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Cognitive abilities and 50 and 100 ms paired-click processes in schizophrenia

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Abstract

Objective—Abnormal 50 and 100ms event-related brain activity derived from paired-click procedures are a well established finding in schizophrenia. There is little agreement on whether ratio score (second click/first click) paired-click group differences reflect an encoding or gating abnormality. In addition, the functional implications of the ratio score deficit remain unclear. In the present study, EEG and MEG were used to examine paired-click measures as well as the cognitive correlates of paired-click activity.

Method—Electroencephalographic (EEG) Cz and whole-cortex magnetoencephalographic (MEG) data were acquired during the standard paired-click paradigm in 73 controls and 79 patients with schizophrenia. Paired-click ratio scores were obtained at 50ms (P50 at Cz, M50 at left and right superior temporal gyrus, STG) and 100ms (N100 at Cz, M100 at left and right STG). Subjects were administered a cognitive battery assessing attention, working memory, and long-delay memory. An IQ estimate was also obtained.

Results—Groups differed on ratio score and S1 amplitude measures. 50ms and 100ms ratio and S1 amplitude scores predicted variance in attention (primarily S1 amplitude), working memory, and long-delay memory. The attention findings remained after removing variance associated with general cognitive ability (i.e., IQ).

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Conclusions—Associations between paired-click measures and cognitive performance in patients supports 50ms and 100ms ratio and amplitude scores as clinically significant biomarkers of schizophrenia. In general, cognitive performance was better predicted by the ability to encode auditory information rather than the ability to filter redundant information.

Descriptors

sensory gating; schizophrenia; P50; N100; M50; M100; magnetoencephalography; cognition

1. Introduction

For more than 25 years the auditory paired-click paradigm has been used to study auditory processes in individuals with schizophrenia (1). Subjects are presented with two clicks (first click=S1, second click=S2) separated by 500ms, and the amplitude of the evoked 50ms (P50) and 100ms component (N100) to each click is typically measured at electrode Cz using EEG. An increased ratio score (S2/S1) is frequently observed in schizophrenia (2). The functional implications of the ratio score deficit are currently in dispute. There is little evidence of a relationship between P50 ratio scores and positive or negative symptoms in schizophrenia (3). A few studies have examined the association between paired-click ratio scores and cognitive measures, with some evidence of a relationship to processing speed (4), attention (5; 6; although see 7), and explicit and implicit memory (8).

There is also ongoing disagreement as to whether patient and control ratio score differences reflect encoding or gating abnormalities. A fundamental question is whether interpretations of ratio score phenomena should focus on S1 or S2. The S1 response is driven by encoding/attention processes, whereas the S2 response primarily reflects sensory gating/filtering. Although the paired-click ratio score deficit is often observed in the absence of group differences in S1, several studies have observed a decreased S1 response in patients at 50ms (e.g., 9; 10; 11; 12) and 100ms (e.g., 9; 13; 14; 15). de Wilde et al. (16) suggested that ratio and amplitude scores should both be investigated (see also 17).

There are at least two basic limitations to linking Cz activity and cognitive dysfunction. P50 recorded at the scalp is multi-determined, making it difficult to identify specific brain-performance relationships (18), and several studies have shown that the P50 Cz ratio score is not a reliable measure in traditional psychometric terms (e.g., 19; 20; 21; although see 22). Both limitations can be overcome using source-localization methods. Recent studies using magnetoencephalography (MEG) to localize sources of brain activity during the paired-click paradigm in controls and schizophrenia focused on M50 and M100, the magnetic manifestations of the P50 and N100 neuroelectric components, and established that bilateral superior temporal gyrus (STG) is the primary area active during the 50ms period (18; 23). Whereas group ratio score differences may be specific to the left-hemisphere STG at 50ms, bilateral STG deficits exist at 100ms (24). In addition, source-localized M50 STG ratios scores are reliable (21). In contrast to paired-click EEG studies, paired-click MEG studies have found relationships with clinical measures: negative symptoms correlated positively with right-hemisphere M50 ratio scores (25).

Since our original study examining the relationship between EEG/MEG 50ms ratio scores and cognitive abilities (26), our sample size has increased approximately fourfold. In addition, the Wisconsin Card Sorting Task, a test sensitive to prefrontal/executive function (27), was added to the cognitive battery. The present study examined the relationship between cognitive measures and EEG/MEG 50 and 100ms ratio scores. Whereas the 50ms component is thought to reflect bottom-up, pre-attentive processes (28; although see 29; 30, 31, 32), 100ms activity may reflect the onset of top-down modulation by frontal cortex (33;

34; 35), a hypothesis supported by studies that show that N100 amplitude is influenced by attentional manipulations (e.g., 33; 36; 37). Thus, 50 and 100ms ratio scores may be differentially related to cognitive tests.

In the present study, MEG and EEG were simultaneously collected during the paired-click paradigm and Cz and MEG-derived STG activity examined to uncover clinical relationships in a relatively large sample of controls and patients. The following hypotheses were pursued: (1) Replicating previous findings, patients with schizophrenia would show abnormally large P50, N100, left M50 and bilateral M100 ratio scores. (2) Based on 100ms paired-click findings reported in previous studies (e.g., 9; 38; 39), 100ms ratio score group differences would reflect an encoding deficit. Given variable 50ms amplitude findings, no predictions were made concerning 50ms S1 and S2 group differences. (3) Given that inadequate inhibition of redundant sensory information is thought to underlie attention dysfunction in patients with schizophrenia and that some studies have observed relationships between P50/M50 ratio scores and attention, higher 50ms and perhaps also higher 100ms ratio scores and S2 amplitudes would be associated with impaired performance on attention measures. (4) As Cz ratio scores are unreliable, P50 and N100 ratio scores would be less (if at all) related to cognitive performance. In contrast, although determined by multiple sources, the reliability of EEG S1 and S2 amplitude scores (20; 21) means that these EEG amplitude measures might show associations with cognitive performance.

2. Methods

2.1 Subjects

Seventy-nine subjects with chronic schizophrenia (17 female) and seventy-three control subjects (20 female) were recruited (Table 1). Recruitment procedures and inclusion/exclusion information are detailed in Edgar et al. (38) and Hanlon et al. (24); see also online Data Supplement Section for additional demographic information. In the patient group, 62 were treated with therapeutic doses of 2nd generation antipsychotics (11 on clozapine, 15 on olanzapine, 8 on aripiprazole, 12 on risperidone, 14 on quetiapine, 2 on ziprasidone), and 17 were receiving therapeutic doses of 1st generation antipsychotics (4 on fluphenazine, 12 on haloperidol, 1 on perphenazine). Fifty-four patients were diagnosed as paranoid subtype, 23 as undifferentiated subtype, and 2 as disorganized subtype.

2.2 Paired-Click Paradigm

The paired-click paradigm followed the protocol of Adler et al. (40), in which 3ms binaural clicks were presented in pairs (S1 and S2) with a 500ms inter-stimulus-interval (ISI) and a variable inter-trial interval (ITI) of 7–11s averaging 9s. The clicks were delivered through Entymotic earphones placed in each ear canal. The peak intensity of the click was presented 30–40dB above hearing threshold. If necessary, intensity was decreased to avoid elicitation of a startle reflex. Click pairs were presented until 150 trials were obtained without MEG/EEG artifact. The time to collect 150 paired-click trials did not differ between groups: control mean = 32.43 minutes, patient mean = 33.49 minutes.

2.3 EEG Data Collection

EEG was collected with Ag/AgCl electrodes. Impedances were below 10k. EEG was recorded using SynAmps and SCAN software (Neuroscan, Herndon, VA) with a bandpass filter (0.03–150Hz) and a 60Hz notch filter. Cz and left mastoid were referenced to right mastoid during recording and re-referenced offline to linked mastoids (41). Electro-oculogram (EOG; bipolar oblique: upper right and lower left sites) and electro-cardiogram (ECG; placed on collarbone) were also collected.

2.4 MEG Data Collection

MEG data were collected using a 122-channel biomagnetometer (NeuroMag Ltd., Helsinki, Finland; Ahonen, Hämäläinen, Kajola, Knuutila & Laine, 1992). EEG and MEG were collected simultaneously using NeuroMag acquisition software and hardware. After a bandpass filter (0.03–150Hz) and a 60Hz notch filter, EEG and MEG signals were digitized at 300, 467, or 500Hz (data acquisition software and hard drive were upgraded during the course of data collection, and digitization rate was increased). After the MEG session, structural magnetic resonance imaging (sMRI) provided T1-weighted, 3-D anatomic images using a 1.5T Picker Edge Imager. Details regarding on-line artifact rejection and other data collection procedures are provided in Hanlon et al. (24).

2.5 EEG ERP Analyses

Cz EEG P50 and N100 data were analyzed using custom Matlab programs. Individual S1 and S2 P50/N100 averages were created by visually inspecting the raw data from each trial offline and discarding trials with ocular or muscle artifact or excessive alpha-band activity occurring from 300ms preceding S1 to 300ms after S2. Filter parameters for P50 were: F_{stop}=3Hz, F_{pass}=5Hz for the high pass, and F_{pass}=50Hz, F_{stop}=60Hz for the low-pass. Filter parameters for N100 were: F_{stop}=1Hz, F_{pass}=2Hz for the high pass and F_{pass}=38Hz, F_{stop}=42Hz for the low pass. Each filter was applied twice, once in the forward and once in the reverse direction, to increase roll-off and preserve latencies. Pre-stimulus baseline activity, computed as the mean amplitude from −100 to −10ms, was removed.

The P50 response to S1 was defined as the most positive peak at electrode Cz occurring between 35 and 75ms post-stimulus. The P50 response to S2 was defined as the most positive peak that occurred within 10ms of S1 peak latency. P50 S1 and S2 amplitudes were scored as the difference between the peak and the preceding negativity (N40) to ensure that the P30 component was not selected (3). The N100 S1 response was defined as the most negative trough at Cz occurring between 75 and 130ms post-stimulus. The N100 S2 response was defined as the most negative trough that occurred within 10ms of S1 peak latency. N100 S1 and S2 responses were scored as the difference between the trough and the preceding positive peak (P50). Ratio scores were calculated for P50 and N100 by dividing S2 scores by S1 scores.

2.6 Magnetic Source Analysis

To coregister MEG and sMRI data, three anatomical landmarks (nasion and right and left preauriculars) as well as an additional 50+ points on the scalp were digitized for each subject using the Probe Position Identification System (Polhemus, Colchester, VT). The three fiducials were identified in the subject's sMRI, and a transformation matrix that involved rotation and translation between the MEG and sMRI coordinate systems was used.

A trial was rejected automatically if there was magnetic activity greater than 1750fT/cm in any MEG channel or if there was electrical activity +/− 110μV peak to peak in the EOG channel. A −100 to −10ms baseline adjustment was applied to averaged MEG data. Prior to source localization, a 4–55Hz bandpass filter was applied for M50 and a 2–40Hz bandpass for M100. In a few subjects, the high-pass filter setting was adjusted +/−1Hz to improve source localization.

Determination of the strength, location, and peak latency of M50 sources (35–75ms post-stimulus) and M100 sources (75–130ms post-stimulus) in left and right hemispheres was accomplished by fitting a dipole separately over the left and right hemispheres using subsets of 34 planar gradiometers over the temporal lobe. For modeling S1 M50 and S1 M100, 10ms of data surrounding the M50 and M100 peaks were selected. Equivalent current

dipoles were determined separately for each hemisphere. Only equivalent current dipoles with goodness-of-fit values (a measure of the correlation between calculated and measured signal) exceeding 70% for S1 were accepted. Peak strength of the source (measured in nano-Ampere-meters, nAm) over the 10ms period was then determined. S2 M50 and S2 M100 measures were identified using a procedure (42) in which the location of the S2 dipole was assumed to be the same as that of the S1 dipole. To assure that the same component was chosen for S2 and S1, S2 latency was required to be within +/− 10ms for M50 and M100. In the event that no identifiable peak was available, S2 amplitude was scored at the same latency as S1. M50 and M100 ratio scores for each hemisphere and component were expressed as S2 dipole peak source strength divided by S1 dipole peak source strength.

2.7 Cognitive Measurements

Both groups were administered cognitive tests to assess several cognitive domains: Wisconsin Card Sorting Test (43), Wechsler Adult Intelligence Scale III Digit Span Back (44), Connors' version of the Continuous Performance Test (45), Trail Making Test part A (46), 4) Rey's Auditory-Verbal Learning Test (47), and 5) Wechsler Memory Scale Visual Reproduction (48). The Shipley Institute of Living Scale (49) was administered to estimate IQ (50). An attention composite was derived from Trails A time (inverse), Continuous Performance Test hit rate, and Continuous Performance Test d'. *A* working memory composite was derived from Wisconsin Card Sorting Task Perseverative Errors (inverse; 27) and Digit Span Back total recall. Finally, a long-delay memory composite was computed from Rey's Auditory-Verbal Learning Test list A delayed recall and WMS-R visual reproduction delayed recall. Composite scores for attention, working memory, and long-delay memory were computed by z-scoring each test, adding z-scores within a domain, and calculating the z-score mean.

2.8 Statistical Analyses

T-tests and ANOVAs examined group effects on Cz and MEG amplitude and ratio score measures. To examine how cognitive ability may differ as a function of psychiatric status and ratio scores, hierarchical regression was done in which ratio score was entered first, Group second, and their interaction last, with each cognitive composite measure (attention, working memory, delayed memory) analyzed separately. For each cognitive measure, regressions were run separately for the two Cz ratio scores (P50 and N100) and four MEG ratio scores (left- and right-hemisphere M50 and M100). In addition, for each cognitive measure, separate regressions were run for S1 and S2 amplitude scores to assess whether relationships were specific to the ratio score or were instead better reflected by S1 or S2. As the primary goal was to identify associations between ratio scores and cognitive performance, ratio scores were entered first in the regressions. Results, however, were essentially the same when group was entered first and ratio scores second. See online Data Supplement for information on outliers and EEG/MEG inter-rater reliability.

3. Results

3.1 P50/N100 Ratio and Amplitude Scores (Table 2)

Cz P50 ratio scores were larger in patients than controls, $t(140)=-2.17$, $p=0.03$. No P50 S1 or S2 amplitude main effects or interactions were observed. Cz N100 ratio scores were larger in patients than controls, $t(144)=-2.63$, $p=0.01$. A Group × Stimulus (S1, S2) ANOVA on N100 source strength, $F(1,144)=12.08$, $p<0.01$, showed a larger S1 response in controls than patients, $F(1,144)=12.67$, $p < 0.01$.

3.2 M50/M100 Ratio and Source Strength (Table 2)

No M50 ratio score main effects or interactions were observed. Dissection of a Group × Hemisphere × Stimulus (S1, S2) M50 source strength interaction, $F(1,135)=3.97$, $p=0.05$, showed a larger M50 S1 minus S2 difference in controls than patients in the left hemisphere, $F(1,135)=4.57$, $p=0.03$. A Group × Hemisphere ANOVA on M100 ratio scores showed a Group main effect (controls < patients), $F(1,121)=11.92$, $p<0.01$. A Group × Hemisphere × Stimulus ANOVA on M100 source strength showed a larger S1 response in controls than patients, $F(1,121)=4.67$, $p=0.03$.

Repeated-measures ANOVAs assessed paranoid and undifferentiated subtype group ratio score differences. There were no significant S1, S2 amplitude, or ratio score group differences (all $p > 0.05$).

3.3 Cognitive Measures

Hierarchical regression analyses examined the relationship between Cz and MEG ratio scores and the three cognitive composites (zero-order correlations between ratio scores and individual cognitive tests are reported in the online Data Supplement). As expected, Group (entered second) accounted for significant incremental variance and showed that patients with schizophrenia performed more poorly than controls on all three cognitive composites (all $p <0.001$; the percentages of variance accounted for by group differ slightly depending on whether P50, N100, M50, or M100 was the predictor added second, because the number of subjects excluded in P50, N100, M50, and M100 analyses differed slightly) even after accounting for variance due to ratio score (Table 3). As N100 and M100 S1 amplitude and M50 S1 and S2 values contributed to group differences in ratio scores (Table 2), hierarchical regressions also examined the relationship between S1 and S2 amplitude and the cognitive composite to characterize ratio score findings (Table 4).

3.3.1 Attention (Tables 3 and 4)—Smaller Cz P50 ratio scores predicted better performance in attention composite scores, $F(1,107)=10.03$, $p<0.01$. Examining P50 S1 and S2 amplitude scores, larger P50 S1 amplitude predicted better performance on attention tests, $F(1,111)=7.05$, $p<0.01$. Smaller Cz N100 ratio scores also predicted better performance on tests of attention, $F(1,111)=4.61$, $p=0.03$. A combination of S1 and S2 amplitude scores seemed to contribute to the N100 ratio score finding, as larger N100 S1 amplitude, $F(1,113)=19.78$, $p<0.001$, and smaller S2 amplitude, $F(1,117)=4.14$, $p=0.04$, predicted better performance on attention tests. Regressions run entering S1 first and S2 second or vice versa indicated that only S1 accounted for significant unique variance in attention.

Similar to Cz P50, smaller left M50 ratio scores predicted better performance in the attention composite, $F(1,107)=8.53$, $p<0.01$. Dissection of a marginal Group × Left M50 S1 source strength interaction, $F(1,107)=3.34$, $p=0.07$, indicated that left M50 S1 source strength correlated with better performance on the attention composite only in patients, $r(55)=0.29$, $p=0.03$. A Group × Right M50 ratio score interaction, $F(1,102)=4.17$, $p=0.04$, indicated that larger right M50 ratio scores were associated with worse performance on attention tests only in patients, $r(53)=-0.27$, $p=0.04$.

Similar to Cz N100, smaller left M100 ratio scores predicted better performance on the attention composite, $F(1,86)=14.81$, $p<0.001$. A left M100 S1 Group × Source Strength interaction, $F(1,84)=5.71$, $p=0.02$, indicated a relationship between S1 source strength and better attention performance only in patients, $r(43)=0.31$, $p=0.04$. A right M100 ratio score interaction term, $F(1,84)=7.33$, $p<0.01$, indicated a relationship between smaller right M100 ratio scores and better performance on attention tests only in patients, $r(43)=-0.39$, $p<0.01$.

Right M100 S1 and S2 amplitude did not predict variance in attention performance. Figure 2 shows S1 amplitude and attention composite scatter plots for 50ms and 100ms Cz S1 scores and for 50ms and 100ms left STG scores (for all other cognitive measures, scatter plots are included in the Online Supplement).

3.3.2 Working Memory (Tables 3 and 4)—Smaller P50 ratio scores predicted better working memory performance, $F(1,95)=10.25$, $p<0.01$, with increased P50 S1 amplitude accounting for this relationship, $F(1,95)=7.05$, $p<0.01$. Smaller N100 ratio scores predicted better working memory performance, $F(1,102)=4.22$, $p=0.04$, with increased N100 S1 amplitude accounting for this relationship, $F(1,100)=5.93$, $p=0.02$.

Left and right M50 ratio scores accounted for variance in the working memory composite (left: $F(1,94)=7.56$, $p<0.01$; right: $F(1,93)=5.39$, $p=0.02$). Left and right M100 ratio scores also accounted for significant variance (left: $F(1,86)=15.51$, $p<0.001$; right: $F(1,86)=4.58$, $p=0.04$). In both groups, smaller left and right M50 and M100 ratio scores were associated with better working memory performance. None of the MEG amplitude measures was associated with working memory.

3.3.3 Verbal and Visual Long-Delay Memory (Tables 3 and 4)—P50 and N100 ratio scores did not predict variance in the long-delay memory composite. For the amplitude scores, only larger N100 S1 amplitude scores predicted better long-delay memory composite scores, $F(1,99)=4.30$, $p=0.04$.

Left/right M50 ratio scores did not predict delayed memory performance. Smaller left and right M100 ratio scores, however, were associated with better performance on delayed memory tests (left: $F(1,83)=4.41$, $p=0.01$; right: $F(1,84)=0.06$, $p=0.03$). None of the S1 or S2 source strength values predicted additional variance in long-delay memory performance.

3.3.4 IQ and Hierarchical Regressions (Table 5)—To assess the degree to which performance in cognitive domains predicted performance in ratio scores after removing variance associated with general cognitive ability, hierarchical multiple regressions were conducted with IQ entered first. In separate tests, in the second block the (1) composite measure of working memory, (2) composite measure of attention, or (3) composite measures of delayed memory was entered. Group was entered third. The Group × Composite score interaction term was entered fourth.

Regression results for the second (Cognitive Composite) and fourth block (Group × Cognitive Composite) are reported in Table 5. With IQ variance removed, the attention composite predicted additional variance in P50 ratio scores, $F(1,106)=5.44$, $p=0.02$. The attention composite score did not predict additional variance in N100 or in left or right M50 ratio scores. The attention composite, however, predicted additional variance in left ($F(1,85)=5.26$, $p=0.02$) and right ($F(1,85)=9.46$, $p<0.01$) M100 ratio scores. The Group × Attention composite score interaction added 5% of the variance in the right M100 ratio scores, $F(1,83)=5.34$, $p=0.02$, with simple-effects analysis showing that attention continued to predict significant variance in the ratio score only in the patient group, $R^2=17\%$, $p< 0.01$.

With IQ variance removed, working memory did not predict variance in P50 or N100 ratio scores. The working memory composite predicted additional variance in right M50 ratio scores, $F(1,92)=3.94$, $p=0.05$, and left M100 ratio scores, $F(1,85)=4.39$, $p=0.04$. The working memory composite did not predict variance in left M50 or right M100 ratio scores. With IQ variance removed, the delayed memory composite did not predict variance in P50, N100, M50, or M100 ratio scores.

4. Discussion

As hypothesized, patients with schizophrenia had larger P50 Cz ratio scores. Although the M50 ratio score Group main effect was not significant, left but not right M50 S1 minus S2 group differences were observed, supporting a left M50 paired-click deficit (Hypothesis 1). Whereas the 50ms S1 and S2 values reported in Table 2 as well as the Figure 1 source waveforms suggest a left M50 S1 effect, analyses indicated that ratio score group differences were not explained solely by either a pure encoding/attention deficit (driven by S1) or a pure gating deficit (driven by S2). As such, present findings do not resolve the 50ms ratio score debate. Patients also showed larger N100 Cz ratio scores. For M100, ratio score group differences were observed bilaterally. As hypothesized, 100ms ratio score group differences were due to a smaller S1 response in patients (Hypothesis 2). Thus, ratio score group differences at 100ms were explained by an encoding/attention deficit.

Turning to the functional significance of the paired-click findings, as 50ms activity is thought to reflect sensory encoding, a relationship between 50ms and perhaps also 100ms paired-click activity and attention was hypothesized, such that the less that redundant sensory information was inhibited (i.e., larger S2), the greater the attentional impairment (Hypothesis 3). In patients and controls, larger Cz P50 and N100 ratio scores were indeed associated with poorer performance on attention tests. For M50 and M100 STG measures, paired-click ratio scores were also associated with the attention composite, with this relationship observed primarily in patients. The second part of Hypothesis 3 was not supported, as worse performance on attention tests was associated with a decreased S1 response rather than an increased S2 response (with the M50 relationship again observed only in patients). Thus, attention performance was predicted by the patient's ability to encode auditory information rather than their ability to filter redundant information. The lack of a STG S1 amplitude/attention association in controls may reflect the fact that most of the control subjects had normal STG activity. In any case, after removing variance in ratio score measures associated with general cognitive ability, many of the 50 and 100ms associations with attention remained, suggesting that the association with attention was somewhat unique.

Ratio scores and amplitudes were also associated with working memory and verbal and visual long-delay memory. Only working memory added significant variance beyond that accounted for by general cognitive ability (IQ). Thus, findings also reveal a nonspecific association between 50 and 100ms electrophysiological measures (primarily S1) and general cognitive ability. Interestingly, associations were observed only with the ratio score or S1, again generally suggesting an association between encoding ability and cognitive performance.

Finally, Hypothesis 4 received moderate support. First, to the extent that the Cz paired-click measure reflects brain activity only from primary/secondary auditory areas (especially true of 50ms activity, see 23), present results indicate that STG findings provide more information about paired-click group differences. For example, although P50 ratio score group differences were observed, analyses of STG sources suggested that this was due to left and not right STG abnormality in patients. In contrast, as M100 STG ratio score group differences were observed in both hemispheres, Cz N100 more directly mirrored STG findings. Second, whereas associations between P50 and N100 Cz ratio and amplitude scores and cognitive abilities were observed, STG sources again provided more information. For example, although P50 and N100 S1 scores were associated with attention (even after removing IQ variance), STG analyses suggested S1 associations only in the left hemisphere and only in patients. To the extent that a detailed understanding of the specific brain areas

that are associated with clinical measures is important, present findings suggest the need to examine source rather than scalp activity.

Although in the present study MEG provided more specific information, MEG and EEG findings were often similar. Thus, it is somewhat puzzling that so few studies have reported associations between paired-click activity and cognitive ability. There may be insufficient power in most EEG studies. To take the most extreme Cz example, although N100 was consistently associated with cognitive measures here, N100 ratio scores explained, at most, 5% of the variance in the cognitive scores. Considering a correlation of 0.22 (~5% of the variance), a minimum of ~150 subjects would be needed to obtain a significant correlation (alpha=0.05, power=0.80), in line with the present sample (controls+patients) but far larger than samples in previous studies (see 3). Present findings suggest a larger effect size and thus a greater chance of observing associations when examining source activity. For example, left M100 R^2 values of ~15% were consistently observed for attention and working memory measures, for which a sample size of 50 subjects would suffice (alpha=0.05, power=0.80). It should be noted that present M50 findings in controls did not replicate Thoma et al. (26), where in a much smaller but overlapping sample of controls worse M50 gating was associated with better working memory performance. The number of control subjects in present analyses has increased fourfold since Thoma et al. Present findings underscore the need to recruit relatively large subject groups to test relationships between paired-click measures and cognitive performance.

Although in the present study associations between auditory brain processes and cognitive ability were observed, the study design precludes causal claims. In addition, it is possible that a third, unstudied measure could account for electrophysiological and cognitive abnormalities. In particular, there is evidence to suggest that the observed relationship between abnormal STG paired-click activity and impairment on cognitive tests in patients with schizophrenia may both be related to abnormal STG anatomy. In particular, decreased STG gray matter is observed in many published studies (e.g., 51; 52; 53; 54; 55). As 50 and 100ms paired-click activity directly reflects gray-matter activity, an examination of the relationship between 50 and 100ms paired-click activity and STG structural measures is of interest. Available evidence also provides support for a relationship between STG gray-matter structural abnormalities and functional impairment as assessed by psychophysiological measures as well as clinical measures. For example, reduced left temporal auditory P300 has been associated with smaller left posterior STG gray-matter volume in chronic (56) and first-episode schizophrenia (57). In addition, left posterior STG gray-matter volume reduction has been associated with severity of thought disorder (58), and a recent MRI study demonstrated that the severity of thought disorder was negatively correlated with activation changes in left BA 22 (59). Thus, gray-matter abnormalities may contribute to abnormal electrophysiology measures as well as to patient symptoms and cognitive abilities. In the present study, the observed left-hemisphere M50 group differences may be due to structural STG hemisphere differences. Finally, it is worth noting that, in the present study, only S1 was associated with cognitive ability. To the extent that S1 activity primarily reflects local processes, whereas S2 may reflect local activity as well as inhibitory activity from the reticular formation and the thalamus (60; 61; 62), hippocampus (63; 64), or frontal cortex (35), S1 and S2 processes would be expected to differentially associate with cognitive measures.

With regard to previous studies, as detailed in the Introduction, a few other studies have observed associations between Cz P50 and attention (4; 5). In the present study a clear association between 50 and 100ms ratio scores and performance on attention tests was observed, although primarily accounted for by S1 amplitude. To our knowledge, few studies have examined relationships between Cz N100 paired click activity and cognitive measures

(with no studies examining associations with attention). Examining controls and patients with schizophrenia, Boutros et al. (65) reported a relationship between N100 ratio scores and prefrontal cortex function (performance on the Wisconsin Card Sorting Task, 27). In the present study, although no significant association was observed between Wisconsin Card Sorting Task performance and N100 ratio scores, an association between Wisconsin Card Sorting Task performance and left and right STG M100 ratio scores was observed in patients (see online Data Supplement). Another study examining only healthy controls observed associations between N100 S1 and ratio scores and a measure of working memory (6), a relationship related more directly to stimulus processing properties (S1) than to N100 sensory gating. Present findings generally replicated this finding, observing an association between Cz N100 S1 amplitude and working memory performance.

In sum, present findings indicate that the paired-click abnormalities predict cognitive deficits. In many instances, cognitive impairments were more closely associated with encoding processes. The use of MEG source localization alongside scalp EEG provides larger effect sizes and more inferential specificity, which may explain why EEG-only studies have been inconclusive regarding an association between paired-click activity and clinical measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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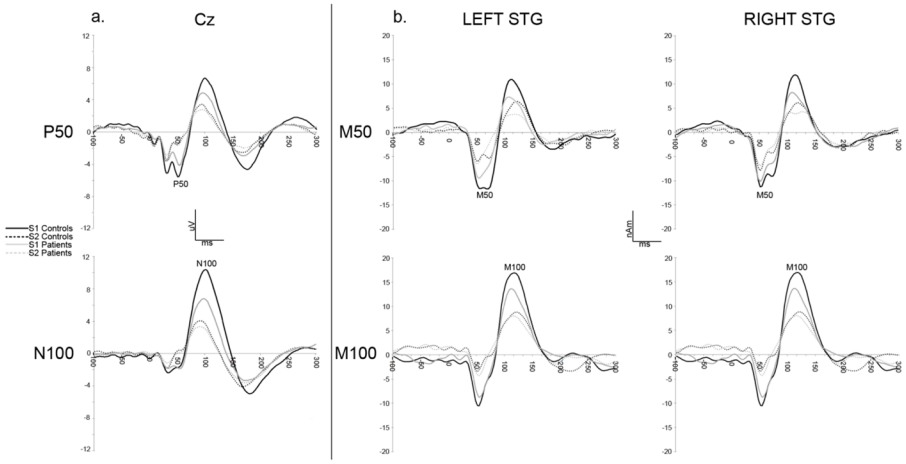

Figure 1. Cz and STG Paired-click Waveforms

Cz (panel a) and left and right superior temporal gyrus (panel b) 50 and 100 ms paired-click waveforms.

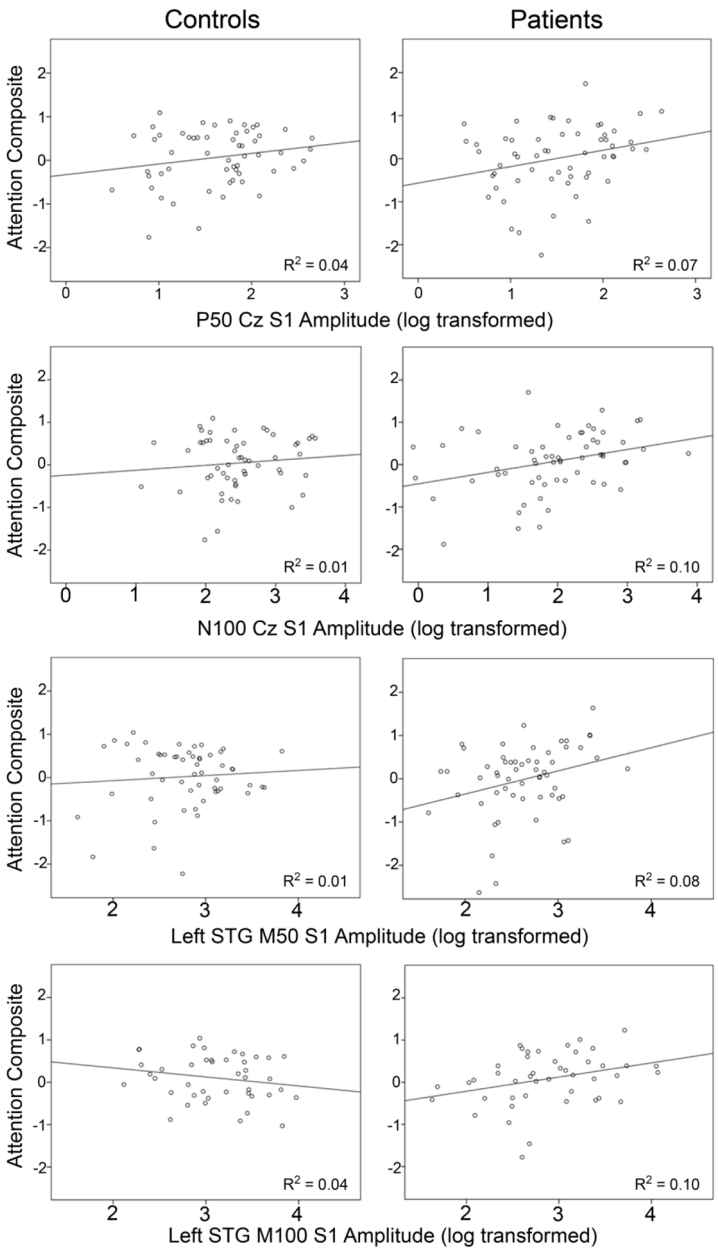

Figure 2. Associations Between First Click (S1) Amplitude and Attention

First click (S1) amplitude and attention composite scatter plots for 50ms and 100ms Cz and for 50ms and 100ms left superior temporal gyrus. Attention performance was predicted by the patient's ability to encode auditory information.

Table 1

Demographic information: Controls and patients

	Controls (N=73***)		Patients (N=79***)	
	Mean	***SD***	**Mean**	***SD***
Age*	41.48	10.44	42.94	10.30
Education (years) **	14.66	2.02	13.10	2.37
Patient SES**[a]	37.97	14.20	58.12	13.16
Parental SES*	37.01	18.30	39.91	20.28

* Group differences in age, $t(150) = -0.87$, and parental SES, $t(135) = -0.88$, were not significant.

** Controls were more educated, $t(149) = 4.35$, $p < 0.001$, and had higher SES, $t(141) = -8.81$, $p < 0.001$.

*** Sample size differed slightly across measures due to missing values.

[a] SES was assessed with Hollingshead, August B. 1957. “Two Factor Index of Social Position,” Mimeo. New Haven, Connecticut: Yale University.

Table 2

First click (S1) and second click (S2) source strength (log transformed), and ratio score group means and standard deviations.

	Amplitude (log transformed μV or nAm)				Ratio Score	
	S1	***SD***	**S2**	***SD***	**S2/S1[a]**	***SD***
Cz P50						
Controls (n = 70)	1.61	*0.54*	1.03	*0.59*	**0.39***	*0.22*
Patients (n = 72)	1.47	*0.55*	1.04	*0.49*	**0.48**	*0.28*
Cz N100						
Controls (n = 71)	**2.36****	*0.66*	1.70	*0.60*	**0.37****	*0.18*
Patients (n = 75)	**1.96**	*0.84*	1.56	*0.60*	**0.45**	*0.19*
LM50						
Controls (n = 67)	2.74	*0.47*	1.99	*0.72*	**0.50***	*0.24*
Patients (n = 70)	2.61	*0.44*	2.05	*0.65*	**0.61**	*0.21*
RM50						
Controls (n = 67)	2.74	*0.49*	2.15	*0.64*	0.61	*0.24*
Patients (n = 70)	2.68	*0.52*	2.06	*0.68*	0.61	*0.27*
LM100						
Controls (n = 62)	**3.05****	*0.49*	2.09	*0.79*	**0.44****	*0.19*
Patients (n = 61)	**2.79**	*0.58*	2.03	*0.88*	**0.56**	*0.27*
RM100						
Controls (n = 62)	3.00	*0.46*	1.97	*0.98*	**0.44****	*0.22*
Patients (n = 61)	2.89	*0.51*	2.11	*0.85*	**0.56**	*0.29*

Significant group differences are bolded (indicated by t-test.

*p ≤ .05;

**p ≤ .01).

[a]Cz P50/N100 ratio scores were log-transformed to normalize the data distribution.

Table 3

Hierarchical regressions with ratio scores and group predicting cognitive composite score

		Ratio Score		Interaction	
	Gating Predictor	**R^2 Change**	***p* =**	**R^2 Change**	***p* =**
Attention	Cz P50	**0.09**	**< 0.01**	0.01	0.31
	Cz N100	**0.04**	**0.03**	0.02	0.13
	Left M50	**0.07**	**< 0.01**	0.02	0.10
	Right M50	0.01	0.36	**0.03**	**0.04**
	Left M100	**0.15**	**< 0.001**	0.02	0.10
	Right M100	**0.11**	**< 0.01**	**0.05**	**< 0.01**
Working Memory	Cz P50	**0.10**	**< 0.01**	0.00	0.53
	Cz N100	**0.04**	**0.04**	0.00	0.56
	Left M50	**0.07**	**< 0.01**	0.01	0.36
	Right M50	**0.06**	**0.02**	0.00	0.64
	Left M100	**0.15**	**< 0.001**	0.00	0.92
	Right M100	**0.05**	**0.04**	0.03	0.09
Long Delay Memory	Cz P50	0.03	0.10	0.00	0.93
	Cz N100	0.01	0.32	0.01	0.24
	Left M50	0.01	0.30	0.00	0.79
	Right M50	0.01	0.35	0.00	0.44
	Left M100	**0.07**	**0.01**	0.01	0.27
	Right M100	**0.06**	**0.03**	0.00	0.69

*All group and full-model R^2 values were significant at $p < 0.001$, except Cz N100 and Working Memory, which were significant at $p < 0.01$.

Table 4

Hierarchical regressions with group, first click (S1), and second click (S2) amplitude predicting cognitive composite score

		Amplitude		Interaction	
	Gating Predictor	**R^2 Change**	***p* =**	**R^2 change**	***p* =**
Attention	Cz P50 S1	**0.06**	< **0.01**	0.01	0.35
	Cz P50 S2	0.00	0.63	0.00	0.46
	Cz N100 S1	**0.15**	< **0.001**	0.01	0.19
	Cz N100 S2	**0.03**	**0.04**	0.01	0.24
	Left M50 S1	**0.06**	**0.01**	0.02	0.07
	Left M50 S2	0.00	0.82	0.00	0.44
	Right M50 S1	0.02	0.13	0.02	0.06
	Right M50 S2	0.00	0.93	0.00	0.96
	Left M100 S1	**0.06**	**0.03**	**0.04**	**0.02**
	Left M100 S2	0.01	0.50	0.01	0.32
	Right M100 S1	0.00	0.68	0.01	0.39
	Right M100 S2	0.02	0.22	0.02	0.12
Working Memory	Cz P50 S1	**0.07**	< **0.01**	0.00	0.70
	Cz P50 S2	0.00	0.92	0.02	0.20
	Cz N100 S1	**0.06**	**0.02**	0.00	0.78
	Cz N100 S2	0.02	0.21	0.00	0.60
	Left M50 S1	0.01	0.39	0.01	0.35
	Left M50 S2	0.01	0.44	0.00	0.65
	Right M50 S1	0.02	0.16	0.01	0.41
	Right M50 S2	0.00	0.98	0.00	0.92
	Left M100 S1	0.01	0.41	0.01	0.47
	Left M100 S2	0.03	0.15	0.00	0.88
	Right M100 S1	0.01	0.33	0.00	0.65
	Right M100 S2	0.00	0.62	0.01	0.43
Delayed Memory	Cz P50 S1	0.01	0.29	0.00	0.91
	Cz P50 S2	0.00	0.84	0.00	0.84

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		Amplitude		Interaction	
	Gating Predictor	**R^2 Change**	***p* =**	**R^2 change**	***p* =**
	Cz N100 S1	**0.04**	**0.04**	0.00	0.87
	Cz N100 S2	0.02	0.16	0.00	0.53
	Left M50 S1	0.00	0.63	0.00	0.62
	Left M50 S2	0.00	0.91	0.00	0.55
	Right M50 S1	0.00	0.86	0.02	0.08
	Right M50 S2	0.00	0.93	0.02	0.17
	Left M100 S1	0.00	0.55	0.00	0.65
	Left M100 S2	0.01	0.38	0.00	0.95
	Right M100 S1	0.01	0.46	0.00	0.88
	Right M100 S2	0.01	0.28	0.00	0.86

* All group and full model R^2 values were significant at $p < 0.001$.

Table 5

Hierarchical regressions with IQ, cognitive composite scores, and group predicting ratio scores.

		Cognitive Domain		**Cognitive Domain * Group interaction**	
	Ratio Score	**R^2 Change**	***p* =**	**R^2 Change**	***p* =**
Attention	Cz P50	**0.05**	**0.02**	0.01	0.34
	Cz N100	0.01	0.32	0.01	0.25
	Left M50	0.03	0.07	0.00	0.97
	Right M50	0.02	0.21	0.03	0.10
	Left M100	**0.05**	**0.02**	0.02	0.19
	Right M100	**0.10**	< **0.01**	**0.05**	**0.02**
Working Memory	Cz P50	0.02	0.15	0.00	0.82
	Cz N100	0.02	0.15	0.00	0.93
	Left M50	0.03	0.10	0.00	0.75
	Right M50	**0.04**	**0.05**	0.00	0.88
	Left M100	**0.04**	**0.04**	0.00	0.73
	Right M100	0.02	0.21	0.03	0.10
Long Delay Memory	Cz P50	0.00	0.63	0.00	0.88
	Cz N100	0.00	0.90	0.01	0.25
	Left M50	0.00	0.99	0.00	0.54
	Right M50	0.00	0.66	0.03	0.08
	Left M100	0.01	0.39	0.01	0.52
	Right M100	0.02	0.20	0.00	0.85