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ORIGINAL ARTICLE

Directional Alpha Frontoparietal Connectivity and Anxiety in Autistic Boys

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Abstract

Describing neural connectivity between pre-frontal and parietal brain regions and anxiety in children and adolescents with Autism Spectrum Disorder (ASD) has the potential to inform diagnosis and treatment decisions. This study aimed to identify the neural connectivity patterns between the prefrontal cortex (PFC) and parietal regions in young autistic males, and to determine if Generalised Anxiety Disorder (GAD) was associated with these communication patterns. Forty-one males with ASD aged between 6 and 18 yr (*M* age = 10.76 yr, SD = 3.14 yr) and their mothers were recruited as volunteer participants from the Gold Coast region, Australia. After assessments, participants received 3 min of eyes-closed and 3 min of eyes-opened EEG data-collection under resting conditions. EEG data from the frontal and parietal regions were investigated for their connectivity via Granger Causality (GC). There were significant correlations between the PFC-to-parietal region GC connectivity indices and total GAD scores, and also for the core components of GAD, but these were restricted to the alpha-wave frequency with only minimal beta-wave significant results. No significant correlations between parietal-to-PFC regions and GAD were present. Communication from the decision-making region (PFC) to the spatial reasoning (parietal) regions appeared to be aimed at instigating increased motor activity associated with GAD.

Keywords Anxiety · Brain connectivity · Autism · Behaviour

Although Autism Spectrum Disorder (ASD) is acknowledged as a neurological disorder (APA, 2022), understanding how the autistic brain works remains a major and unfulfilled research target (Guo et al., 2020), although the general hypothesis is

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towards problems in connectivity across brain regions (Guo et al., 2020; Picci et al., 2016). Brain region connectivity has been associated with deficits in social interaction and communication (Yao et al., 2021) and also restricted and repetitive behaviour (McKinnon et al., 2019), the key diagnostic indicators of ASD (APA, 2022), thus providing a basis for investigation of connectivity in autistic youth. Concurrently, it is well-recognised that anxiety is a major confounding factor for autistic youth that may influence their social interaction and communication, and restricted and repetitive behaviour (Vasa et al., 2020). The interaction between anxiety and brain connectivity (Chen et al., 2021) has been reported as a potential link that may help explain the way that the autistic brain develops the elevated levels of anxiety that are observed in that population (Vasa et al., 2020). A common tool used to measure connectivity is electroencephalography (EEG).

Although EEG-based research often uses the overall strength of an isolated EEG signal from a single selected brain region (i.e., power spectra) as an index of specific brain site activity, EEG connectivity refers to the strength of the communication between two EEG sites obtained from different areas of the brain (Bowyer, 2016; Schomer & Lopes da Silva, 2017). Thus, EEG connectivity data are of value because they can provide detailed information regarding short-range and long-range neural activity as an interactional process (Sporns, 2014). In terms of particular brain regions to examine, there is an established neurological association between anxiety and connectivity across the prefrontal and parietal regions of the brain (Cole et al., 2014).

The prefrontal region of the brain is implicated in cognitive control and the 'top-down' (i.e., from cognition to behaviour) processing of behaviour, particularly in relation to maintaining attention and achieving tasks or goals (Christoff & Gabrieli 2000; Miller & Cohen, 2001). This process is enabled by the sending of information from the prefrontal cortex (PFC) to other brain regions (i.e., temporal, occipital, and parietal lobes) and the receiving of information from those regions by the PFC (Miller & Cohen, 2001). By comparison, the parietal (P) cortex is associated with sensory and spatial processing, attention, motor planning, perception, and decision-making (Bisley & Goldberg, 2010; Whitlock et al., 2008). Thus, the *frontoparietal* system may be considered to be a flexible control system, regulating and communicating to meet task demands (Cole et al., 2014; Genovesio et al., 2014; Ma et al., 2019; Marek & Dosenback 2018; Sylvester et al., 2012). As such, it has a *prima facie* potential association with anxiety and anxious responses, particular when the task demands produce psychophysiological arousal and feelings of anxiety, to which the individual must respond. Initial support for this hypothesis comes from studies in which frontoparietal connectivity has been correlated with Generalised Anxiety Disorder (GAD) in a non-autistic sample (Li et al., 2023).

EEG data from brain activity within specific frequencies has the potential to inform the connectivity-anxiety hypothesis. In particular, alpha activity (8 to 13 Hz) has been associated with relaxed states (i.e., not present during anxiety), and beta activity (13-18 Hz) has been associated with concentrated mental activity that might occur during anxious states (Schomer & Lopes da Silva, 2017). Detection of EEG connectivity at these different frequencies has the potential to further illuminate the kinds of brain activities that are associated with GAD.

As mentioned above, autistic youth exhibit elevated anxiety (Vasa et al., 2020) compared to their non-autistic peers (Matson & Nebel-Schwalm, 2007; Steensel & Heeman, 2017; Steensel et al., 2011; White et al., 2009). Although various manifestations of anxiety may occur in autistic youth, the most common is GAD (Bitsika & Sharpley, 2015), which is a function of two major diagnostic criteria (Excessive anxiety and worry; Difficulty in controlling the worry) and six ancillary symptoms, including restlessness, fatigue, irritability, and others (APA, 2013). There are also some GAD-like behaviours that are similar to the diagnostic criteria for ASD, such as strict adherence to rituals (Gotham et al., 2013) or fear of social situations (Renno & Wood, 2013), but a recent network analysis found that anxiety was "not a central and inextricable part of the autism realm" (Montazeri et al., 2019, p. 2227).

The collection of EEG connectivity data may be undertaken under a variety of experimental conditions, including task-solving or rest. Of these, rest provides the most relevant indication of a person's 'background' mental state, relatively free from distraction, called 'resting EEG' (Wang et al., 2013a). Resting EEG can be measured during an eyes-closed condition (i.e., participants sit still with their eyes closed) or an eyes-opened condition (i.e., participants sit still with their eyes open, typically looking at a black computer screen) (Barry et al., 2009).

Therefore, the current study aimed to investigate the association between GAD and EEG connectivity between the prefrontal and parietal regions in a sample of autistic youth. Several methodological decisions were made prior to undertaking the study in order to reduce the possible sources of external invalidity. Those methodological decisions were: (i) recruitment of autistic males because of the preponderance of ASD among males (APA, 2022), using the current diagnostic guidelines, and thus maximising generalisability of the results; (ii) restriction of the sample to males between the ages of 6 yr and 18 yr, as these are the years during which children attend school in Australia (this study was part of a larger investigation in progress of anxiety among school-age autistic youth (Bitsika & Sharpley, 2016)); (iii) participants were restricted to those with 'mild impairment' in order to homogenise the sample, and so a minimum IQ of 70 was set as an inclusion criterion; (iv) collection of EEG signals from the prefrontal and parietal regions to allow testing of the hypothesis that PFC-P connectivity is associated with GAD; (v) because previous studies of GAD and EEG connectivity in autistic youth examined functional connectivity (i.e., between PFC and P) only (Saunders et al., 2016), calculation of EEG connectivity in the present study was performed by Granger Causality (Brovelli et al., 2004), one of the most common effective connectivity methods that allows directional connectivity indices (i.e., PFC to P, as well as P to PFC) to be calculated; (vi) comparison of eyes-open and eyes-closed conditions so that any effect due to involuntary visual stimuli could be identified; (vii) collecting EEG data only when the participants were at rest (i.e., not engaged in any specific activity during eyes-closed and eyes-opened conditions) to follow previous studies of 'resting EEG'; and (viii) using GAD data collected from the autistic youths' parents about their autistic sons as one of the most commonly-used sources of information about this aspect of autistic youth (Steensel & Heeman, 2017; Steensel et al., 2011). Additionally, although theta-wave activity (i.e., between 4 and 7 Hz) has also been implicated in EEG studies investigating GAD symptoms in participants (Adhikari et al., 2010; Jacinto et al., 2016; Xing et al., 2017), one of the

aims of the current study was to explore participants' GAD scores and PFC-P connectivity under periods of typically increased relaxation (associated with alpha-wave) and mental activity (associated with beta-wave), as has been observed using the eyes-closed and eyes-opened conditions (Barry et al., 2007). As such, PFC-P connectivity was calculated for alpha-wave and beta-wave frequency ranges. It was hypothesised that there would be a significant inverse correlation between PFC-P connectivity and GAD. To further extend previous research, the directional testing of this hypothetical association with GAD (i.e., PFC → P *vs* P → PFC) was undertaken. Finally, because GAD is diagnosed by reference to eight heterogeneous symptoms (APA, 2013), the association between EEG connectivity and GAD was undertaken at the total GAD score level and also for the core components of GAD in the sample of autistic male youth to be recruited.

Material and Methods

Participants

Following a priori power analysis, 41 male autistic participants aged between 6 and 17 years were recruited for the study. One parent of each child was also recruited to provide diagnostic data on their child's ASD and anxiety. Participants were recruited from responses to publicity about the study delivered to autism support groups on the Gold Coast, Australia. Inclusion criteria were that autistic participants were male, aged between 6 and 18 years (M age = 10.76 yr, SD = 3.14 yr), had a formal diagnosis of ASD, and an IQ ≥ 70. Exclusion criteria included history of epilepsy or schizophrenia, and intake of anticonvulsant medication that may have influenced EEG signal validity. Among the 41 participants, 26 had additional diagnoses (primarily ADHD, OCD, anxiety, and depression) and 29 participants were medicated, seven for anxiety. There was no significant difference in the CASI-4 GAD total scores for the participants who were taking medication for anxiety, those who were taking medication for reasons other than anxiety, or those who were not taking medication $F(2,41) = 1.777$, $p = 0.183$, partial eta squared = 0.086. During the assessment period, participants were also screened for any visual sensitivities.

All behavioural and neurophysiological data were collected at the Centre for Autism Spectrum Disorder at Bond University and data analyses were conducted in the Behavioural Neuroscience Laboratory at the University of New England.

Instruments

Autism Diagnostic Interview – Revised (ADI-R)

All the autistic youth had been diagnosed with ASD several years previously by a registered paediatrician or psychiatrist, and these diagnoses were confirmed during study recruitment using the *ADI-R*. The *ADI-R* is a standardised and semi-structured interview with the participant's parent to assess previous and current autistic symptoms,

following ICD-10 and DSM-IV criteria (Lord et al., 1994). Lord, Rutter (Lord et al., 1994) have demonstrated interrater reliability coefficients for the majority of the *ADI-R* items to be over 0.70, with no item coefficients below 0.60. Test–retest reliability for the *ADI-R* ranges from 0.93 to 0.97 (Lord et al., 1994). The *ADI-R* has also been shown to have satisfactory diagnostic, construct and convergent validity (Lecavalier et al., 2006; Saemundsen et al., 2003; Tuschiya et al., 2013).

Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)

The WASI-II is a standardised test of general cognitive functioning (Wechsler, 2011). Scores on four WASI-II subtests are summed to provide a measure of Verbal Comprehension and Perceptual Reasoning, which are then combined to provide a Full Scale IQ (FSIQ) (Wechsler, 2011). The WASI-II can be administered to children and adults between ages 6 and 90 years. Internal consistency coefficients for the subtests range from 0.87 to 0.91 for the child sample (ages 6 to 16 years) and 0.90 to 0.92 for the adult sample (ages 17 to 90 years) (Wechsler, 2011). Test–retest reliability coefficients for the WASI-II subtests range from 0.79 to 0.90 for children and 0.83 to 0.94 for adults; inter-scorer reliability coefficients range from 0.98 to 0.99 for the Block Design and Matrix Reasoning subtests, 0.97 for Vocabulary, and 0.94 for the Similarities subtest (Wechsler, 2011). The WASI-II has also been shown to have strong validity with the WISC-IV in autistic samples with an IQ ≥ 70. (Minshew et al., 2005).

Child and Adolescent Symptom Inventory, Fourth Revision (CASI-4)

The CASI-4 (Gadow & Sprafkin, 2010) is a 173-item rating scale which may be completed by parents or other caregivers, and is based on the diagnostic criteria for emotional and behavioural disorders outlined in the DSM-TR (APA, 2022). The CASI-4 is intended to evaluate relevant symptoms in children between 5 to 18 years. The GAD subscale of the CASI-4 contains eight items drawn from the DSM-IV (and which are current for the DSM-5-TR) measuring the presence of concentration problems, severe worry, difficulties controlling worry, restlessness, irritability, tension, sleeping difficulties, and fatigue. Participants may respond to the CASI-4 GAD items by ratings of 0 (never), 1 (sometimes), 2 (often), or 3 (very often) about their child's 'overall behavior' (Gadow & Sprafkin, 2010), thus providing a measure of severity beyond that from categorical assessment procedures. Psychometric data are satisfactory (Gadow & Sprafkin, 2010) and include test–retest reliability of $r = 0.67$ ($p < 0.001$) over a six-week period, and internal consistency of 0.74 (Gadow & Sprafkin, 2010).

Procedure

The autistic boys were administered the WASI-II by a research-capable assistant, while their parents completed the ADI-R and CASI-4 with another research-capable assistant at the first author's laboratory. During this first visit, parents and their sons

were shown the EEG equipment and given an outline of the experimental procedure, so that they could ask any questions and give their consent (all parents and boys aged 15 years or more) or assent (boys aged 6 years to 14 years) to the procedure. Following confirmation of the boys' suitability for participation, parents and their sons (the latter will be referred to as 'participants' in the following sections) attended the laboratory on a subsequent day for the EEG session.

Experimental Setting

The sensory stimuli were presented to participants in a sound-attenuated laboratory approximately 4 m x 5 m, with the EEG recording equipment set behind the participant, who was sitting on a sofa chair. A PC screen showing the various stimuli described below was set approximately 0.90 m in front of the participants. Participants were video-taped with a Logitech HD Webcam camera to identify their responses, monitor their overt anxious behaviour during the experiment, and to observe any physiological artifacts during signal processing.

Experimenter

The experimental protocol was conducted by a doctoral student in clinical psychology who had several years' experience working with autistic children. The experimenter sat behind the participant to monitor his behaviour and EEG recordings.

Experimental Phases

1. Adaptation (15 min): Participants had the EEG cap and electrodes fitted, were settled into the chair, and engaged in minor conversation with the experimenter to ensure that they were calm and prepared for the rest of the protocol.
2. Resting eyes-closed condition (3 min): Participants sat still in the chair with their eyes closed for a period of three minutes, as has been done in previous studies (Duffy & Als, 2012; Wang et al., 2013b).
3. Resting eyes-opened condition (3 min): Participants were asked to look at the PC screen in front of them with their eyes opened for three minutes. The screen displayed a black screen with a white circle in the centre of the screen. This condition was congruent with those used in previous studies where participants looked at a dot on a blank screen or just a black screen (Machado et al., 2015; Mathewson et al., 2012) in order to keep participants' reactions to stimuli at a minimal level but also to direct their focus.

Data Acquisition and Pre-processing

The EEG signal was measured using a 40-channel NuAmps EEG amplifier from *Compumedics NeuroScan, Compumedics Ltd*, three Quik-Caps, *Compumedics Ltd.* (varying in size from small, to medium, and large) with 34 sintered Ag/AgCl electrodes, four drop-down integrated electrodes, and two auricle electrodes. The electrode cap included the following electrodes: FP1, F7, F3, FT9, FT7, FC3, T3, C3,

TP7, CP3, T5, P3, O1, PO1, Fz, FCz, Cz, CPz, Pz, Oz, FP2, F4, F8, FC4, FT8, FT10, C4, T4, CP4, TP8, P4, T6, PO2, O2. Cz was chosen as the reference electrode. Curry 7 is the seventh version of the Curry Neuroimaging Suite developed by Compumedics Ltd, and is the software associated with NuAmps and Quik-Caps. Signal pre-processing in Curry 7 included common average referencing (CAR), Bandpass filter (with default low and high pass frequencies ranging from 0 to 30 Hz). The sampling rate was 1 kHz. Impedances for the current study for most participants were set at or below 5 kΩ. Due to sensory sensitivities that are characteristic in this group of participants, the experimenter was mindful to limit abrasion to the scalp.

EEG Signal Processing

All EEG data collected from the two experimental conditions were treated with a constant baseline correction and filter parameters, which included the Notch filter with harmonics (frequency: 50 Hz; slope: 1.5 Hz) and the Bandpass with both low (frequency: 0.5 Hz; slope: 2 Hz) and high (frequency: 30 Hz; slope: 5 Hz) filter settings. Data tapering with a Hann filter (width: 5%) was used to assist in frequency smoothing. The general procedure included visual inspection to identify and reject any bad blocks, plus artifact reduction using automatic features offered in Curry 7. Typical artifacts detected came from ocular (eye blinks, lateral or roving eye movements), electrode, and muscle sources. All datasets were passed through the same artifact correction pipeline, using Curry 7 automatic reduction techniques: Subtraction, Covariance, Principal Component Analysis (PCA), and Independent Component Analysis (ICA).

All connectivity measurements were calculated using MATrix LABoratory (MATLAB) R2018b for academic use. The MATLAB toolboxes used for connectivity analysis were EEGLAB (Delorme & Makeig, 2004) and FieldTrip (Oostenveld et al., 2011). EEGLAB was used to convert the Curry 7 data format to a compatible version that was accepted by FieldTrip for Granger Causality (GC) analyses. Using the same filter parameters in Curry 7 to identify remaining artifacts, EEGLAB was used to delete bad blocks that were not identified during Curry 7 artifact reduction. FieldTrip was used to calculate connectivity via GC (Brovelli et al., 2004) due to its wide usage in EEG effective connectivity research, and in research on the autistic population (Nolte et al., 2010; O'Reilly et al., 2017; Pollonini et al., 2010; Schwartz et al., 2017). GC determines if one brain region's electrical activity influences another brain region's electrical activity (Brovelli et al., 2004; Ding et al., 2006), and can therefore provide greater insight into the *direction* of the connectivity. Because the current study was focused on the frontoparietal and parietal systems in the alpha and beta frequency ranges, a measure of directional connectivity was determined to provide more meaningful information in the ways these selected brain regions interacted and were influenced by each other.

The first step in using FieldTrip to calculate GC involved data pre-processing and redefining trials, where each dataset was used in its cleaned format (using Curry 7 or EEGLAB file formatting) and redefined as having four-second epochs. The number of available epochs ranged from 35 to 40, depending on the quality of data for each participant. The second step involved frequency analysis of the redefined

dataset, where the multi-taper frequency transformation method was chosen to calculate the power spectra (Oostenveld et al., 2011). Fourier spectral analysis was designated as the desired output, with Hann tapering applied with a width of 5%. The frequencies of interest were 8 Hz to 13 Hz (alpha) and 13 Hz to 30 Hz (beta). However, GC calculations required the frequency of interests to range from 0 to the Nyquist frequency, which is half the frequency of the sampling rate (Oostenveld et al., 2011). Spectrally resolved GC was calculated (Brovelli et al., 2004). All relevant mathematical calculations were embedded within the FieldTrip toolbox and did not require user input.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS), version 25. *G-Power* 3.1 power analysis showed that, for a correlational study (i.e., the major statistical procedure used to test for associations between GAD and connectivity in this study), a sample size of 40 was sufficient to detect a 'moderate' effect (Cohen, 1988) of $r = 0.30$ to 0.49 (i.e., accounting for between 9.0% and 24.0% of the variance) with $\alpha = 0.05$ and Power = 0.95. Appropriate Bonferroni corrections for family-wise error rate were conducted to reduce the likelihood of a Type I error where applicable. However, when there were so many correlation coefficients that the adjusted p value was unnecessarily restrictive (i.e., tended towards a Type II error instead of a Type I error), results were principally evaluated via consideration of the Effect Size (ES), as described by Cohen (Cohen, 1988). It was decided that a moderate ES (i.e., r of at least 0.3) was the lower cutoff value to be accepted, as recommended by Cone and Foster (Cone & Foster, 2008).

PFC-P connectivity was defined as the connectivity between each of the two preFrontal sites Fp1 and Fp2 with each of the three Parietal sites P3, Pz and P4, measured for alpha (i.e., 8–12.9 Hz) and three beta frequency ranges (i.e., 'low' = 13 to 17.75 Hz; 'medium' = 18 to 23.75 Hz; 'high' = 24 to 30 Hz). Using GC, these connectivity indices were calculated for each direction of association (i.e., PFC → P and P → PFC) in these frequency ranges.

Results

Descriptive Analysis

Table 1 presents the means and standard deviations of the ADI-R, WASI-II Full Scale Scores (FSIQ), and CASI-4 GAD total scores. Internal consistency (Cronbach's Alpha) was 0.814 for the eight GAD items. There was no significant correlation between participants' CASI-4 GAD total scores and their age ($r = 0.174$, $p = 0.276$), WASI-II FS IQ ($r = -0.278$, $p = 0.078$), ADI-R Social ($r = 0.277$, $p = 0.080$), Verbal ($r = 0.090$, $p = 0.577$), or Repetitive and Restrictive Behaviour ($r = 0.090$, $p = 0.577$) subscale scores.

Table 1 Means and Standard Deviations for Participant Age, WASI-II FSIQ[a], ADI-R[b] Domains, and CASI-4 GAD[c]

Instrument	Variable	*M*	SD
	Participant Age	10.76	3.14
WASI-II	FSIQ-4	102.10	14.46
ADI-R	Social	19.12	5.11
	Verbal	14.49	4.78
	Restricted and Repetitive Behaviour	6.71	2.35
CASI-4 GAD	GAD Total scores	10.10	5.13

N = 41. [a]Wechsler Abbreviated Scale of Intelligence-revised, Full Scale Score;

[b]Autism Diagnostic Interview – Revised; [c]Child and Adolescent Symptom Inventory, Fourth Revision, General Anxiety Disorder subscale total score

Univariate normality testing was conducted for both CASI-GAD total scores and EEG power values from cleaned data after signal processing across eyes-closed and eyes-opened conditions. The Kolmogorov–Smirnov (K-S) statistic for the CASI-GAD total scores was non-significant and therefore met the criteria for normality. The K-S statistic demonstrated that only 24.1% of EEG power spectra data met the criteria for normality, but transforming data to meet the criteria for normality may in fact distort the original data and increase the likelihood of misinterpreting the results (Tabachnick & Fidell, 2014). In particular, log transformations of data that is sometimes performed for EEG data (e.g., Machado et al., 2015, Simon et al., 2017, Isler et al., 2010) may make the data more skewed or lead to incorrect inferences regarding the original data (Feng et al., 2014; Robert & Casella, 2004). In addition, a minor degree of non-normality is not a necessary source of confound for correlational analyses (Norris & Aroian, 2004). For these reasons, no transformation of EEG data was undertaken.

GAD Total Score and F-P Connectivity

Pearson correlations were calculated between CASI-4 GAD total score and PFC-P connectivity values obtained via Granger Causality (GC). Applying the Bonferroni-adjusted p value of $0.05/48 = 0.0010$ (for directional PFC-P connectivity in alpha frequency and the three beta frequency ranges) would have increased the likelihood of a Type II error, and so the presence of an ES that was at least moderately robust, (i.e., $r \geq 0.30$) plus the traditional $p < 0.05$ level of significance was accepted as indication of significant and meaningful correlations between CASI-4 GAD total score and EEG data. For the PFC → P direction of connectivity in the alpha frequency, eyes-closed condition, there were several correlations that met this criterion: between sites Fp1 → P3: $r = -0.309$, $p = 0.049$; Fp2 → Pz: $r = -0.415$, $p = 0.002$; Fp2 → P4: $r = -0.462$, $p = 0.002$, but there were no significant and meaningful effects for any of the three beta frequencies. There were no significant and meaningful correlations between CASI-4 GAD total scores and any of the connectivity indices for

either alpha or the three beta frequencies for P → PFC GC in the eyes-closed condition. There were no significant and meaningful correlations in either PFC → P GC or P → PFC GC directions for alpha or any of the three beta frequencies for the eyes-open condition.

Core GAD Symptoms and F-P Connectivity

In order to detect any significant and meaningful correlations between the CASI-4 GAD items and PFC → P GC or P → PFC GC connectivity under the eyes-open and eyes-closed conditions, it was necessary to firstly identify the core components of the CASI-4 GAD scale, i.e., which CASI-4 GAD items were the most representative of these participants' GAD total score. Factor analysis of the eight CASI-4 GAD items was conducted for this purpose. There is some debate regarding the sample size needed to conduct factor analysis, but recent comments focus instead upon the presence of sufficiently robust (i.e., $r = 0.3$ or larger) intercorrelations between the items (Tabachnik & Fidell, 2013). Additionally, Bartlett's' test of Sphericity and the Kaiser–Meyer–Olkin measure of sampling accuracy are valuable indicators of the suitability of the data for factor analysis. In the current sample, over 60% of the item intercorrelations were greater than 0.3, Bartlett's test was significant (Chi square = 394.644, $p < 0.001$), and the Kaiser–Meyer–Olkin test was 0.734, greater than the 0.6 value recommended (Tabachnik & Fidell, 2013). Direct Oblimin rotation of the 8 CASI-GAD items revealed a single-factor solution (Eigenvalue = 3.670, 45.879% of the variance explained), confirmed by the scree plot and parallel analysis. When the Component Matrix was inspected (Table 2), it was apparent that CASI-4 GAD item 3 (*Difficulty controlling worries*) and item 6 (*Extremely tense and unable to relax*) loaded most strongly on that single factor. These two CASI-4 GAD items therefore represent the 'core' symptoms of GAD as it was expressed in the responses of this sample of autistic boys, and so were selected for investigation in terms of their association with PFC-P connectivity. Indicative of their association as core components of GAD here, they significantly correlated with each other at $r = 0.742$, $p < 0.001$.

Table 2 Component Matrix for CASI-4 GAD[a] Items

CASI-4 GAD Item	Component 1
Has difficulty paying attention to tasks or activities	.561
Is overconcerned about abilities in school, athletic, work, or social activities	.533
Has difficulty controlling worries	.846
Acts restless or edgy	.772
Is irritable for most of the day	.717
Is extremely tense or unable to relax	.865
Has difficulty falling asleep or staying asleep	.428
Has low energy level or is tired for no apparent reason	.562

[a]Child and Adolescent Symptom Inventory, Fourth Revision, General Anxiety Disorder subscale total score

Pearson correlations between the two CASI-4 GAD core items and PFC → P direction connectivity in the alpha frequency under the eyes-closed condition are shown in Table 3, and indicate that seven of the 12 correlation coefficients reached the criteria of $p < 0.05$ and also $r \geq 0.3$ (these are bolded in Table 3). For the beta frequency range under this eyes-closed condition, only the correlation between CASI-4 GAD item *Has difficulty controlling worries* and Fp1 → Pz connectivity in the very high beta frequency range (24-30 Hz) reached significant and meaningful size: $r = -0.389$, $p = 0.012$; a similarly powerful correlation was found between CASI-4 GAD item *Extremely tense and unable to relax* and Fp2 → P4 connectivity in the lowest beta frequency range (13–18 Hz): $r = 0.343$, $p = 0.028$. There were no other significant and/or meaningful correlations between either of these two CASI-4 GAD items and any of the connectivity indices in the PF → P or P → PF directions under either the eyes-open or eyes-closed conditions. The directionality (arrows), strength (correlation coefficient), and location (EEG sites) of the connectivity indices that were significantly and meaningfully associated with the two CASI-GAD core items are shown colour-coded in red (*Difficulty controlling worries*) and blue (*Being extremely tense or unable to relax*) in Fig. 1 for ease of comprehension. The correlations between CASI-4 GAD total score are also shown in Fig. 1 colour-coded in green.

Discussion

Although one major finding from this study was a confirmation of the correlation between anxiety and PFC-P connectivity that had previously been reported in non-ASD youth (Ball et al., 2013; Etkin et al., 2009; Liao et al., 2013; Sylvester et al., 2012), the use of GC to detect the direction of that connectivity was an extension on previous work. There was a minor difference in the role played by the left frontal site versus the right frontal site, which will be discussed below. However, the overall finding was that, as connectivity between the general PFC region towards the parietal region (i.e., PFC → P) increased in strength in the alpha frequency, total GAD scores (as per items using the CASI-4 checklist) decreased. There was no significant association between GAD and communication from the parietal area towards the PFC region (P → PFC).

Table 3 Pearson correlations for PFC → P[a] direction connectivity under the eyes closed condition in the alpha frequency for two 'core' CASI-GAD[b] items

CASI-4 GAD items		**Fp1P3**	**Fp1Pz**	Fp1P4	Fp2P3	**Fp2Pz**	**Fp2P4**
Has difficulty controlling worries	*r*	**-.313**	**-.344**	-.225	-.288	**-.362**	**-.313**
	p	**.046**	**.028**	.157	.068	**.020**	**.047**
Is extremely tense or unable to relax	*r*	-.287	**-.319**	-.272	-.282	**-.353**	**-.414**
	p	.069	**.042**	.085	.074	**.024**	**.007**

Bolded figures represent medium strength correlations

[a]Prefrontal cortex to Parietal regions; [b]Child and Adolescent Symptom Inventory, Fourth Revision, General Anxiety Disorder subscale total score

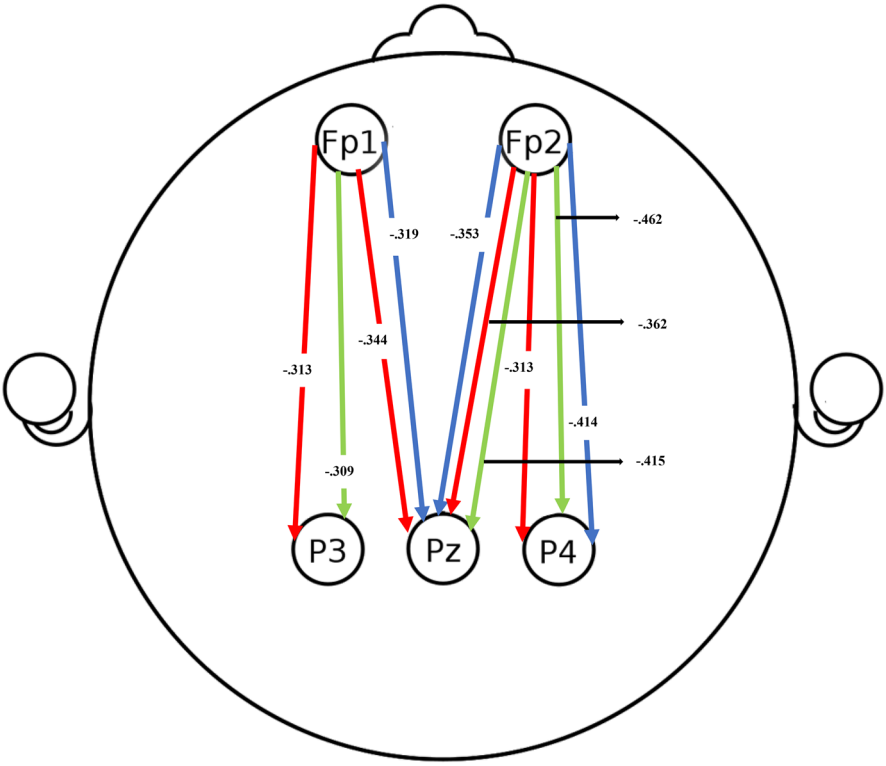

Fig. 1 Significant ($p < .05$) and Meaningful ($r > .29$) Correlations between PFC-P Granger Causality and CASI-4 GAD Items. *Note.* Based on the International 10–20 System. Red lines indicate correlations between PFC-P connectivity and the GAD item regarding *Difficulty controlling worries*. Blue lines indicate correlations between PFC-P connectivity and the GAD item regarding *Being extremely tense or unable to relax*. Green lines refer to correlations between PFC-P connectivity and the *CASI-4* GAD total score

Concerning the significant inverse association between PFC→P EEG alpha-wave connectivity and GAD total score, the more anxious the young autistic males were, the less they demonstrated alpha frequency connectivity from the PFC to the parietal regions. If the 'causal' properties of GC connectivity were considered, this finding may indicate that the 'decision-making' PFC region communicated to the 'motor-activations' parietal region of anxious boys to respond with less alpha activity while participants were at rest and with their eyes closed. Because alpha activity is most often associated with relaxation, this interpretation is plausible if EEG data had been collected at the PFC region or the parietal regions separately and in isolation from each other, but the finding that the PFC→P connectivity was the means by which the parietal region may have been induced to reduce alpha activity is a new finding for autistic youth.

The Introduction to this paper described how the PFC communicates to various other brain regions to establish a cognitively-controlled processing of behaviour, particularly in relation to maintaining attention and achieving tasks or goals (Miller &

Cohen, 2001). These results demonstrate how the PFC does that in regard to the parietal region, where attention, motor planning, perception, and decision-making occur (Bisley & Goldberg, 2010; Whitlock et al., 2008), and they also emphasise the regulatory nature of the frontoparietal system in helping the individual meet task demands (Cole et al., 2014; Genovesio et al., 2014; Ma et al., 2019; Marek & Dosenback, 2018; Sylvester et al., 2012). The 'core' GAD components identified for this sample of autistic males were their control of worrying (i.e., a cognitive control process) and their inability to relax (i.e., related to motor activity), incorporating both the PFC and parietal regions, and plausibly doing so via their EEG connectivity.

Those results were for the total CASI-4 GAD score, but that metric represents the sum of eight heterogeneous symptoms of anxiety. The core components of GAD in this sample of autistic young males included one of the two key symptoms of GAD (i.e., *Difficulty controlling worries*), suggesting that this central aspect of GAD was influential upon the way that the PFC and parietal regions communicated in these autistic boys. The second CASI-GAD item that was found to constitute the 'core' elements of GAD in this sample was concerned with their physiological state (*Being extremely tense or unable to relax*). Again, there is some evidence that higher scores on this symptom of GAD were also associated with reduced likelihood of the PFC influencing alpha activity in the parietal region. There is a theoretical link between these two GAD symptoms because difficulty in controlling worrying may lead to a state of physiological arousal in which relaxation is difficult to achieve; evidence of that link is the presence of a significant correlation between those two GAD symptoms in this study.

The 'source' PFC and 'target' parietal regions that were associated with the two GAD 'core' item-connectivity correlations are also of interest. For example, previous data indicated that EEG activity in P3 is associated with the *precuneus* area of the brain, which is the site of self-regulation (Cavanna & Trimble, 2006). By contrast, the P4 region is the inferior parietal region of the brain, and the site of motor planning and action-related functions (Caspers et al., 2013), and the Pz is the superior parietal region, found to be linked to working memory (Koenigs et al., 2009). The frontal region FP1 has been hypothesised to be the site of activation of the behavioural *approach* system (responsible for *engaging* with pleasant stimuli) (Davidson, 1998), whereas FP2 reflects the behavioural *withdrawal* system (responsible for *disengaging or avoiding* aversive stimuli) (Henriques & Davidson, 1997). Although it would be beyond the reach of the present data to hypothesise the functions of aspects of PFC-P pathways at this level of specificity, it is apparent from Fig. 1 that, for the GAD symptom that measured participants' ability to *control their worries,* the PFC region's communication reached all three parietal sites, but for the GAD symptom of *being extremely tense or unable to relax,* that communication reached only to P4 and Pz sites. Whether that difference also relates to the underlying actions of those three parietal regions remains to be demonstrated, as does the possible effect of the behavioural approach versus withdrawal systems, and these remain possible targets for future research.

These findings were predominantly for alpha-wave activity, with only two relatively isolated significant results for beta-wave activity, one of which showed a significant direct association (FP2 to P4 for *being tense or unable to relax*) but the

other showed a significant inverse association (FP1 to Pz for *difficulty controlling worries*). Alpha frequency is generally associated with lower arousal states, and so the present findings agree in general with those from Oathes et al. (Oathes et al., 2008) who also failed to find major associations between GAD and beta-wave activity. The role of alpha appears to be more powerful than that exerted by beta in relation to GAD states, but that may also have arisen because of the fact that the significant alpha and beta results were isolated to the eyes-closed condition, wherein alpha is more likely to be generated (Barry et al., 2009).

Finally, all the significant correlations between GAD and EEG connectivity were in the PFC→P direction, as indicated by Granger Causality, which allowed for an extension of previous studies when only functional connectivity was reported. The fact that there was no significant communication from the parietal area to the PFC (P→PFC) region argues for the dominance of the PFC in the association between PFC-P connectivity and GAD. This, it might be initially hypothesised that PFC-based cognitions influenced GAD-related behaviours rather than vice-versa.

Clinical Implications

Several psychosocial therapies may be used to help autistic youth reduce their anxiety (Kester & Lucyshyn, 2018; White et al., 2018), and exercise may be valuable in helping these children and adolescents cope with environmental stressors (Tse, 2020), but one direct treatment (i.e., which focusses upon the brain connectivity itself) is neurofeedback. Neurofeedback is an EEG-based neurophysiological intervention by which neuronal communication patterns can be altered (Biofeedback, 2016; Hoogdalem et al., 2020) through provision of visual and/or auditory representations of their brain wave activity, which they are encouraged to control while being exposed to varying tasks and demands. A recent systematic review by van Hoogdalem, Feijs (Hoogdalem et al., 2020) found that 19 out of the 20 studies that applied neurofeedback with autistic children reported positive long-term outcomes in relation to challenging, sensory motor, social, and communicative behaviours associated with ASD. Of particular interest to the current study, neurofeedback has been found to be successful in long-term treatment of individuals with GAD (Biofeedback, 2016; Clark et al., 2009; Micoulaud-Franchi et al., 2021; Moardi et al., 2011). As well as helping to increase functional integration, cognitive control and task adaptation, which have been associated with PFC-P connectivity (Marek & Dosenback, 2018), neurofeedback might also potentially decrease some of the anxiety symptoms (e.g., *controlling worries* and *decreasing tension*) that may be present in autistic children with GAD.

Limitations

The sample size was adequate to detect moderate effects via Pearson correlational analysis, and so the absence of significant findings for most of the beta-wave connectivity and for alpha in the P→PFC direction was unlikely to be due to inadequate statistical power alone. However, the sample was not comprehensive, and so restrictions on generalisability to other geographical, cultural, and ability samples of autistic males

must be acknowledged. Similarly, the restriction of the recruiting process to autistic males calls for extension of this study to mildly-impaired autistic girls, as well as more severely impaired autistic boys and girls. The experimental conditions were purposely structured to allow collection of resting EEG data, but implementation of an active task-solving setting could provide information about how autistic youth responds in actual anxiety-provoking situations. EEG data provide a valuable insight into the brain's activity, but concomitant collection of other physiological data that are related to stress and anxiety (e.g., heart rate, skin conductance) could help in understanding the actual anxiety state of the research participant during the experiment itself.

Conclusion

These data offer an insight into the way that anxiety may be initiated and maintained in male autistic youth, and confirm some previous correlations between PFC-P connectivity and GAD in non-autistic samples, but with the extension of those findings to the diagnostic symptoms of GAD rather than the total GAD score. As such, these findings help understanding of the way the autistic brain develops anxiety, and suggest some treatment possibilities for alleviating that state, particularly via direct (i..e, neurofeedback) strategies.

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Data Availability Data are available from the first author on request. Data citation: (Bitsika & Sharpley, 2016).

Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest or any competing financial or other competing interests.

Ethical Approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bond University Human Research Ethics Committee, Approval Number: 15786, March 2017, and the University of New England Human Research Ethics Committee, Approval Number: HE17-208, June, 2017.

Informed Consent Parents gave their written consent for all children to participate in this study. In addition, children aged 12 or more also gave their written consent, and younger children gave their verbal assent.

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