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Machine Learning Identification of EEG Features Predicting Working Memory Performance in
Schizophrenia and Healthy Adults

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4 ABSTRACT
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7 **Background:** With millisecond-level resolution, electroencephalographic (EEG) recording
8 provides a sensitive tool to assay neural dynamics of human cognition. However, selection of
9 EEG features used to answer experimental questions is typically determined *a priori*. The utility
10 of machine learning was investigated as a computational framework for extracting the most
11 relevant features from EEG data empirically.
12

13 **Methods:** Schizophrenia (SZ; n=40) and healthy community (HC; n=12) subjects completed a
14 Sternberg Working Memory Task (SWMT) during EEG recording. EEG was analyzed to extract
15 5 *frequency components* (theta1, theta2, alpha, beta, gamma) at 4 *processing stages* (baseline,
16 encoding, retention, retrieval) and 3 scalp sites (frontal-Fz, central-Cz, occipital-Oz) separately
17 for correctly and incorrectly answered trials. The 1-norm support vector machine (SVM) method
18 was used to build EEG classifiers of SWMT trial accuracy (correct vs. incorrect; Model 1) and
19 diagnosis (HC vs. SZ; Model 2). External validity of SVM models was examined in relation to
20 neuropsychological test performance and diagnostic classification using conventional
21 regression-based analyses.
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24 **Results:** SWMT performance was significantly reduced in SZ ($p < .001$). Model 1 correctly
25 classified trial accuracy at 84% in HC, and at 74% when cross-validated in SZ data. Frontal
26 gamma at encoding and central theta at retention provided highest weightings, accounting for
27 76% of variance in SWMT scores and 42% variance in neuropsychological test performance
28 across samples. Model 2 identified frontal theta at baseline and frontal alpha during retrieval as
29 primary classifiers of diagnosis, providing 87% classification accuracy as a discriminant
30 function.
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33 **Conclusions:** EEG features derived by SVM are consistent with literature reports of gamma's
34 role in memory encoding, engagement of theta during memory retention, and increased resting
35 low-frequency activity in schizophrenia. Tests of model performance and cross-validation
36 support the stability and generalizability of results, and utility of SVM as an analytic approach for
37 EEG feature selection.
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41 **Keywords:** EEG, gamma frequency, support vector machine (SVM), machine learning,
42 Sternberg task, working memory, schizophrenia
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INTRODUCTION

Electroencephalographic (EEG) recording, when combined with experimental tasks, can provide powerful methodology for studying neural dynamics of human cognition. EEG data is dimensional and complex, based on a time series of events sampled with high temporal resolution and distributed spatially across multiple scalp locations. Given that research-grade EEG systems are capable of sampling at 1000 samples per second and higher, a simple 10-minute experiment could feasibly produce 600,000 discrete data points per channel of acquired data even before considering spatial characteristics or signal extraction methods (e.g., amplitude, spectral power, coherence) that further add to possible number of variables produced. Analysis of such data requires many decisions about the time points and signal extraction methods used to best characterize the psychophysiological phenomena under investigation. Without standardized procedures for EEG experimentation or data extraction across laboratories, how are these decisions to be made? It seems that in most cases, investigators defer to methods of prior studies for guidance on new studies. While this approach may provide important replication of prior results and incrementally advance knowledge, it may also limit EEG analyses to a relatively small portion of the data collected, overlook important features of data not previously discovered, and constrains science to a confirmatory and deductive, rather than data inductive, position.

The primary measure of EEG activity used in psychophysiological research is the event-related potential (ERP). ERPs are defined by stereotyped patterns of voltage change time-locked to stimulus events and are quantified by peak amplitudes measured in averaged waveforms. ERP analysis may therefore focus narrowly on a time window containing a specific peak and leave a large portion of the EEG record discarded from further analysis. However, in addition to the event-related activity driven exogenously by stimulus events, these data contain neural activity generated endogenously that is not captured by averaged waveforms, as well as activity during pre-stimulus and inter-trial intervals that may reveal important differences in how

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4 the brain prepares for and carries out task-related processes. The importance of pre-stimulus
5 activity, for example, is illustrated in work relating the amplitude of ERPs to resting EEG
6 recorded in a passive state prior to the experiment (T. W. Lee, Yu, Wu, & Chen, 2011) and in
7 demonstrations of how ERP amplitudes can be altered experimentally by modulating pre-
8 stimulus activity through non-invasive neural stimulation (Keeser et al., 2011). Accordingly,
9 individual differences in task-related ERP measures, as well as group-wise differences, could be
10 influenced by features of neural oscillatory activity that are inadvertently excluded from
11 conventional ERP analysis. Increased use of time-frequency analysis over the past 10 years
12 (Makeig, Debener, Onton, & Delorme, 2004; Roach & Mathalon, 2008), and associated
13 measures of coherence and phase synchrony, further extend the range of features that can be
14 extracted from standard ERP experiments and the number of variables that can potentially be
15 submitted to statistical analysis. Given the many sources on information that can be gleaned
16 through various signal processing approaches, there is increased need for computational
17 frameworks capable of mining large datasets to identify features most relevant to questions
18 asked of EEG data.

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20 Machine learning encompasses a body of statistical approaches that can be used to
21 discover knowledge from data through mathematical modeling, wherein pattern recognition is
22 optimized by allowing the program to adjust actions accordingly to new information. Machine
23 learning methods are becoming more commonly used in medical sciences, outperforming
24 classical regression approaches when applied to prediction and diagnostic classification
25 decisions (Khosla et al., 2010; Singal et al., 2013). The Support Vector Machine (SVM)
26 approach, in particular, has proven useful for clinical classification problems based on brain
27 imaging data (Orru, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). SVM provides
28 individual-level classification and, therefore, can be applied to questions pertaining to diagnosis,
29 prediction of treatment response, and progression to illness based on preclinical indicators.
30 Furthermore, because SVM is inherently multivariate, it is an appropriate method for separating

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4 unique from redundant sources of variance in spatially distributed, yet variably dependent,
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6 patterns of brain activity.
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9 As a method of EEG feature selection, SVM could provide a powerful tool for reducing
10 large data arrays of scalp locations, frequency bands, and temporal windows to those most
11 pertinent to a classification question. For clinical purposes, this approach could be used to build
12 classifiers of known diagnostic categories based on latent patterns of EEG activity, to refine
13 classifiers iteratively through cross-validation, and ultimately to apply validated classifiers to new
14 clinical samples. In experimental research, these methods can be used to identify the EEG
15 features most related to task behavior, thereby allowing the researcher to empirically develop
16 neural models of human behavior without *a priori* knowledge of task-related activity.
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27 The current study aimed to demonstrate the utility of SVM as a data inductive solution
28 for EEG feature selection. The sample consisted of individuals with schizophrenia and healthy
29 community members who performed a Sternberg working memory task during EEG recording.
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31 The Sternberg task can be analyzed over stages of encoding, retaining, and retrieving
32 information from short-term memory, each involving different sources and components of brain
33 activity, with all contributing to successful task performance. Therefore, multiple spectral-
34 frequency, temporal, and spatial characteristics must be considered simultaneously in order to
35 answer questions about patterns of optimal task-related brain activity and differences in
36 schizophrenia. Questions asked of these seem most amenable to empirical approaches of
37 feature selection as (a) the number of variables that could be conceivably extracted from these
38 data far exceed the number of comparisons that would be advisable if tested independently, and
39 (b) the dynamics of EEG, involving changes and interactions in sources of brain activity that co-
40 vary with individual differences in task performance, can only be resolved in multivariate space
41 where hierarchical relationships within and between features are compared over repeated
42 observations. SVM may provide an appropriate, albeit novel, data reduction and classification
43 approach for this type of analytic problem.
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4 Using a supervised learning approach, given that information about task performance
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6 and diagnostic group membership is known, what EEG features would SVM be expected to
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8 identify? Working memory is a core domain of neurocognitive impairment in individuals with
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10 schizophrenia, found across various task versions administered in auditory and visual modalities
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12 (Forbes, Carrick, McIntosh, & Lawrie, 2009; J. Lee & Park, 2005). Working memory requires
13
14 network-level activation and coordination of neural activity between pre-frontal cortical and
15
16 cortical association areas involved in sensory and attentional processes (Daskalakis et al.,
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18 2008; Intaite, Koivisto, & Castelo-Branco, 2014; Wang, 2010). The cortical distribution of neural
19
20 activity during working memory performance has been studied extensively using EEG recording
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22 (Boonstra, Powell, Mehrkanoon, & Breakspear, 2013; Herrmann, Senkowski, & Rottger, 2004;
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24 Hsieh, Ekstrom, & Ranganath, 2011), demonstrating that optimal behavioral performance can
25
26 be predicted on the basis of neural dynamics (Klimesch, 1997, 1999). Although these
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28 interrelations are complex, and may interact differently depending on memory load and
29
30 individual differences in performance, task-related changes in oscillatory activity in theta, alpha,
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32 and gamma frequencies have been consistently reported (Roux & Uhlhaas, 2014). Theta
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34 frequency (e.g., 4-8Hz) activity is associated with hippocampal-cortical communication during
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36 encoding (Tesche & Karhu, 2000) and increases with higher memory load (Boonstra, et al.,
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38 2013). In a model based on the interrelationship of theta and alpha, performance is suggested
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40 to be optimal when pre-trial baseline EEG contains low tonic theta but high phasic alpha, and
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42 when encoding is accompanied by event-related increases in theta with reductions in alpha
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44 (Klimesch, 1999). A shift to alpha frequency (e.g., 8-12Hz) is then associated with subsequent
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46 memory retention and retrieval processes (Herrmann, et al., 2004) involving thalamo-cortical
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48 networks (Hindriks & van Putten, 2013). Gamma frequency (e.g., > 30Hz) activity is generally
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50 associated with integrative multi-modal sensory processes and, in memory tasks, appears to
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52 couple in-phase with theta activity (Kiri-hara, Rissling, Swerdlow, Braff, & Light, 2012). As with
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54 theta, event-related increases in gamma are normally observed with higher memory load
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4 (Howard et al., 2003; Meltzer et al., 2008). While related in phase, gamma and theta activity
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6 have been associated with distinct functional roles in memory processing, with gamma
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8 supporting short-term maintenance and theta supporting the organization of sequentially
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10 ordered information into memory (Roux & Uhlhaas, 2014). Importantly, while up regulation of
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12 gamma may indicate the recruitment of additional cognitive resources required to meet higher
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14 task demands, individuals with schizophrenia appear to have a limited capacity to modulate
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16 gamma in this way (Basar-Eroglu, Brand, Hildebrandt, Karolina Kedzior, et al., 2007; Schmieidt,
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18 Brand, Hildebrandt, & Basar-Eroglu, 2005).
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22 In addition to features embedded in task-related activity, it is also important to consider
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24 the possibility that neural activity unrelated to demands of the task, but perhaps reflecting traits
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26 of illness, can also affect performance in schizophrenia. For instance, resting state EEG in
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28 schizophrenia is commonly characterized by abnormal elevations in theta and alpha, which
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30 persist during experimental conditions where suppression of this activity normally occurs (Hong,
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32 Summerfelt, Mitchell, O'Donnell, & Thaker, 2012). Based on the previously described neural
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34 dynamics model of memory (Klimesch, 1999), high levels of tonic (i.e., task independent) theta
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36 and failure to down regulate alpha during encoding would predictably result in impaired memory
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38 function. Taken together, these findings provide basis for predicting that differences in EEG
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40 activity during Sternberg task performance will be characterized by elevated low-frequency
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42 activity at the pre-stimulus baseline period and by reductions in event-related theta and gamma
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44 activity during encoding in schizophrenia. Alternatively, optimal performance should be
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46 predicted by increased theta and gamma during encoding, and alpha activity at the retrieval
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48 stage. Given these predictions, the primary question pertaining to SVM-based analysis is
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50 whether these same features emerge as most critical to Sternberg performance and diagnostic
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52 differences when tested within a relatively large array (n=60) of EEG features.
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METHOD

Participants

Forty individuals meeting DSM-IV-TR criteria for schizophrenia (SZ) and 12 healthy comparison (HC) participants were enrolled in a registered clinical trial (identifier: NCT00923078, <https://clinicaltrials.gov>) at time of this analysis. For purposes of the current analysis, only data collected at study intake will be presented. The study was conducted under oversight of VA Connecticut Healthcare System (VACHS) Human Studies Subcommittee (HHS protocol # 01245) and Yale University Human Investigation Committee (HIC protocol # 1003006388) institutional review boards. All participants provided written informed consent prior to initiating any study procedures and were compensated \$75 for data collected at study intake assessment. Recruitment of HC participants was conducted according to match (age, gender, race) with SZ participants. Sample descriptive statistics are presented in Table 1.

Inclusion was limited to individuals aged 18 and 70, native English speaking, with stable housing for minimum of 30 days. In addition, SZ sample members had minimum of 30 days since discharge from last hospitalization, 30 days since last change in psychiatric medications, and were receiving mental health services through VACHS or Yale affiliated outpatient facilities. Individuals were excluded based on current (past 30 days) diagnosis of alcohol or substance abuse disorders, history of brain trauma or neurological disease, mental retardation or premorbid intelligence ≤ 70 , and auditory or visual impairment that would interfere with study procedures. In addition, any current or past DSM-IV Axis I diagnosis was exclusionary for HC sample enrollment.

Clinical Assessment Measures

All participants underwent a clinical interview to obtain treatment, substance use, medical, legal, employment, and psychosocial background information. Diagnosis of SZ sample participants was confirmed using the Structured Clinical Interview for DSM-IV-TR (SCID-I/P; First, Spitzer, Gibbon Miriam, & Williams, 2002), administered by a licensed clinical

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4 psychologist. The Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998)
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6 was administered to healthy volunteers to screen for psychiatric conditions that would be
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8 exclusionary. The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was administered
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10 to all participants to obtain an estimate of premorbid intellectual endowment and the MATRICS
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12 Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) was used to test current
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14 cognitive ability across multiple domains. Age- and gender-corrected t-scores for MCCB
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16 Working Memory Composite and Continuous Performance Test–Identical pairs (CPT-IP)
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18 subtest were used in the current analysis to cross-validate SVM-derived models of EEG activity
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20 related to working memory.
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23 24 EEG Data Collection Procedures

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26 Participants were seated in front of a 24” LCD monitor (1920x1200 pixels, 75 Hz refresh
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28 rate) at a viewing distance of 100 cm in a dimly lit room. EEG was recorded using a 64-channel
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30 BioSemi ActiveTwo (BioSemi B.V., Amsterdam, Netherlands) bio-amplifier and electrode
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32 system with sensors located according to the 10-20 system. Additional electrodes were placed
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34 bilaterally at mastoids (reference), the outer canthi of both eyes (horizontal electrooculogram;
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36 HEOG), and above and below the right orbit (vertical electrooculogram; VEOG). Continuous
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38 EEG was monitored online in ActiView V6.05 and acquired at a 1024 Hz sampling rate with a
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40 bandpass filter setting of 0.16-100 Hz. The Sternberg task was administered using NBS
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42 Presentation software (Neurobehavioral Systems, Inc., Albany, CA), with behavioral responses
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44 captured using two buttons of a Cedrus RB-834 response pad (Cedrus Corporation, San Pedro,
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46 CA). Total EEG set up time was approximately 30 minutes, and the Sternberg task was
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48 administered in three blocks of interspersed between blocks of two additional auditory ERP
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50 tasks (not included in current report).
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53 54 Sternberg Working Memory Task

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56 A version of the Sternberg working memory task (SWMT), modified from Rajhavarachi
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58 and colleagues (2001), was used in the present study. Stimuli consisted of sequentially
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4 presented letters (200ms duration, 1200ms ISI), spanning sets of 4-8 letters each, randomly
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6 generated from an array of 12 letters. For each trial the stimulus set was followed by a 3200ms
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8 retention period that terminated with a response probe letter. Participants were instructed to
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10 press one of two response pad buttons, using right or left index finger, to indicate whether the
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12 probe letter was or was not presented in the preceding set. The response probe remained
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14 present for the duration of the response window, up to 3500ms, and terminated at time of button
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16 press. Auditory feedback was given to indicate correct, incorrect, or time-out (after 2000ms) on
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18 each trial. Feedback was followed by 1000ms of black screen and a fixation “+” cross for
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20 another 1000ms preceding the first stimuli of the next set. A total of 90 trials was administered
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22 over three blocks of 30 trials, each block lasting approximately 8 minutes.
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25 26 EEG Signal Processing

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28 Data analysis was conducted using BrainVision Analyzer software v2.0 (Brain Products,
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30 Munich, Germany). SWMT EEG data was re-referenced offline to the average mastoid,
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32 broadband filtered from 1-70 Hz (12 dB/oct) with a notch filter at 60 Hz, and segmented
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34 according to four stages of processing (Figure 1); pre-stimulus baseline (500 - 1200ms relative
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36 to fixation), encoding (-200 - 8000ms relative to fixation), retention (-3400 - 800ms relative to
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38 probe), and retrieval (-200 - 800ms relative to probe). The analysis window selected for the
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40 encoding stage spanned the first 5 letters (or all 4 when span = 4) of each trial. This window
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42 was selected to optimize the amount of information that could be consistently extracted across
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44 trials varying in length based on span.
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49 Following segmentation, ocular artifact correction was applied (Gratton, Coles, &
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51 Donchin, 1983) and segments containing activity $\pm 75\mu\text{V}$ at electrodes Fz, Cz, and Oz were
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53 excluded. Time-frequency extraction was applied to single trial data using Morlet continuous
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55 wavelet transform (parameter $c = 3.8$) over 20 frequency steps from 4-50 Hz. Data at encoding
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57 and retrieval stages was averaged to extract event-related spectral perturbations (ERSP),
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59 elicited in response letter memory and probe stimuli, respectively. Encoding stage frequency
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4 extraction was baseline normalized to a window of -200 to -50ms relative to fixation cross, while
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6 retrieval was normalized to a window of -200 to -50ms relative to response probe onset. The
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8 same wavelet transform was applied to EEG data at pre-stimulus baseline and retention stages
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10 without normalization. Time-frequency data was output in the form of squared wavelet
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12 coefficients (μV^2) binned and averaged according to response accuracy (correct vs. incorrect),
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14 and exported in five frequency bands at each of the four stages of processing: Theta 1 (θ_1),
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16 centered at 4.00 Hz (range: 3.12 - 4.88); Theta 2 (θ_2), centered at 6.42 Hz (range: 5.01 - 7.83);
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18 Alpha (α), centered at 11.26 Hz (range: 8.79 - 13.73); Beta (β), centered at 18.53 Hz (range:
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20 14.46 - 22.59); Gamma (γ), centered at 40.32 Hz (range: 31.48 - 49.16). Time-frequency values
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22 were exported for statistical analysis based in the following windows: pre-stimulus baseline (500
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24 - 1200ms relative to fixation); encoding (1000 - 7000ms relative to fixation); retention (-3000 -
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26 0ms relative to probe); and retrieval (0 - 600ms relative to probe). All statistical analyses were
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28 conducted on spectral power measured at three midline electrode locations: Frontal (Fz),
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30 Central (Cz), and Occipital (Oz).
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33 Machine Learning Feature Selection

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35 From a machine learning point of view, our analysis is a variable selection problem that
36
37 aimed to identify the EEG features most relevant to SWMT performance and diagnostic group
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39 differences. Variable selection methods are often divided along two lines: filter and wrapper
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41 methods (Kohavi & John, 1997). The filter approach of selecting variables serves as a
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43 preprocessing step to the model construction. The main disadvantage of the filter approach is
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45 that it ignores the effects of the selected variable subset on the performance of the classification
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47 algorithm. The wrapper method searches the optimal variable subsets using the estimated
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49 classification accuracy, as the measure of *goodness*, when the subset of variables is used in
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51 classification. Thus, the variable selection is being “wrapped around” a particular classification
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53 algorithm. Wrapper methods typically outperform filter methods (Guyon & Elisseeff, 2003).
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4 For the current analysis variable selection was conducted using a wrapper method that
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6 is wrapped around the so-called 1-norm SVM (Bi, Bennett, Embrechts, Breneman, & Song,
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8 2003). SVM is a supervised learning method which has the ability to weigh input features
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10 according to their relevance to the classification target, as determined through the learning
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12 process. Most SVMs, including the one implemented in this study, construct a linear classifier
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14 that predicts, by thresholding the classifier real-valued output, whether new cases of data will
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16 fall into one of two categories. The classifier used in the current analysis was based on a linear
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18 function of the form of $\mathbf{w}^T \mathbf{x} + b$, where \mathbf{w} is the weight vector to be determined, \mathbf{x} is the input
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20 vector representing EEG features and $\mathbf{w}^T \mathbf{x}$ represents the dot product between the two vectors.
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22 It obtains the best model coefficients in \mathbf{w} by minimizing the following regularized risk function:
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$$25 \sum_{j=1}^d |w_j| + C \sum_{i=1}^n \varepsilon_i$$

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27 where d represents the number of variables (i.e., EEG features) in total, n represents the
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29 number of records collected in the training set, and $\varepsilon_i = \max\{0, 1 - y_i(\mathbf{w}^T \mathbf{x}_i + b)\}$ denotes the
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31 so-called hinge loss to measure the training error (Vapnik & Vapnik, 1998), where y_i represents
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33 the class label, such as “correct response” versus “incorrect response” of the record i that is
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35 numerically characterized by an input vector \mathbf{x}_i (i.e., the vector of features extracted from that
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37 record).
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45 A record consisting of 60 features of EEG data was extracted for each participant,
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47 including five frequency bands (theta 1, theta 2, alpha, beta, and gamma), three scalp locations
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49 (frontal, Fz; central, Cz; occipital, Oz), and four information processing stages (pre-stimulus
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51 baseline, encoding, retention, and retrieval). Features were binned separately based on trial
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53 accuracy and assigned a binary label indicating whether trials received correct (+1) or incorrect
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55 (-1) responses. Accordingly, EEG features receiving positive valence weightings can be
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57 interpreted as more highly predictive of correct trial performance, with those receiving negative
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4 valence predictive of incorrect performance. The SVM algorithm was applied in two models: (1)
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6 to classify correct vs. incorrect trial performance within each sample, referred to hereafter as
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8 *Model 1*, and (2) to classify between SZ and HC groups across correct and incorrect trials,
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10 referred to as *Model 2*.

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13 Although the current analysis was based on a small study (12 HC and 40 SZ), a large
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15 number of EEG features (60) were used to represent each case. This circumstance poses risk
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17 for over-fitting, meaning that the resultant classifier could achieve good accuracy during training
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19 but poor validation accuracy. According to statistical learning theory (Vapnik & Vapnik, 1998),
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21 regularization is the most effective way to control over-fitting. SVM methods optimize a
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23 regularized loss function for the best classifier where either the two-norm regularizer $\|w\|^2 =$
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25 $\sum_{j=1}^d w_j^2$ or one-norm regularizer $\|w\|_1 = \sum_{j=1}^d |w_j|$ is used. In the current implementation, the 1-
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27 norm regularizer was chosen because this regularizer enforces sparsity of the weight vector w ,
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29 meaning many entries of w will be zeros. More precisely, although 60 features were used in the
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31 SVM classifier training, when the classifier is built by SVM, only 3~10 features were actually
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33 used by the classifier because other features received zero weights in the model.
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38 The parameter C in the 1-norm SVM was tuned in a 3-fold cross validation process
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40 where the respective data set was evenly split into 3 disjoint subsets. At each fold, we tested on
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42 a subset of the data the classifier obtained by SVM from the remaining data. Receiver operating
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44 characteristics (ROC) curves were used to examine the performance of the classifiers.
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46 Specifically, the area under the curve (AUC) was reported. We average the AUC values over
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48 the three folds for each choice of C in a range from 0.1 to 10 with a step size of 0.1. The value
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50 of C that produced the best cross validation performance was used to train the final classifier
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52 from all records. The cross validation performance for SVM with the chosen C value was also
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54 reported. In addition to AUC values, precision, recall, and F1 score were computed.
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4 The analysis of *Model 2* presented an unbalance classification problem due to far fewer
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6 HCs (n=12) than SZs (n=40). Therefore, a commonly used procedure in SVM was adopted to
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8 balance the sample size. Specifically, the analysis penalized errors that occurred in the HC
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10 samples 3 times more than the errors in the SZ samples. This created the similar effect as up-
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12 sampling HC three times. Mathematically, this procedure corresponded to revising the
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14 regularized loss function as follows:
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$$\sum_{j=1}^d |w_j| + C \left(3 \sum_{i \in \{HN\}} \varepsilon_i + \sum_{i \in \{SZ\}} \varepsilon_i \right)$$

22 RESULTS

23 Behavioral Data

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27 Group comparison on SWMT behavioral data revealed overall lower accuracy in SZ than
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29 HC (Table 1). As a group, working memory performance was impaired in SZ participants based
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31 on MCCB WM composite score, but visual attention was within normal range based on the
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33 CPT-IP. Groups did not differ in basic demographic composition. SZ participants were estimated
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35 to have average range of IQ but, overall, scored lower than HC.
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37 Model 1: Classification of SWMT Performance Accuracy

38 *Healthy Normal Sample*

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42 SVM Model 1 identified frontal (Fz) gamma activity during encoding and occipital (Oz)
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44 theta 2 during retrieval as the primary EEG features associated with SWMT accuracy in the HC
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46 sample (Table 2). Additional features retained in the model had weightings of .10 or less and
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48 were not regarded as meaningful for further analysis. The negative valence of feature weights
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50 indicated that higher values for each preceded incorrect behavioral responses. Model
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52 classification accuracy was 84% and all additional performance statistics (F1 score = 0.96,
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54 precision = 0.92, recall = 1.0, estimated AUC of ROC = 0.98), suggested excellent model fit and
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56 stability. Cross-validation of this model applied to SZ data yielded lower, yet acceptable model,
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4 classification accuracy (74%) and performance statistics (F1 score = 0.77, precision = 0.68,
5 recall = 0.9, estimated AUC of ROC = 0.84). Accordingly, primary features determining SWMT
6 performance in HC also applied to SZ; however, an overall decrease in model performance
7 suggested that other or additional features were explanatory for SZ.
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11 To further assess the stability of SVM Model 1 based on HC data, the analysis was
12 repeated with features entered separately by stage of WM processing (i.e., baseline, encoding,
13 retention, retrieval). This analysis was conducted to determine whether experimenter decisions
14 regarding method of feature entry (i.e., 60 features entered simultaneously vs. 15 features
15 entered into 4 separate models) would substantially influence the outcome of feature selection.
16 Overall, the two approaches converged on the same features (Table 3). As observed with
17 simultaneous entry of 60 EEG features, frontal gamma during encoding was the feature most
18 highly weighted in predicting SWMT accuracy. Notably, the only two features identified at the
19 encoding stage with non-zero weightings both involved gamma activity, the second feature
20 being centrally distributed gamma, and together predicted SWMT trial performance with 96%
21 accuracy. Retrieval stage features also predicted SWMT with high accuracy (88%) based
22 primarily on occipital activity in gamma and theta 2 ranges (Table 3). In this case, the ordering
23 of features differed slightly from the model constructed by simultaneous entry in that theta 2,
24 rather than gamma, was most highly weighted. Furthermore, modeling data independently
25 according to WM stage identified features that were evidently suppressed by the primary
26 features of the original model. No feature representing the pre-trial baseline stage entered the
27 original model when applied to HC data; however, a contribution of baseline activity accounted
28 for almost entirely by central theta (feature weight = -1.13), in association with inaccurate
29 performance, was identified when modeled independently. Finally, the contribution of retention
30 stage activity to performance was best characterized by central theta 1, both when features
31 were modeled simultaneously (Table 2, 3rd ranked feature) and independently according to WM
32 stage.
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Schizophrenia Sample

Many more features entered the model with non-zero weighting In the SZ sample data (Table 4), with central and frontal gamma during encoding identified as the primary classifiers of SWMT accuracy. As observed in the HC sample data, the valence of coefficients indicated that higher values for these features preceded incorrect behavioral responses. Interestingly, beta activity during retrieval was also identified as a predictor of trial accuracy but with a positive coefficient, indicating that higher activity preceded correct behavioral responses. Theta 1 during retention and theta 1 and gamma activity during retrieval entered as negative predictors of trial accuracy with weightings above .5. Overall classification accuracy was 80% and model performance statistics (F1 score = 0.80, precision = 0.78, recall = 0.83, estimated AUC of ROC = 0.88) suggested good fit and stability. Importantly, although SVM modeled directly on SZ data performed slightly better than when parameters extracted from HC Model 1 were applied to SZ data (i.e., F1 scores of 0.80 and 0.77, respectively), gamma activity at encoding received the highest weightings in both cases.

Model 2: Classification of Diagnostic Status

Features selected by SVM models used to classify diagnostic status (SZ labeled +1 and HC labeled -1) based on correct and incorrect behavioral responses are presented in Tables 5 and 6, respectively. Overall classification accuracy of 79% was achieved by EEG features selected from correct response trials, with higher values of frontal and central theta at baseline associated with SZ group membership (Table 5). Gamma activity during retrieval and encoding stages also entered the model but with relatively low weightings. Performance statistics of this diagnostic classification model were acceptable (F1 score = 0.87, precision = 0.77, recall = 1, estimated AUC of ROC = 0.77). SVM modeled on incorrect trials (Table 6) identified frontal alpha at retrieval as the highest weighted feature, with a near-zero contribution of central gamma during encoding. The valence of coefficients indicated that higher values were associated with HC group membership. Performance statistics of this diagnostic classification

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4 model using incorrect trial data were exactly identical to those of the other model using correct
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6 trial data. Taken together, these findings are interpreted to suggest that SZ is generally
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8 distinguished from HC by elevations of low-frequency (theta 1) activity at pre-trial baseline, and
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10 evidence less engagement of alpha during retrieval than HC, particularly when WM load
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12 exceeds capacity (i.e., incorrect responses).
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14 Concurrent and External Validity

15 *SVM Model 1*

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18 As a test of concurrent validity based on classification method, EEG features selected by
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20 SVM Model 1 in HC data (Table 2) were submitted to stepwise linear regression as predictors of
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22 SWMT total score in the full sample of HC and SZ participants (N=52). The model was highly
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24 statistically significant ($F_{(4, 47)} = 37.67, p < 0.0005, R = 0.87$) and explained 76% of the variance
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26 in SWMT score (Figure 2). Central theta 1 activity during retention in correct trials entered as
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28 the first step, frontal gamma activity during encoding in correct trials as the second step, frontal
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30 gamma activity during encoding in incorrect trials as the third step, and central theta 1 activity
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32 during retention in incorrect trials as the fourth and final step (Table 7). Obtained beta and
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34 partial correlation coefficients suggested that when participants answered incorrectly,
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36 presumably challenged by higher WM load, performance was associated with increases in
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38 frontal gamma during encoding and central theta 1 during retention (beta = 0.38 and 0.39,
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40 partial $r = 0.51$ and 0.48 , respectively), while lower activation of these features was required on
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42 trials answered correctly (beta = -0.44 and -0.55, partial $r = -0.62$ and -0.61 , respectively). The
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44 same EEG features were retained, with exactly the same model coefficients, when the
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46 regression analysis was repeated by replacing the predictors with the 1st ranked feature of each
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48 WM stage (Table 3).
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55 To examine external validity of the EEG features derived by SVM, the same regression
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57 model was repeated to predict MCCB WM Composite (Figure 3) and CPT-IP (Figure 4) scores
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59 in separate analysis. MCCB WM Composite score was predicted ($F_{(2, 49)} = 17.39, p < 0.0005, R$

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4 = 0.64) with 42% of variance explained by two features; frontal gamma activity during encoding
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6 in correct trials ($R^2 = 0.31$, $F_{(1, 50)} = 23.92$, significant F change < 0.0005) and central
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8 theta 1 activity during retention in correct trials ($R^2 = 0.42$, R^2 change = 0.09, $F_{(1, 49)} =$
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10 7.67, significant F change = 0.008). The direction of association was consistent with previous
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12 models, with frontal gamma at encoding (beta = -0.59, partial $r = -0.61$) and central theta 1 at
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14 retention (beta = -0.30, partial $r = -0.37$) associated negatively with working memory test
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16 performance. The CPT-IP was selected as an additional cross-validation measure due to
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18 dependence of this task on visual encoding and retrieval processes similar to the SWMT. CPT-
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20 IP performance was predicted with 39% of variance explained ($F_{(3, 48)} = 10.15$, $p < 0.0005$, $R =$
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22 0.62) based on three features; frontal gamma activity at encoding in correct trials as the first
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24 step ($R^2 = 0.19$, $F_{(1, 50)} = 11.54$, significant F change = 0.001), central theta 1 activity at
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26 retention in correct trials as the second step ($R^2 = 30$, R^2 change = 0.11, $F_{(1, 49)} = 7.90$,
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28 significant F change = 0.007), and occipital gamma activity at retrieval in incorrect trials as the
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30 third step ($R^2 = 39$, R^2 change = 0.09, $F_{(1, 48)} = 6.89$, significant F change = 0.012).

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32 Consistent with prior models, beta and partial correlations for frontal gamma during encoding
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34 and central delta during retention in correct trials were negatively associated with CPT-IP AGT
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36 (beta = -0.45 and -0.32, partial $r = -0.50$ and -0.37, respectively) while occipital gamma during
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38 retrieval in incorrect trials entered with positive coefficients (beta = 0.30, partial correlation =
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40 0.35). These results confirmed that EEG features modeled on SWMT performance are
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42 generalizable with respect to neuropsychological measures of working memory and visual
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44 attention.
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50 51 *SVM Model 2*

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53 To cross-validate the diagnostic classification accuracy of SVM Model 2, derived
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55 features (Tables 5 and 6), were submitted to discriminant function analyses of diagnostic
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57 membership (i.e., HC vs. SZ) using stepwise entry. The overall Wilk's lambda, $\Lambda = 0.59$, $\chi^2(df =$
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59 4) = 25.67, $p < 0.0001$, indicated that there was a significant group-wise difference by diagnosis
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4 across four retained EEG features, with group centroids of 1.43 and -.48 for HC and SZ,
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6 respectively. The correlation structure of the discriminant function (Table 8) indicates that HC
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8 was classified with higher frontal alpha at retrieval and central gamma at encoding on incorrect
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10 trials, while SZ was associated with higher frontal theta 1 at baseline and central gamma at
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12 retrieval on correct trials. Overall diagnostic classification accuracy in the full sample was 87%
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14 (sensitivity 90%, specificity 77%) with positive predicative power (SZ diagnosis) of 92% and
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16 negative predictive power of 71% probability. Leave-one-out cross-validation of this model
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18 replicated classifications with 83% accuracy.
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24 **DISCUSSION**

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26 The primary aim of the current study was to evaluate the utility of machine learning
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28 methodology, specifically SVM, as a novel approach of EEG feature selection. EEG data
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30 involves many more variables than can be feasibility evaluated using conventional between-
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32 groups statistical contrasts, a problem that requires experimenter decisions guiding *a priori*
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34 selection of features submitted to hypothesis testing. In doing so, questions remain as to
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36 whether the selected features, among an extensive range of possibilities, are indeed those most
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38 critical to the questions asked of the data. Machine learning approaches, in contrast, offer the
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40 benefit of considering all data and empirically determining the most relevant features from all
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42 possible solutions. In this way, machine learning solutions represent a paradigm shift from
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44 rationally deductive to data inductive methodology.
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49 The current study employed machine learning classification to identify (1) EEG features
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51 predictive of SWMT accuracy in healthy adults, (2) EEG features predictive of SWMT accuracy
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53 in schizophrenia, and (3) controlling for SWMT accuracy, EEG features that distinguished
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55 healthy from schizophrenia group status. Using 1-norm SVM classification, and 60 features
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57 based on SWMT stage (4; baseline, encode, retain, retrieve), EEG frequency band (5; theta 1,
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59 theta 2, alpha, beta, gamma), and electrode site (3; Fz, Cz, Oz), frontal gamma-band activity at
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4 encoding was identified as the primary classifier of trial accuracy (Tables 2 & 3), while frontal-
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6 central gamma also contributed substantially to classifiers constructed by diagnostic status
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8 (Table 8). In addition, the presence of low-frequency activity during the pre-stimulus baseline
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10 and activation of alpha during memory retrieval were identified as important diagnostic
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12 differences (Tables 5 & 8). In each case model performance was assessed by cross-validation
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14 and determined to adequately fit the data based on several metrics (i.e., F1-score, precision,
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16 recall, and estimated area under the ROC curve). Importantly, the EEG features identified by
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18 SVM seem both plausible and generalizable given prior literature reports regarding the role of
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20 gamma and alpha activity in working memory function and commonly higher low frequency
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22 activity in resting EEG of individuals with schizophrenia.
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27 Published reports describe an upward modulation of gamma activity in response to
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29 higher working memory load in healthy participants, and an overall attenuation of gamma with a
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31 failure to modulate at higher memory loads in schizophrenia (Basar-Eroglu, Brand, Hildebrandt,
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33 Kedzior, et al., 2007). Our data partially support this finding but with an important difference in
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35 interpretation. As shown in Figure 5, significant upward modulation of frontal gamma in *incorrect*
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37 relative to *correct* trials is evident in schizophrenia and healthy samples alike. When tested
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39 statistically, encoding gamma was found to be significantly increased in incorrect relative to
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41 correct trials for both groups (paired-samples t tests; HC, $t(11) = 5.37, p < 0.0005$; SZ, $t(39) =$
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43 $7.01, p < 0.0005$); however, the strength of this upward modulation was significantly greater in
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45 healthy participants (multivariate tests; a significant Correct-Incorrect x Group interaction effect,
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47 Wilk's $\Lambda = 0.86, F(1, 50) = 8.46, p = 0.005$). However, of note, gamma modulation with accuracy
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49 appears to be evident by the time the first stimulus of the memory set is presented (i.e., by 1200
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51 ms). Therefore, current results are not interpreted purely in context of a memory load effect.
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54 Rather, given that differences in gamma preceding correct and incorrect trials are already
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56 present and persist in the early stage of encoding, elevations of gamma may reflect changes in
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58 cognitive preparedness that occur from trial to trial. This interpretation is not entirely inconsistent
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4 with prior findings associating upward modulation of gamma at increased memory load with
5 better working memory function. We suggest that the early presence of increased gamma
6 preceding incorrect trials could indicate that gamma has already elevated to peak level, limiting
7 the ability to further increase gamma with encoding of new information and, thereby, reducing
8 trial accuracy. Further examination of reasons for elevated gamma preceding incorrect trials is
9 beyond the scope of the current analysis, but possible explanations could include the extended
10 maintenance of information, or perhaps cognitive response to error feedback, from the
11 preceding trial. Pertinent to the current analysis, it would appear that individual differences in the
12 overall magnitude of encoding gamma, found to be greater in healthy than schizophrenia
13 groups, is better represented in incorrect than correct trials and, for this reason, activity
14 preceding incorrect trials was found most predictive of SWMT performance in both groups.
15 Consistent with prior findings (Basar-Eroglu, Brand, Hildebrandt, Karolina Kedzior, et al., 2007;
16 Schmiedt, et al., 2005), it does appear that working memory impairment in schizophrenia does
17 relate, in part, to a restriction of range in the ability to upregulate gamma in response to
18 cognitive challenge.

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38 Furthermore, SVM also identified central gamma activity during encoding as the most
39 highly weighted feature predicting SWMT performance in schizophrenia, suggesting gamma
40 activity extended over greater cortical areas than in healthy participants. Studies of postmortem
41 brain tissue have provided strong evidence that the GABAergic system of left DLPFC is
42 impaired in schizophrenia (Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991; David A.
43 Lewis, Curley, Glausier, & Volk, 2012; D. A. Lewis & Gonzalez-Burgos, 2008). GABAergic
44 interneurons appear to be crucial elements in the generation of synchronous neuronal activity in
45 the gamma bands of EEG (Hajos et al., 2004; Klausberger et al., 2003; McBain & Fisahn, 2001;
46 Traub et al., 2001; Whittington & Traub, 2003). Results of phase locking and coherence
47 analyses in schizophrenia patients further suggest that neuronal network functioning is impaired
48 due to a failure of neuronal synchrony in gamma frequency band (Spencer et al., 2003). Based
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4 on present and previous studies, we speculate that extension of gamma activity from frontal to
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6 central cortical areas in patients may be compensatory in response to inefficiency of frontal
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8 activity generated in the DLPFC (Chen et al., 2014; David A. Lewis, et al., 2012).
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11 Data-driven approaches for EEG feature selection would seem particularly useful, if not
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13 essential, when working with complex cognitive experiments that entail several stages of
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15 information processing, as well as for common experiments that can nonetheless be analyzed
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17 based on spectral decomposition of EEG in multi-channel recordings of spatially disparate
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19 events. Although 1-norm SVM classification was selected for the current study, this is by no
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21 means the only approach to consider and research in this area could be expanded by
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23 comparing and optimizing other machine learning approaches for use with EEG data. Graphical
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25 models, which take into account some network correlations, or Gaussian Process regression,
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27 which can identify nonlinear relationships in the data, may be other promising approaches. A
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29 future direction for analysis based on SVM is to develop new machine learning methods that
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31 can optimize simultaneous modeling of the spatial and temporal distribution of the EEG
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33 features, to better account for change in EEG frequency amplitude at different scalp locations
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35 over time. Feature selection using such spatial-temporal modeling will become more precise by
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37 accommodating single-trial data and larger electrode arrays.
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42 The current study was limited in terms of sample size, particularly of healthy community
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44 participants and, therefore, models derived may not be optimized for the broad range of abilities
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46 represented in the population at large. Our objective in analyzing the current data set was
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48 primarily to demonstrate how SVM could be applied to data analytic questions that involve many
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50 potential dependent measures. As an analytic solution for big data problems, the performance
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52 of SVM improves with larger and, presumably, more stable datasets inclusive of the full range of
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54 possible values on the parameters involved. Nevertheless, cross-validation of the features
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56 selected by SVM with regard to external measures of working memory performance and
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58 diagnostic classification by discriminant function suggested that the derived models performed
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4 well within the constraints of the current sample. EEG data modeled on SWMT performance in
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6 healthy participants explained 76% of variance in task performance across samples and
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8 demonstrated a linear relationship that appeared a good fit for schizophrenia data over the full
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10 range of performance (Figure 2). Of note, healthy participants generally responded to at least 70
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12 of 90 trials correctly, representing 78% accuracy. Individuals with schizophrenia who performed
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14 in this range also exhibited neural activity in the average to above-average range (i.e., standard
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16 score values of 0 and above) relative to the sample distribution, while EEG values were
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18 generally within 1 standard deviation below average for those performing below 78% accuracy.
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20 With larger samples, contributing to better overall normative estimates, it would be conceivable
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22 to construct neurophysiological test batteries comparable to standard neuropsychological tests
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24 that provide individual measures of performance on multiple domains based on precise
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26 measures of neural activity. This information could inform treatment selection and outcome
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28 measurement of interventions targeting cognitive impairment through computer-based training
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30 as well as task-related neurofeedback methods (Mishra & Gazzaley, 2014; Thomas, Vinod, &
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32 Guan, 2013).

37 **CONCLUSIONS**

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39 In summary, we conclude that SVM successfully identified EEG features associated with
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41 working memory performance that are consistent with, and rationally predicted, based on prior
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43 literature. Selected features highlight the roles of gamma activity during encoding and theta
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45 during memory retention as EEG components contributing similarly to Sternberg performance in
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47 both healthy and schizophrenia study samples. Importantly, these same features explained
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49 substantial portions of variance in working memory and visual attention ability when assessed
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51 by standardized neuropsychological tests, lending support to the external validity of these
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53 findings. Furthermore, SVM produced a diagnostic classifier achieving 87% accuracy in
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55 distinguishing individuals with schizophrenia. Gamma activity during encoding remained to be a
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57 primary feature distinguishing groups, with lower alpha during retrieval and increased theta
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4 during pre-stimulus baseline as additional features characterizing schizophrenia. These results,
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6 based only on data collected using the Sternberg task, compare favorably with another recent
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8 example of SVM applied to P300 and mismatch negativity task data, where nearly 85%
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10 classification accuracy was achieved (Laton et al., 2014), as well as to prior efforts to enhance
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12 diagnostic classification using multiple EEG experiments and traditional regression approaches
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14 (Johannesen, O'Donnell, Shekhar, McGrew, & Hetrick, 2013). Taken together, machine learning
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16 approaches, such as SVM, show considerable potential as an adjunctive analytic strategy for
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18 data reduction and feature selection of complex EEG datasets.
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Conflict of Interest

Authors JKJ, CMC, JR, JGK, and JB declare they have no conflict of interest.

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