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Abnormal Auditory Pattern Perception in Schizophrenia

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Abstract

Mismatch negativity (MMN) in response to deviation from physical sound parameters (e.g., pitch, duration) is reduced in individuals with long-term schizophrenia (Sz), suggesting deficits in deviance detection. However, MMN can appear at several time intervals as part of deviance detection. Understanding which part of the processing stream is abnormal in Sz is crucial for understanding MMN pathophysiology. We measured MMN to complex pattern deviants, which have been shown to produce multiple MMNs in healthy controls (HC). Both simple and complex MMNs were recorded from 27 Sz and 27 matched HC. For simple MMN, pitch- and duration-deviants were presented among frequent standard tones. For complex MMN, patterns of five single tones were repeatedly presented, with the occasional deviant group of tones containing an extra sixth tone. Sz showed smaller pitch MMN ($p=.009$, ~110ms) and duration MMN ($p=.030$, ~170ms) than healthy controls. For complex MMN, there were two deviance-related negativities. The first (~150ms) was not significantly different between HC and SZ. The second was significantly reduced in Sz ($p=.011$, ~400ms). The topography of the late complex MMN was consistent with generators in anterior temporal cortex. Worse late MMN in Sz was associated with increased emotional withdrawal, poor attention, lack of spontaneity/conversation, and increased preoccupation. Late MMN blunting in schizophrenia suggests a deficit in later stages of deviance processing. Correlations with negative symptoms measures are preliminary, but suggest that abnormal complex auditory perceptual processes may compound higher-order cognitive and social deficits in the disorder.

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Contributions

Sarah M Haigh helped run the study, analyzed and interpreted the data, and wrote the manuscript

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Timothy K Murphy–designed and ran the study, and helped interpret the data

Christiana D Butera–ran the study and helped interpret the data

Dean F Salisbury–designed the study, helped interpret the data and write the manuscript

All authors reviewed the manuscript before submission

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Keywords

mismatch negativity; schizophrenia; complex-pattern deviant; perceptual grouping

1. Introduction

Schizophrenia is associated with auditory abnormalities, including auditory verbal hallucinations and sensory perceptual deficits. Individuals with schizophrenia show reduced neural responses in auditory event-related potential (ERP) studies (Rosburg et al., 2008; Salisbury et al., 2009), suggesting abnormal cortical sensory-perceptual processing.

One such ERP component, mismatch negativity (MMN), is robustly reduced in long-term schizophrenia (for a review see Umbricht & Krjles, 2005). MMN appears in response to infrequent deviant stimuli, for example, rare 1.2kHz tones played among 1kHz standard tones. MMN amplitude correlates with the ability to match two tones after a short delay, and both MMN and tone matching thresholds are reduced in schizophrenia (Javitt et al., 2000). Therefore, reduction in MMN amplitude may indicate a deficit in detecting deviant stimuli in schizophrenia; however, the mechanisms behind MMN generation are debated.

MMN was originally proposed to reflect pre-attentive sensory-memory (Näätänen, 1990). More recently, MMN was re-conceptualized into a computational model of error-detection (Winkler, 2007; Winkler et al., 2009) where parts of auditory cortex form predictions about the auditory environment. Predictions feed-back to sensory areas and are compared to the incoming signal. MMN reflects prediction error, used to update the predictive model. The error-detection model of MMN therefore reflects communication between (at least) two separate cortical modules (sensory-memory related that may be dissociable from sensory responses, and cognitive). While MMN is typically reported to be around 150ms after deviant-onset, several studies have reported multiple MMNs at later time intervals (~350ms; Zachau et al., 2005; Korpilahti et al., 2001), indicating an auditory system hierarchy (Escera & Malmierca, 2014; Grimm & Escera, 2012).

One theory for MMN generation posits that MMN reflects release from stimulus-specific adaptation (SSA). According to this theory, MMN is essentially a large, delayed N1 response to a new deviant tone (May & Tiitinen, 2007; 2010). Single cell recordings have found SSA and MMN both increase in amplitude with decreased stimulus probability (Ulanovsky et al., 2003). However, SSA and N1 originate from temporal lobe (Javitt et al., 1994; Hari et al., 1980), whereas MMN may originate from outside primary auditory cortex (Korzyukov et al., 1999; Rosburg et al., 2004). Enlarged N1 also does not explain how MMN has been reported outside of the N1 time window. Although SSA/N1 may contribute to simple MMN responses, and may contribute to the sensory-memory component of deviance detection, there is likely a second separate source, which may reflect a cognitive component.

Deviation from complex-patterns also evokes MMN. Measuring —complex MMN responses may better elucidate deficits in the underlying mechanisms of deviance detection dysfunction in schizophrenia, by avoiding release from SSA, and isolating the cognitive

component of deviance detection. Complex MMN has been reported in healthy populations. For example, deviant groups of five tones compared to standard groups of six produce complex MMN, suggesting that deviants from purely temporal patterns can evoke MMN, even when no stimulus is presented (Salisbury, 2012). MMN to deviant paired-tones also appeared at the expected 140ms time window, but there was a second MMN reported at 350ms (Zachau et al., 2005). MMN to language deviants also produced the expected MMN at 150ms, but also a second MMN around 400ms (Korpilahti et al., 2001), creating the possibility of an early (perhaps sensory-memory) MMN that is separate to a later (perhaps cognitive) MMN.

Little work has investigated complex MMN in schizophrenia. Alain and colleagues (1998) found no significant reduction in MMN (~150ms) in schizophrenia to a complex pattern comprising two alternating tones, with the occasional repeated tone as a deviant. Rudolph and colleagues (2015) extended their previous findings by measuring MMN to a missing stimulus in schizophrenia, and found, compared to controls, significantly blunted MMN (~150ms) in individuals who are in their early course psychosis. These results are inconclusive, highlighting the need for further exploration of complex MMN in schizophrenia.

We measured complex MMN to an extra sixth tone among groups of five tones. We predicted that the Gestalt principle of grouping by proximity would lead to a predictive coding model of five tones per group, and that a sixth tone would generate complex MMN due to violation of the abstract model. All tones were the same pitch and duration, hence ruling out any release from SSA. In fact, since the deviant was an extra repeated tone, adaptation demands that any evoked response should be smaller. We predicted that individuals with schizophrenia would show reduced complex MMN compared to controls, particularly in late MMN, indicating a deficit in the detection of deviation from a complex perceptual grouping rule.

2. Methods and Materials

2.1 Participants

Twenty seven participants with schizophrenia (Sz) were compared with 27 healthy control (HC) participants. Sz had at least 5 years length of illness or were hospitalized at least three times for psychosis. Twenty-two Sz had a diagnosis of schizophrenia (undifferentiated=7; paranoid=7; residual=7; disorganized=1), five had schizoaffective disorder (bipolar=3; depressed=2).

All subjects had normal hearing as assessed by audiometry, at least nine years of schooling, and an estimated IQ over 85. None of the participants had a history of concussion or TBI with sequelae, history of alcohol or drug addiction, or detox in the last five years, or neurological or psychiatric comorbidity. Groups were matched for age, gender, handedness, estimated premorbid IQ, and parental socioeconomic status (Table 1).

All participants provided informed consent after receiving a complete description of the study, and were paid for participation. Procedures were approved by the University of Pittsburgh IRB.

2.2 Diagnostic Assessments

Diagnosis was based on the Structured Clinical Interview for DSM-IV (SCID-P). Symptoms were rated using the Positive and Negative Symptom Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS), and the brief UCSD Performance-based Skills Assessment (UPSA-B; for psychosocial functioning). All tests were conducted by an expert diagnostician. Sz were medicated, and moderately symptomatic.

2.3 Neuropsychological Tests

All participants completed the MATRICS Cognitive Consensus Battery. Sz also completed the Brief Assessment of Cognition in Schizophrenia (BACS). In addition, all participants completed the Wechsler Abbreviated Scale of Intelligence (WASI), and the 4-factor Hollingshead Scale to measure socioeconomic status (SES) in the participant and in their parents. As expected, Sz had lower SES than HC, consistent with social and occupational impairment as a disease consequence.

2.4 Procedure

Stimuli were generated with Tone Generator (NCH Software), and presented in Presentation (Neurobehavioral Systems, Inc.). Binaural auditory stimuli were presented using Etymotic 3A insert earphones, with loudness confirmed with a sound meter. Participants were instructed to concentrate on the silent movie and ignore the tones, which were played over earphones.

2.4.1 Stimuli for Simple MMN Protocol—Tones of 1kHz of 50ms duration with 5ms rise/fall times were presented on 80% of trials. Pitch-deviants (1.2kHz, 50ms, 5ms rise/fall) and duration-deviants (1kHz, 100ms, 5ms rise/fall) were each presented 10% of the time. At least two standard tones preceded a deviant tone. Tones had a stimulus-onset-asynchrony (SOA) of 330ms.

2.4.2 Stimuli for Complex MMN Protocol—Physical parameters of all tones used in the complex MMN protocol were the same (1kHz, 50ms pips with 5ms rise/fall times). Temporal proximity was used to form discrete groups, with a SOA within groups of 330ms. Groups were separated by an ITI of 800ms. Five tones formed the standard group. The deviant group included an additional tone, and were presented 10% of the time, with a total of 100 deviant groups. Deviant groups never followed one another.

2.5 Electroencephalogram (EEG) Recording

EEG was recorded from a custom 72 channel Active2 high impedance system (BioSemi), comprising 70 scalp sites including the mastoids, 1 nose electrode, and 1 electrode below the right eye. The EEG amplifier bandpass was DC to 104 Hz (24 dB/octave rolloff) digitized at 512Hz, referenced to a common mode sense site (near PO1). Processing was done off-line

with BESA 6 (BESA GMBH) and BrainVision Analyzer2 (Brain Products GMBH). First, using BESA, EEG was filtered between 0.1 and 20Hz; the low cutoff was to remove DC drifts and skin potentials, the high cutoff was to remove muscle and other high frequency artifact. Data were visually examined and bad channels were interpolated. ICA (InfoMax) was used to isolate and remove one vertical and one horizontal EOG component from the first 600 seconds of the EEG recording. In BrainVision Analyzer2, data were rereferenced to averaged mastoids (complex MMN was larger with a clearer topography, than with nose reference). Epochs (400ms for the analysis of the simple MMN, and 700ms for the complex MMN) were extracted from the EEG based on stimulus triggers, including a 50ms prestimulus baseline. Epochs were baseline corrected, and DC detrended between baseline (−50 to 0) and the last 50ms of the epoch to ensure that the data were not skewed by skin potentials and steady-state drift. Epochs were subsequently rejected if any site contained activity $\pm 50\mu\text{V}$.

2.6 Data Analysis

2.6.1 MMN Measurement for Simple Single-Tone Deviants—MMN waveforms were calculated by subtracting the ERP waveform in response to the immediately preceding standard tone from the deviant tone ERP waveform. This ensured equal signal-to-noise ratios across deviant and standard averages. The window for calculating MMN amplitude depended on the maximal response for both SZ and HC in the grand averages. For MMN to pitch-deviants, the average voltage was calculated between 105–125ms. HC and SZ did not significantly differ in the number of epochs included in the averages (HC: 151.6 (18.8); Sz: 152.0 (27.2); $t(50)=.06, p=.951$). For the duration-deviant, the response was calculated between 165–185ms. HC and SZ did not differ in the number or trials included in averages (HC: 147.8 (21.9); Sz: 152.5 (26.8); $t(50)=.06, p=.951$). Two Sz were not tested on the simple MMN paradigm due to time constraints.

2.6.2 MMN Measurement for Complex Extra-Tone Deviant—Complex MMN waveforms were calculated by subtracting the ERP waveform in response to the last tone in the immediately preceding standard group from the deviant extra-tone ERP waveform. Again, this ensured equal signal-to-noise ratios across deviant and standard averages. Due to the potential for multiple MMNs we took an agnostic approach with regards to the timings of MMNs. Subtraction waveforms showed two deviant-related negativities: the first within the time window expected for MMN (150–170ms), and a second later negativity (380–430ms). HC and SZ did not differ in the number of trials included in averages (HC: 92.5 (24.8); Sz: 84.4 (22.9); $t(52)=1.24, p=.220$).

2.7 Statistics

Analysis was performed at electrodes F1, Fz, F2, FC1, FCz and FC2, where MMN is largest, using mixed models ANOVA with the Huynh-Feldt epsilon correction for factors with more than 2 levels. Group (HC, Sz) was used as the between-subjects factor, and electrode chain (frontal and frontocentral chains) and laterality (left, central, and right electrodes) as within-subjects factors. Only significant effects are reported. Cohen's d effect sizes were calculated for group comparisons. MMNs were subjected to current source density (CSD) analysis to infer source-sink topography. Interpolation was done using spherical splines, with the order

of splines set to 4, the maximum degree of Legendre polynomials set to 10, and a default lambda of 1e-5. Spearman correlations measured the relationship between simple pitch and duration MMNs and complex extra MMNs for each group (HC, Sz) separately.

Exploratory Spearman correlations examined relationships between MMN responses at FCz (where MMN amplitude was largest) and medication dosage, length of illness, items in the MATRICS, PANSS, SAPS, SANS, UPSA, (including summary scores on these scales), and WASI. Correlations were conducted separately for simple pitch and duration MMN, and complex extra-tone MMNs. Only significant correlations are reported.

3. Results

3.1 Simple MMN to Pitch and Duration Deviants

The pitch deviant tone produced a negative deflection in HC (Figure 1A) and in Sz (Figure 1B) not seen to the standard tone. MMN was significantly larger in HC (-4.9 (1.9) μ V) than in Sz (-2.8 (1.9) μ V; $F(1,50)=15.12, p<.001$; $d=1.08$). There were no significant differences between HC and SZ in their responses to the standard tone in the MMN latency range ($t(50)=0.86, p>.05$). Scalp topography and CSD maps showed the expected MMN distribution, suggesting sources in temporal cortex (Figure 1C). Difference between HC and SZ was significantly larger at frontocentral chains compared to frontal chains ($F(1,50)=5.42, p=.024$). For both HC and SZ, MMN was largest at central electrode sites ($F(1.9,92.7)=4.93, p=.009$) compared to left and right hemisphere sites. There was also an interaction between electrode chain and laterality ($F(2,100)=6.7, p=.002$), with maximal MMN at FCz.

The duration deviant tone produced a negative deflection in HC (Figure 2A), and in Sz (Figure 2B), not seen to the standard tone. MMN amplitude was significantly larger in HC (-3.1 (2.6) μ V) compared to Sz (-1.6 (1.6) μ V; $F(1,50)=6.60, p=.013$; $d=0.70$). Scalp topography and CSD maps showed the expected distribution for bilateral sources in the temporal lobe (Figure 2C). Difference between HC and SZ trended to be larger at frontocentral chains compared to frontal chains ($F(1,50)=3.92, p=.053$). For both HC and SZ, MMN was largest at central electrode sites ($F(1.7,85.3)=6.1, p=.005$) compared to left and right hemisphere sites, and maximal MMN at FCz (electrode chain x laterality interaction; $F(2,100)=3.4, p=.039$).

3.2 Complex MMN to the Extra Tone

The extra tone deviant produced two negative deflections not seen to the standard waveform (compare Figure 3A and 3B). The first negativity (early MMN) was similar in amplitude in HC (-1.0 (1.3) μ V) and Sz (-0.9 (1.3) μ V; $F(1,52)=0.09, p=.763$; $d=0.08$; Figure 3C). The second negativity (late MMN) was significantly larger in HC (-1.1 (1.0) μ V; Figure 3A) than in Sz (-0.1 (1.0) μ V; $F(1,52)=11.96, p=.001$; $d=0.94$; Figure 3B and 3C). Importantly, HC showed significantly different from zero late MMN at all sites ($p<.001$), but no site was significantly different from zero in Sz ($p>.446$). There were no significant differences between HC and SZ in their responses to the standard tone in the complex pattern in the MMN latency range ($t(52)=1.47, p>.05$). In HC, scalp topography maps showed fronto-

central distributions, and CSD maps indicated temporal source activity more anterior than for simple MMN. Sz CSD and topography maps show that there is no obvious MMN-like activity at the same time point (Figure 3C; cf. Figure 1C and Figure 2C).

3.3 Correlations between MMN measures

For HC, there was a significant correlation between pitch and duration MMN ($r(23)=.52$, $p=.008$), whereas the correlation was weaker in Sz and not significant ($r(25)=.32$, $p=.104$). There was no significant correlation between pitch or duration MMN and the late complex MMN for HC (pitch: $r(23)=-.21$, $p=.314$; duration: $r(23)=.11$, $p=.601$) or for Sz (pitch: $r(25)=-.01$, $p=.961$; duration: $r(25)=-.13$, $p=.518$). There was a significant correlation between early complex MMN and duration MMN for HC ($r(23)=.44$, $p=.028$), but this was not significant for pitch MMN ($r(23)=-.04$, $p=.849$), and neither correlation was significant in Sz (pitch: $r(25)=.16$, $p=.435$; duration: $r(25)=-.26$, $p=.190$).

3.4 Correlations with Clinical and Cognitive Variables

For HC, there was no significant correlation between any of the MMN responses and any neuropsychological test.

3.4.1 Simple MMN—In Sz, pitch MMN at FCz were significantly correlated with working memory scores in the MATRICS ($r(25)=-.47$, $p=.019$), and with financial measures on UPSA ($r(25)=-.45$, $p=.029$). Duration MMN did not significantly correlate with any neuropsychological test, but did with medication ($r(25)=.43$, $p=.037$).

3.4.2 Complex MMN—Despite there being no significant late MMN in Sz at the group level, there was some variability in late MMN responses within the Sz group. Therefore, correlations between late MMN and symptomology were calculated. For the early MMN in Sz, there was a significant correlation with social cognition in the MATRICS ($r(25)=-.45$, $p=.023$), and a significant negative correlation with medication ($r(25)=-.44$, $p=.032$).

Correlations between the late MMN in Sz and PANSS scores showed significant positive correlations with emotional withdrawal ($r(25)=.41$, $p=.038$), lack of spontaneity and flow of conversation ($r(25)=.40$, $p=.046$), and poor attention ($r(25)=.54$, $p=.005$; Figure 4).

4. Discussion

Sz showed reductions in simple pitch and duration MMN (pitch $d=1.08$, duration $d=0.7$). For the complex pattern, there were two deviance-related negativities. The first was in the N1 time window (~150ms), and both HC and Sz produced similar MMN amplitudes (~-1 μ V). In Sz, the early MMN did not correlate with symptoms or cognitive measures, except social cognition. The second deviance-related negativity appeared later (~400ms), and was significantly reduced in Sz ($d=0.94$). Exploratory correlations showed that late MMN correlated with emotional withdrawal, lack of spontaneity and flow of conversation, poor attention, and preoccupation in the PANSS, suggesting that the less symptomatic the individual, the more negative their late MMN. While these results are correlational, there is a recent understanding that deficits in perceptual processing likely impacts cognitive and social behavior (Javitt, 2009). For example, difficulty in decoding modulation of pitches and

emphasis in speech can lead to impaired social cognition due to failure to appreciate emotional cues (Leitman et al., 2005). Similarly, failure to parse perceptual objects into larger meaningful groups may undermine the cognition needed to navigate the social environment.

Late MMN may be a part of the hierarchical deviant detection system (Escera & Malmierca, 2014; Grimm & Escera, 2012), and maybe delayed due to the recruitment of more cognitive areas of the cortex to recognize the deviant. Consistent with previous studies (Zachau et al., 2005; Korpilahti et al., 2001), there was an early MMN that located to temporal lobe, and a late MMN that was qualitatively more anterior in location than early MMN (CSD maps in Figure 3C), either suggesting different MMN generators, or that the MMNs have relatively different activation weights in a distributed MMN system. In addition, the significant correlation between pitch and duration MMN in HC but not between simple MMN and late complex MMN, supports the theory that late MMN has differential activation from simple MMN. This could indicate an early sensory-memory component and a later cognitive component.

The early MMN cannot be due to release from adaptation as all tones were identical, and so there may be a deviance detection circuit within temporal lobe that evokes the early MMN. This response appears to be intact in Sz, which is consistent with previous findings (Alain et al., 1998). While simple MMN was significantly larger in HC than in Sz, the early complex MMN was not, despite being measured at a similar time point. The reason for this is unclear. It is possible that there is an additional sensory signal that amplifies the simple MMN in HC, and it is this signal that is abnormal in Sz – the simple MMN is three to five times larger than the early complex MMN in HC. Another possibility is that the cognitive (late) MMN is delayed on the complex pattern task, but coincident with the early MMN on the simple task. This would lead to a larger simple MMN in HC than Sz.

Late MMN may be an interesting tool for understanding the pathophysiology of Sz as it may be impinging on cognitive and social functioning in the disease. The late MMN correlated with several item measures on the PANSS. While these correlations are exploratory and require further investigation, they were not significantly correlated with early MMN or simple MMN, suggesting that there is something specific about the late MMN that is reflecting a certain subset of behavioral symptoms. Sz also show other impairments in auditory processing such as the ability to segregate auditory information (Ramage et al., 2012; Weintraub et al., 2012), and in ERP measures of auditory grouping (Coffman et al., 2016), which may be related to the deficits in deviance detection.

In summary, the late MMN to complex pattern deviants is significantly blunted in Sz and preliminary analysis suggest that late MMN is associated broadly with negative symptoms. The late MMN may reflect a cognitive component of deviance detection compared to the early MMN, which may be more related to sensory-memory. In addition, MMN to a complex pattern deviant cannot be due to SSA, showing that the late MMN reflects deviant-detection abilities. The blunted late MMN in Sz demonstrates a deficit in pure deviance detection.

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Figure 1.

Waveforms to the pitch-deviant (red) and the preceding standard tone (black) in (A) HC, and (B) Sz at FCz. (C; Left to Right) Current source density (CSD) and scalp topography maps of MMN in HC; MMN in HC (black) and Sz (red) at FCz (peak indicated by arrow); CSD and topography maps of MMN in Sz. Scales of maps adjusted to accurately reflect distribution in each group unconfounded by main effect.

Figure 2.

Waveforms to the duration-deviant (red) and the preceding standard tone (black) in (A) HC, and (B) Sz at FCz. (C; Left to Right) CSD and scalp topography maps of MMN in HC; MMN in HC (black) and Sz (red) at FCz (peak indicated by arrow); CSD and topography maps of MMN in Sz. Scales of maps were adjusted to accurately reflect distribution in each group unconfounded by main effect.

Figure 3.

Waveforms to the extra-tone deviant (red) and the last tone from the preceding standard trial (black) in (A) in HC, and (B) Sz at FCz. (C; Left to Right) CSD and scalp topography maps of the late MMN in HC; MMN in HC (black) and Sz (red) at FCz. Early MMN indicated by the grey arrow, and late MMN indicated by the black arrow. CSD and topography of the late MMN in Sz. Scales of maps were adjusted to accurately reflect distribution in each group unconfounded by main effect.

Figure 4.

Late MMN amplitude positively correlated with scores on PANSS tests: emotional withdrawal, lack of spontaneity and flow of conversation, and poor attention.

Demographic and diagnostic information for the Sz and HC groups, with t /chi-square statistics and p-values for group comparisons. Medication is listed in Chlorpromazine (CPZ) equivalents.

Table 1

Age	36.00	(7.85)	Sz	HC	(11.2)	Statistics
Gender	16 M /11 F	14 M /13 F				$\chi^2(3)=0.03, p=.584$
% Right handed	25 M /2 L	23 R /4 L				$\chi^2(3)=0.59, p=.442$
SES	34.08	(13.96)		42.41	(11.1)	$t(52)=2.66, p=.010$
Parental SES	37.69	(13.41)		42.30	(12.7)	$t(52)=1.61, p=.113$
IQ	99.81	(18.78)		104.85	(8.3)	$t(52)=1.28, p=.206$
MATRICES	50.96	(16.41)		57.19	(5.7)	$t(52)=2.14, p=.037$
Medication (CLZ mg/day)	799.26	(648.53)				
Length of illness (days)	775.28	(439.96)				
PANSS total	63.00	(21.91)				
PANSS positive	16.15	(6.27)				
PANSS negative	17.54	(5.30)				
SAPS (global items)	3.59	(3.17)				
SAPS (symptom items)	8.81	(9.97)				
SANS (global items)	11.26	(3.34)				
SANS (symptom items)	33.93	(8.96)				
UPSA communication	78.70	(13.07)				
UPSA financial	85.61	(13.11)				