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RESEARCH ARTICLE

Dynamic functional connectivity in the right temporoparietal junction captures variations in male autistic trait expression

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Abstract

Autistic individuals can experience difficulties with attention reorienting and Theory of Mind (ToM), which are closely associated with anterior and posterior subdivisions of the right temporoparietal junction. While the link between these processes remains unclear, it is likely subserved by a dynamic crosstalk between these two subdivisions. We, therefore, examined the dynamic functional connectivity (dFC) between the anterior and posterior temporoparietal junction, as a biological marker of attention and ToM, to test its contribution to the manifestation of autistic trait expression in Autism Spectrum Condition (ASC). Two studies were conducted, exploratory (14 ASC, 15 TD) and replication (29 ASC, 29 TD), using resting-state fMRI data and the Social Responsiveness Scale (SRS) from the Autism Brain Imaging Data Exchange repository. Dynamic Independent Component Analysis was performed in both datasets using the CONN toolbox. An additional sliding-window analysis was performed in the replication study to explore different connectivity states (from highly negatively to highly positively correlated). Dynamic FC was reduced in ASC compared to TD adults in both the exploratory and replication datasets and was associated with increased SRS scores (especially in ASC). Regression analyses revealed that decreased SRS autistic expression was predicted by engagement of highly negatively correlated states, while engagement of highly positively correlated states predicted increased expression. These findings provided consistent evidence that the difficulties observed in ASC are associated with altered patterns of dFC between brain regions subserving attention reorienting and ToM processes and may serve as a biomarker of autistic trait expression.

Lay Summary

Autistic individuals may have difficulties with redirecting their attention and understanding others' thoughts and it is possible that there is a direct link between the interaction of these two functions and the level of social difficulties in autism. One way to test this link is by assessing how different brain regions associated with these functions are communicating with each other and working in synchrony. The present study focused on two subdivisions of a brain region called

the temporoparietal junction, which has been associated with attention and understanding others' thoughts. Our aim was to assess the dynamic communication between these subdivisions in autistic and non-autistic individuals and whether differences in this dynamic communication might be related to higher or lower expressions of social difficulties. Using brain scans from two different groups of 29 and 58 participants, we found that communication between these brain regions was less dynamic in autistic individuals in both groups. Moreover, reduced dynamic communication between these two subdivisions of the temporoparietal junction was associated with greater social difficulties. Across the two groups, we show consistent results whereby some of the social difficulties observed in autistic individuals might arise from reduced dynamic communication between brain areas linked to attention and understanding of others' thoughts. This insight adds to our understanding of how the spectrum of autistic traits might be rooted in the brain's communication patterns and advances the search for biological markers of autism.

KEYWORDS
attention reorienting, autism spectrum condition (ASC), dynamic functional connectivity (dFC), mentalizing, resting-state fMRI (RSfMRI), right temporoparietal junction (TPJ), theory of mind (ToM)

INTRODUCTION

Autism spectrum condition (ASC) is a neurodevelopmental condition characterized by difficulties in social interaction, communication, and repetitive, restricted behaviors (American Psychiatric Association, 2013). Within the wide spectrum of autistic traits, atypicalities in Theory of Mind (ToM)/mentalizing and attention reorienting, including the possible link between them, have been reported by an extensive body of behavioral and neuroimaging research (Keehn et al., 2010; Lai et al., 2014; Leekam, 2016; Spaniol et al., 2021). ToM refers to the ability to understand and infer the mental states—beliefs, intentions, emotions—of oneself and others, and to use this information to predict behavior (Baron-Cohen et al., 1985; Hill & Frith, 2003; Jones et al., 2018). Previous studies have consistently reported difficulties in the behavioral performance of ASC groups compared to typically developing (TD) controls during ToM tasks (such as false beliefs tasks; Abu-Akel & Bailey, 2001; Wimmer & Perner, 1983). These behavioral effects are also mirrored in the decreased activation and reduced functional connectivity (FC) in ASC of the neural network underpinning ToM (Castelli et al., 2002; Cole et al., 2019; Ilzarbe et al., 2020; Kana et al., 2015), which chiefly consists of the medial prefrontal cortex, the temporal pole, the posterior cingulate cortex, and the temporoparietal junction (TPJ).

Attention atypicality in orienting, disengaging, and reorienting attention when presented with novel relevant stimuli (i.e., "attention shifting" or "attention reorienting") has also been consistently demonstrated in ASC (Abu-Akel et al., 2018; Keehn et al., 2013). For instance, using a peripheral cueing paradigm (Posner et al., 1980), Keehn et al. (2010) showed that autistic participants were significantly slower than TD participants in orienting their attention to a validly cued target. Likewise, several studies have found that ASC participants shifted their attention toward both social and non-social stimuli less frequently than TD participants (Dawson et al., 2004; Mo et al., 2019). Here too, neuroimaging studies in ASC have shown atypical activation in regions associated with attention orienting and reorienting, mainly within the ventral frontoparietal attention network. Reduced activation of the inferior frontal gyrus and the supramarginal gyrus in response to the appearance of social cues were recorded in ASC (Greene et al., 2011), as well as both under- and over-reactivity in the prefrontal cortex and the inferior parietal lobule for passive or active novelty detection, respectively (Gomot et al., 2006; Gomot et al., 2008).

The ability to shift attention to new relevant stimuli both in social and non-social contexts could be a prerequisite for infants' development of ToM (Mundy & Newell, 2007), premised on the notion that shifting attention between different spatially distinct external stimuli is similar to the requirement to shift attention between your own and another person's point of view (Corbetta et al., 2008; Decety & Lamm, 2007). Evidence for the association of early manifestation of attention disengagement difficulties (between 6 and 12 months) and later diagnosis of ASC at 24 months (Zwaigenbaum et al., 2005) has increased the interest in the link between ToM and attention difficulties in ASC (Devaney, 2018; Keehn et al., 2013; Kubit & Jack, 2013).

The involvement of the right TPJ (rTPJ) in both reorienting attention and ToM processes has been consistently documented (Abu-Akel et al., 2017; Bzdok et al., 2013; Devaney, 2018; Kubit & Jack, 2013; Mars et al., 2012; Schuwerk et al., 2017). For example, brain

stimulation over the rTPJ has been shown to impair both attention-shifting performance (using a visual cueing paradigm) and ToM performance (increased error rates in a false belief task; Krall et al., 2016). A closer inspection of the rTPJ using diffusion-weighted imaging tractography-based parcellation (Mars et al., 2012) found that the right anterior TPJ (raTPJ) is connected with the ventral prefrontal cortex and anterior insula (parts of the attention network), while the right posterior TPJ (rpTPJ) shows stronger connectivity with the posterior cingulate cortex, temporal pole and medial prefrontal cortex (parts of the ToM network). Corresponding with this structural parcellation, Krall et al. (2015) reported functional evidence showing higher activation of the raTPJ during attention-reorienting tasks and higher activation of the rpTPJ during ToM tasks.

Subsequent resting-state FC studies have revealed an antagonistic relationship between the raTPJ and rpTPJ (Bzdok et al., 2013; Fox et al., 2005; Jack et al., 2012; Kubit & Jack, 2013). For example, using coactivation-based parcellation, Bzdok et al. (2013) found the attention network to be both positively correlated with the raTPJ and anti-correlated with the rpTPJ; whereas the social cognition network showed a positive correlation with the rpTPJ and negative correlation with the raTPJ. Accordingly, the authors proposed that the posterior and anterior rTPJ belong to two antagonistic brain networks (Bzdok et al., 2013). It is evident that two distinct and possibly antagonistic brain networks, with a focus on the TPJ, support attention orienting and ToM. It is, therefore, possible that an important proxy for understanding the manifestation of autistic expression, which is associated with atypicalities in both of these processes, can be found in the functional connectivity between the raTPJ (attention) and rpTPJ (ToM) parcellations of the right TPJ region.

Previous FC studies in ASC are inconsistent and tend to split between a hypo- (Alaerts et al., 2014; Lau et al., 2020) and hyper- (Chien et al., 2015; Li et al., 2020) connectivity pattern in the social cognition network of ASC participants compared to neurotypical individuals. These inconsistencies may point to the limitations of static FC studies especially in the context of neural networks underlying complex cognitive processes, such as attention and ToM (Allen et al., 2014; Calhoun et al., 2014; Hutchison, Womelsdorf, Gati, et al., 2013). In contrast to the traditional static FC, *dynamic* FC tracks the temporal variations in FC resulting in different brain state configurations (connectivity patterns) among neural networks at different time points (Allen et al., 2014; Calhoun et al., 2014; Hutchison, Womelsdorf, Allen, et al., 2013). Thus, for instance, at the beginning of a scan, a pair of regions of interest (ROIs) could show a high positive correlation, whereas later in the scan they could be negatively correlated. Existing dynamic FC research demonstrates its utility in several domains, including for predicting behavior (Chen, Nomi, et al., 2017), classifying bipolar disorder (Rashid et al., 2018), and detecting abnormal connectivity patterns associated with dysfunctional thoughts in major depression disorder (Kaiser et al., 2016) and with clinical symptoms in schizophrenia (Rabany et al., 2019).

The limited extant research using dynamic FC studies in ASC has successfully highlighted group differences, particularly in the average time spent in each state of connectivity (i.e., mean dwell time, MDT) between ASC and TD participants (Yao et al., 2016). In a recent paper (Li et al., 2020), both group differences in overall dynamic FC variability in some regions (e.g., in the saliency and default mode networks) and differences in specific connectivity states (specifically the time spent in and the likelihood of transitioning into a hyper-connected state) were documented and were also associated with autistic traits on the individual level (Li et al., 2020). Thus, dynamic FC investigations are important in ASC in both highlighting global differences in the overall dynamic nature of connectivity (i.e., whether connections remain constant or change during rest) and in the specific connectivity states that occur during rest, including the time a person "spends" in a particular state or the likelihood they will transition into that state.

In the current study, we focus on the dynamic resting-state FC between the anterior and posterior subdivisions of the rTPJ as a window into the relationship between attention reorienting and social cognition in autistic compared to TD individuals (Kubit & Jack, 2013). For this purpose, dynamic independent component analysis (dyn-ICA) was used on two resting-state fMRI datasets from the Autism Brain Imaging Data Exchange (ABIDE) database (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al., 2014; Martino et al., 2017), with the first serving as an exploratory and the second as a replication. dyn-ICA was used to assess general variability in functional connectivity (i.e., a measure of the degree to which functional connectivity changes throughout the resting-state scan). In addition, we assessed specific connectivity states (from highly negatively correlated to highly positively correlated) in the larger replication dataset using a sliding-window approach (Kaiser et al., 2016). The latter enables us to identify the underlying source of the global functional connectivity variability difference. Previous research argued that integration processes would be enhanced by higher FC variability (Hellyer et al., 2015; Shine et al., 2016). Since we understand attention orienting to be intrinsically linked to ToM (Mundy & Newell, 2007), we expect the two networks to be supported by a degree of functional connectivity variability, and therefore atypicalities in attention and ToM (as in ASC) should be associated with reduced variability. In our analysis, this should be evidenced in decreased dynamic resting-state FC between the raTPJ and rpTPJ in the ASC group. In addition, as previous research

pointed to the antagonistic relation between the networks—although this is in static connectivity—we expected ASC participants to show a reduced likelihood of entering into a high negative correlation state of the raTPJ and rpTPJ. Finally, both the reduction in variability and the reduced likelihood of negative states are expected to predict increased manifestation of autistic traits on the individual level, which may support the dimensional notion of ASC (Abu-Akel et al., 2019; Li et al., 2020; Rabany et al., 2019; Yao et al., 2016).

METHODS

Participants

Original fMRI and phenotypic data were obtained from the open-access ABIDE repository (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al., 2014; Martino et al., 2017). Participants eligible for inclusion in both the pilot/exploratory and replication analyses were adults aged 18 years and above. The selection process considered fMRI scanning parameters, specifically the length of the repetition time (TR), as a crucial factor in capturing dynamic changes in FC. A shorter TR was prioritized to enhance temporal resolution, enabling the detection of rapid alterations in brain connectivity patterns. For the pilot study, participants included autistic adults and typically developing controls with equal group sizes and average Full-Scale Intelligence Quotient (FIQ) scores. The availability of Social Responsiveness Scale (SRS) scores was also included as an inclusion criterion as this measure is important for assessing autistic trait expression, particularly related to mentalizing processes (which are particularly relevant here). In the replication analysis, a larger sample size was prioritized while maintaining phenotypic characteristics consistent with the pilot study (male autistic adults, average FIQ, and SRS scores).

A first exploratory study was conducted using the University of Leuven Sample 1 dataset (subsequently referred to as Exploratory), which includes the resting-state fMRI data of 14 autistic males (21.7 ± 4.0 years) and 15 typically developing (TD) matched controls (23.3 ± 2.9 years). A second study was conducted using the Barrow Neurological Institute dataset (subsequently referred to as Replication) to replicate and expand the first findings in a larger cohort. The Replication dataset includes the resting-state fMRI data of 29 autistic males (37.4 ± 16.1 years) and 29 TD-matched controls (39.6 ± 15.1 years).

Clinical assessment

Across both datasets, autistic trait expression was assessed with the self-report Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005), which significantly discriminated between groups. The SRS measures social difficulties related to ASC and quantifies their levels of expression. The scale includes a total score and five subscales that assess social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Higher SRS scores indicate higher expression of autistic traits. Demographics and clinical characteristics are available in Table 1 in the Results section.

Data acquisition

Data acquisition parameters for the Exploratory and Replication datasets are available in Supporting Information and were obtained from http://fcon_1000.projects.nitrc.org/indi/abide: ABIDE I University of Leuven Sample 1 and ABIDE II Barrow Neurological Institute repositories, respectively.

Data preprocessing and Denoising

Functional data was analyzed in the CONN toolbox 19.c (https://www.nitrc.org/projects/conn/) (Whitfield-Gabrieli & Nieto-Castanon, 2012), an open-source software based on Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) and MATLAB (MathWorks, Natick, MA). Data preprocessing and denoising were performed using batch scripts (available online at https://github.com/laurabravo97/Preprocessing-Denoising-CONN-toolbox-) following the CONN default pipelines (Nieto-Castanon, 2020) with minimal adjustments. Please see Supporting Information for details on the preprocessing and denoising steps.

Dynamic independent component analysis (Dyn-ICA)

Two ROI masks for the raTPJ and the rpTPJ (see Figure 1a) were obtained from the study by Mars et al. (2012) and are available at http://www.rbmars.dds.nl/CBPatlases.htm. Fslmaths (FMRIBS's Software Library, https://fsl.fmrib.ox.ac.uk, version 6.0.1) was used to remove the overlap between them. ROI-to-ROI dynamic resting-state FC analysis was performed using the dyn-ICA approach available in the CONN toolbox. Dyn-ICA is a data-driven approach that returns spatial maps containing connectivity patterns that can be interpreted as building blocks of dynamic FC (Nieto-Castanon, 2020). In this case, because two seeds are introduced in the analysis, we obtain one component/circuit timeseries that explains most of the variance across the 2 × 2 dynamic FC matrix.

In the Exploratory dataset, a temporal modulation smoothing kernel of 37.4 s (i.e., 22 TRs) was defined in

TABLE 1 Demographic characteristics and autistic trait expression (both datasets).

	Exploratory			Replication		
	ASC ($n = 14$) Mean ± SD	**TD ($n = 15$) mean ± SD**	***p*-Value**	**ASC ($n = 29$) mean ± SD**	**TD ($n = 29$) mean ± SD**	***p*-Value**
Age (years)	21.7 ± 4.0	23.3 ± 2.9	0.223	37.4 ± 16.1	39.6 ± 15.1	0.604
Sex	All males	All males		All males	All males	
FIQ	107.9 ± 13.9	114.8 ± 12.8	0.160	107.8 ± 13.7	112.4 ± 12.1	0.175
SRS—Total (self-report)	76.9 ± 24.2	43.6 ± 21.7	<0.001	106.3 ± 30.4	27.9 ± 17.9	<0.001
SRS *subscales*						
Social awareness	9.2 ± 3.1	6.8 ± 2.8	0.03	11.4 ± 4.5	5.2 ± 2.8	<0.001
Social cognition	14.5 ± 4.8	7.2 ± 4.8	<0.001	19.7 ± 6.3	4.7 ± 4.3	<0.001
Social communication	25 ± 6.9	14.4 ± 8.1	<0.001	35.8 ± 10.9	7.6 ± 6.6	<0.001
Social motivation	15 ± 4.8	7.9 ± 4.8	<0.001	18.9 ± 6.3	6.4 ± 4.8	<0.001
Autistic mannerisms	13.1 ± 5.1	7.1 ± 4.5	0.002	20.3 ± 6.8	4.1 ± 3.6	<0.001

Note: Higher scores in SRS represent higher autistic trait expression.
Abbreviations: FIQ, full-scale IQ; SRS, Social Responsiveness Scale.

the *Dyn-ICA* tab of the CONN toolbox, and the raTPJ and rpTPJ masks were introduced as seeds. In the Replication dataset, the temporal window was set to 39 s (i.e., 13 TRs). The dyn-ICA analysis is performed in different steps. First, fMRI data is concatenated across subjects and iterative dual regression is used to estimate the subject-specific matrix of connectivity changes and the subject-specific timeseries of the temporal modulatory component. Next, fast independent component analysis is used to obtain the dynamic, data-driven, independent component. Finally, generalized psychophysiological interaction (gPPI) back-projection is implemented to obtain each subject's dyn-ICA matrix (connectivity values between raTPJ and rpTPJ), with the estimated component as the gPPI psychological factor (Nieto-Castanon, 2020).

Dynamic FC analysis in the replication dataset (sliding-window approach)

An ROI-to-ROI sliding-window dynamic FC analysis (Allen et al., 2014; Hutchison, Womelsdorf, Allen, et al., 2013) was additionally carried out in the Replication dataset to expand the results obtained with the dyn-ICA approach. ROI-to-ROI dynamic FC analyses return connectivity matrices representing the temporal variability in dynamic FC between pairs of seeds. The window length was set to 13 TRs (39 s) with a sliding window step of 1 TR (3 s) to ensure smooth transitions between windows, producing 108 temporal windows in total (120 volumes − 13 TRs + 1). These parameters were selected in order to find a balance between the sensitivity and specificity of the window, that is, to define a window short enough to capture rapidly shifting dynamics of FC but long enough to avoid spurious fluctuations (Leonardi & Van De Ville, 2015; Preti et al., 2017).

For the first level analysis, the FC values (Fisher's z transformed correlation coefficient; z-scores) between the pair of ROIs were computed for each sliding window and each subject. This yielded a set of beta-maps per subject that were introduced into a general linear model for ROI-to-ROI group-level analysis. Effects were considered significant if $p_{\text{uncorrected}} < 0.01$ (two-sided) and p-false discovery rate (FDR) $_{\text{corrected}} < 0.05$.

In order to investigate the states of connectivity, FC patterns were estimated by classifying each subject's ROI-to-ROI connectivity values from each of the 108 windows into five states to match previous similar approaches (Kaiser et al., 2016): high negative (z-scores < -0.50), moderate negative ($-0.5 \leq z$-scores < -0.25), low-uncorrelated ($-0.25 \leq z$-scores ≤ 0.25), moderate positive ($0.25 < z$-scores ≤ 0.50) and high positive (z-scores > 0.5). It is important to note that these category boundaries are not reflective of inherent biological constructs but rather serve as methodological tools for capturing diverse connectivity patterns. Nevertheless, especially the higher negatively and positively correlated states can be interpreted as effective states of communication between the two right TPJ subdivisions. We then extracted three indices quantifying the connectivity states. These included the proportion of windows that fell into each particular state (Proportion); the average number of continuous windows attributed to the same state (Mean Dwell Time—MDT) (Allen et al., 2014), and the probability of entering a specific connectivity state (Probability of Transition—PT), which was depicted by the number of times a participant entered that specific state of connectivity over the total number of state changes (Li et al., 2020). All indices were computed using in-house

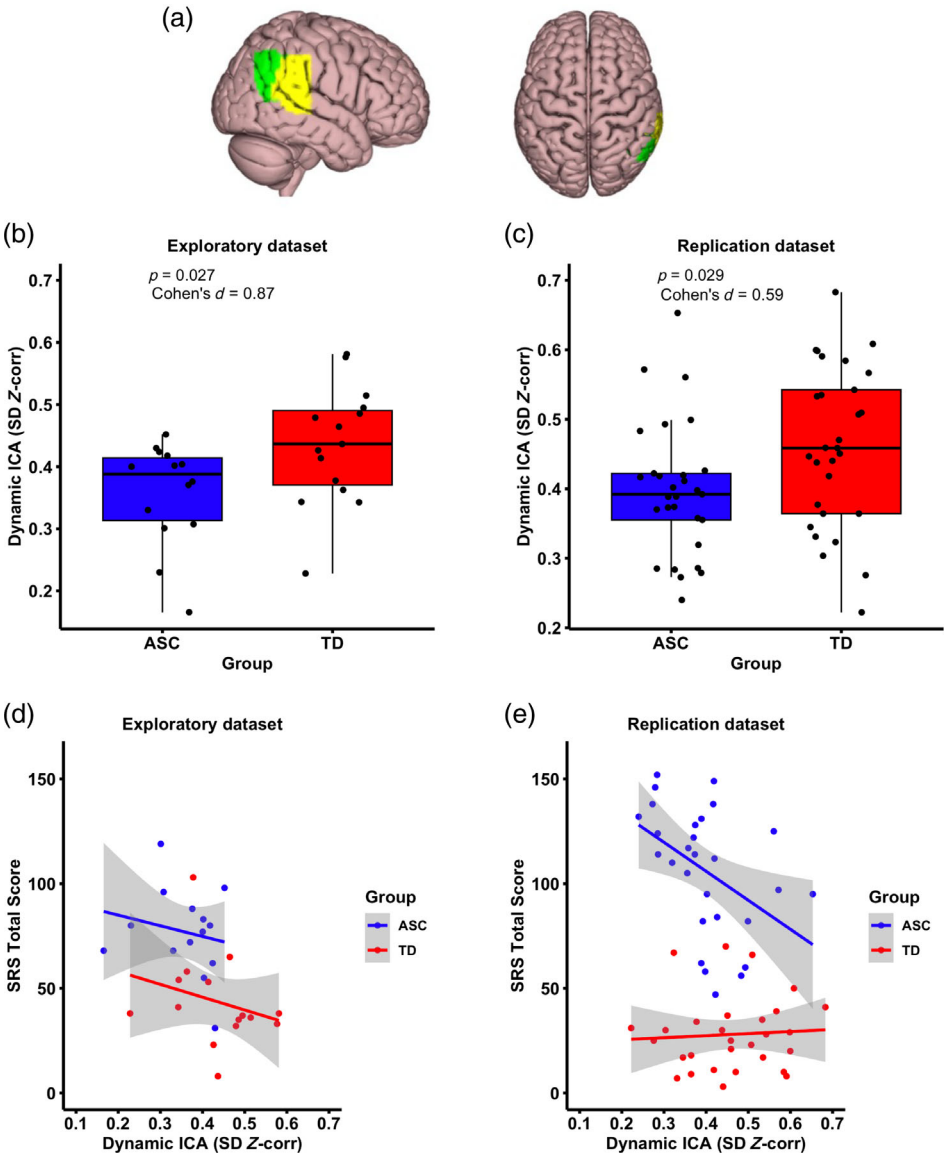

FIGURE 1 Dynamic resting-state functional connectivity (FC) between the anterior and posterior subdivisions of the right temporoparietal junction (raTPJ and rpTPJ respectively) in ASC and typically developing (TD) individuals. (a) The raTPJ (yellow) and rpTPJ (green) seed ROIs superimposed on the Oren-Nayer brain surface in Surf Ice viewer. Centre of gravity (in MNI space) for the raTPJ: $x = 59$, $y = -37$, $z = 30$; and for the rpTPJ: $x = 54$, $y = -55$, $z = 26$. (b, c) The group differences in dynamic FC between raTPJ and rpTPJ in the Exploratory and Replication datasets, respectively. SD *Z*-corr refers to the standard deviation in *Z* correlation coefficients, which is the output measure from the Dynamic ICA analysis. SD *Z*-corr quantifies the dynamic variability in the strength of functional connectivity between raTPJ and rpTPJ over time. Higher SD *Z*-corr values represent more dynamic functional connectivity between raTPJ and rpTPJ. (d, e) The association and corresponding 95% Confidence Intervals between dyn-ICA and autistic traits, were measured with the Social Responsiveness Scale (SRS) total scores in the Exploratory and Replication datasets, respectively.

scripts (available online at https://github.com/laurabravo97/dynamic_functional_connectivity_analysis) written in Python (https://www.python.org/).

Following suggestions by anonymous reviewers, we repeated our analyses across the entire sample encompassing both the exploratory and replication datasets to boost sample size. The analyses of the combined datasets are included in Supporting Information.

Static FC analysis

Static FC was also assessed to ascertain whether stationary and dynamic FC analyses produce complementary or overlapping information. For the first-level analysis, the correlation coefficients between the full-time series of the raTPJ and the rpTPJ were obtained for each subject. The resulting static beta maps were introduced into a general linear model for ROI-to-ROI group-level analysis and, similar to dynamic FC analyses, effects were considered significant if $p_{\text{uncorrected}} < 0.01$ and $p_{\text{FDR corrected}} < 0.05$.

Statistical analyses

A two-sample *t*-test was used to compare demographic characteristics and autistic traits between the ASC and TD groups. Group differences in dyn-ICA and static FC were assessed using independent samples *t*-test. Pearson's correlation analyses between dyn-ICA and connectivity state indices (i.e., Proportion, MDT, and PT) were performed in the Replication dataset to further explore the dynamic relationship between raTPJ and rpTPJ functional connectivity. Multiple comparison correction (false discovery rate, FDR) was performed for all connectivity matrices (dyn-ICA, proportion of windows, MDT, and PT) using the Benjamini–Hochberg procedure. In addition, three repeated measures ANOVAs were performed in the Replication dataset to explore group differences in

the proportion of windows, MDT, and PT; with "group" as the between-subject variable and "state of connectivity" (i.e., high negative, moderate negative, low uncorrelated, moderate positive and high positive) as the within-subject variable (Rabany et al., 2019).

In both datasets, the association between autistic traits (quantified with SRS Total scores) and dyn-ICA was examined using Pearson's correlation analyses for the entire samples. These analyses were followed by general linear models (GLM) to explore the main effects and interaction effects of dyn-ICA and group in predicting SRS total scores. Similarly, in the Replication dataset, Pearson's correlation analyses were performed to examine the association between SRS total scores and connectivity state indices. Significant results were followed by GLMs to evaluate between-subjects effects of connectivity state indices, group, and their interaction in predicting SRS Total scores. All p-values reported are FDR-corrected unless otherwise stated. The additional analyses conducted with the combined datasets were done in a similar way (see Supporting Information for full details of the analyses conducted in the combined sample).

RESULTS

Participant characteristics

Table 1 summarizes demographic characteristics and autistic traits measured with the SRS in both the Exploratory and Replication datasets. Two-sample *t*-tests showed no differences between the ASC and TD groups in age or Full Scale IQ (FIQ) in either dataset. Across the two datasets, however, the ASC group scored significantly higher on the SRS Total and all subscales (all p_s <0.05).

Group differences in dynamic FC

Independent samples *t*-tests revealed significant differences between the ASC and TD groups in the dynamic connectivity between raTPJ and rpTPJ in both the exploratory ($t = -2.34$, $p = 0.027$, Cohen's $d = 0.88$, Figure 1b) and replication datasets ($t = -2.21$, $p = 0.031$, Cohen's $d = 0.60$, Figure 1c). In line with our prediction, in both datasets, the ASC group showed decreased dynamic resting-state FC (i.e., lower temporal variability) between the anterior and posterior subdivisions of the rTPJ. A similar finding was obtained in the combined dataset analyses (see Figure S2).

Association between autistic traits and dynamic FC

Pearson correlation was used to assess the association between autistic traits (SRS total scores) and dynamic FC between raTPJ and rpTPJ (quantified with SD in *Z*-correlation coefficients, that is, output measure from dyn-ICA analyses) in both the Exploratory and Replication datasets. The analysis revealed a significant negative correlation in the Exploratory ($r = -0.43$, $p = 0.02$) and Replication dataset ($r = -0.35$, $p = 0.007$). Thus, in line with our predictions, increased temporal variability in FC between the raTPJ and rpTPJ was associated with reduced autistic trait expression. To assess for possible group differences in this association, we further conducted regression analyses in the two datasets with dyn-ICA, group, and their interaction as predictors and the SRS total score as the outcome measure. In the Exploratory dataset, the regression yielded a significant model, $F\ (3,\ 25) = 6.26$, $p = 0.003$, $\eta_p^2 = 0.429$, but no significant main effects or interaction effects were found, probably due to the small sample size. Subsequently, a main effect-only model ($F\ (2,\ 26) = 9.76$, $p = 0.001$, $\eta_p^2 = 0.429$) revealed a main effect of group, β(se) = 28.92(8.62), $t = 3.35$, $p = 0.02$, $\eta_p^2 = 0.302$, such that the ASC group presented significantly higher autistic traits (see Figure 1d). In the Replication dataset, the model ($F\ (3, 53) = 56.30$, $p < 0.001$, $\eta_p^2 = 0.761$) revealed a significant interaction between dyn-ICA and group in predicting autistic traits, $F\ (1,\ 53) = 6.08$, $p = 0.017$, $\eta_p^2 = 0.103$ (see Figure 1e). Specifically, higher dynamic FC was associated with reduced autistic traits in individuals with ASC, β(se) = −138.51(54.91), $t = -2.52$, $p = 0.018$, $\eta_p^2 = 0.197$, but not in the TD controls, $p = 0.75$. Interestingly, in the combined dataset a significant model yielded the main effects of groups and dyn-ICA but no interaction (i.e., dyn-ICA predicted SRS scores across both ASC and TD in the entire cohort).

Specific connectivity states (in replication dataset)

Repeated measures ANOVAs of the connectivity state indices (Proportion, Mean Dwell Time, and Probability of Transition) highlighted a global difference in these metrics as a function of connectivity state (all p_s <0.001) but this did not change based on group and there was no interaction between state and group either (results of the ANOVAs are presented in Table S1 and graphed together in Figure S1).

To further assess the dynamic connectivity between the raTPJ and rpTPJ and its association with autistic traits, we first performed Pearson correlations across the replication sample between the connectivity state indices and SRS total scores. Pearson correlations revealed that autistic trait expression was *negatively* correlated with the Probability of Transition to and Proportion of high negative connectivity states ($r_{PT} = -0.31$, $p = 0.02$, and $r_{proportion} = -0.35$, $p = 0.007$). This suggests that individuals for which the high negative state (antagonistic relation) was more prominent tended to show lower levels of autistic traits. In addition, autistic trait expression was

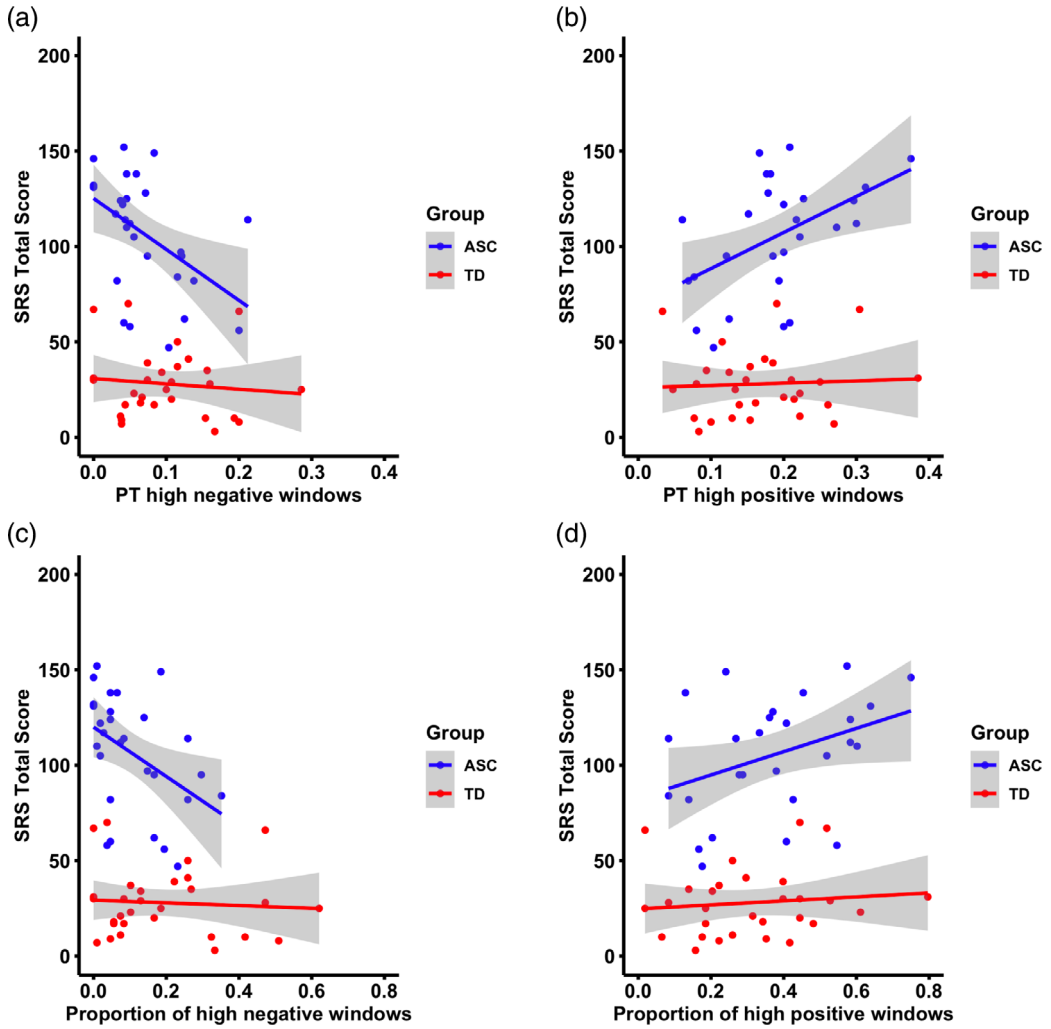

FIGURE 2 Association between temporal variability metrics (probability of transition, PT, and proportion of windows) and autistic trait expression in both high negative and high positive connectivity states in the ASC and the typically developing (TD) groups of the Replication dataset. Autistic trait expression is quantified with the total score of the Social Responsiveness Scale (SRS). (a) The association of PT with SRS total scores in the high negative connectivity state; (b) the association of PT with SRS total scores in the high positive connectivity state; (c) the association of the proportion of windows with SRS total scores in the high negative connectivity state; and (d) the association of proportion of windows with SRS total scores in the high positive connectivity state. All regression lines are depicted with the corresponding 95% Confidence Intervals.

also *positively* correlated with the Probability of Transition to and Proportion of high positive states ($r_{PT} = 0.33$, $p = 0.01$ and $r_{proportion} = 0.32$, $p = 0.01$). Thus, individuals for which the high positive state was more prominent tended to show higher levels of autistic traits. There were no significant correlations between the Mean Dwell Time of any of the five states and total SRS scores ($-0.22 <$ Pearson r correlation coefficients <0.25, all $p_s > 0.057$).

Next, we used regression analyses to establish whether these significant associations between connectivity metrics and autistic traits are dependent on the group. We, therefore, used group, index of connectivity state, and their interaction to predict autistic trait expression in each of the connectivity states separately (see Table S2 for full details of the regression models). Results in the high negative connectivity state (see Figure 2a, c) revealed significant interactions between group and Probability of Transition, F (1, 53) $= 5.29$, $p = 0.025$, $\eta_p^2 = 0.091$, and proportion of windows, F (1, 53) $= 5.77$, $p = 0.020$, $\eta_p^2 = 0.098$. Examining the interaction effects revealed that lower Probability of Transition to (β(se) $= -267.20(97.60)$, $t = -2.74$, $p = 0.020$, $\eta_p^2 = 0.19$) and lower Proportion of (β(se) $= -129.25$ (52.37), $t = -2.472$, $p = 0.018$, $\eta_p^2 = 0.197$) the high negative connectivity state were associated with increased autistic trait expression in ASC participants, but not in TD controls ($p_{PT} = 0.58$ and $p_{proportion} = 0.72$). In the high positive connectivity state (Figure 2b, d), the models revealed only a significant main effect for group (Probability of transition: F (1, 53) $= 12.18$, $p = 0.001$, $\eta_p^2 = 0.187$; Proportion of windows: F (1, 53) $= 20.82$, $p < 0.001$, $\eta_p^2 = 0.282$), such that autistic trait expression was higher in the ASC than in the TD group. Thus, it

appears that prominence of the high negative state is associated with reduced autistic traits and that this is particularly pronounced in the ASC group.

Results from the supplementary analyses in the combined sample largely replicated our initial findings in the replication dataset. Repeating the ANOVA in the combined sample yielded significant main effects of connectivity state indices (see Table S6 and Figure S3), and pairwise comparisons show that individuals engaged more in highly correlated connectivity states than in moderate or low-uncorrelated states (see Table S8). Regression analysis in the combined sample yielded significant main effects of group and connectivity state indices (i.e., the proportion of windows and probability of transition to high negative and high positive states) in predicting SRS Total Scores (see Figure S4 and Table S7). However, no interaction effect was found between group and connectivity states in predicting SRS total scores, suggesting that the association between high negative and high positive correlation states and autistic trait expression is not exclusive to ASC participants but instead observed in both ASC and TD groups. Full details of the results from the combined sample analysis are available in the Supporting Information.

Finally, we assessed the possible link between the dyn-ICA measure representing the global temporal variability in functional connectivity and the specific states of connectivity (from high negative to high positive). To this end, we assessed the Pearson correlations between dyn-ICA and the three indices of the five connectivity states. The analysis revealed a significant *positive* correlation between dyn-ICA and the probability of transitioning to a high negative connectivity state ($r = 0.43$, $p_{FDR} = 0.003$), suggesting that increased global temporal variability was associated with a stronger tendency for the raTPJ-rpTPJ connectivity to move towards a high negatively correlated (antagonistic) state. In addition, we observed a significant *negative* correlation between dyn-ICA and the probability of transitioning to a high positive connectivity state ($r = -0.42$, $p_{FDR} = 0.003$). Thus, increased global temporal variability was also associated with a decreased tendency for the raTPJ-rpTPJ connectivity to shift towards a highly positively correlated state (see Table S3 for full details of the correlations between dyn-ICA and connectivity state indices). Similar findings were obtained in the combined sample analysis (see Table S5).

Static functional connectivity

To assess whether static functional connectivity could also be useful here, we repeated the same analyses we reported with the dyn-ICA metric with the static functional connectivity between the raTPJ and the rpTPJ. We observed no significant differences in static FC between the ASC and TD groups in either the Exploratory ($t_{df=27} = 0.71$, $p = 0.482$), the Replication ($t_{df=56} = 1.37$, $p = 0.176$), or the combined ($t_{df=85} = 1.51$, $p = 0.134$) datasets. There were also no significant correlations between static FC and SRS total scores in either the Exploratory ($r = 0.11$), the Replication ($r = 0.25$), or the Combined ($r = 0.23$) dataset ($p_{FDR} > 0.05$).

DISCUSSION

The present study is the first to explore the dynamic FC between the anterior and posterior subdivisions of the rTPJ in ASC and neurotypical adults as a window to understanding the relationship between attention reorienting and ToM in ASC. For this purpose, the dynamic ICA (Nieto-Castanon, 2020) and the sliding window (Allen et al., 2014; Calhoun et al., 2014) approaches were used in two datasets (Exploratory and Replication) to yield specific metrics of dynamic functional connectivity both on the global level (dyn-ICA) and on specific connectivity state level (proportion of windows, Mean Dwell Time, and Probability of Transition). Consistent with our predictions, the results in the Exploratory dataset highlighted a decreased dynamic FC between the posterior and anterior divisions of the right TPJ in the ASC group. This finding was then corroborated in the Replication dataset, with a similar reduction in global dynamic FC in ASC compared to neurotypical controls. Moreover, this global signal of dynamic functional connectivity was associated with autistic trait expression so reduced dynamic functional connectivity was associated with higher autistic traits. Furthermore, the reduction in the global dynamic functional connectivity signal appeared to be translated to a reduction in the prominence of a specific connectivity state—a less prominent highly negatively correlated state was similarly associated with higher autistic traits.

The reduced dyn-ICA signal in ASC we report here fits with similar findings regarding dynamic FC in this population (although previously a whole-brain analysis has been the most common approach). For example, Yao et al. (2016) performed time-varying FC analyses in ASC and found reduced dynamic connectivity within the DMN (between the posterior and anterior hubs) which was also associated with social difficulties. This is consistent with the idea that a more variable connectivity between regions contributes to enhanced cognitive processing (Allen et al., 2014) and enables networks to jointly function when a task is presented (Nguyen et al., 2017; Uddin, 2021). Moreover, considering the importance of dynamic connectivity between brain regions for integrative functions (Shine et al., 2016), the decreased dynamic FC between raTPJ (part of the attention reorienting network) and rpTPJ (part of the ToM network) shown here by the ASC group may point to the importance of integrative attention and ToM processes in driving successful social interaction. It is therefore

plausible that at least some of the difficulty in social interaction in ASC might be explained by such reduced integration of the attention and ToM processes. It is not clear, however, if this is a consequence of separately or independently impaired attention or ToM in ASC (e.g., the precursory nature of attention-shifting problems in ASC; Kubit & Jack, 2013) or that the integration itself is the source of the social interaction impairment irrespective of the attention and ToM processes per se.

Previous research in static FC observed an antagonistic relationship between attention and ToM networks (Fox et al., 2005) and between the raTPJ and rpTPJ specifically (Bzdok et al., 2013). Using the sliding window approach here we were able to identify a more intricate set of functional connectivity states that are important for social interactions. Still, the antagonistic state (the highly negatively correlated state) appeared to be particularly important. While we reported no significant group differences in this state (although such an effect seems to emerge in the combined datasets), we were able to demonstrate its association with autistic trait expression. Reduced prominence of the high negative state (expressed in reduced proportion of windows and probability of transition) was associated with increased expression of autistic traits (increased total SRS). Interestingly, this was also complemented (although in a less pronounced way) by the association between increased prominence of the high positive state and higher autistic traits, thus pointing to the intricate relationship between raTPJ and rpTPJ.

A few previous studies utilizing different versions of a sliding window approach with a whole brain analysis have identified not only reduced functional connectivity but also a tendency in ASC to spend more time in a weak FC state (or a state of underconnectivity) compared to TD individuals (Chen, Nomi, et al., 2017; Yao et al., 2016). Rabany and colleagues (Rabany et al., 2019), for instance, compared the temporal variability and connectivity patterns between 56 independent components in individuals with ASC, schizophrenia and typically developing and reported a generally decreased dynamic FC in the ASC population due to an increased dwell time in a state of underconnectivity. While we did not find evidence for such a group difference in an uncorrelated state in our study, it is worth noting that our focus on the raTPJ and rpTPJ meant the most indicative correlation states were the high negative and high positive states. The present results showed that individuals spent significantly more time in both highly negative and highly positive connectivity states compared to an uncorrelated state (see Figure S1B and Table S4 for pairwise comparisons). While not expressed statistically, it is possible that in the case of the raTPJ and rpTPJ a balance between high negative and high positive states is the important feature, but this turns into an imbalance (a bias in favor of the high positive state) in high expression of autistic traits (see Figure S1A).

The relevance of this balance between the high negative and high positive correlation states was also exemplified through their association with global dynamic FC. Correlation analyses revealed that increased dynamic FC was associated with a greater probability of transition to the high negative connectivity state but also a reduced probability of transition to the high positive connectivity state. Generally, across the various FC state indices, when moving from high negative to high positive states (through the intermediary connectivity states) there is a gradual shift from positively correlated to negatively correlated dynamic FC (see Table S3). Thus, dynamic FC between the raTPJ and rpTPJ seems to be associated with a balance between high negative and high positive states. However, when participants present with a shift away from this balance (away from the negative state and toward the positive state), they seem to also show reduced dynamic FC, as well as increased autistic trait expression.

One intriguing aspect of our findings (especially in the replication dataset) is the exclusive nature of the association between dynamic FC metrics and autistic trait expressions in the ASC but not in the TD group. Notably, the ASC group exhibited a broader spectrum of SRS scores, possibly contributing to the more pronounced manifestation of this association within this cohort. However, our supplementary analysis, encompassing the entire sample, revealed that both dyn-ICA and the high negative and high positive correlation states were associated with SRS scores across all participants (see Table S7). This therefore suggests that while the expression of this association seems heightened in ASC it may not be exclusive.

The present study confirmed the importance of investigating FC between interrelated neural networks from a time-varying perspective. Indeed, while we report significant differences (both on a group and an individual level) using dynamic FC metrics, using a static FC metric did not yield significant findings. This is perhaps not surprising given the inconsistent findings regarding the status of FC in ASD (Alaerts et al., 2014; Chien et al., 2015; Lau et al., 2020; Li et al., 2020). Moreover, previous static FC investigations focusing on connectivity between raTPJ and rpTPJ indicated an anticorrelated pattern (Bzdok et al., 2013), but our dynamic FC analyses have revealed that the relationship between these regions is not so straightforward and that high positive states also play an important role. It is therefore possible that inconsistencies in previous research looking at FC in ASC relate to the limitation of the static FC approach to capture different connectivity states present throughout the scan.

The present findings highlight the potential utility of decreased dynamic FC between raTPJ and rpTPJ, as well as altered connectivity state patterns, as biomarkers for ASC symptomatology. These neurobiological markers could contribute to the stratification of ASC subtypes, perhaps through combination with more comprehensive

behavioral assessments and multi-modality approaches. Additionally, our findings could inform future targets for interventions, such as closed-loop non-invasive brain stimulation aimed at increasing the antagonistic relationship between these subdivisions of the right temporoparietal junction (or decreasing the likelihood of the positive state) to reduce mentalizing difficulties in autistic individuals. Investigating the longitudinal stability of these connectivity patterns and their responsiveness to therapeutic interventions could also prove effective and lead to more personalized treatment approaches, ultimately improving outcomes for autistic individuals.

LIMITATIONS

Given the lack of standardization of MRI acquisition parameters across sites in the ABIDE repository, a cautious approach was followed here through exploratory and replication analyses in independent samples. This meant that the study sample sizes were relatively small. However, following reviewer suggestions, the main analyses were repeated over the combined datasets and largely replicated the initial findings across the whole sample. Regardless, interpretation of these results should be made with the caveat that different scanning parameters could have introduced some confounds (although the dataset as a parameter yields no significant effects or interactions). Additionally, due to the limited number of female participants in the ABIDE repository, only male adults were selected for this study, which limits the ability to analyze gender differences in autistic trait expression and generalize the findings to the broader autistic population. In addition, this study focused exclusively on the rTPJ given its relevance as a possible interaction point between attention reorienting and mentalizing (Devaney, 2018; Kubit & Jack, 2013). Nevertheless, future research should assess whether this pattern of reduced dynamic FC extends to other regions of the neural networks underpinning attention and social cognition (such as the insula), as well as assess the connectivity of these seed regions across the whole brain. Moreover, although the field of dynamic FC is rapidly growing there are still some uncertainties about the methodology and neurocognitive implications of this analysis (Chen, Rubinov, & Chang, 2017), and consequently a lack of standardized optimal parameters for the sliding-window technique (especially window length and sliding step). Finally, while the SRS is commonly used to evaluate autistic trait expression, particularly social functioning, its suitability as a transdiagnostic measure may be limited, and it may not fully capture the diverse range of individual differences influencing functional connectivity patterns. Future studies could address this by integrating a more comprehensive assessment battery covering cognitive, emotional, and sensory domains to better capture the nuanced and heterogeneous nature of individual differences in the context of dynamic functional connectivity.

CONCLUSIONS

The present study suggests that difficulties in social interaction in autistic individuals could be linked to an atypical interaction between the ToM and attention-orienting networks, expressed as reduced dynamic functional connectivity between the anterior and posterior subdivisions of the right TPJ. We suspect that this reduced decreased dynamic connectivity hinders the integrative process of ToM and attention orienting, which combined contribute to the manifestation of social difficulties (Ramot et al., 2020). It appears that the reduced dynamic FC is associated with an imbalance between positive and negative connectivity states. Importantly, both the reduced dynamic FC and the reduced prominence of a high negative connectivity state are predictive of increased autistic trait expression. This work confirms the importance of investigating the interrelationship between cognitive processes at the neural level as a vehicle for designing more integrated models of neurodevelopmental conditions that better account for the vast heterogeneity observed in the expression of their traits. Our findings also provide strong support for the importance of assessing dynamic FC in ASC and the sensitivity of this measure to individual differences in social abilities. With future research, the present findings may contribute substantially to the neuro subtyping and biomarker literature in autism.

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CONFLICT OF INTEREST STATEMENT

The authors report no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in ABIDE at https://fcon_1000.projects.nitrc.org/indi/abide/.

ETHICS STATEMENT

ABIDE I and II: All contributions were based on studies approved by the local Institutional Review Boards. In accordance with the Health Insurance Portability and Accountability (HIPAA) guidelines, both datasets were deidentified (no protected health information included and defaced structural images). Further ethical information available at http://fcon_1000.projects.nitrc.org/indi/abide/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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