Published in final edited form as:

Psychiatry Res. 2009 January 30; 165(1-2): 27–37. doi:10.1016/j.psychres.2008.04.013.

The profile of auditory information processing deficits in schizophrenia

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Abstract

Schizophrenia patients exhibit abnormalities in several different auditory ERP measures. It is unclear how these abnormalities relate to each other, since multiple measures are rarely acquired from the same sample. This study addressed two related questions: 1) Are specific auditory ERP measures differentially impaired in schizophrenia? 2) Do abnormalities co-aggregate within the same patients? Nine auditory ERP measures were acquired in a single testing session from 23 schizophrenia patients and 22 healthy subjects. Hierarchical oblique factor analysis revealed that these measures aggregated into 4 factors, with each loading primarily on a single factor. Patient deficits were observed for two independent factors: N100/MMN and P3a/P3b. N100/MMN abnormalities were associated with symptoms of alogia and formal thought disorder. P3a/P3b abnormalities were associated with avolition, attentional disturbances and delusions. We conclude that deficits in different ERP measures of early sensory processing at the level of the auditory cortex co-occur in patients. These likely represent a single differential deficit indexing the physiological abnormality underlying impaired language and verbal processing. This is relatively independent of a higher cortical deficit that mediates cognitive stimulus evaluation and underlies deficits in motivation, attention and reality testing. Such multidimensional profiling of ERP abnormalities may help to clarify the clinical and genetic heterogeneity of schizophrenia.

Keywords

evoked potentials; schizophrenia; P50; PPI; N100; mismatch negativity; P300

1. Introduction

Although the clinical symptoms and course of schizophrenia are heterogeneous, most patients exhibit cognitive deficits that are present at the onset of illness and persist following improvement in psychotic symptoms (Saykin et al., 1994). Of these, disturbances in attention and memory appear to be most prominent (Saykin et al., 1991). Event-related potentials (ERPs) are commonly used to study the physiological correlates of these behavioral impairments, and ERP abnormalities have been widely reported, particularly in response to auditory stimuli

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(McCarley et al., 1991). The range of auditory ERP deficits extends from early pre-attentive stages of information processing to relatively late higher-level evaluative processes. It has been suggested, however, that a breakdown in processes that regulate the inflow of information from the environment is fundamental (Venables, 1964). Successful stimulus encoding requires the ability to screen out or inhibit responses to redundant or irrelevant inputs and, reciprocally, to enhance or facilitate responses to novel or salient stimuli. There is evidence to suggest that both of these processes are impaired in schizophrenia. Auditory ERP abnormalities that have been commonly associated with schizophrenia include: pre-pulse inhibition of startle (PPI) (Braff et al., 1978) and P50 auditory evoked potential suppression (Adler et al., 1982), two different measures of neuronal inhibition; N100, a measure of basic auditory sensory perception (O'Donnell et al., 2004); mismatch negativity (MMN), a measure of automatic deviance detection (Javitt et al., 1994); and P300, a composite measure of cognitive orienting (P3a) and contextually salient identification (P3b) of deviant stimuli (Turetsky et al., 1998).

Although the evidence supporting each of these deficits is substantial, the question of how these physiological abnormalities might relate to each other remains unaddressed. Only rarely have more than one of these measures been acquired contemporaneously in the same patient sample (Louchart-de la Chapelle et al., 2005; Braff et al., 2006; Price et al., 2006). It is not clear whether patients who exhibit abnormalities on one physiological measure also exhibit abnormalities on other measures, or whether different abnormalities manifest themselves in different patients. This is a question that has important implications for understanding both the neurophysiological and genetic bases of the illness. Multiple deficits that co-aggregate in the same patients may reflect a single underlying auditory information processing deficit that, in turn, denotes a single common variant of genetic risk for the disorder. In this case, a composite or multivariate measure derived from multiple ERP indices may be a more robust endophenotypic marker of genetic vulnerability than any single measure (Price et al., 2006). Conversely, deficits that are distinct and dissociable may reflect different neurophysiological abnormalities that arise, in turn, from independent variants of genetic vulnerability (Braff et al., 2006). In this case, the presence of unique profiles of ERP deficits in different subsets of patients could facilitate both physiological and genetic subtyping of the disorder.

Alternatively, the co-aggregation of multiple ERP abnormalities within the same patients may reflect a global or non-specific deficit associated with more severe forms of the illness. It is important, therefore, to also consider the question of whether related measures all exhibit comparable levels of impairment, or whether one or more might represent differential or selective deficits that manifest against a backdrop of more global impairment. To the extent that such selective deficits can be identified, these may denote specific aspects information processing that are more closely linked to the neuropathological and genetic substrates of the illness than other correlated measures. Such is the case, for example, for the various domains of neuropsychological functioning. Although schizophrenia patients are impaired across multiple cognitive domains, they exhibit selective (i.e., more severe) impairments in learning and memory, consistent with greater involvement of the temporal-hippocampal system in the pathogenesis of the illness (Saykin et al., 1991).

The current study was designed to address these two related but distinct questions: 1) Do specific auditory ERP measures show evidence of differential or selective impairment in schizophrenia? 2) Do different auditory ERP abnormalities manifest themselves within the same patients or within different subsets of patients? Multiple ERP measures, including PPI, P50 suppression, MMN, N100, P3a and P3b, were acquired from a sample of schizophrenia patients and healthy comparison subjects in a single testing session. Two statistical procedures, profile analysis and hierarchical oblique factor analysis, were employed to answer these two questions.

2. Methods

2.1. Subjects

Participants were recruited by the Conte Center for Neuroscience of Mental Disorders, in the Neuropsychiatry Division of the Department of Psychiatry at the University of Pennsylvania. The sample consisted of 23 patients (14 males, 9 females) with a diagnosis of schizophrenia and 22 healthy individuals (14 males, 8 females) with no family history of an Axis I psychotic disorder. All subjects received a semi-structured psychiatric interview (DIGS, Diagnostic Interview for Genetic Studies), the Family Interview for Genetic Studies (FIGS) and a medical evaluation, including complete blood count, electrolyte panel, liver function tests, thyroid function tests and urine analysis prior to enrollment. A urine toxicology screening test was also performed on the day of electrophysiological testing. All patients met DSM-IV diagnostic criteria for schizophrenia, based on a consensus case conference of research psychiatrists, with no other concurrent Axis I diagnoses. Healthy comparison subjects were excluded based on any Axis I or Axis II Cluster A (i.e. schizotypal, schizoid, or paranoid personality disorder) diagnosis. Subjects with a history of neurological disorder, head trauma with loss of consciousness, substance abuse, or other medical condition that might affect brain functioning were excluded from participation in the study. Subjects were also excluded for a hearing threshold greater than 40 dB at 1000 Hz. Eleven patients and 4 comparison subjects indicated that they were active smokers.

Patients were all stable outpatients at the time of testing. Eighteen were being treated with antipsychotic medications at the time of testing. Of these, three were also taking adjunctive antidepressants and one was taking an anticholinergic agent. One patient was being treated with only a benzodiazepine and four were entirely unmedicated. Specific medications and dosages are presented in the on-line supplementary material (Supplementary Table 1). Patients were rated on several scales: the Brief Psychiatric Rating Scale [BPRS] (Overall and Gorham, 1980), the Scale for Assessment of Negative Symptoms [SANS] (Andreasen, 1983) and the Scale for Assessment of Positive Symptoms [SAPS] (Andreasen, 1984). Ratings were completed by investigators trained to a minimum criterion reliability of 0.90 (intraclass correlation). Clinical characteristics of the patient sample, by gender, are presented in Table 1. Total BPRS, SANS, and SAPS scores suggest that overall symptom severity was relatively mild in this patient sample.

The two groups were comparable in both gender distribution [$\chi^2(1)=0.037$, $P=0.85$] and age [$t(43)=1.36$, $P=0.18$]. Mean patient age was 37.7 ± 10.3 (sd) years (range: 23–66), compared to 33.5 ± 10.4 (sd) years (range: 20–66) for healthy controls. They also did not differ on handedness [$\chi^2(1)=1.19$, $P=0.27$] (Raczkowski et al., 1974).

2.2. Experimental Protocol

Each subject participated in 4 consecutive experiments in a fixed order: 1) mismatch negativity with both pitch deviant and duration deviant stimuli, 2) P50 auditory gating 3) a 3-stimulus P300 task with both infrequent targets and novel stimuli, 4) pre-pulse inhibition of startle. This specific task order was selected to minimize potential confounding effects of any given task on subsequent tasks. In particular, the PPI task was placed last so that any increase in arousal following exposure to startling stimuli would not affect any of the other tasks. This was particularly important for the P50 task, as increased arousal can disrupt auditory sensory gating (Waldo et al., 1992). Similarly, the MMN experiment, in which a subject's attention is directed away from the auditory stimuli, was placed before any of the other tasks that might have increased the likelihood of attending to the stimuli. All tests were administered in a single session that lasted approximately two hours. Subjects maintained their usual smoking and caffeine habits prior to arrival at the EEG laboratory. They refrained from all smoking and

caffeine intake from the time of arrival until the completion of all studies, including approximately one hour prior to the start of testing.

Electrophysiological recordings were acquired with an Easy-Cap electrode cap (Herrsching-Breitbrunn, Germany) fitted with sintered Ag/AgCl electrodes and a Synamps amplifier and Scan software system (Compumedics, El Paso, TX, USA). Bipolar electrodes placed superior and lateral to the left eye monitored eye movement activity. Amplifier gain was set to 1000 (range: 5.5 mV, resolution: 0.084 μ V). Impedances were below 10 kOhms at all electrode sites. A TTL timing pulse marked the presentation of each stimulus in the EEG record. Data were continuously sampled and written to disk for post-processing offline. Digital sampling rate, filter settings, electrode montage and post-processing procedures were all task-specific, as described below.

2.2.1. Mismatch negativity—A 1000Hz, 80 dB SPL, 50ms duration “standard” tone was repeatedly presented binaurally through ear-insert headphones, with a 520ms inter-stimulus interval. For every set of 24 tones, the 12th tone was a 50ms 2000Hz pitch deviant and the 24th tone was a 1000Hz 100ms duration deviant tone. Total number of tones was 966, including 40 presentations of each deviant stimulus. Subjects were shown a silent video to direct attention away from the auditory stimuli. EEG was recorded with 0.1–100 Hz analog filter settings and digitally sampled at 500Hz. Post-acquisition, the EEG data were digitally filtered with a 1–30Hz zero phase-shift bandpass filter (–24dB/octave), corrected for EOG activity using an established algorithm (Semlitsch et al., 1986), and visually scanned to identify and exclude intervals contaminated by movement or other recording artifacts. Continuous recordings were then segmented into individual epochs beginning 100ms pre-stimulus and ending at 400ms post-stimulus. Average evoked potential waveforms were derived for the pitch-deviant and duration-deviant tones and for the standard tone immediately preceding each type of deviant. Difference waveforms were derived by subtracting the preceding standard waveform from each deviant waveform. For the purposes of this analysis, MMN was defined as the minimum amplitude in this difference waveform, between 100 and 250ms post-stimulus, at the Fz electrode site.

2.2.2 P50 auditory sensory gating—Rarefaction clicks of 0.1 ms duration and 85dB SPL were generated by a Neurostim audio stimulator. A total of 120 pairs of clicks were presented, with 500 ms within-pair interstimulus interval and 8000 ms between-pairs intervals. Amplifier analog filter settings were 0.5–300 Hz and digital sampling rate was 1000Hz. Subjects were seated in a reclining position and instructed to remain awake with eyes fixated at a distant target. Data were digitally filtered with a 10–100Hz bandpass and segmented into individual trial intervals from -200 to 900 ms, relative to the onset of the first click of each pair. The single trial data from Cz and EOG channels were visually inspected for artifacts prior to averaging. Trial rejection criteria included EEG activity >30 μ V, eye blink response, movement artifact, or prominent alpha activity in the 0–100ms interval following each click. The amplitude of the P50 response to the first click was defined, in the Cz average waveform, as the peak response in the 40–80 ms post-stimulus interval, relative to the preceding negative trough. The P50 response to the second click was measured similarly, with the added constraint that its latency varied by less than 10 ms from that of the first click. The percentage of P50 auditory sensory gating was then computed as 1 minus the ratio of the amplitude of the second click to the amplitude of the first click. Although it is usually not computed in this way, subtracting the ratio from 1 scales the auditory P50 gating measure so that smaller values represent less inhibitory gating and its interpretation parallels that of PPI.

2.2.3 Three-stimulus P300—75 dB SPL, 100 ms duration tones were presented binaurally with inter-trial interval jittered between 1500 and 1600 ms. A 1000 Hz “standard” tone was presented randomly on 70% of the trials and a 2000 Hz “target”, to which subjects responded

with a button press, was presented 15% of the time. The remaining trials consisted of unexpected complex deviant sounds, each of which was presented only once (“novel”). To ensure comprehension and acceptable performance, subjects were trained on the target discrimination and motor response prior to data acquisition, but were not pre-exposed to the novel stimuli. The experiment terminated after presentation of 45 target and 45 novel stimuli. EEG was digitally sampled at 250 Hz and bandpass filtered between 1 and 50 Hz. Following EOG correction and visual inspection, the continuous EEG was segmented into artifact-free single trials from –200 to +800 ms, relative to stimulus onset. Separate average waveforms were then derived for each of the 3 stimulus conditions. The amplitudes three ERP components were defined as follows: N100 -the negative trough between 75 and 125 ms at Cz in the standard condition; P3a – the peak response between 250 and 400 ms at Cz in the novel condition; P3b – the peak response between 250 and 400 ms at Pz in the target condition.

2.2.4 Pre-pulse inhibition of startle—Against a background of continuous 70dB white noise, acoustic startle stimuli consisting of 40 ms bursts of 110dB white noise were presented binaurally, with an 8–16 second variable inter-stimulus interval. A total of 72 startle stimuli were presented. Half of these were preceded randomly by a 20 ms 85dB white noise pre-pulse that occurred 30, 60 or 120 ms prior to the startling stimulus (12 each). Subjects were instructed simply to listen to the sounds and to fixate on a distant object. The startle response was recorded from two 4mm eletromyographic (EMG) electrodes positioned below and lateral to the right eye over the obicularis oculi muscle. The EMG activity was digitally sampled at 2500Hz and filtered with a zero-phase shift bandpass of 1–1000Hz. The amplitude of the rectified EMG response to each startling stimulus was measured as the peak response between 18 and 150 ms. Trials exhibiting voluntary or spontaneous eye blinks prior to the onset of the startle response or other artifacts were excluded. Mean startle amplitudes were computed for each of the four trial types (startle alone, startle with 30, 60, or 120 ms pre-pulse). PPI was computed as 1 minus the ratio of the startle response following a pre-pulse divided by the magnitude of the startle alone response. To limit the number of dependent measures, only the 120 ms PPI measure was included in the analyses. However, comparable results were obtained for all three pre-pulse intervals.

2.3 Statistical analyses

Nine primary measures were included in the analyses: P50 amplitude (based on the 1st-click response), P50 ratio, pitch-deviant MMN, duration-deviant MMN, N100 amplitude, P3a amplitude, P3b amplitude, startle amplitude and PPI. To facilitate comparisons across measures, each was converted to a standardized z-score, such that control subjects had a mean score of 0 and a standard deviation of 1 on each measure. Patients were assigned z-scores relative to this control sample distribution. The sign of each measure was adjusted so that the expected patient deficits were expressed as negative z-score values across all measures. The analysis then proceeded in two steps, to address each of the 2 questions of interest. Step 1 was a profile analysis test of parallelism across all nine dependent measures. Profile analysis is a multivariate analysis of dependent variables that are all measured on the same scale, as is the case when z-scores are used in the analysis. It provides a formal test of two null hypotheses: 1) the multivariate response profiles of two different groups are parallel; 2) the response profiles are flat (i.e., the various dependent measures elicit the same average responses). Profile analysis has the advantage of being very robust to violations of multivariate normality and having more power than univariate repeated measures tests adjusted for sphericity violations. In this particular case, since control group values were already scaled to have a flat profile (mean=0 across all measures), the two hypotheses reduced to one. That is, if the group profiles were not parallel, it implied that the mean deviations in the patient profile were not flat. So the test of parallelism between patient and control responses became a formal test for the presence of one or more selective impairments. Post-hoc comparisons within the patient group could then be

used to identify those measures that deviated from the others, consistent with a differential deficit.

Step 2 was a hierarchical analysis of oblique factors extracted from the nine dependent variables. Traditional principal components analysis requires that derived factors be completely independent or orthogonal to each other. This tends to be an unrealistic assumption, particularly with regard to ERP measures that are usually highly correlated with each other. The orthogonality constraint may therefore result in misspecification of the underlying factor structure. Oblique factor analyses do not impose this requirement, but non-orthogonal factor rotations often produce correlated factors that share many cross-loadings and are difficult to interpret. Hierarchical factor analysis is an alternative to both oblique and orthogonal factor analysis. This is a two-stage approach in which discrete clusters of variables are first identified and non-orthogonal axes are rotated through these clusters. The correlations between oblique factors are then computed and this correlation matrix is further factor analyzed to yield an orthogonal set of factors in which the variability of the measures is divided into shared or common variance (secondary factors) and unique variance arising from clusters of related variables (primary factors) (Wherry, 1959). The result is a set of independent factors that are relatively easy to interpret, without the model misspecification that arises from misallocation of correlated variance (Dien, 1998). The hierarchical factor analysis was implemented using the Kaiser criterion of eigenvalue > 1 to specify the number of retained factors (Kaiser, 1960).

3. Results

Means and standard deviations of the untransformed dependent variables are presented in Table 2, and the profiles of the standardized z-scores are depicted in Figure 1. Grand averages of the waveforms used to derive these measures are presented in the online supplementary material (Supplementary Figures 1 – 9). Plots of individual subject scores on all measures are presented in Supplementary Figures 10 – 18). Individual t-tests comparing patients and controls revealed significant group differences on 4 of the 9 measures: pitch MMN [$t(43)=4.06$, $P<0.001$], P3a amplitude [$t(43)=2.12$, $P<0.05$], P3b amplitude [$t(43)=4.21$, $P<0.001$] and N100 amplitude [$t(43)=3.36$, $P<0.01$]. Three of the other measures - duration MMN [$t(43)=2.00$, $P=0.052$], P50 amplitude [$t(43)=0.15$, $P=0.88$] and P50 gating [$t(43)=0.87$, $P=0.39$] – had group means that were in the expected direction of a patient deficit but were not significantly different. Contrary to our expectations, mean startle amplitude [$t(43)=1.08$, $P=0.29$] and PPI [$t(43)=1.25$, $P=0.22$] were both actually larger in the patient sample, though not significantly so. Given the fact that antipsychotic medications have been reported to affect several of these measures (Coburn et al., 1998; Kumari et al., 1999; Light et al., 2000; Weike et al., 2000; Kumari et al., 2002), we assessed potential medication effects by examining the correlation between daily antipsychotic medication dosage (expressed as chlorpromazine equivalents) and each evoked potential measure. Two measures, P3a amplitude [$r = -0.52$, $P<0.01$] and PPI [$r = 0.47$, $P<0.05$] exhibited significant medication effects. However, the directions of the two effects were opposite. Increasing medication dosage resulted in reduced (i.e., more abnormal) P3a amplitude, but increased (i.e., less abnormal) pre-pulse inhibition of startle. The normalization of PPI with antipsychotic medication, independent of dosage, was confirmed by the comparison between medicated and unmedicated patients. Mean PPI for medicated patients was 0.61; for unmedicated patients it was 0.11 [$t(21)=3.74$; $P<0.001$]. The comparable group comparison for P3a amplitude was not significant [$t(21)=1.73$, $P=0.10$], suggesting that this relationship was dosage dependent.

3.1. Profile analysis

Consistent with the variability of the univariate test results, the multivariate profile test of parallelism was highly significant [Wilks' $\lambda(8,36)=0.574$, $P<0.01$], confirming differential patient responses across the measures. Deviation contrasts, within the patient sample, were then used to identify those variables that exhibited abnormalities that were significantly different from the grand mean value across all measures. Significant deviations were observed for 3 of the 4 measures that were abnormal in the patients: pitch MMN [$t(22)=4.55$, $P<0.001$], P3b amplitude [$t(22)=5.59$, $P<0.0001$] and N100 amplitude [$t(22)=2.87$, $P<0.01$]. These 3 ERP components, therefore, were selectively impaired relative to the other measures. P3a, however, did not differ significantly from the overall mean response [$t(22)=1.24$, $P=0.23$], indicating that even though patients were abnormal on this measure, this did not represent a differential deficit.

To rule out the possibility that the results of the deviation contrasts were influenced by the inclusion of several measures on which the patients were not impaired, we repeated the deviation contrast analysis using only the 4 measures that exhibited significant univariate deficits. That is, we compared each of the 4 abnormal measures, individually, to the grand mean response across the remaining measures. The result was the same: P3a amplitude deviated significantly from the other measures [$t(22)=2.62$, $P<0.05$], indicating that it was significantly less impaired. However, levels of impairment of the other 3 components remained indistinguishable from each other.

3.2. Hierarchical factor analysis

The hierarchical analysis of oblique factors yielded 4 unique primary factors and two secondary or general factors containing shared variance. These accounted, collectively, for 70.8% of the total sample variance. The factor loadings for each variable on each of the four primary factors are presented in Table 3. An examination of this table reveals that each dependent measure had a relatively high loading (>0.5) on only one primary factor. Factor 1 included N100 amplitude and both the pitch and the duration MMN measures. N100 and MMN share the common feature of originating, to a large extent, from generators in the auditory cortex. Factor 1 may therefore be interpreted as an index of sensory processing deficits at the level of primary and secondary auditory cortex. P50 gating was the only variable to load strongly on factor 2. Factor 3 included P50 amplitude, startle amplitude and PPI of startle. These 3 ERPs are either generated in, or modulated by, subcortical nuclei (Turetsky et al., 2007). Specifically, PPI is regulated by cortico-striato-pallido-pontine circuitry that converges with the primary startle circuitry at the nucleus reticularis pontis caudalis (Swerdlow et al., 2001), while P50 amplitude is regulated by hippocampal and thalamic inputs (Tragellas et al., 2007). Factor 3 may therefore be understood as an index of relatively early subcortical modulation of sensory stimulus processing. Factor 4 contained the two late endogenous P300 measures, suggesting that this is an index of more controlled stimulus evaluation and discrimination processes.

Factor scores were computed for each subject for each of the 4 primary factors. These are depicted in Figure 2 as standardized Z-scores. Consistent with the findings for the individual measures, group comparisons of the factor scores indicated significant patient-control differences for Factor 1 [$t(43)=3.35$, $P<0.01$] and Factor 4 [$t(43)=2.64$, $P<0.05$], but not for Factor 2 [$t(43)=0.84$, $P=0.41$] or Factor 3 [$t(43)=0.38$, $P=0.57$]. Figure 3 is a scatterplot of the z-transformed individual patient scores on these 2 abnormal factors. The correlation between these 2 sets of factor scores within the patient sample was $r=0.008$ [$P=0.97$], consistent with the hypothesis that the stimulus processing abnormalities indexed by these 2 factors manifest themselves relatively independently within different patient subgroups.

The results of any factor analysis are dependent upon the specific variables and subjects entered into the analysis. To assess the stability of these factor loadings, we repeated the analysis using only the 5 variables for which patients exhibited significant impairments. In this case, two factors with virtually identical loadings to factors 1 and 4, above, explained 72.4% of the total variance. These factor loadings are presented in the online supplementary material (Supplementary Table 2). This indicates that the factor structure of MMN, N100 and P300 patient abnormalities was not dependent on the inclusion of PPI and P50 measures. We also repeated the original factor analysis after excluding the 5 unmedicated patients. The factor loadings for this analysis are presented in Supplementary Table 3. Except for PPI and startle, which loaded more heavily on the P50 gating factor (Factor 2), the factor structure for this reduced sample was virtually identical to that of the sample as a whole. So, except perhaps for the startle response, the underlying factor structure was not overly determined by the subset of unmedicated patients.

We also considered, in an exploratory manner, whether patients who exhibited impairments on either of these two auditory ERP factors could be distinguished on the basis of any specific clinical characteristics. Patients' scores on each factor were correlated with age of illness onset, illness duration, total BPRS score, and SANS and SAPS subscale scores. A one-tailed significance threshold of $P < 0.05$ was used to test the hypothesis that greater ERP impairment was associated with more severe clinical symptomatology. Abnormalities on Factor 1 were associated with selective deficits on the SANS alogia [$r = 0.41$, $P = 0.027$] and the SAPS positive thought disorder [$r = 0.39$, $P = 0.031$] rating scales. In contrast, abnormalities on Factor 4 were associated with increased levels of avolition [$r = 0.46$, $P = 0.013$], attentional disturbance [$r = 0.41$, $P = 0.026$] and delusional thought content [$r = 0.42$, $P = 0.022$].

4. Discussion

This study addressed two related questions: 1) Are there selective impairments of specific auditory ERP measures; 2) Do these specific impairments reflect a single underlying auditory processing deficit? With respect to the first question, the answer appears to be "yes". N100 amplitude, pitch MMN and P3b amplitude were differentially impaired in this patient sample. With respect to the second question, the factor analysis indicates that these abnormalities coalesce into two distinct and relatively independent auditory processing deficits. One, encompassing the N100 and MMN, appears to be a relatively focal disturbance of early sensory processing at the level of the auditory cortex, which can be linked clinically to the positive symptom of thought disorder and the reciprocal negative symptom of alogia. The other, represented by abnormal P300 amplitude, denotes a disturbance of higher-order cognitive processes of stimulus evaluation, discrimination and salience detection, which is linked to clinical disturbances in motivation, attention and reality testing. Our results indicate, therefore, that there are at least 2 distinct auditory processing deficits in schizophrenia, one early and one late, and that these are likely to reflect different neurobiological and/or genetic substrates that contribute to the heterogeneity of the illness (Turetsky et al., 2007).

This finding of two discrete deficits is consistent with the relatively limited data that exist concerning the co-aggregation of auditory ERP abnormalities in schizophrenia. Two recent studies examined P50 gating, P300 and MMN in the same subjects, one in schizophrenia patients and their unaffected 1st-degree relatives (Price et al., 2006) and one in healthy monozygotic and dizygotic twins (Hall et al., 2006). Although all three measures were found to be both heritable and abnormal in patients, none of them were correlated with each other. Four studies have examined P50 gating and PPI in the same subjects, one in schizophrenia patients (Braff et al., 2006) and three in healthy individuals (Schwarzkopf et al., 1993; Oranje et al., 1999; Oranje et al., 2006). Again, there were no consistent associations between the two measures, even though both have been conceptualized as indices of inhibitory failure in

schizophrenia. Unfortunately, although there have been numerous studies of P300 in schizophrenia, and N100 amplitude measures are routinely acquired during these studies and often reported as abnormal (e.g., Ford et al., 2001), we are unaware of any previous investigations of the relationship between these 2 patient abnormalities. Our data, though, suggest that the N100 amplitude decrement is similarly independent of other auditory ERP abnormalities, except for MMN.

There are a number of caveats and possible limitations of this study that must be emphasized. In particular, there is our failure to observe any patient abnormalities in either P50 auditory sensory gating or PPI - two measures that have been commonly reported as abnormal in schizophrenia - despite there being significant deficits in other measures of auditory sensory processing. As detailed in Table 2, the principal difference between our measurements and those of previous studies was reduced PPI and P50 gating in control subjects, rather than increased PPI and P50 gating in patients. This suggests that methodological differences, rather than patient biases, may have contributed most to our failure to observe a patient deficit. There are a number of ways in which this study differed from prototypical P50 and PPI studies.

First, these measures were not acquired in isolation, but as part of a more extensive battery of auditory processing tasks. We employed a fixed test order that was selected to minimize carryover effects from one task to another and maintain the psychophysiological construct validity of each measure. Nevertheless, the use of multiple tests in this particular order may have affected measures that are relatively sensitive to state effects. It is notable, in this regard, that a recent study employing a broad test battery found significant effects of test order on PPI in a healthy control sample (Swerdlow et al., 2007). Specifically, PPI was reduced in healthy men when testing occurred later in the test battery. This is especially pertinent since PPI was the last experiment in our protocol. Similarly, P50 has been shown to be altered in a state-dependent manner, in healthy subjects, by changes in levels of arousal and stress (Johnson and Adler, 1993). It may be that control subjects, who have no intrinsic deficit, are more sensitive to the disruptive effects of such state factors than schizophrenia patients.

Second, because the profile and factor analyses require that each subject have data on all measures of interest, we did not exclude so-called “non-responders”, as is often done for PPI and P50 (e.g. Braff et al., 2007). Rather, we measured responses in all subjects without regard for a threshold response level. The inclusion of subjects with relatively small P50 and PPI amplitudes would likely result in increased mean gating ratios, due to smaller denominator values. Although this remains a possibility, we would note that none of the subjects in our sample would have been excluded using the thresholds specified by Braff et al. (2007) ($P50 < 1.0 \mu V$, startle amplitude $< 13 \mu V$).

Third, there may have been undetected effects of other potential confounds, such as smoking and nicotine withdrawal, female menstrual cycle, and psychotropic medications other than antipsychotics. Consistent with the standard practice for most PPI and P50 studies, we allowed subjects to maintain their usual smoking habits prior to arrival at the laboratory, but we did not allow any smoking breaks during the test session. It may be that any effects of acute nicotine withdrawal were exacerbated by our more protracted test session. However, this was unlikely to have contributed to our atypical control subject measures, as only 4 of the 22 healthy subjects smoked at all. Similarly, although antidepressants and anxiolytics can alter both PPI and P50 (e.g., Schächinger et al., 1999; Quednow et al., 2004; Hammer et al., 2007), only 4 of 23 patients were actually taking these types of medications. So, the likelihood that the use of these medications substantially affected our measurements is small. Phase of the female menstrual cycle can also affect PPI (Jovanovic et al., 2004), with PPI being reduced in the luteal phase. We did not assess menstrual phase in our female subjects; rather, we treated it as a random factor that was not expected to contribute to any between-group differences. This is fairly

standard practice. However, we cannot rule out the possibility that undetected differences in menstrual phase between female patients and female controls contributed to our failure to observe a group difference.

In addition to these potential confounds, a selection bias may have contributed to the lack of a patient deficit. Our sample was a community-based outpatient sample with quite low levels of acute symptomatology and relatively high levels of functioning. Most of the published studies have examined chronic patients with greater levels of clinical impairment. Finally, a recent meta-analysis of published P50 studies noted large variability in P50 gating among healthy control subjects, and sensitivity of the measure to fairly subtle differences in experimental methodology. Overall, approximately 40% of control subjects had P50 gating ratios within 1 standard deviation of the patient mean (Patterson et al., in press). So, relatively low statistical power may have also contributed to our failure to detect a deficit.

It should also be noted that, despite these various confounds, our PPI data are in at least one respect representative of the literature. The small group of unmedicated patients in our sample exhibited a nearly complete failure of PPI, which was offset by normal PPI (relative to this control sample) among the medicated patients. Normalization of PPI with atypical antipsychotic medication has been observed previously (Kumari et al., 2002; Swerdlow et al., 2006), although not uniformly for all agents (Oranje et al., 2002). It is likely that this, too, contributed to the lack of an observed abnormality in our sample. Some studies have also reported partial-to-full normalization of P50 gating with other atypical antipsychotics, in addition to clozapine (Yee et al., 1998; Light et al., 2000; Adler et al., 2004). Although we did not observe a robust effect of medication on P50 in our sample, the use of atypical antipsychotics may have also partially attenuated the gating deficit in these subjects - which was, in fact, in the expected direction.

Nevertheless, even in this sample of patients with relatively low levels of clinical symptomatology, active treatment with atypical antipsychotic medications, potential confounds, and normal PPI and P50 gating, there were robust deficits in both early auditory sensory and subsequent cognitive processing that were entirely independent of our assessment of PPI and P50. The clustering of these deficits suggests two discrete independent neurobiological substrates that may represent different illness subtypes. In particular, early sensory processing deficits at the level of the primary and secondary auditory cortex may be an index of the physiological abnormality underlying clinical symptoms of impaired language and verbal processing, while later deficits in cognitive stimulus evaluation may index more frontally mediated impairments in motivation and attention. Future studies should similarly focus on the assessment of multiple measures in the same individuals, to enable us to better understand both the heterogeneity and underlying etiologic mechanisms of the disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by National Institutes of Health grant 5P50MH064045.

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Figure 1.

Standardized z-scores for each of the 9 auditory ERP measures. Data were scaled so that control subjects had mean $z=0$ and standard deviation=1 for each measure, and patient deficits were scored as negative values. Error bars represent the standard error of the mean.

Figure 2. Standardized z-scores for each of the 4 primary factors identified by the hierarchical oblique factor analysis. Data were scaled so that control subjects had mean $z=0$ and standard deviation=1 for each measure. Patient deficits were scored as negative values. Error bars represent the standard error of the mean.

Figure 3.

Scatterplot of patient z-scores for factors 1 versus factor 4. Solid line represents the regression fit between the two variables. The dotted lines represent the 95% confidence interval of this fit. The lack of association between the two sets of factor scores indicates that the ERP abnormalities indexed by these two factors manifest themselves independently in different patient subgroups.

Table 1

Clinical Characteristics of Patient Sample (mean±s.d.)

	Males	Females
Age of Onset (yrs)	21.8 ± 5.7	30.4 ± 9.2
Duration of Illness (yrs)	12.2 ± 8.3	10.3 ± 10.7
SANS Total	23.8 ± 21.1	15.3 ± 11.8
SAPS Total	17.3 ± 12.6	16.0 ± 19.6
BPRS Total	30.1 ± 8.6	28.8 ± 8.6
Deficit/Non-deficit (#)	4/10	2/7
Medicated/Unmedicated (#)	11/3	7/2
Dosage (mg CPZ equivalents)	234 ± 176	169 ± 156

Table 2

Auditory Evoked Potential Measures (mean±s.d.)

	Patients	Controls	Effect Size
P50 Amplitude	3.54±1.87	3.62±1.78	0.04
P50 Gating	0.42±0.29	0.49±0.28	0.25
Pitch MMN	4.04±2.31	7.07±2.69	1.21 ***
Duration MMN	6.99±2.79	8.56±2.46	0.60 ⁺
P3a Amplitude	9.19±4.41	12.15±4.96	0.63 *
P3b Amplitude	4.60±2.47	9.15±4.53	1.26 ***
N100 Amplitude	4.95±2.35	7.55±2.84	1.00 **
Startle Amplitude	195.2±213.21	140.0±114.21	0.32
Pre-Pulse Inhibition	0.50±0.33	0.38±0.29	0.39

Patient-Control Difference:

⁺
p=.052*
p<.05**
p<.01***
p<.001

Table 3

Hierarchical Factor Analysis Factor Loadings

	Primary 1	Primary 2	Primary 3	Primary 4
P50 Amplitude	-0.028	0.311	0.658	0.047
P50 Gating	0.038	0.843	0.064	0.001
Pitch MMN	0.619	0.065	0.089	-0.046
Duration MMN	0.671	-0.091	0.045	-0.047
P3a Amplitude	0.004	0.172	-0.008	0.694
P3b Amplitude	0.049	-0.246	-0.001	0.618
N100 Amplitude	0.515	0.042	-0.137	0.112
Startle Amplitude	-0.030	-0.333	0.569	0.181
Pre-Pulse Inhibition	0.063	-0.059	0.576	-0.214

Factor loadings > 0.5 are highlighted in bold.