The Viability of the Frequency Following Response Characteristics for use as Biomarkers of
Cognitive Therapeutics in Schizophrenia

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Abstract

Deficits in early auditory information processing contribute to cognitive and psychosocial disability; this has prompted development of interventions that target low-level auditory processing, which may alleviate these disabilities. The frequency following response (FFR) is a constellation of event-related potential and frequency characteristics that reflect the processing of acoustic stimuli at the level of the brainstem and ascending portions of the auditory pathway. While FFR is a promising candidate biomarker of response to auditory-based cognitive training interventions, the psychometric properties of FFR in schizophrenia patients have not been studied. Here we assessed the internal consistency characteristics and magnitude of group differences across 18 different FFR parameters to determine which of these parameters demonstrate adequate internal consistency. Electroencephalography from 40 schizophrenia patients and 40 nonpsychiatric comparison subjects was recorded during rapid presentation of an auditory speech stimulus (6,000 trials). Patients showed normal response amplitudes but longer latencies for most FFR peaks and lower signal-to-noise ratios (SNRs) than healthy subjects. Analysis of amplitude and latency estimates of peaks, however, indicated a need for a substantial increase in task length to obtain internal consistency estimates above .80. In contrast, excellent internal consistency ($> .95$) was shown for FFR sustained responses. Only SNR scores reflecting the FFR sustained response yielded significant group differences and excellent internal consistency, suggesting that this measure is a viable candidate for use in clinical treatment studies. The present study highlights the use of internal consistency estimates of FFR to guide future intervention studies interested in individual differences among patients.

Keywords: internal consistency, frequency following response (FFR), event-related brain potential (ERP), schizophrenia, auditory processing

Cognitive impairment is a robust predictor of psychosocial disability and functional outcomes in schizophrenia (Elvevag & Goldberg, 2000; Green, Kern, Braff, & Mintz, 2000; Green & Nuechterlein, 1999). Substantial evidence has accumulated linking cognitive impairment to deficits in lower-level auditory information processing via a variety of measures (Javitt, 2009; Kirihaara, Rissling, Swerdlow, Braff, & Light, 2012; Koshiyama et al., 2020; Rissling et al., 2014; Thomas et al., 2017). Abnormalities in auditory information processing are documented in patients prior to symptom onset (i.e., in clinical high risk populations), in early stage illness, and in chronic disease (Erickson, Ruffle, & Gold, 2016; Hamilton, Boos, & Mathalon, 2020). Due to the congruence of these observations, electroencephalographic (EEG) biomarkers, which index auditory information processing, are increasingly being promoted to identify and optimize novel pro-cognitive therapeutics. For example, auditory information processing EEG biomarkers have been used to identify response to putative pro-cognitive medications and novel “bottom-up” auditory-based targeted cognitive training (TCT) interventions (Light et al., 2020).

An EEG measure that has been relatively unexplored in the context of pro-cognitive therapeutic development is the frequency-following response (FFR). FFR—also referred to as the auditory brainstem response to complex sounds (cABR)—is an event related brain potential (ERP) that reflects early sound-evoked synchronous neural activity that tightly corresponds to the acoustic properties of a stimulus (Kraus & White-Schwoch, 2015, 2017). FFR primarily represents a manifestation of auditory midbrain activity, and this activity is sensitive to changes in a distributed auditory system that includes cortical and subcortical sources, such as the auditory nerve, inferior colliculus, cochlear nucleus, thalamus, and primary auditory cortex (Coffey et al., 2019). The 40-ms ‘da’ stimulus is among the most frequently used speech

stimulus to elicit FFR and consequently has particular nomenclature for its ERP peaks (e.g., see Figure 1). In short, FFR purportedly provides a neural representation of auditory perceptual encoding (Kraus & White-Schwoch, 2015, 2017).

Measures of FFR are sensitive to short- and long-term auditory training interventions in healthy participants and children with language disorders and changes in cognitive functioning, demonstrating that FFR is malleable (Elmer, Hausheer, Albrecht, & Kühnis, 2017; Russo, Nicol, Zecker, Hayes, & Kraus, 2005; Skoe, Krizman, Spitzer, & Kraus, 2013; Song, Skoe, Wong, & Kraus, 2008). However, it is unknown whether FFR measures collected from patients with schizophrenia are sensitive to intervention. FFR measures may also be useful in predicting treatment response to pro-cognitive approaches that leverage complex sounds, such as in auditory-based TCT. Although auditory TCT appears effective at a group level, there is substantial variability in response to treatment among individual patients (Murthy et al., 2012; Thomas et al., 2018), with some studies showing little or no benefit even after 100h of treatment (Fisher, Holland, Subramaniam, & Vinogradov, 2010). To date only a single pilot study of FFR has been conducted in schizophrenia patients which demonstrated that a 15-minute task was well tolerated (Tarasenko, Swerdlow, Makeig, Braff, & Light, 2014).

In order to determine the suitability of FFR to act as a predictive biomarker of pro-cognitive interventions, the primary goal of this study was to characterize the psychometric properties of individual constituent measurements of the FFR response in both schizophrenia and healthy nonpsychiatric comparison subjects. We also sought to determine whether FFR measures are abnormal in schizophrenia. Lastly, we aimed to explore whether FFR measures were related to traditional measures of speech perception, cognition, and clinical variables.

2. Method

2.1 Participants

Study enrollment included 40 treatment-refractory patients with schizophrenia or schizoaffective disorder and 40 healthy controls. Patients were recruited from a community-based inpatient treatment program and deemed clinically stable by their treatment team, and healthy controls were recruited from the community via internet advertisements and bulletin boards. The research was approved by the Institutional Review Board of the University of California, San Diego (IRB#130874). All participants provided written informed consent and subsequent written approvals from public guardians/conservators were also obtained for all patients.

Psychiatric diagnoses were assessed using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (SCID; First, Spitzer, Gibbon, & Williams, 1996). Exclusion criteria for all participants included an inability to understand the consent process and/or provide consent, not being a fluent English speaker, auditory detection threshold above 40 dB at 1 kHz, head injury with loss of consciousness exceeding thirty minutes, neurological illness, severe systemic illness, or current mania.

2.2 Experimental Task

Participants listened to binaurally presented stimuli via insert earphones (Etymotics ER-3A earphones) at 75 dB SPL while seated comfortably in a reclining chair watching a silent cartoon. Stimuli comprised 6,000 five-formant synthesized speech sounds (i.e., speech syllable ‘da’) presented for a duration of 40 ms with an inter-stimulus interval of 90 ms (see Klatt, 1980; Krizman & Kraus, 2019). The ‘da’ stimulus was presented in alternating polarity, which is recommended practice for recording FFR (Krizman & Kraus, 2019). FFRs to either polarity are nearly identical, and for the purposes of this study the polarity of the stimulus was ignored

during data analysis. The fundamental frequency (F_0 : 103 to 125 Hz) and first three formants (F_1 : 220 to 720 Hz, F_2 : 1,700 to 1,200 Hz, F_3 : 2,580 to 2,500 Hz) changed linearly over the course of a stimulus. F_4 and F_5 remained constant at 3,600 Hz and 4,500 Hz, respectively (see Krizman, Skoe, & Kraus, 2012).

2.3 Electrophysiological Data Recording and Reduction

Continuous EEG was recorded using an ActiveTwo BioSemi amplifier (BioSemi, Amsterdam, Netherlands), which uses active Ag/AgCl sintered electrodes. EEG signals were digitized at a sampling rate of 8,192 kHz with a 24-bit analog-to-digital converter (least significant bit: 31.25 nV). EEG was recorded from 64 active scalp electrodes placed based on the 10/20 system using a custom cap (Cortech Solutions, Wilmington, North Carolina, USA). Additional sensors were placed on the left and right mastoids and above and below the left eye and near the outer canthi. Channels were referenced online to a common mode sense electrode. Lastly, the audio input was also digitally encoded on a dedicated A/D channel, event markers were adjusted to the onset of the audio stimulus recorded in the A/D channel.

EEG data were subsequently re-referenced to algebraically linked mastoids and filtered offline using an infinite impulse response Butterworth filter implemented in ERPLab v6.1.4 (Lopez-Calderon & Luck, 2014). The fourth-order highpass filter (24 dB/oct) used a half-amplitude cutoff at 100 Hz, and the sixth-order lowpass filter (36 dB/oct) used a half-amplitude cutoff at 400Hz. Stimulus-locked epochs were then extracted using a temporal window of 15 ms prior to stimulus onset to 60 ms following stimulus onset. Epochs were rejected if a voltage difference of more than 23.8 μ V was detected at Cz within any given epoch, and this 23.8- μ V cutoff is the standard threshold for rejecting artifact when recording FFR (e.g., Krizman, Bonacina, & Kraus, 2019; Otto-Meyer, Krizman, White-Schwoch, & Kraus, 2018). The period

from 15 ms to 0 ms prior to the onset of the audio stimulus was used for baseline adjustment. All ERP measurements were extracted at channel Cz. Healthy controls had an average of 5,997 trials (min to max: 5,963 to 6,000) and patients with schizophrenia had an average of 5,995 trials (min to max: 5,933 to 6,000).

2.4 Broadband Timing and Response Magnitude

There is no empirically derived consensus regarding the optimal approach for measuring FFR (for review, see Krizman & Kraus, 2019). Some of the most common time-domain measures of FFR are broadband timing and broadband response magnitude estimates.

2.4.1 Broadband timing. Broadband timing is analyzed by extracting the latencies of each peak following the auditory stimulus. The latency of Peak V was extracted as the time point at which the peak amplitude reached the minimum voltage between 3 and 5.5 ms from single trials. For the remaining peaks, the time point at which peak amplitude reached the maximum voltage was extracted. Peak A was measured between 5.5 and 9 ms, Peak C between 15 and 18 ms, Peak D between 19.5 and 25 ms, Peak E between 28.5 and 33 ms, Peak F between 37 and 41.5 ms, and Peak O 44.5 and 49.5 ms.

2.4.2 Broadband response magnitude. Measures of broadband response magnitude focus on the amplitude of the ERP following the auditory stimulus. The amplitude of Peak V was quantified as the absolute minimum amplitude between the specified latency window. The absolute maximum amplitude was extracted for the remaining positive-going peaks using the specified latency windows. The root mean square (RMS) of amplitude measurements between -15 and 0 ms prior to presentation of the audio stimulus and between 19.5 and 44.2 ms following presentation of the audio stimulus were extracted. These RMS measurements were then used to create a measure of relative magnitude called the signal-to-noise ratio (SNR). The SNR is

computed by first dividing post-stimulus RMS activity by pre-stimulus RMS activity. This score is converted to dB by computing 20 times the base log 10 of this score (i.e., dB SNR).

2.5 Speech Perception in Noise

Two measures of speech perception in noise were administered and included the Words-in-Noise (WIN) test from the NIH Toolbox (Zecker et al., 2013) and the Quick Speech-in-Noise Test (QuickSIN, Killion, Niquette, Gudmundsen, Revit, & Banerjee, 2004). Tests were modified to allow for binaural presentation. The WIN tests the ability to recognize single words presented amid varying volume levels of background conversation noise. Thirty-five words are presented in seven blocks of five items while SNR decreases (26 dB, easy, to -2 dB SNR, difficult). The number of correctly recognized words is multiplied by 0.8 and subtracted from 26 to convert the raw scores to dB SNR thresholds, which was the primary measure of interest for the present study. During the QuickSIN, participants are tested on their ability to remember five key words of a sentence amid varying volume levels of background conversation noise (four-talker babble). Thirty total words are presented across six sentences while SNR decreases (25 dB, easy, to 0 dB, difficult). The total recalled words were subtracted from 25.5 to convert to an SNR Loss score, which was the primary measure of interest.

2.6 Cognitive and Clinical Assessments

All participants completed the MATRICS Consensus Cognitive Battery (MCCB) to assess cognitive functioning (Nuechterlein & Green, 2006). The primary measure of interest for the MCCB was overall neurocognitive composite scores, which were converted into standardized *T* scores ($M = 50$, $SD = 10$) and adjusted for age and gender (Kern et al., 2008). Psychiatric symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1984a, 1984b).

2.7 Data Analysis

Single-trial measurements were averaged for statistical analysis, so analyses reflect the data that contribute to the reliability estimates. However, peak amplitude and latency measurements are susceptible to trial-by-trial fluctuations in background EEG (Clayson, Baldwin, & Larson, 2013). Therefore, trial-by-trial variability was likely obscured in grand average waveforms (see Figure 1), but they are reflected in the within-trial standard deviations discussed in sections 3.3.1 and 3.3.2.

First, one-sample t tests against zero for averaged single-trial peak amplitudes was conducted for each group as a validity check to determine whether expected peaks were present. Equal variances were not assumed, and pooled standard deviations were used in the calculation of effect sizes (Bonett, 2008).

Next, separate 2-Group (controls, patients) robust analyses of variance (ANOVAs) were performed on averaged single-trial ERP latencies. A 2-Group x 7-Peak (V, A, C, D, E, F, O) robust ANOVA was performed on ERP amplitudes. Then, separate 2-Group x 2-Timing (pre-stimulus, post-stimulus) robust ANOVAs were performed on RMS scores. Next, 2-Group robust ANOVAs were conducted on SNR and dB SNR scores.

To avoid the biasing effects of non-normality and (co)variance heterogeneity (see Dien, 2017; Dien & Santuzzi, 2005; Keselman, Wilcox, & Lix, 2003), robust ANOVAs were implemented within R (R Development Core Team, 2018) using the library `welchADF` (Villacorta, 2017). Robust ANOVAs used trimmed means (2.5% from each tail) and Winsorized (co)variances to calculate test statistics ($T_{WJ/c}$). Follow-up contrasts to significant interactions used a bootstrapped critical value to maintain a family wise error rate of .05. Although effect size calculations are not available for omnibus analyses, effect sizes ($\hat{\delta}_j^{(R)}$) are reported for follow-up

contrasts (Keselman, Algina, Lix, Wilcox, & Deering, 2008). The number of iterations used for bootstrapping was 50,000, and the starting seed for the random number generator was set to 1,000 for all analyses.

2.8 Internal Consistency

To circumvent issues related to selecting any particular internal consistency threshold, the numbers of trials needed for each FFR measurement for multiple thresholds (.70, .80, .90, and .95) were estimated to provide guideposts for future studies of FFR in schizophrenia.

Generalizability theory was used to calculate dependability (ϕ), which is a measure of internal consistency analogous to Cronbach's alpha from classical test theory (see Baldwin, Larson, & Clayson, 2015; Brennan, 2001; Clayson, Brush, & Hajcak, 2020; Shavelson & Webb, 1991). Dependability as a function of the number of trials needed for a stable average for each ERP component and group was examined using the ERP Reliability Analysis (ERA) Toolbox v 0.5.0 (Clayson, Carbine, Baldwin, Olsen, & Larson, 2020; Clayson & Miller, 2017a). The ERA Toolbox used CmdStan v 2.21.0 (Stan Development Team, 2019) to implement the analyses in Stan (Carpenter et al., 2017). To estimate variance components, the Markov chain Monte Carlo estimation procedures used 3 chains and 10,000 iterations each.

3. Results

3.1 Sample Characteristics

Table 1 provides demographic summary information for both groups. Patients were younger, scored lower on the WRAT, and performed worse on all scales of the MCCB, and patients had lower personal, but not parental, levels of education than nonpsychiatric comparison subjects. For the speech-in-noise measures, patients performed worse on the QuickSIN (higher

scores reflect worse performance), but significant group differences were not observed for the WIN.

Grand average waveforms for healthy controls and patients with schizophrenia are shown in Figure 1, and summary scores for averaged single-trial ERP measurements are shown in Table 2. All amplitude scores from both groups were significantly different from zero ($|ts| > 5.6$, $ps < .001$, $ds > 2.8$) and passed the validity check.

3.2 Initial Pattern of Effects

Next, the pattern of responding across groups was examined for estimates of broadband timing and estimates of broadband response magnitude.

3.2.1 Broadband timing. Patients with schizophrenia showed longer latencies for Peaks C, D, E, F, and O than healthy controls ($T_{WJt/cs} > 5.9$, $ps < .02$; see Figures 2 & 3). Significant group differences were not observed for Peaks V or A ($T_{WJt/cs} < 1.7$, $ps > .21$).

3.2.2 Broadband response magnitude. A 2-Group x 7-Peak robust ANOVA on peak amplitudes yielded a main effect of peak, $T_{WJt/c}(6.0, 198.8) = 332.97$, $p < .001$; see Figures 2 & 3. Peak V was more negative than each other peak ($T_{WJt/cs} > 317$, $ps < .001$), which is expected as Peak V is the only negative deflection. The remaining significant contrasts are shown in Table 3. The main effect of group and Group x Peak interaction were not significant, $T_{WJt/c}(1.0, 373.7) = 0.69$, $p = .41$; $T_{WJt/c}(6.0, 198.8) = 1.60$, $p = .14$, respectively.

A 2-Group x 2-Timing robust ANOVA on RMS scores yielded no significant effects ($T_{WJt/cs} < 0.5$, $ps > .48$; see Figure 4). Healthy controls showed larger SNR scores than patients with schizophrenia, $T_{WJt/c}(1.0, 61.06) = 4.16$, $p = .048$, but significant differences were not observed for dB SNR, $T_{WJt/c}(1.0, 55.05) = 1.84$, $p = .20$.

3.3 Internal Consistency

The overall dependability estimates for each measure and group are shown in Table 4. Dependability estimates reflect the internal consistency of the measurements are derived using generalizability theory. For transient response scores (latency and amplitude estimates of individual peaks) the numbers of trials needed to obtain internal consistency thresholds of .70 and .80 are summarized below. For sustained response scores (pre-stimulus RMS, post-stimulus RMS, SNR, and dB SNR) the numbers of trials needed to achieve internal consistency thresholds above .95 are summarized below, because high reliability was easily obtained using the current task length. Between- and within-person standard deviations are reported in Table 5, and variance components are reported in Table 6.

3.3.1 Broadband Timing. Dependability estimates for peak latencies ranged from .80 to .90 for healthy controls and from .70 to .84 for patients. The numbers of trials needed to obtain dependability estimates of .70 was 1,419 to 3,273 for healthy controls and 2,410 to 5,669 for patients, which indicates the current task length is sufficient to achieve a .70 reliability threshold in both groups.

In order to achieve a dependability threshold of .80 for each peak latency, 2,432 to 5,610 trials were needed for healthy controls, and 4,132 to 9,718 trials were needed for patients with schizophrenia. For patients there were too few trials in the current task for Peaks V, A, C, and D.

Generally speaking, peak latency estimates yielded lower internal consistency in patients than in healthy controls. Based upon visual inspection of the between- and within-person standard deviations this appeared to be the result of lower between-person standard deviations in patients than in controls. This indicates that within-person variance (i.e., measurement error) was comparable across groups. Lower between-person variance in patients than controls suggests that

patients yielded single-subject average estimates that were more similar to each other than controls did.

3.3.2 Broadband Response Magnitude. Dependability estimates were very low for Peak V amplitude scores for both groups (controls = .07, patients = .28). Given how low dependability estimates of Peak V amplitudes were compared to other peaks, Peak V is excluded from the remainder of this summary.

For the remaining peak amplitude scores dependability estimates for controls ranged from .64 to .93 and estimates for patients ranged from .60 to .84. Most amplitude scores achieved the .70 internal consistency threshold using the present task length of 6,000 trials.

Amplitude scores for Peaks C, E, F, and O from the control and Peak O from the patient group were the only peaks to obtain the .80 internal consistency threshold using the current task length. For all ERP amplitude measures of Peaks A, C, D, E, F, and O to obtain an internal consistency of at least .80, it was estimated that 12,188 trials would be needed for healthy controls, and 14,321 trials would be needed for patients.

For most amplitude scores, between-person standard deviations were numerically larger for the healthy control group than for the patient group. This suggests that there is more variability in person-specific averages in the control group than in the patient group, which leads to higher internal consistency estimates for controls. Within-person standard deviations were also generally smaller in the healthy control group than in the patient group. This smaller variability in between-trial amplitude scores leads to smaller error variance in the internal consistency estimates for the healthy control group, which results in higher internal consistency estimates. Taken together, higher internal consistency estimates in the healthy control group than in the

patient group were typically due to larger between-person differences in average scores and smaller between-trial differences in amplitude scores.

The four remaining broadband response magnitude measures (i.e., pre-stimulus RMS, post-stimulus RMS, SNR, dB SNR) obtained very high internal consistency using the current task length. Overall dependability was high and ranged from .98 to >.99 for healthy controls and ranged from .96 to >.99 for patients. In order to obtain dependability estimates above .70, only 10 to 205 trials were needed for healthy controls, and 11 to 480 trials were needed for patients. To obtain a .80 threshold, 17 to 352 trials were needed for healthy controls, and 12 to 480 trials were needed for patients.

For pre- and post-stimulus RMS, patients showed numerically similar between-person standard deviations to controls but larger within-person standard deviations. Although patients showed smaller within-person standard deviations than controls for SNR and dB SNR scores, healthy controls showed proportionally large between-person standard deviations, which led to improved reliability estimates with relatively fewer trials than patients.

3.4 Age Subset Analyses

The oldest third of controls and youngest third of patients were removed to create group subsets that did not significantly differ on age, $t(50) = 1.20$, $p = .24$. Twenty-six participants remained in each group. Patients with schizophrenia still showed longer latencies for Peaks D, E, F, and O than healthy controls ($T_{WJt/cs} > 4.0$, $ps < .05$). However, significant group differences were not observed for any other latency or amplitude measure ($T_{WJt/cs} < 3.7$, $ps > .05$).

3.5 Exploratory Analyses

Exploratory analyses were conducted by examining the relationships between each FFR measurement and external correlates, and this was done separately for patients (see Table 7) and

controls (see Table 8). External correlates included scores from the WRAT, QuickSIN, WIN, and MCCB, and scores from the SANS and SAPS were also examined in patients. In patients, larger Peak A was related to better performance on the MCCB, and higher pre-stimulus and post-stimulus RMS were related to lower scores on the WRAT. Additionally, smaller SNRs were related to higher SANS scores. A different pattern of relationships was observed in healthy controls (see Table 8). None of the correlations were significant at a Bonferroni-corrected threshold ($p < .00028$).

4. Discussion

The primary purpose of the current study was to evaluate internal consistency estimates of FFR scores in healthy controls and in participants with schizophrenia in order to advance the use of FFR as a potential predictive biomarker of treatment response for pro-cognitive interventions. To our knowledge, this study is the first reported investigation of speech elicited FFR in schizophrenia, and there are several important implications of our findings.

Group differences in most latency estimates of broadband timing (Peaks C, D, E, F, and O) and an estimate of broadband response magnitude (SNR) suggest that patients with schizophrenia show deficits in this very early stage of auditory information processing. Longer latencies of FFR peaks likely reflect slower transmission of information across the ascending auditory pathway, and reductions in SNR in patients might reflect lower-fidelity neural signaling. Other studies of click ABR in schizophrenia have observed mixed findings, with some showing deficits (e.g., Hayashida et al., 1986; Igata, Ohta, Hayashida, & Abe, 1994) while others show intact responses (e.g., Brecher & Begleiter, 1985; Pfefferbaum, Horvath, Roth, Tinklenberg, & Kopell, 1980). It is possible that speech elicited FFRs might be more sensitive than click ABR in detecting brainstem dysfunction, which is consistent with suggestions from a study of autism that

demonstrated intact click ABRs and aberrant speech-elicited FFRs (Russo et al., 2008).

Schizophrenia research using other ERPs related to auditory processing consistently show impaired responses in patients (e.g., Joshi et al., 2018; Light et al., 2015), and it is suggested that these auditory perceptual processing deficits contribute to higher-level cognitive deficits (Thomas et al., 2017). Present findings mirror the deficits in FFR measures of auditory processing shown in autism (e.g., Chen et al., 2019). Brainstem-mediated auditory processing deficits in autism are thought to reflect abnormal speech perception, which can lead to delayed language development. In schizophrenia, deficits in early stages of auditory processing indexed by FFR might similarly reflect abnormal speech perception.

The measures of the sustained FFR responses (pre-stimulus RMS, post-stimulus RMS, SNR, and dB SNR) yielded very high internal consistency estimates ($\phi_s > .95$) in both groups, and these estimates were easily obtained using the current task length of 6,000 trials (approximately 13 minutes). Hence, SNR values were sensitive to both between- and within-group differences. SNR measures reflect the ratio of post-stimulus RMS amplitude (i.e., signal) to pre-stimulus RMS amplitude (i.e., background noise), and they are a measure of the sustained response to the auditory stimulus. Large SNR scores are thought to reflect high accuracy of phase locking of single auditory nerve fibers or a large proportion of fibers phase locking to the stimulus (Carcagno & Plack, 2017). In healthy participants, reductions in SNR were observed when irrelevant ambient background noise was presented concurrently with the auditory stimulus, suggesting the background noise degrades discrimination of the auditory signal (Prévost, Laroche, Marcoux, & Dajani, 2013; Russo, Nicol, Musacchia, & Kraus, 2004).

There are at least three possible reasons that patients with schizophrenia showed smaller SNR scores than healthy participants. First, patients might show lower auditory processing

fidelity (i.e., larger pre-stimulus RMS), which would suggest that the auditory system is not adequately suppressing task-irrelevant auditory inputs. Second, the auditory system might be inadequately sharpening sensory representations of the stimulus. Third, it is possible that both previous explanations contribute to low SNR scores in patients. The present study was not able to determine the contribution to low SNR scores because significant group differences were not observed for pre- or post-stimulus RMS scores. Future research might consider investigating quiet and varying noise conditions to determine whether changes in SNR in schizophrenia are due to poor suppression of background noise, a failure to “tune into” the auditory signal, or a combination of both (for such a study of healthy controls, see Prévost et al., 2013).

With regards to behavioral tasks, group differences were observed when participants were required to repeat sentences (QuickSIN), but not single words (WIN), heard amid background noise. It is likely that the added cognitive demands (e.g., attention, immediate memory recall) associated with repeating complete sentences, rather than simple words, contributed to these group differences. For correlational analyses, lower SNR scores were related to higher negatives symptom ratings on the SANS, which is consistent with prior research relating ERPs of auditory processing to negative symptoms (e.g., Fisher et al., 2010), but this relationship is inconsistently observed (e.g., Jahshan, Wynn, & Green, 2013). However, these correlational analyses were exploratory, and none of these relationships were significant after correcting for multiple comparisons.

An optimized FFR paradigm may be deployed as part of a biomarker battery in schizophrenia translational research and may eventually be helpful in identifying optimal candidates for TCT. However, the relationship between FFR characteristics and TCT has yet to be examined. Other ERP indices of auditory processing, such as mismatch negativity (MMN)

and P3a, have demonstrated acute sensitivity and are highly predictive of clinically relevant outcomes in schizophrenia patients. For example, features of the mismatch negative (MMN) and P3a response complex are abnormal in schizophrenia, but these ERPs represent activity from broadly distributed neural sources and reflect a slightly later stage of cortical processing than FFRs (Rissling et al., 2014; Takahashi et al., 2013). In contrast to tone-based stimuli that are most commonly used to evoke MMN or P3a, FFRs to speech sounds are more spectrally and temporally complex and may therefore be more ecologically valid (Russo, Nicol, Trommer, Zecker, & Kraus, 2009; Wible, Nicol, & Kraus, 2004), and they are a promising candidate for the precise evaluation of speech-sound encoding in clinical populations (Skoe & Kraus, 2010). FFRs represent manifestations of focal neural activity and objectively represent the neural encoding of acoustic properties of an auditory stimulus (Kraus & White-Schwoch, 2015, 2017). In light of these considerations, FFR represents a potential candidate biomarker of treatment response following auditory TCT.

There are some limitations to note. First, there are numerous approaches to quantifying FFR and different stimuli that might produce more desirable psychometric properties for further research (see Krizman & Kraus, 2019), and it is our hope that the present study does not constrain such exploration. Second, the internal consistency of measures is the property of the data in hand, not a property of a measure in some general sense. Present estimates should be used as guideposts when planning future studies, but they should not be used to infer reliability in future research (see Clayson, 2020; Clayson & Miller, 2017b). The schizophrenia patients from this study represent a chronically impaired and significantly disabled cohort mandated to long-term locked care, and they were significantly younger than healthy controls. Studies of normal-hearing adults show longer FFR latencies and reduced neural synchronization (i.e., smaller SNR)

in older than in younger adults (for review, see Anderson & Karawani, 2020). Nonetheless, patients showed longer latencies and smaller SNR than healthy controls despite being significantly younger, suggesting that age-related changes did not account for present group differences in FFR. Fourth, it is possible that EEG equipment that is better optimized for recording FFR responses may yield more favorable psychometric properties (e.g., an even higher sampling rate to improve measurement precision of latency estimates). Nonetheless, EEG response biomarkers should be reasonably robust to variations in equipment, stimulus parameters, and analytic approaches.

In conclusion, broadband response measures of the sustained FFR response obtained in the present study show promise as individual difference measures under current data recording and processing practices. Of these estimates, however, only SNR scores yielded significant group differences. Hence, SNR scores appear to be the most promising candidate for auditory TCT intervention studies. The choice of which measure to use should also be guided by the extent to which scores relate to clinically meaningful outcomes in schizophrenia. Although some latency and amplitude measurements of the FFR transient response showed statistically significant group differences, these measurements showed widely variable dependability estimates. If measurements of the FFR transient response are highly sensitive to clinically meaningful variables, particularly as they are related to treatment response, then the present study suggests more trials than are typically recorded are needed to use transient response scores.

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Table 1

Summary of Demographics and Clinical Symptoms

Characteristic	Controls		Patients			
	<i>n</i> = 40		<i>n</i> = 40			
	<i>n</i>		<i>n</i>			
Female/Male	23/17		19/21		$X^2 = 0.45, p = .50$	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>t</i>	<i>p</i>
Age (yrs.)	52.5	17.2	33.6	10.4	5.90	< .001
Education (yrs.)	15.6	2.5	11.7	2.1	7.46	< .001
Parental Education (yrs.) ¹	14.1	4.0	13.8	3.3	0.38	.70
WRAT	108.9	9.6	93.3	13.4	5.98	< .001
Quick Speech-in-Noise ²	2.2	2.0	3.7	3.5	-2.21	.03
Words-in-Noise ³	6.4	2.9	6.1	2.6	0.46	.65
Duration of illness (years) ⁴	-	-	14.7	11.5	-	-
Chlorpromazine equivalents (mg/day)	-	-	1,108	842	-	-
MCCB ²						
Attention/Vigilance	53.1	9.3	31.8	13.7	8.07	< .001
Reason and Problem Solving	50.1	10.3	40.9	9.6	4.12	< .001
Speed of Processing	53.9	11.1	28.5	14.7	8.65	< .001
Working Memory	52.7	10.4	33.8	14.7	6.62	< .001
Verbal Learning	50.4	11.5	33.2	5.4	8.51	< .001
Visual Learning	54.1	14.3	32.0	11.6	7.55	< .001
Neurocognitive Composite	53.3	11.2	24.8	13.8	10.08	< .001
Symptoms						
SANS Global Score	-	-	13.8	4.1	-	-
SAPS Global Score	-	-	6.8	5.1	-	-

Note: Chlorpromazine equivalents were calculated using formulas from Woods (2003) and summarize information for the 33 patients who were taking medication at the time of testing.

¹Information is missing for four patients. ²Information is missing for one control. ³Information is missing for one control and one patient. ⁴Information is missing for one patient. SANS = Scales for the Assessment of Negative Symptoms; SAPS = Scales for the Assessment of Positive Symptoms

Table 2

Summary Event-Related Potential (ERP) Measurements as a Function of Measurement and Group

Measurement		Healthy Controls			Patients		
		<i>M</i>	<i>SD</i>	ϕ	<i>M</i>	<i>SD</i>	ϕ
Peak V	Amplitude	-.11	0.038	0.07 (0.00, 0.31)	-.11	0.052	0.28 (0.01, 0.57)
	Latency	4.40	0.031	0.85 (0.77, 0.91)	4.41	0.022	0.70 (0.54, 0.82)
Peak A	Amplitude	0.23	0.079	0.69 (0.54, 0.82)	0.20	0.069	0.60 (0.40, 0.77)
	Latency	7.37	0.041	0.83 (0.74, 0.90)	7.38	0.032	0.73 (0.59, 0.84)
Peak C	Amplitude	0.13	0.133	0.88 (0.83, 0.93)	0.08	0.088	0.73 (0.59, 0.84)
	Latency	16.59	0.046	0.90 (0.85, 0.94)	16.61	0.026	0.70 (0.55, 0.82)
Peak D	Amplitude	0.14	0.073	0.64 (0.47, 0.79)	0.16	0.087	0.74 (0.61, 0.84)
	Latency	22.34	0.052	0.80 (0.70, 0.88)	22.38	0.047	0.75 (0.63, 0.85)
Peak E	Amplitude	0.21	0.111	0.85 (0.77, 0.91)	0.21	0.078	0.68 (0.52, 0.81)
	Latency	30.77	0.061	0.89 (0.84, 0.93)	30.82	0.051	0.84 (0.77, 0.91)
Peak F	Amplitude	0.22	0.161	0.93 (0.89, 0.96)	0.19	0.086	0.72 (0.59, 0.83)
	Latency	39.34	0.058	0.88 (0.82, 0.93)	39.36	0.050	0.84 (0.76, 0.90)
Peak O	Amplitude	0.21	0.159	0.93 (0.89, 0.96)	0.20	0.111	0.84 (0.76, 0.90)
	Latency	47.15	0.068	0.90 (0.84, 0.94)	47.19	0.050	0.81 (0.71, 0.89)
Pre-stimulus RMS		2.49	0.907	>.99 (>.99, >.99)	2.49	0.919	>.99 (>.99, >.99)
Post-stimulus RMS		2.61	0.961	>.99 (>.99, >.99)	2.57	0.945	>.99 (>.99, >.99)
SNR		1.14	0.059	0.99 (0.98, 0.99)	1.12	0.042	0.98 (0.98, 0.99)
dB SNR		0.50	0.341	0.98 (0.98, 0.99)	0.39	0.210	0.96 (0.95, 0.98)

Note: Summary scores represent averaged single-trial estimates. The overall dependability (ϕ) represents the dependability point estimates and their 95% credible intervals for data including all trials. Amplitude measurements are in μV , and latency measurements are in ms. RMS = root mean square; SNR = signal-to-noise; dB = decibel

Table 3

Summary of Significant Pairwise Contrasts for the Main Effect of Peak in the Robust Analysis of Variance

Comparison	$T_{WJ/c}$	df	$\hat{\delta}_j^{(R)}$
C < O	44.53	1, 109.84	-2.21
C < F	48.89	1, 129.95	-2.27
C < E	88.34	1, 123.18	-3.06
D < E	21.44	1, 133.81	-1.49
A > D	21.40	1, 134.98	1.49
C < D	21.79	1, 128.70	-1.51
A > C	85.31	1, 126.33	3.00

Note. Peak V was the only negative-going peak, and was more positive than each other peak, which were all positive-going peaks ($T_{WJ/c} > 317$, $ps < .001$). The comparison column indicates the direction of effect, and $\hat{\delta}_j^{(R)}$ represents a measure of effect size. Follow-up contrasts used a bootstrapped critical value to maintain a family wise error rate of .05, and all of the effects shown are significant, $p < .05$. The remaining pairwise contrasts were not significant, $ps > .05$.

Table 4

Dependability as a Function of Peak and Group

		Healthy Controls				Patients			
Measurement		.70 Trial Cutoff	.80 Trial Cutoff	.90 Trial Cutoff	.95 Trial Cutoff	.70 Trial Cutoff	.80 Trial Cutoff	.90 Trial Cutoff	.95 Trial Cutoff
Peak V	Amplitude	153,700	263,485	592,841	1,251,552	29,869	51,204	115,209	243,218
	Latency	2,380	4,079	9,177	19,374	5,669	9,718	21,865	46,159
Peak A	Amplitude	5,686	9,747	21,931	46,298	8,354	14,321	32,222	68,023
	Latency	2,677	4,589	10,325	21,797	4,860	8,330	18,742	39,567
Peak C	Amplitude	1,728	2,962	6,663	14,065	4,842	8,300	18,674	39,422
	Latency	1,419	2,432	5,470	11,548	5,509	9,444	21,247	44,855
Peak D	Amplitude	7,110	12,188	27,423	57,893	4,507	7,727	17,384	36,700
	Latency	3,273	5,610	12,622	26,646	4,277	7,331	16,495	34,822
Peak E	Amplitude	2,407	4,126	9,282	19,595	6,098	10,453	23,519	49,651
	Latency	1,623	2,781	6,257	13,208	2,410	4,132	9,296	19,625
Peak F	Amplitude	1,040	1,783	4,011	8,467	4,956	8,496	19,114	40,352
	Latency	1,823	3,125	7,030	14,841	2,475	4,243	9,545	20,151
Peak O	Amplitude	1,041	1,785	4,015	8,476	2,511	4,305	9,685	20,445
	Latency	1,542	2,644	5,947	12,555	3,074	5,269	11,856	25,028
Pre-stimulus RMS		10	17	37	78	12	21	46	96
Post-stimulus RMS		9	15	34	71	11	18	41	86
SNR		139	238	535	1,128	218	373	840	1,772
dB SNR		205	352	791	1,669	480	823	1,851	3,907

Note. Trial cutoffs represent the number of trials needed to obtain a dependability estimate of .70, .80, .90, and .95. Trial cutoffs over 6,000 are extrapolations beyond the number of presented trials and should be interpreted cautiously. RMS = root mean square; SNR = signal-to-noise; dB = decibel

Table 5

Between- and Within-Person Standard Deviations as a Function of Peak and Group

		Healthy Controls		Patients	
Measurement		$\sigma_{Between}$	σ_{Within}	$\sigma_{Between}$	σ_{Within}
Peak V	Amplitude	0.01 (< .01, 0.03)	3.32 (3.31, 3.33)	0.03 (< .01, 0.05)	3.36 (3.35, 3.37)
	Latency	0.03 (0.02, 0.04)	0.96 (0.96, 0.96)	0.02 (0.01, 0.03)	0.95 (0.95, 0.96)
Peak A	Amplitude	0.07 (0.05, 0.09)	3.40 (3.39, 3.41)	0.06 (0.04, 0.08)	3.36 (3.35, 3.37)
	Latency	0.04 (0.03, 0.05)	1.32 (1.31, 1.32)	0.03 (0.02, 0.04)	1.30 (1.30, 1.30)
Peak C	Amplitude	0.13 (0.10, 0.17)	3.53 (3.52, 3.54)	0.08 (0.06, 0.10)	3.56 (3.55, 3.57)
	Latency	0.04 (0.03, 0.06)	1.11 (1.11, 1.12)	0.02 (0.02, 0.03)	1.11 (1.10, 1.11)
Peak D	Amplitude	0.06 (0.04, 0.08)	3.37 (3.36, 3.38)	0.08 (0.06, 0.10)	3.45 (3.44, 3.46)
	Latency	0.05 (0.04, 0.06)	1.84 (1.84, 1.85)	0.04 (0.03, 0.06)	1.84 (1.83, 1.84)
Peak E	Amplitude	0.11 (0.08, 0.14)	3.42 (3.41, 3.43)	0.07 (0.05, 0.09)	3.43 (3.42, 3.44)
	Latency	0.06 (0.05, 0.08)	1.58 (1.58, 1.59)	0.05 (0.04, 0.06)	1.58 (1.57, 1.58)
Peak F	Amplitude	0.16 (0.13, 0.21)	3.42 (3.41, 3.43)	0.08 (0.05, 0.10)	3.51 (3.50, 3.52)
	Latency	0.06 (0.04, 0.07)	1.59 (1.59, 1.59)	0.05 (0.04, 0.06)	1.58 (1.57, 1.58)
Peak O	Amplitude	0.16 (0.12, 0.20)	3.37 (3.36, 3.38)	0.11 (0.08, 0.14)	3.49 (3.48, 3.50)
	Latency	0.07 (0.05, 0.09)	1.71 (1.71, 1.72)	0.05 (0.03, 0.06)	1.71 (1.71, 1.72)
Pre-stimulus RMS		0.95 (0.76, 1.21)	1.93 (1.93, 1.94)	0.94 (0.73, 1.22)	2.13 (2.12, 2.13)
Post-stimulus RMS		1.00 (0.80, 1.24)	1.94 (1.93, 1.94)	0.98 (0.81, 1.24)	2.09 (2.08, 2.10)
SNR		0.06 (0.05, 0.08)	0.47 (0.47, 0.47)	0.04 (0.04, 0.06)	0.43 (0.42, 0.43)
dB SNR		0.35 (0.28, 0.45)	3.31 (3.30, 3.32)	0.21 (0.17, 0.27)	3.09 (3.08, 3.10)

Note. $\sigma_{Between}$ = between-subject standard deviation; σ_{Within} = within-subject standard deviation; RMS = root mean square; SNR = signal-to-noise; dB = decibel

Table 6

Between- and Within-Person Variances as a Function of Peak and Group

		Healthy Controls		Patients	
Measurement		$\sigma_{Between}^2$	σ_{Within}^2	$\sigma_{Between}^2$	σ_{Within}^2
Peak V	Amplitude	< .001 (< .001, 0.001)	11.003 (10.942, 11.064)	0.001 (< .001, 0.003)	11.306 (11.243, 11.369)
	Latency	0.001 (0.001, 0.002)	0.919 (0.914, 0.925)	< .001 (< .001, 0.001)	0.911 (0.906, 0.917)
Peak A	Amplitude	0.005 (0.002, 0.009)	11.583 (11.518, 11.648)	0.003 (0.001, 0.006)	11.303 (11.239, 11.368)
	Latency	0.001 (0.001, 0.003)	1.731 (1.721, 1.741)	0.001 (< .001, 0.001)	1.692 (1.683, 1.702)
Peak C	Amplitude	0.017 (0.010, 0.028)	12.491 (12.423, 12.561)	0.006 (0.003, 0.011)	12.694 (12.623, 12.765)
	Latency	0.002 (0.001, 0.003)	1.239 (1.232, 1.246)	0.001 (0.000, 0.001)	1.227 (1.220, 1.234)
Peak D	Amplitude	0.004 (0.002, 0.007)	11.341 (11.277, 11.406)	0.006 (0.003, 0.011)	11.887 (11.820, 11.956)
	Latency	0.002 (0.001, 0.004)	3.394 (3.375, 3.414)	0.002 (0.001, 0.003)	3.381 (3.362, 3.401)
Peak E	Amplitude	0.011 (0.006, 0.019)	11.667 (11.602, 11.731)	0.004 (0.002, 0.008)	11.750 (11.682, 11.818)
	Latency	0.004 (0.002, 0.006)	2.509 (2.494, 2.523)	0.002 (0.001, 0.004)	2.489 (2.475, 2.504)
Peak F	Amplitude	0.026 (0.016, 0.042)	11.664 (11.598, 11.731)	0.006 (0.003, 0.010)	12.308 (12.238, 12.379)
	Latency	0.003 (0.002, 0.005)	2.527 (2.513, 2.541)	0.002 (0.001, 0.004)	2.484 (2.470, 2.498)
Peak O	Amplitude	0.025 (0.015, 0.041)	11.329 (11.266, 11.392)	0.011 (0.006, 0.019)	12.179 (12.112, 12.247)
	Latency	0.004 (0.003, 0.007)	2.933 (2.916, 2.950)	0.002 (0.001, 0.004)	2.938 (2.922, 2.955)
Pre-stimulus RMS		0.905 (0.584, 1.466)	3.727 (3.707, 3.748)	0.881 (0.528, 1.489)	4.519 (4.494, 4.544)
Post-stimulus RMS		1.001 (0.637, 1.549)	3.744 (3.723, 3.766)	0.962 (0.654, 1.535)	4.368 (4.343, 4.394)
SNR		0.004 (0.002, 0.006)	0.222 (0.221, 0.223)	0.002 (0.001, 0.003)	0.181 (0.180, 0.182)
dB SNR		0.123 (0.078, 0.199)	10.957 (10.896, 11.019)	0.046 (0.029, 0.075)	9.554 (9.501, 9.608)

Note. Decimals to three places are used due to the small nature of some estimates. $\sigma_{Between}^2$ = between-subject variance; σ_{Within}^2 = within-subject variance; RMS = root mean square; SNR = signal-to-noise; dB = decibel

Table 7

Pearson Correlations Between FFR Measures and External Correlates for Patients with Schizophrenia

Measurement		WRAT	QuickSIN	WIN	MCCB	SANS	SAPS
Peak V	Amplitude	.02	-.12	-.10	.01	.02	.07
	Latency	.13	-.16	-.14	.00	.22	.04
Peak A	Amplitude	.15	-.15	.18	.36*	-.01	.04
	Latency	-.22	.08	.04	.02	.12	.02
Peak C	Amplitude	-.15	-.17	-.11	.17	-.06	.07
	Latency	-.02	.14	.01	-.23	.08	.08
Peak D	Amplitude	.11	-.03	.05	-.06	.08	-.06
	Latency	.19	.07	.05	-.25	.04	.18
Peak E	Amplitude	-.15	.14	.19	.11	.02	-.14
	Latency	.05	.02	.17	.06	.16	.07
Peak F	Amplitude	-.02	.16	.19	.15	-.02	-.01
	Latency	-.10	.10	.11	.12	.10	.18
Peak O	Amplitude	.09	-.16	-.07	.14	-.07	-.06
	Latency	-.08	-.05	.08	.10	.16	.25
Pre-stimulus RMS		-.46*	.28	-.02	-.12	.10	-.16
Post-stimulus RMS		-.45*	.26	-.04	-.11	.08	-.16
SNR		-.26	-.11	-.28	.02	-.31*	.15
dB SNR		-.07	-.25	-.25	.17	-.30	.11

Note: WRAT = single-word reading scores from the Wide Range Achievement Test-Reading; QuickSIN = Quick Speech-In-Noise; WIN = Words-In-Noise; MCCB = neurocognitive composite scores from the MATRICS Consensus Cognitive Battery; SANS = Scales for the Assessment of Negative Symptoms; SAPS = Scales for the Assessment of Positive Symptoms; RMS = root mean square; SNR = signal-to-noise; dB = decibel. * $p < .05$.

Table 8

Pearson Correlations Between FFR Measures and External Correlates for Healthy Participants

Measurement		WRAT	QuickSIN	WIN	MCCB
Peak V	Amplitude	.15	.13	.08	.17
	Latency	-.14	.06	-.11	.01
Peak A	Amplitude	-.05	-.29	-.24	.04
	Latency	-.05	.11	.06	-.21
Peak C	Amplitude	-.18	-.05	-.18	.03
	Latency	.02	.14	.18	.03
Peak D	Amplitude	.09	-.36*	-.31	.20
	Latency	.08	.09	.36*	-.15
Peak E	Amplitude	-.08	-.29	-.21	.22
	Latency	-.07	.17	.28	-.39*
Peak F	Amplitude	-.02	-.25	-.06	.12
	Latency	-.11	.13	-.15	-.19
Peak O	Amplitude	-.16	-.32*	-.45*	.18
	Latency	-.05	.20	-.06	-.35*
Pre-stimulus RMS		.04	.06	.29	-.19
Post-stimulus RMS		.03	.04	.24	-.19
SNR		.08	-.14	-.11	-.02
dB SNR		.00	-.12	-.19	-.01

Note: WRAT = single-word reading scores from the Wide Range Achievement Test-Reading; QuickSIN = Quick Speech-In-Noise; WIN = Words-In-Noise; MCCB = neurocognitive composite scores from the MATRICS Consensus Cognitive Battery; RMS = root mean square; SNR = signal-to-noise; dB = decibel. * $p < .05$.

Figure Captions

Figure 1. Grand average waveforms for controls (top) and patients (bottom) at recording site Cz averaged across alternating polarities of the ‘da’ stimulus. RMS = root mean square

Figure 2. Single-subject amplitude and latency scores for Peaks V, A, C, and D for each group. Box and whiskers plots represents the median (middle line), the two hinges represent the 25th and 75th percentiles, respectively, and the two whiskers extend from the hinge to the largest value or no farther than 1.5 times the interquartile range. Note the different scale for each plot.

Figure 3. Single-subject amplitude and latency scores for Peaks E, F, and O for each group. Box and whiskers plots represents the median (middle line), the two hinges represent the 25th and 75th percentiles, respectively, and the two whiskers extend from the hinge to the largest value or no farther than 1.5 times the interquartile range. Note the different scale for each plot.

Figure 4. Single-subject pre-stimulus root mean square (RMS) amplitude, post-stimulus RMS, signal-to-noise ratio (SNR), and dB SNR for each group. (SNR and dB SNR are unitless measurements and the axis units are not labeled.) Box and whiskers plots represents the median (middle line), the two hinges represent the 25th and 75th percentiles, respectively, and the two whiskers extend from the hinge to the largest value or no farther than 1.5 times the interquartile range. Note the different scale for each plot.

Figure 1

Figure 2

Figure 3

Figure 4