Frontal Alpha Asymmetry in Youth at Clinical High Risk for Psychosis

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Abstract

Purpose of Review Negative symptoms are highly predictive of whether individuals at clinical high risk (CHR) develop a psychotic disorder. However, little is known about pathophysiological mechanisms underlying negative symptoms during this period. The current study examined neurophysiological mechanisms underlying negative symptoms in CHR individuals using electroencephalography frontal alpha asymmetry power, a biomarker of approach and avoidance motivation.
Recent Findings People with schizophrenia display abnormal patterns of frontal alpha asymmetry indicative of reduced approach motivation. However, it is unknown whether similar abnormalities occur in CHR youth that predict negative symptoms.
Summary Results indicated that CHR and healthy controls did not differ in frontal alpha asymmetry scores. However, in CHR youth, frontal alpha asymmetry was inversely correlated with the motivation and pleasure dimension of negative symptoms, which was accounted for by mood symptoms. Findings suggest that depression contributes to reduced approach motivation in CHR youth that manifests clinically as negative symptoms.

Keywords Frontal alpha asymmetry · Negative symptoms · Anhedonia · Avolition · Psychosis · Prodrome

Introduction

Psychotic disorders are costly and the leading cause of medical disability in the USA [1]. Given that few individuals achieve recovery after illness onset, there has been increasing interest in the early identification and prevention of psychosis. The prodromal stage retrospectively refers to the 1-to-2-year period preceding the onset of a psychotic disorder, characterized by functional decline and subthreshold positive symptoms. It is now possible to identify a group of clinical high-risk (CHR) youth who will go on to develop a psychotic disorder using state-of-the-art clinical interviews that evaluate attenuated positive symptom criteria. Several processes have been found to predict CHR status, including affect, cognition, perception, motor behavior, and volition [2, 3]. Despite these advances, the majority of individuals meeting CHR status do not develop a psychotic disorder within 2 years, and it remains unclear which pathophysiological processes are most predictive of psychosis risk. To develop novel treatment targets for early intervention and prevention, the field is in need of new approaches that evaluate alternate pathophysiological processes that might give rise to psychotic disorders.

In the current study, we took a novel approach to enhancing psychosis risk prediction by investigating pathophysiological mechanisms underlying negative symptoms. In the prodromal phase, negative symptoms (e.g., anhedonia, avolition, asociality) are highly prevalent (e.g., occurring in 82% of cases [4]) and one of the earliest indicators of risk, typically appearing years before the emergence of attenuated positive symptoms [3] [6]. They are often the reason why youth at CHR for psychosis and their families seek initial contact with the treatment system [5], and one of the strongest predictors of conversion to psychosis [6]. However, exploration into the mechanisms underlying negative symptoms in youth at CHR for psychosis has yet to be accomplished, despite significant advances in conceptual models of negative symptoms that have been developed for understanding negative symptoms in adults with schizophrenia [7–10].

To index the motivational system that underlies negative symptoms, we are examining a well-validated electroencephalography (EEG) measure of frontal alpha asymmetry, which refers to the lateralization of alpha power on either right or left

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This article is part of the Topical Collection on *Psychosis*

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frontal regions, where alpha power relates inversely to neural activity [11]. As such, negative values on the asymmetry index indicate greater relative right activation and positive values indicate greater relative left activation. EEG has been used to examine resting frontal asymmetry as a potential trait measure of motivation and affect, where greater left lateralized activity (i.e., greater right alpha power) is believed to reflect positive affect and approach tendencies, and greater right lateralized activity (i.e., greater left alpha power) is believed to reflect negative affect and withdrawal [12, 13]. To test these hypotheses, past studies have examined the relationship between frontal asymmetry and the behavioral activation and inhibition systems (BIS and BAS [14, 15]) using measures like the BIS/BAS scales [16]. Indeed, the results of these studies indicate an association between greater left activation and BAS scores [17–19] and greater right activation and BIS scores [18], though evidence for the latter is less consistent [19].

Theoretical frameworks implicate elevated BIS sensitivity as a risk factor for the development of mood and anxiety disorders [20]. Indeed, meta-analytic findings suggest that both anxiety and depressive disorders are characterized by increased right lateralized activation, reflecting greater withdrawal motivation and negative affect [21]. Despite the prevalence of motivational deficits in schizophrenia, few studies have examined whether individual differences in frontal alpha asymmetry predict the severity of clinically rated negative symptoms. Horan et al. [22] reported that patients with schizophrenia had lower left frontal activation than controls, consistent with reduced approach motivation, though asymmetry scores were not found to correlate significantly with BAS scores or negative symptoms. Jetha et al. [23] did not include a healthy control comparison group but found that greater left lateralized activation was associated with increased severity of positive symptoms. Correlations between negative symptoms and frontal alpha asymmetry were non-significant, although negative symptom severity was low and unvaried in this sample [23]. Notably, these associations were stable over a 3-year period [24]. Only one study has examined frontal alpha asymmetry in individuals within their first episode of psychosis, also finding reduced left frontal activation [25]. Collectively, these studies provide inconsistent results regarding associations between frontal alpha asymmetry and negative symptoms of schizophrenia; however, the strong links between motivation and frontal alpha asymmetry in the literature on healthy individuals and people with mood disorders suggest that these EEG-based biomarkers may be a valuable tool for probing the motivational system in individuals at CHR.

The following primary hypotheses were made based on prior research in individuals with schizophrenia [22, 23, 25] and mood disorders [21]: (1) youth at CHR for psychosis will have diminished frontal alpha asymmetry scores (i.e., reduced left lateralized regional activation), consistent with reduced approach motivation; (2) lower frontal alpha asymmetry scores (i.e., reduced left lateralized regional activation) will be associated with greater negative symptom severity, particularly the motivation and pleasure (MAP) dimension, which reflects the aspect of negative symptoms most clinically similar to the approach motivation construct. Given the high rates of depression in CHR individuals and evidence that depressive symptoms can underlie negative symptoms [26•, 27], we also examined the secondary hypothesis that elevated mood symptoms might account for the association between lower frontal alpha asymmetry scores (i.e., reduced left lateralized regional activation) and greater negative symptom severity.

Method

Participants

The participant sample consisted of 21 CHR and 24 healthy control (CN) participants. Two participants in the CHR group and three participants in the CN group were eliminated due to unusable EEG data (artifacts in > 50% of data). Among participants in the final sample of $n = 19$ CHR and $n = 21$ CN, groups did not significantly differ on age, ethnicity, sex, personal education, or parental education (see Table 1).

The CHR group consisted of individuals recruited from a psychosis risk evaluation program in New York state where they received diagnostic assessment and monitoring evaluations per referrals from local clinicians (e.g., Psychiatrists, Psychologists, Social Workers, School Psychiatrists). Youth at CHR for psychosis were also recruited via online and print advertisements, in-person presentations to community mental health centers, and calls or in-person meetings with members of the local school system (e.g., superintendent, principals). All CHR participants met criteria for a prodromal syndrome on the Structured Interview for Prodromal Syndromes [28], including Attenuated Positive Symptoms (i.e., SIPS score of at least 3–5 on at least one positive symptom item, with worsening symptoms over the past year) ($n = 17$) or Genetic Risk and Deterioration Syndrome, which was defined as having a first-degree relative with a psychotic disorder and decline in global functioning over the past year ($n = 2$). By definition, youth in the CHR group did not meet lifetime criteria for a DSM-IV-TR psychotic disorder as determined via SCID interview [29]. Additionally, none of the CHR participants had ever been prescribed antipsychotic medication.

CN participants were recruited from the local community using posted flyers, newspaper advertisements, and electronic advertisements. Exclusionary criteria for CN participants consisted of current Axis I or II DSM-IV diagnoses as established by the SCID-I and SCID-II [29, 30], family history of psychosis, and currently taking psychotropic medications. All participants were free from lifetime

Table 1 Participant demographics

	UHR ($n = 19$)	CN ($n = 21$)	Test statistic, p value
Age	19.5 (1.74)	19.4 (1.25)	$F_{(1,39)} = 0.04$, $p = 0.84$
Participant education	13.5 (1.78)	13.6 (1.50)	$F_{(1,39)} = 0.04$, $p = 0.85$
Parental education	15.3 (2.39)	15.0 (2.36)	$F_{(1,39)} = 0.13$, $p = 0.73$
% Male	31.6	19.0	$X^2_{(1)} = 0.84$, $p = 0.36$
Ethnicity %			$X^2_{(4)} = 5.78$, $p = 0.22$
Caucasian	81.0	68.4	
African-American	0.0	9.5	
Latin-American	10.5	4.8	
Asian	15.8	0.0	
Native American	0.0	0.0	
Mixed race	5.3	4.8	

UHR clinical high risk for psychosis, *CN* healthy control

neurological disease. Participants provided written informed consent for a protocol approved by the Binghamton University Institutional Review Board and received monetary compensation for their participation.

Procedures

Prior to completing resting-state EEG, all participants completed a diagnostic assessment consisting of the SCID-I, SCID-II, and SIPS with examiners who were trained to reliability standards (ICC > .80). Examiners received training to administer the SIPS under the supervision of a clinical psychologist with previous SIPS training (GPS), which incorporated in-person and gold-standard training videos. Either the PI or a clinical psychology doctoral student conducted the SIPS interviews. In cases of the latter, the PI was consulted to establish consensus. Symptom severity in the CHR group was assessed via clinical interview, which informed ratings on the Brief Negative Symptom Scale (BNSS: [31]).

EEG Recording, Data Reduction, and Analysis

EEG Recording The resting EEG consisted of four 1-min segments with eyes open and four 1-min segments with eyes closed in one of two orders that were counterbalanced across participants. No relaxation procedures were completed prior to the recording. The EEG was recorded from a subset of 64 Ag/AgCl electrodes (Fp1, Fp2, F3, F4, Fz, Fc1, Fc2, C3, C4, Cz, Cp1, Cp2, P3, P4, Pz, O1, O2, Oz) mounted in an elastic cap from manufactured by BrainVision (ActiCap model). Online EEG was referenced to the right mastoid electrode and re-referenced offline to the average of all electrodes. The horizontal electrooculogram (EOG) was used to measure horizontal eye movements and was recorded by placing two electrodes lateral to the external canthi. The vertical EOG was used to detect eye blinks and vertical eye movements and

was recorded from electrodes above and beneath the left eye. All electrode impedances were maintained below 15 kΩ. The EEG and EOG were amplified by a BrainVision actiCHamp amplifier with a gain of 5000, a bandpass filter of 0.05–100 Hz, and a 60-Hz notch filter. The amplified signals were digitized at 500 Hz and averaged offline.

EEG Data Reduction All signal processing and analysis procedures were performed in Matlab using EEGLAB [32] and the ERPLAB toolboxes [33]. Recordings were divided into 480 overlapping epochs of 1.198 s duration and zeroed with respect to average microvolt activity within the epoch window. A bandpass filter using a zero-shift Butterworth filter with cutoffs of 1–100 Hz and a 60 Hz notch filter were applied. Epochs containing muscle artifact and extreme offsets were identified by visual inspection and rejected. Independent component analysis (ICA) was conducted to identify and remove components from the data that were associated with eye movements and eye blinks. A fast Fourier transform (FFT) was then performed on the artifact-free epochs. Average power in the alpha (8–13 Hz) frequency band for the LH and RH was measured at F3 and F4, respectively; finally, an asymmetry index (F4-F3) was calculated. Asymmetry was also calculated between electrodes P4 and P3, which served as nonfrontal control comparisons.

Data Analysis

One-way ANOVA was used to test the hypothesis that CHR would have lower frontal alpha asymmetry scores than CN, and that there would be no group differences in the parietal asymmetry control condition. Spearman correlations were conducted to examine whether frontal and parietal asymmetry scores were associated with BNSS total, BNSS motivation and pleasure dimension (MAP: average of anhedonia, avolition, asociality items), and BNSS expression dimensions

(EXP: average of alogia and blunted affect items). Exploratory correlations were also conducted to examine associations with frontal alpha asymmetry scores and SIPS positive dimension (average of all SIPS P items), SIPS disorganization dimension (average of all SIPS D items), and SIPS item G2 (dysphoric mood). Partial correlation was used to determine whether mood (SIPS item G2) was accounting for variance in the association between negative symptoms and frontal alpha asymmetry.

Results

One-way ANOVA indicated that the groups did not significantly differ in frontal asymmetry, F (1, 38) = 1.72, p = 0.20 (CN: M = − 0.02, SD = 0.11; CHR: M = 0.01, SD = 0.07), or the comparison analysis used for parietal asymmetry F (1, 38) = 3.09, p = 0.09 (CN: M = 0.17, SD = 0.29; CHR: M = 0.04, p = 0.16).

Frontal alpha asymmetry was significantly correlated with BNSS total score (r = −0.53, p = 0.019) and the BNSS MAP dimension (r = −0.46, p = 0.049), but not the EXP dimension (r = −0.39, p = 0.10). There was a trend toward a significant correlation with the dysphoric mood item on the SIPS (r = − 0.45, p = 0.06). When dysphoric mood (item G2) was controlled for using partial correlations, the BNSS total (r = − 0.37, p = 0.13) and MAP (r = − 0.23, p = 0.35) were no longer significant, suggesting that mood may be accounting for some proportion of variance in the observed negative symptom associations.

Frontal alpha asymmetry was not significantly correlated with SIPS Positive or SIPS Disorganized dimensions. There were no significant correlations between parietal asymmetry scores and clinical outcomes.

Discussion

This was the first study to examine frontal alpha asymmetry as a biomarker of motivational impairment in individuals at CHR for psychosis. Contrary to our hypotheses and past results comparing resting frontal alpha asymmetry in individuals diagnosed with schizophrenia to healthy controls [22, 25], there was no evidence for group differences in frontal alpha asymmetry between youth at CHR for psychosis and CN. These findings suggest that, on the whole, the neural mechanisms underlying approach motivation may be intact in CHR individuals. This is perhaps surprising given the high frequency of negative symptoms in CHR individuals [4], as well as the high prevalence of comorbid mood disorders that are known to produce motivational impairments.

However, correlational analyses indicated that the subset of youth at CHR for psychosis with clinically significant

negative symptoms did indeed display abnormalities in neural mechanisms of approach motivation. Specifically, lower frontal alpha asymmetry scores were associated with elevated total and MAP dimension scores on the BNSS, whereas associations with the EXP dimension were non-significant. The specificity of these correlational analyses is intriguing. The aspect of clinically rated motivational deficits that most closely maps onto the neurobehavioral concept of approach motivation showed an association with reduced lateralization of left frontal activity, whereas the dimension of negative symptoms that is less relevant to this conceptualization and more closely aligns with communication disturbances did not. Our results expand upon the literature in three important ways. First, they indicate that the link between frontal alpha asymmetry and negative symptoms is not due to illness chronicity or the consequences of having a serious mental illness (e.g., reduced resources, impoverished environment) that contribute to functional disability. Second, since all CHR participants were antipsychotic naïve, our findings suggest that the association between elevated RH alpha power and negative symptoms is likely not a byproduct of medication effects. Third, our data revealed that when dysphoric mood symptoms were added as a covariate, the association between negative symptoms and frontal alpha asymmetry became non-significant. These observations suggest that mood symptoms may therefore play a significant role in the reductions in approach motivation that are observed in individuals at CHR. This finding is consistent with prior reports of high rates of depression and anxiety in the CHR population (41% and 15%, respectively [34]), as well as results of two prior studies indicating that diminished hedonic response that is observed in CHR individuals and associated with negative symptoms is driven by depressed mood and anxiety [35•, 36•].

The above findings raise an important interpretive question: to what extent are negative symptoms driven by mood symptoms in CHR participants? In adults with schizophrenia, a distinction has been made between negative symptoms that are primary (i.e., idiopathic) and those that are secondary (i.e., due to other factors, such as depression, anxiety, psychosis). Distinct pathophysiological processes are thought to contribute to negative symptoms that are primary versus secondary in adults with schizophrenia [27], and it is reasonable to expect that this division would hold in CHR populations too. Unfortunately, very little research has examined whether subgroups of individuals at CHR can be identified whose negative symptoms are due to primary or secondary sources. One study by Azar et al. [26•] indicated that the proportion of youth at CHR for psychosis with primary negative symptoms was 32.7%, consistent with adults with schizophrenia, while the majority could be considered to result from secondary sources, particularly mood and anxiety symptoms. These findings and the current results highlight the need for additional studies that aim to determine whether neural mechanisms

associated with primary versus secondary negative symptoms are capable of differentially predicting clinical trajectory toward a psychotic versus mood and other disorders. We suspect that biomarkers of negative symptoms, such as frontal alpha asymmetry, may be useful tools for improving risk measurement: some adding positive predictive value and the transition to a psychotic disorder, and others demonstrating negative predictive value and indicating a course of illness that features depression. It remains to be seen for which of these avenues frontal alpha asymmetry may hold promise.

Several limitations should be considered. First, this was a cross-sectional study, and we could not make conclusions about whether frontal alpha asymmetry is a significant predictor of clinical trajectory. Prospective longitudinal studies are needed that identify CHR individuals in the earliest stage possible (i.e., when negative symptoms have emerged, but positive symptoms may not have), characterize them at baseline using neurobehavioral probes of the motivational system, and follow them longitudinally to determine whether baseline scores predict the development of psychotic versus mood and other disorders. Second, although smaller sample sizes are not uncommon for studies examining CHR populations that are difficult to obtain, our results may have been underpowered to detect small to medium symptom correlations. Replication of these results is therefore warranted. With larger sample sizes and increased power, it is possible that the association between frontal alpha asymmetry and the EXP dimensions would have also become significant. Third, although we used one of the two most conceptually up-to-date negative symptom scales (BNSS), our assessment of approach motivation was limited to a single measure. Future studies may choose to include other scales, such as the BIS/BAS self-report. Fourth, frontal alpha asymmetry can be affected by confounding variables that we did not assess (e.g., fatigue, hunger [37]) and we can therefore not rule out such influences.

Conclusions

The current findings provide an important extension to the research on negative symptoms in schizophrenia, providing novel evidence that neurophysiological impairments in approach motivation (indexed via frontal alpha asymmetry) are also associated with negative symptoms in CHR individuals. These results are important because they suggest that the motivational system may be compromised prior to the onset of psychotic illness, potentially serving as one of many other factors that combine to increase risk for developing a psychotic disorder. Motivational impairments may therefore be a relevant target for prevention.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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