

Mid-frontal Theta as a Measure of Attention and Cognitive Control During New Auditory WM tasks: Preliminary Findings for Healthy Adults and Schizophrenia Patients

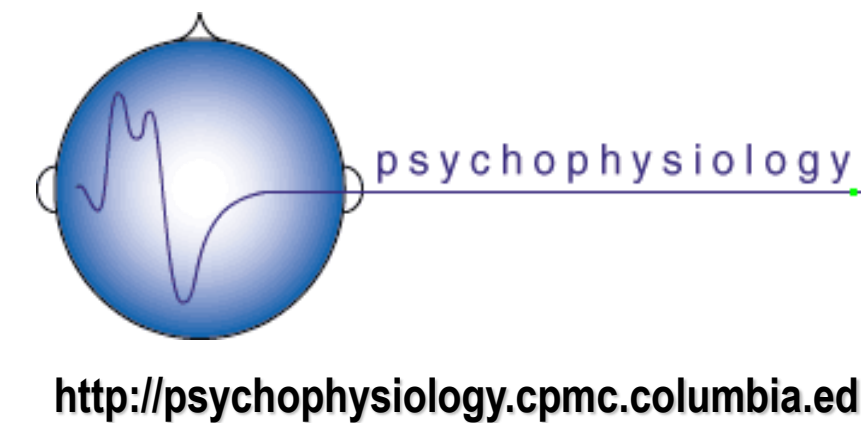
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<http://psychophysiology.cpmc.columbia.edu/mmedia/IOP2018/AWM-MFT.pdf>

Abstract

Introduction: Proactive control, namely the ability to represent and manipulate goal information in working memory (WM), may be a common mechanism that drives cognitive deficits in schizophrenia (SZ). While studies have generally relied on visual WM paradigms, functional deficits in SZ, including hallucinations, are more prevalent and severe for the auditory than visual modality. We developed auditory analogs of visual Ignore/Suppress tasks conducted in conjunction with event-related potentials (ERPs) and oscillations (EROs) to examine the effects of selective attention and inhibitory control on auditory WM in SZ patients and healthy controls (HC). **Methods:** ERPs (72 sites) were recorded from 31 HC and 10 SZ patients 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 (Fig. 1). 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). ERO measures were quantified for the entire 10-s trial interval after reference-free scalp current source density (CSD) transformation using frequency principal components analysis (PCA). The CSD-PCA solution identified a distinct factor with a spectral loadings peak at 6 Hz and maximum factor scores at mid-frontal sites (AFz, Fz, F1/2), which were used for statistical evaluation with non-parametric permutation tests. **Results:** Distinct task-specific modulations of prominent mid-frontal theta (MFT) were seen for HC (Fig. 5), revealing significant event-related synchronization (ERS) of MFT during encoding (I only) and maintenance (I, S, R). Furthermore, MFT was selectively enhanced in HC for S compared to I and R during maintenance (i.e., this enhancement was not due to task difficulty or source memory requirements). In contrast, despite clear presence of MFT, SZ patients failed to show significant MFT ERS or task-specific MFT modulations. **Conclusions:** These findings support previous evidence suggesting that MFT oscillations are closely related to WM processes in HC. Our new auditory WM paradigm allowed a functional dissociation of attentional "bottom-up" (I) and cognitive "top-down" (S) control processes, strongly implicating MFT as an electrophysiological correlate of inhibition of information stored in WM. Inasmuch as these measures represent or mediate proactive control processes, SZ patients exhibited robust functional deficits of proactive control during these auditory WM tasks.

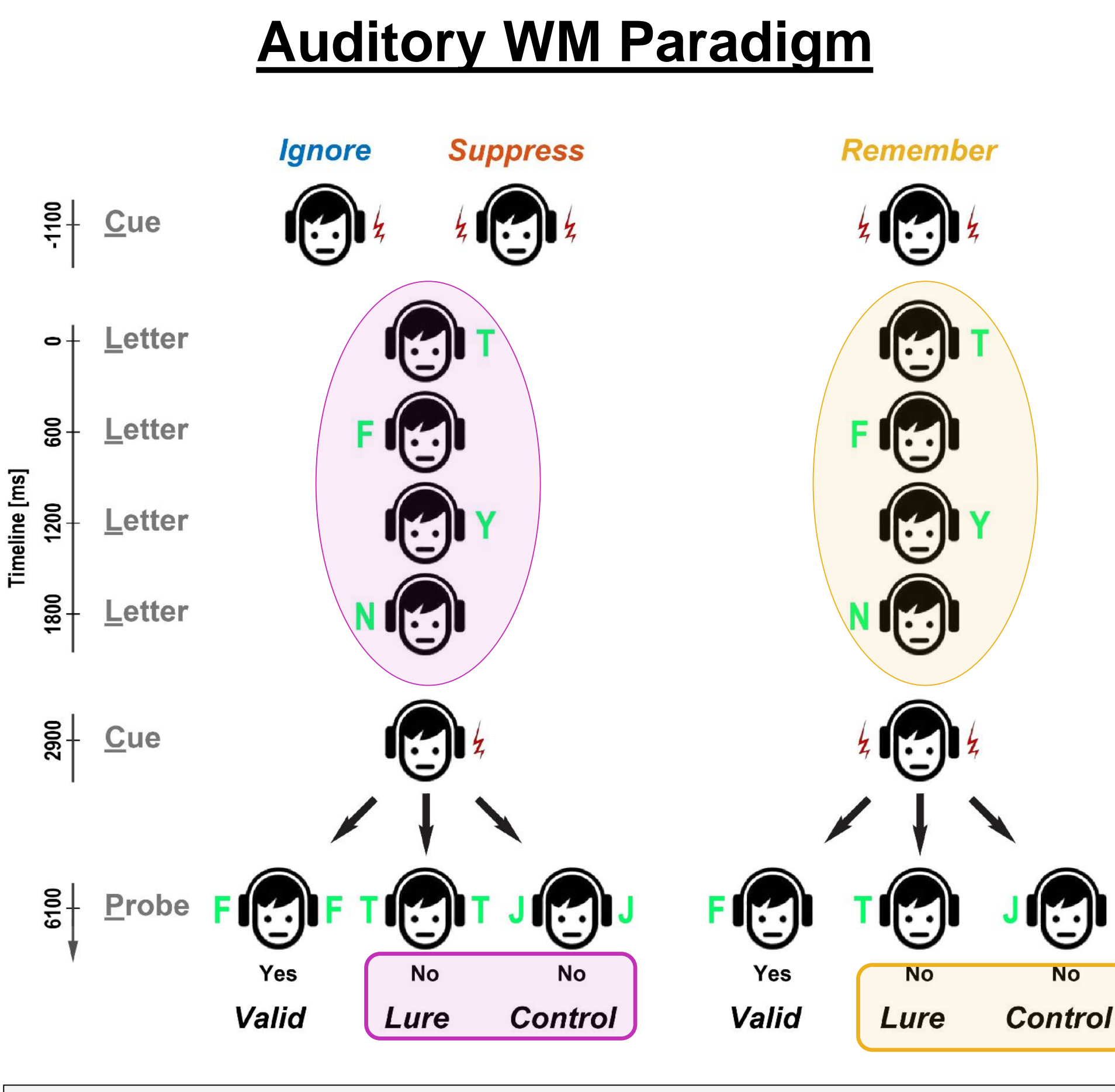


Fig. 1. Schematic for Ignore, Suppress and Remember tasks.

Ignore/Suppress/Remember Auditory WM Tasks

- Auditory analogs of visual Ignore/Suppress tests¹⁴⁻¹⁵, which manipulate interference control during WM¹⁶⁻¹⁷, were supplemented by a Sternberg-like Remember tests designed as a Suppress control condition (Fig. 1)
- WM tests combine advantages of serial position¹⁸ and dichotic listening tasks¹⁹
- 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. 6)
- 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 Laplacian²¹⁻²³) 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. 4A) and cue #2 (Fig. 4B)
- CSD-ERSP: event-related spectral perturbations (ERSP²⁴) obtained from CSD epochs via FFT power spectra (zero-padding ratio of 4) relative to the pre-stimulus baseline²⁵⁻²⁷; 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^{25,28}
- identify factor loadings; Fig. 2) and measure factor scores; Fig. 3) **neuronal generator patterns** corresponding to midfrontal theta ERSP^{25,28}
- statistically probe **theta modulations** (i.e., change to baseline theta, differences between tasks) via **nonparametric permutation tests**²⁹⁻³⁰ (Fig. 5)

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 modality²⁻⁴
- Auditory hallucinations may result from a deficit in cognitive control⁵
- 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 schizophrenia¹
- 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 oscillations (EROs)** unfolding across the trial timeline as a function of task (I, S, R)
- The a priori focus was on midline frontal theta (MFT; 4-8 Hz) oscillations, which serve a crucial function for memory and cognition in healthy individuals (HC)⁶

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

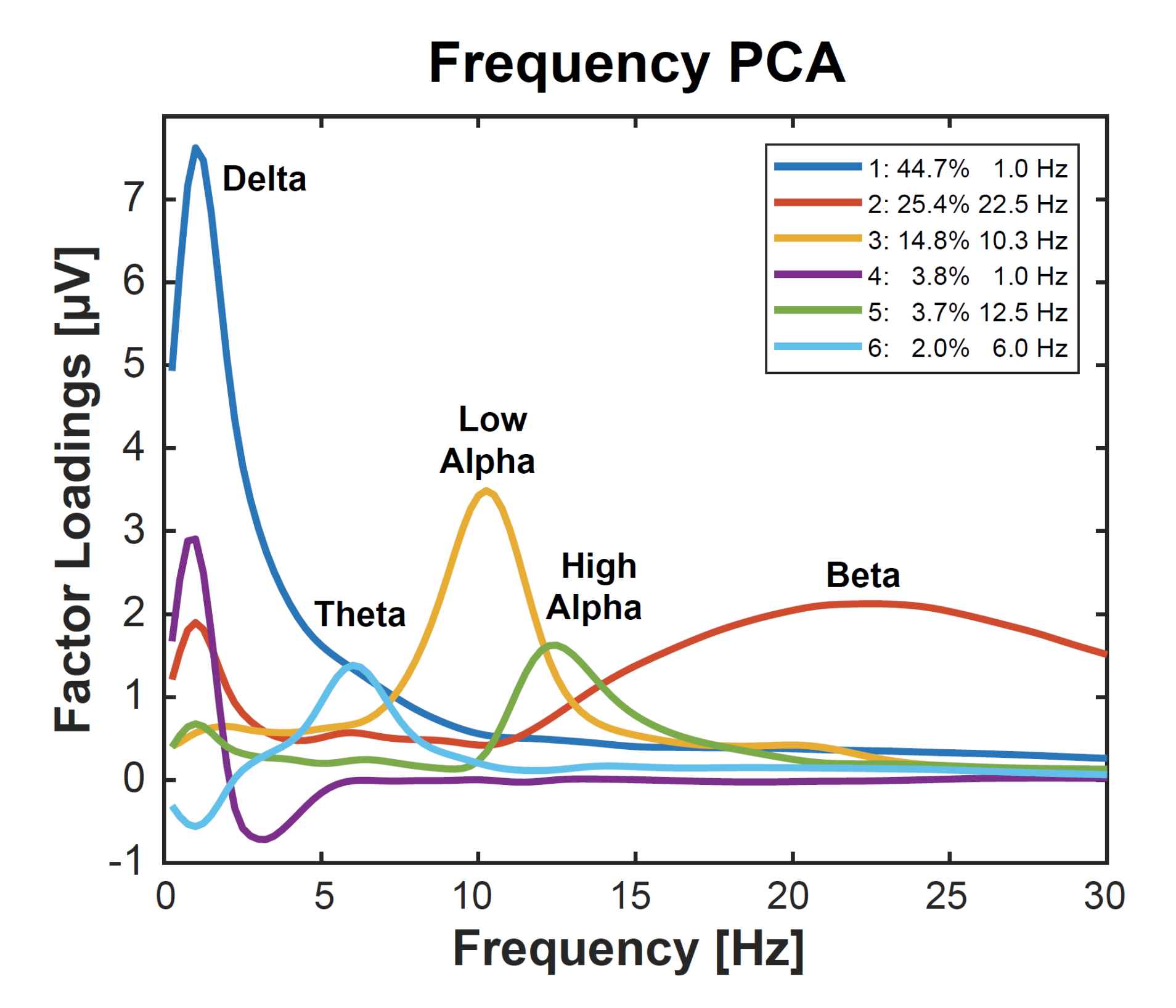


Fig. 2. Factor loadings corresponding to known spectral bands, including 4-8 Hz theta (spectral loadings peak at 6 Hz).0

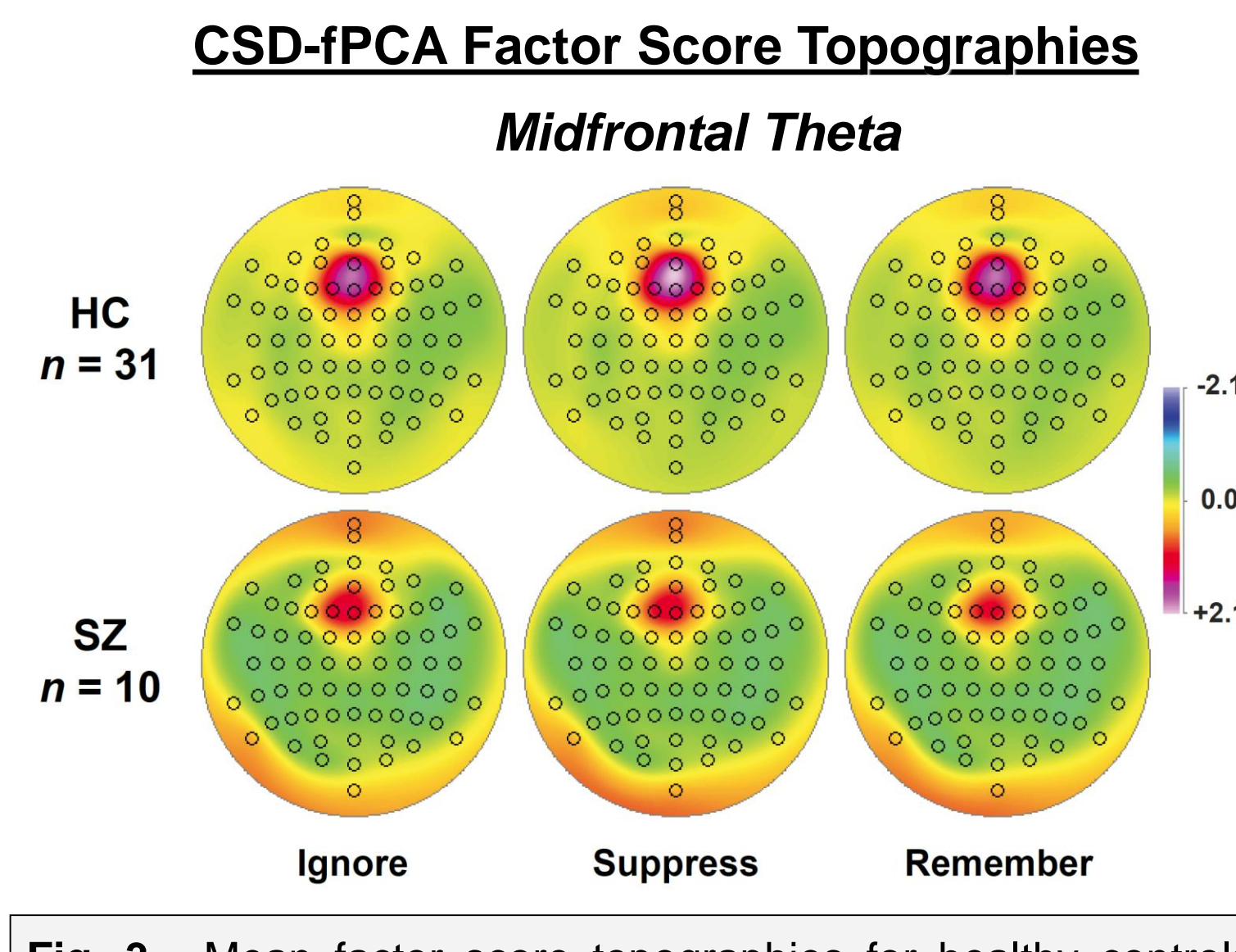


Fig. 3. Mean factor score topographies for healthy controls (HC) and schizophrenia patients (SZ) for each task, revealing midfrontal maxima (AFz, Fz, F1, F2).

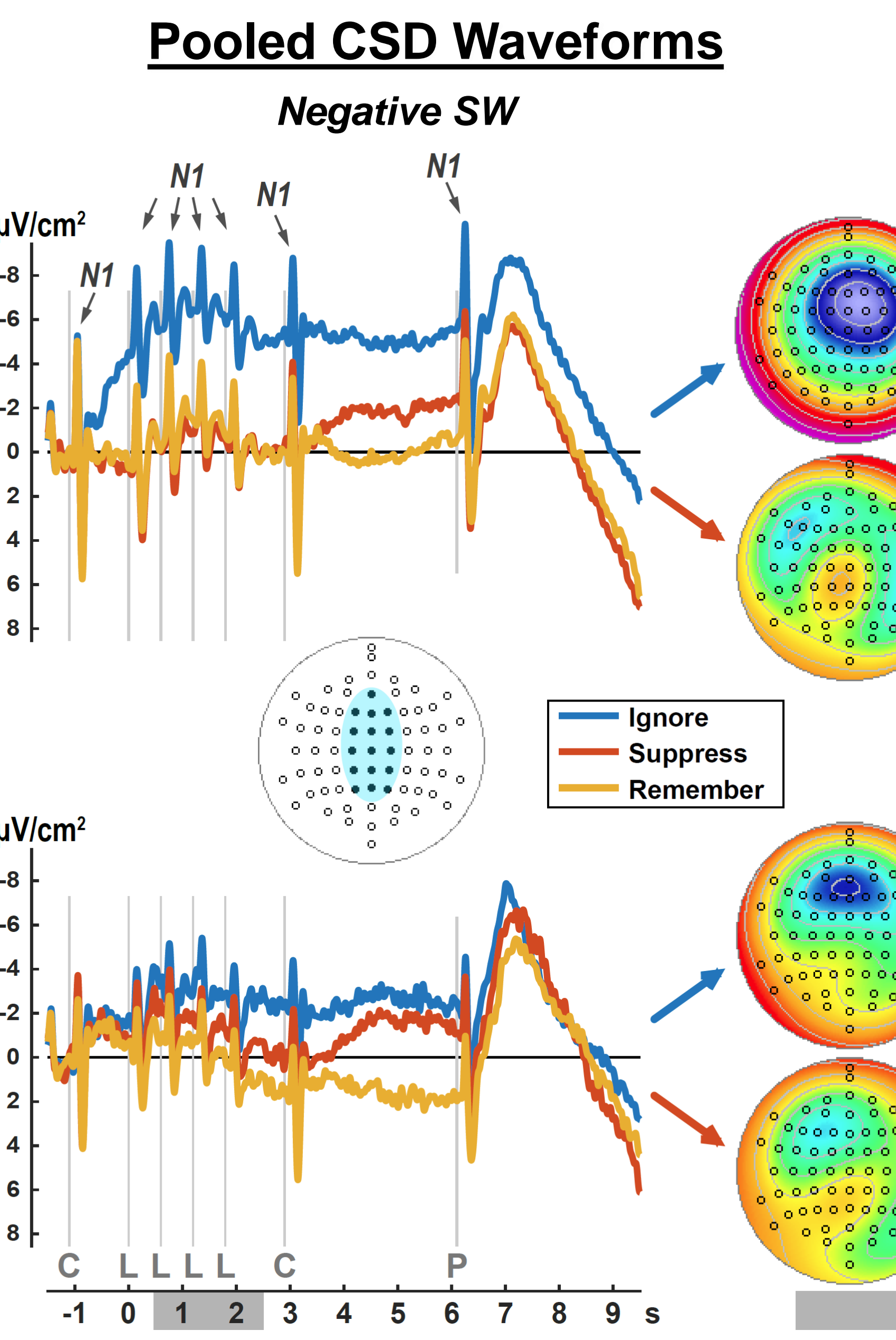


Fig. 4A. Grand mean current source density (CSD) [µV/cm²] waveforms (-1500 to 9500 ms), pooled across 20 medial sites (marked near legend), for Ignore, Suppress, and Remember tasks for HC (top) and SZ (bottom). Prominent N1 sinks after each auditory stimulus (cue [C], letter [L], probe [P]) are superimposed 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.

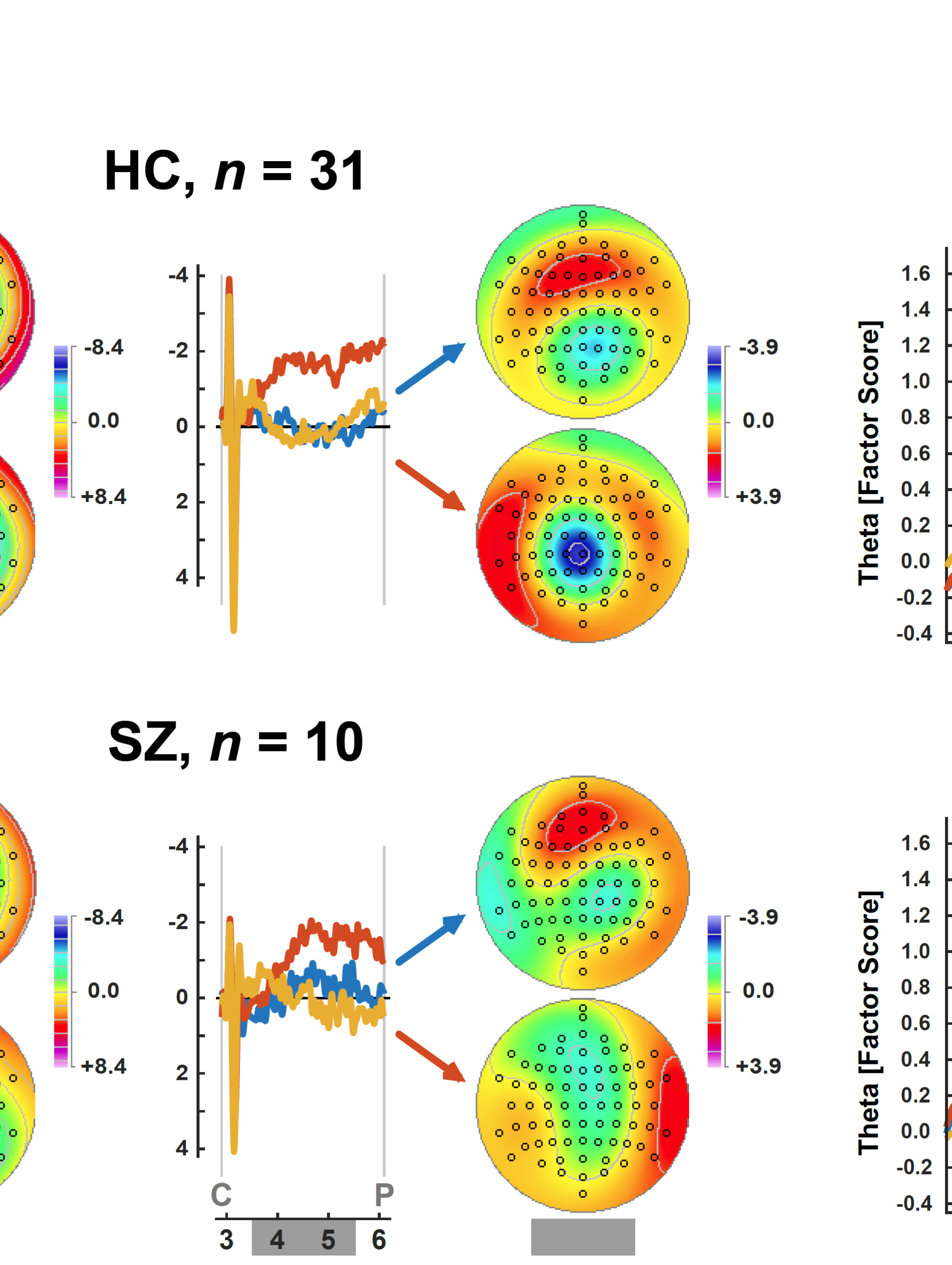


Fig. 4B. CSDs (2750 to 6250 ms) baseline-corrected to cue #2, revealing a sustained mid-frontal negativity during maintenance, particularly for Suppress (i.e., when participants inhibit irrelevant information from WM). This is not seen for Remember despite equal memory load. Topographies show mean CSD amplitudes during maintenance (3500 to 5500 ms) for Ignore and Suppress, indicating a sustained negative SW with a mid-parietal maximum.

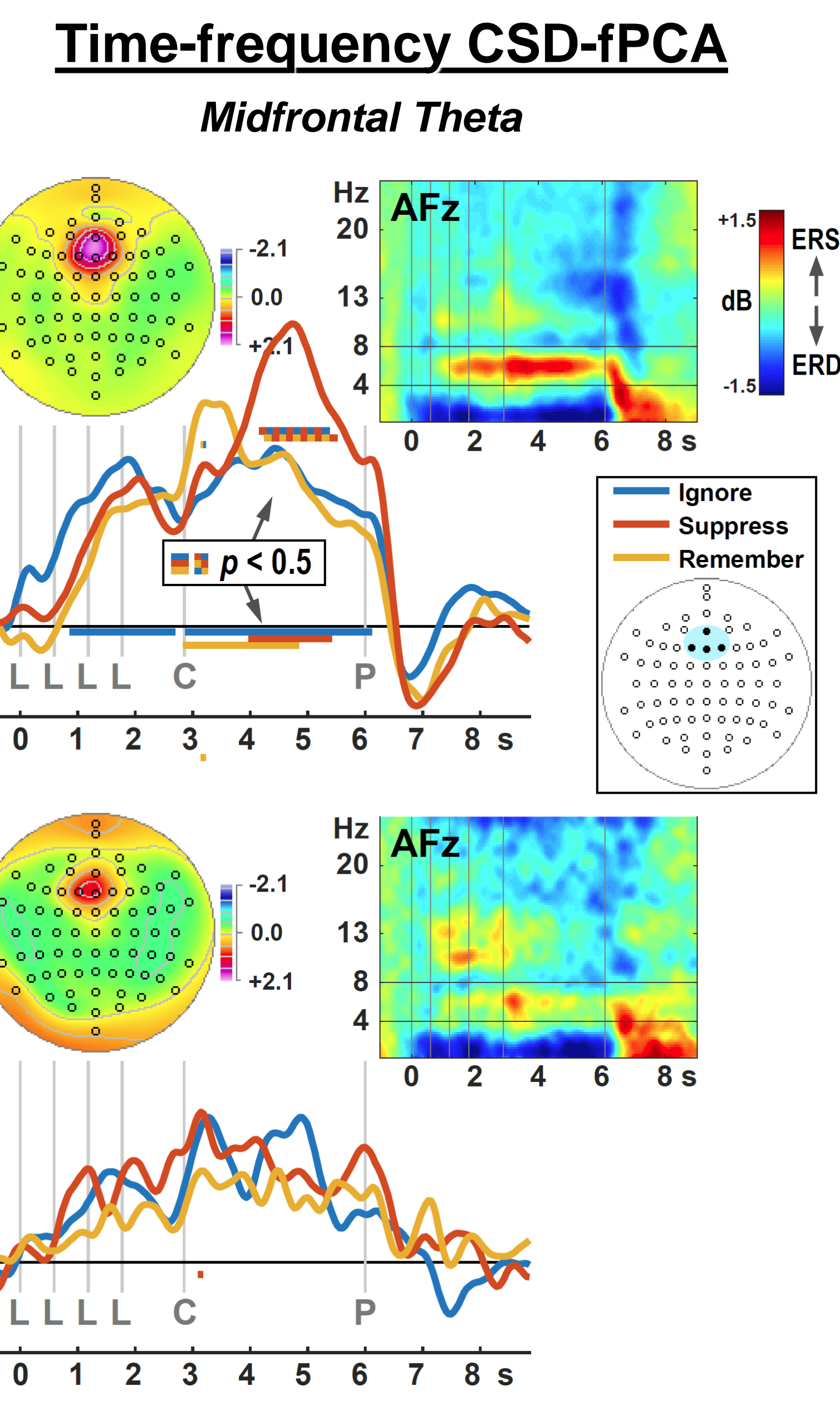


Fig. 5. Task-related modulations of MFT (fPCA factor 6) pooled across 4 mid-frontal sites (marked near legend). Insets show overall MFT factor score topographies and time-frequency ERSPs at AFz. Significant MFT ERS from baseline was seen for HC: (1) during encoding for Ignore only; (2) during maintenance for all tasks. Significant ERS differences between tasks were found for HC during maintenance due to greater MFT ERS for Suppress than Ignore and Remember. No such MFT ERS was observed for SZ, except for a brief increase from baseline for Suppress after the second cue.

Participants

Variable	Schizophrenia Patients (SZ) (n = 10; 2 female, 20%)			Healthy Controls (HC) (n = 31; 17 female, 54.8%)			p ^d
	Mean / n	SD	Range	Mean / n	SD	Range	
Age (years)	35.1	10.7	20-52	30.9	10.2	18-55	n.s.
EHI LQ ^a	70.7	11.9	50-89.5	80.3	24.8	20-100	n.s.
Education (years)	13.5	2.5	9-16	15.1	2.0	12-19	.048
NART ^b	22.9	12.7	9-42	34.3	9.3	16-55	.004
Parental SES ^c	30.7	12.1	16-53	42.0	17.2	7.5-66	.065
Race/Ethnicity							
Native American	0			1			
Asian	0			5			
Black / African American	4			10			
White / Caucasian	3			11			
More than one race	2			4			
Unknown	1			0			
BPRS ^e	32.8	7.4	19-43				
PANSS ^f							
Positive symptoms	12.3	4.3	7-22				
Negative symptoms	16.1	4.0	9-24				
General psychopathology	26.9	6.0	19-34				
SANS ^g							
Affective flattening	1.52	0.8	0.38-2.88				
Alogia	0.62	0.6	0-1.60				
Avolition / apathy	1.57	1.2	0.33-3.83				
Sociality / anhedonia	1.60	1.3	0-3.80				
Attention	1.20	1.0	0-3.00				
SAPS ^h							
Hallucinations	0.47	0.8	0-2.14				
Delusions	0.28	0.4	0-1.08				
Bizarre behavior	0.26	0.5	0-1.00				
Thought disorder	0.30	0.4	0-1.11				

Note. ^a Edinburgh Handedness Inventory (EHI)⁷ laterality quotient (LQ) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). ^b National Adult Reading Test (NART) scores⁸ used for an estimate for premorbid intelligence. ^c Parental Socioeconomic Status (SES)⁹, n = 27. ^d ANOVA significance level comparing SZ and HC. ^e Brief Psychiatric Rating Scale (BPRS)¹⁰. ^f Positive and Negative Syndrome Scale (PANSS)¹¹. ^g Scale for the Assessment of Negative Symptoms (SANS)¹². ^h Scale for the Assessment of Positive Symptoms (SAPS)¹³.

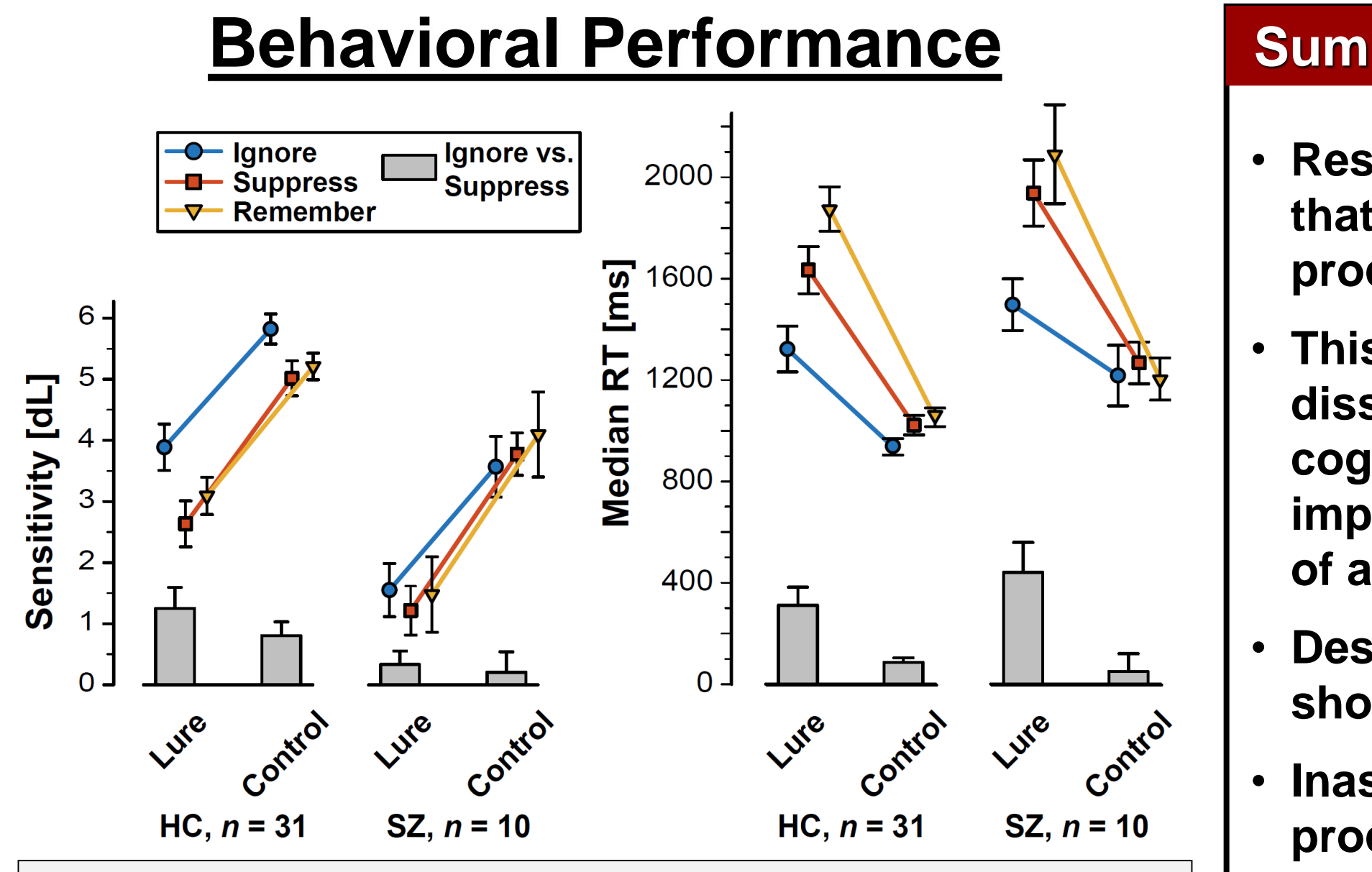


Fig. 6. Mean (±SEM) d'-like sensitivity measure d' (no response bias)²⁰ and median latency to correct responses for all task and both groups. Compared to HC, SZ had poorer performance.

Summary and Conclusions

- Results confirm and extend prior findings suggesting that MFT oscillations are closely related to WM processes in HC
- 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
- Despite clear evidence of MFT, SZ patients failed to show significant task-dependent modulations of MFT
- Inasmuch as these measures reflect proactive control processes, SZ patients exhibited robust functional deficits of proactive control during these auditory WM tasks

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