**Fig. 2**)
- Perfectly selecting only letters on the attended or remembered side would produce no performance difference for lures and controls; if selection is poor, the difference between them will be large

EEG/ERP Recording and Analysis



- 72-channel EEG (nose reference)
- Biosemi, DC-51.3 Hz, 1024 samples/s
- **spatial SVD blink reduction** (continuous EEG)
- long **11 s epochs** (baseline-corrected for cue *N1*)
- ***reference-free* current source densities (CSD)** (spherical splines surface Laplacian[18-20]) computed for each EEG epoch (sharpen topographies, eliminate volume-conducted activity)
- ERP averages (artifact-free trials), low pass at 12.5 Hz (-24 dB/oct.), 300 ms baseline correction at cue #1 (**Fig. 5A**) and cue #2 (**Fig. 5B**)
- **CSD-ERSP**: event-related spectral perturbations (ERSP[21]) obtained from CSD epochs via FFT power spectra (zero-padding ratio of 4) relative to the pre-stimulus baseline[22-24] (**Fig. 5C**); normalized ERS/ERD measures, reduced via bilinear interpolation to 120-by-225 matrices to reflect spectral (0.25 to 30 Hz) and temporal (-1 to 9 s) ranges of interest
- CSD amplitude spectra for each time point, condition, electrode and participant submitted to ***unrestricted* frequency PCA (fPCA)**, followed by Varimax rotation of covariance loadings[22,25]
- identify (factor loadings; **Fig. 3**) and measure (factor scores; **Fig. 4**) **neuronal generator patterns** corresponding to midfrontal theta ERSP[22,25]
- statistically probe **theta modulations** (i.e., change to baseline theta, differences between tasks) via **nonparametric permutation tests**[26-27] (**Fig. 5C**)

Summary and Conclusions

- **Results confirm and extend prior findings suggesting that NSW and MFT are closely related to WM processes in healthy participants**
- **This new auditory WM paradigm revealed a functional dissociation of attentional *"bottom-up"* (*Ignore*) and cognitive *"top-down"* (*Suppress*) control processes, implicating MFT as an electrophysiological correlate of active WM inhibition**
- **Differences between *Ignore*/*Suppress* tasks are not due to memory load or contextual (source) memory effects, given the behavioral and electrophysiological findings for the *Remember* control task**
- **MFT oscillations appear to reflect proactive control processes during these auditory WM tasks**
- **Paradigmatic effects for behavioral and electrophysiological measures are robust (good to excellent 1-wk test-retest reliability)**

Frequency PCA

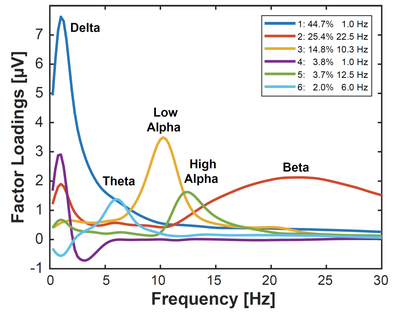


Fig. 3. Factor loadings corresponding to known spectral bands, including 4-8 Hz theta (spectral loadings peak at 6 Hz).

CSD-fPCA Factor Score Topographies

Midfrontal Theta

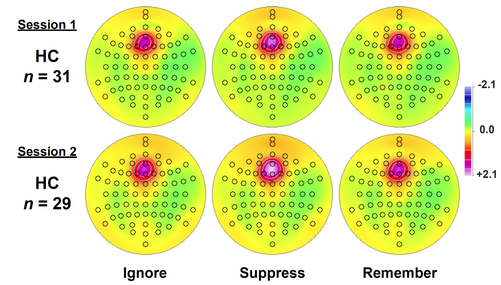


Fig. 4. Mean factor score topographies for healthy control (HC) participants for each task at test and 1-wk retest sessions, revealing midfrontal maxima (AFz, Fz, F1, F2).

Pooled CSD Waveforms

Negative SW

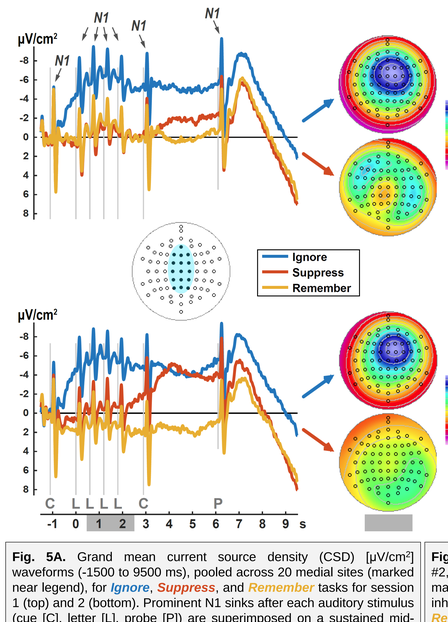


Fig. 5A. Grand mean current source density (CSD) [µV/cm²] waveforms (-1500 to 9500 ms), pooled across 20 medial sites (marked near legend), for ***Ignore***, ***Suppress***, and ***Remember*** tasks for session 1 (top) and 2 (bottom). Prominent N1 sinks after each auditory stimulus (cue [C], letter [L], probe [P]) are superimposed on a sustained mid-frontal negative slow wave (SW) that develops during encoding, particularly for ***Ignore***. Topographies show mean CSD amplitudes during encoding (500 to 2500 ms) for ***Ignore*** and ***Suppress***.

Time-frequency CSD-fPCA

Midfrontal Theta

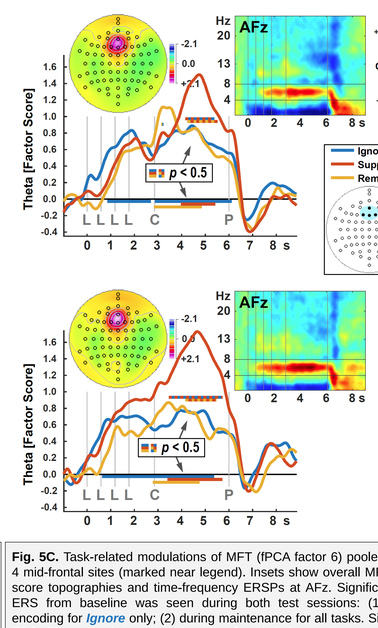


Fig. 5B. CSDs (2750 to 6250 ms) baseline-corrected to cue #2, revealing a sustained mid-frontal negativity during maintenance, particularly for ***Suppress*** (i.e., when participants inhibit irrelevant information from WM). This is not seen for ***Remember*** despite equal memory load. Topographies show mean CSD amplitudes during maintenance (3500 to 5500 ms) for ***Ignore*** and ***Suppress***, indicating a sustained negative SW with a mid-parietal maximum.

Fig. 5C. Task-related modulations of MFT (fPCA factor 6) pooled across 4 mid-frontal sites (marked near legend). Insets show overall MFT factor score topographies and time-frequency ERSPs at AFz. Significant MFT ERS from baseline was seen during both test sessions: (1) during encoding for ***Ignore*** only; (2) during maintenance for all tasks. Significant ERS differences between tasks were found during maintenance due to greater MFT ERS for ***Suppress*** than ***Ignore*** and ***Remember***, whereas ***Ignore*** and ***Remember*** did not differ from each other.

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