Resting-state dynamic functional connectivity of the right temporoparietal junction in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is characterised by impairments in attention reorienting (i.e. shifting attention to unexpected stimuli) and mentalizing (i.e. understanding and making inferences about the mental states of oneself and others). Despite evidence suggesting that the ability to shift the focus of attention is necessary to successfully understand the mental states of other people, the interconnection between these cognitive processes has been neglected by previous research not only in ASD but also in the neurotypical population. Therefore, the present study aimed to explore the dynamic functional connectivity (FC) between the anterior and posterior subdivisions of the right temporoparietal junction (rTPJ), two regions involved in attention reorienting and mentalizing, respectively. For this purpose, the sliding-window and dynamic ICA approaches were used to measure temporal patterns of FC in resting-state fMRI data of 14 high-functioning ASD versus 15 neurotypical adults, obtained from the ABIDE I public data set. The results revealed a decreased dynamic FC in individuals with ASD, which further showed to be associated with greater symptom severity. Statistical analyses failed to show significant differences between groups in the dwell time and transitions of different connectivity states. However, a significant association was also found between spending more time in a high positive FC state and greater ASD severity, which further suggests the possibility of an aberrant high positive connectivity between the anterior and posterior rTPJ in the ASD population. This study provided initial evidence that the atypicalities observed in ASD are associated with abnormal patterns of dynamic functional connectivity between brain regions involved in integrating attention reorienting and mentalizing processes.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by impairments in social interaction, communication, and repetitive, restricted behaviours (American Psychiatric Association, 2013). Within the wide symptomatology of ASD, abnormalities in various domains of social cognition and attention reorienting have been reported by an extensive body of behavioural and neuroimaging research (Keehn, Lincoln, Müller & Townsend, 2010; Lai, Lombardo & Baron-Cohen, 2014).

On the one hand, social and emotional impairments in ASD have been associated with deficits in the mentalizing process (or Theory of Mind), i.e. the ability to understand and infer the mental states (e.g. beliefs, intentionality, emotions and desires) of oneself and others (Baron-Cohen, Leslie & Frith, 1985; Hill & Frith, 2003). In this regard, previous studies have consistently informed of deficits in the behavioural performance of the ASD group compared to healthy controls during social cognition tasks (e.g. false beliefs tasks, unexpected contents and false photographs tasks) as well as decreased activation and functional connectivity (FC) of the neural network underpinning theory of mind (Castelli, Frith, Happe & Frith, 2002; Dichter, 2012; Kana et al., 2009).

On the other hand, dysfunctionalities in disengaging and redirecting attention when presented with novel relevant stimuli (i.e. “attention shifting” or “attention reorienting”) have been demonstrated in ASD (Keehn, Müller & Townsend, 2012). Using a cue-type paradigm (Posner et al., 1980), Keehn and colleagues (2010), showed that individuals with ASD were significantly slower than typically developed (TD) subjects in reorienting their attention to the target when both valid and invalid cues were presented. In addition, several studies have found that subjects with ASD fail in shifting their attention towards social and non-social stimuli more frequently than TD participants (Dawson, Meltzoff, Osterling, Rinaldi & Brown, 1998; Dawson et al., 2004). These findings have also been supported by neuroimaging studies showing less activation of the attention network upon presentation of social cues in individuals with ASD (Greene et al., 2011).

Evidence of a functional link between attention reorienting and mentalizing has been provided by both behavioural and neuroimaging studies (Devaney, 2018, Kubit & Jack, 2013). Mundy and Newell (2007) found that, in order to adequately develop theory of mind, infants must first be able to redirect their attention to new relevant stimuli when social and non-social cues are presented. In this regard, a facilitative function of attention reorienting over social cognition performance has been proposed, given the similarities between shifting spatial attention and shifting to another person's point of view (Corbetta et al., 2008, Decety and Lamm, 2007). Moreover, research in

neuroimaging has shown that attention shifting and social cognition tasks activate and suppress the same brain regions (Jack et al., 2012), with the neural networks underpinning these two processes being negatively correlated (Fox et al., 2005).

Research in cognitive neuroscience has consistently shown the involvement of the right temporoparietal junction (rTPJ), an area located at the intersection of the superior temporal sulcus, inferior parietal lobe and lateral occipital cortex, in both reorienting attention and mentalizing processes; suggesting it could be an important interaction point between these two functions (Abu-Akel et al., 2016; Bzdok et al., 2013; Devaney, 2018; Kubit & Jack, 2013; Mars et al., 2012). Consequently, an anatomical and functional division of the rTPJ into primarily two subregions have been proposed, the anterior and the posterior rTPJ (Decety & Lamm 2007; Mars et al., 2012). Using diffusion-weighted imaging tractography–based parcellation, Mars and colleagues (2012) found that the right anterior TPJ (raTPJ) interacted with the ventral prefrontal cortex and anterior insula (parts of the attention network), while the right posterior TPJ (rpTPJ) interacted with the posterior cingulate cortex (PCC), temporal pole and medial prefrontal cortex (parts of the mentalizing network). In line with these findings, other research modalities have also evidenced that the raTPJ and rpTPJ are involved in attentional and social cognition processes, respectively. Functional magnetic resonance imaging (fMRI) has revealed higher activation of the raTPJ during attention reorienting tasks and higher activation of the rpTPJ during mentalizing using false belief tasks (Krall et al., 2015). Moreover, brain stimulation over the rTPJ impaired performance in attention shifting using a visual cueing paradigm and increased error rates in a false belief task (Krall et al., 2016).

Resting-state functional connectivity (RSFC) studies have not only identified that the anterior and posterior regions of the rTPJ are part of two different cortical networks, but more interestingly, that they are also in tension with each other (Kubit & Jack, 2013). Using coactivation-based parcellation, Bzdok et al. (2013) conducted a data-driven characterization of the rTPJ and found that the raTPJ increased activity in conjunction with the primary motor cortex, midcingulate cortex, and anterior insula/inferior frontal gyrus, associated with attention and action execution; and decreased activity concomitantly with the precuneus, inferior parietal cortex and right middle temporal gyrus, associated with mentalizing and retrieval of episodic memory. In turn, the rpTPJ showed the exact opposite pattern. Furthermore, the attention network was both positively correlated with the raTPJ and anticorrelated (i.e. negative correlation) with the rpTPJ; whereas the social cognition network showed positive correlation with the rpTPJ and negative with the raTPJ. Accordingly, the authors proposed that the posterior and anterior rTPJ belong to two antagonistic brain networks engaged in the processing of internal versus external salient information, respectively (Bzdok et al., 2013).

Investigating the FC between raTPJ and rpTPJ in the ASD population could contribute to a better understanding of their deficits in attention reorienting and mentalizing. However, findings from FC studies have been divided between a hypo (Alaerts et al., 2014; von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013) and hyper (Chien, Lin, Lai, Gau & Tseng, 2015; Li et al., 2020) connectivity pattern in the social cognition network of participants with ASD compared to neurotypical individuals. These inconsistencies have led some researchers to believe that static FC studies are not sufficient to understand the intricacies of neural networks underlying complex cognitive processes, such as attention and mentalizing (Allen, Damaraju, Plis, Erhardt, Eichele, & Calhoun, 2014; Calhoun, Miller, Pearlson & Adali, 2014; Hutchison, Womelsdorf, Gati, Everling & Menon, 2013).

RSFC refers to the temporal correlation between fMRI blood oxygenation level dependant (BOLD) time courses of spatially distant regions in the brain during rest. For a long time, FC has been assumed as a static/stationary phenomenon over time (i.e. throughout the full scanning period) (Allen et al. 2014). In recent years, a new dynamic functional connectivity analysis has emerged, following evidence of temporal variations in RSFC across time resulting in different brain state configurations (connectivity patterns) among neural networks (Allen et al., 2014; Calhoun et al., 2014; Hutchison et al. 2013a). Thus, for instance, at the beginning of the scan, a pair of regions of interest (ROIs) could show a strong positive correlation, whereas two minutes later they could be negatively correlated. Although much remains to be understood about time-varying connectivity networks (Preti et al., 2017), existing research highlights the superiority of dynamic RSFC analysis in several domains. Promising results have been found for predicting behaviour (Chen, Nomi, Uddin, Duan, & Chen, 2017), classifying bipolar disorder (Rashid et al., 2016), 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 vast majority of RSFC studies in ASD use a static approach and even though they provide useful insights, ignoring the dynamics of intrinsic network connectivities could be an oversimplification and is likely one of the reasons behind some of the inconsistencies reported in the FC of clinical populations (Preti et al., 2017; Wee, Yap & Shen, 2016). Nevertheless, in recent years the number of dynamic FC studies in ASD has grown. Yao et al. (2016) found significant differences in the average time spent in each state of connectivity (i.e. mean dwell time, MDT) between ASD and TD participants. In a recent paper (Li et al., 2020), the ASD group showed increased dynamic FC variability in some regions implicated in emotion and saliency processing, and part of the default mode network. These findings were associated with ASD symptom severity, and a higher average dwell time and transitions into a hyper-connected state (Li et al., 2020).

Surprisingly, there is not much neuroimaging literature addressing the relationship between attention reorienting and social cognition in ASD or the neurotypical population (Kubit & Jack, 2013). Therefore, this study aims to shed some light on this issue and overcome the inconsistencies found in the FC of ASD individuals by investigating the dynamic RSFC between raTPJ and rpTPJ in high-functioning ASD versus TD adults. For this purpose, the sliding-window and dynamic independent component analysis approaches will be used and different connectivity patterns (brain states) present throughout the scan will be determined.

In line with previous research showing that integration processes (in this case, the facilitating role that redirecting attention plays on mentalizing) would be enhanced by higher FC variability and more frequent transitions between connectivity states (Hellyer et al., 2015; Shine et al., 2016), decreased dynamic RSFC between the raTPJ and rpTPJ is expected in the ASD group. Furthermore, taking into account the antagonistic relationship between the raTPJ and rpTPJ (Bzdok et al., 2013), the ASD group is expected to spend more time "stuck" in a state of weak FC (Rabany et al., 2019; Yao et al., 2016) and the TD group is expected to spend more time in an anticorrelated state. Finally, an association between dynamic FC atypicalities and ASD symptom severity is also predicted (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 Autism Brain Imaging Data Exchange I repository (ABIDE I; Di Martino et al., 2014). Fourteen high-functioning adult males with ASD (21.7 ± 4.0 years) and 15 typically developed (TD) matched controls (23.3 ± 2.9 years) were included from the University of Leuven Sample 1 data set. Autistic traits were measured with the Autism Quotient Questionnaire (AQ) (Baron-Cohen et al., 2001) and the self-report Social Responsiveness Scale (SRS) (Constantino and Gruber, 2005). Both scales significantly discriminated between groups. The demographic information of participants is available in Table 1.

Data acquisition parameters

Data acquisition parameters were obtained from the ABIDE I, University of Leuven Sample 1 repository. The high-resolution T1-weighted structural volume was acquired with the following parameters: slice thickness = 1.2mm; repetition time (TR) = 9.7ms; echo time (TE) = 4.6ms; matrix size = 256x256; field of view (FOV) = 250x250mm^2; acquisition time = 6 min 38 s. The resting-state fMRI,

T2*-weighted images, were acquired with the following parameters: TR = 1700ms, TE = 33ms; matrix size = 64x64, FOV = 230mm; flip angle 90°; slice thickness = 4mm; number of slices = 32; slice scan order = ascend; functional volumes = 250; acquisition time = 7min.

Table 1. Participant Demographics

	ASD (*n* = 14) Mean ± SD	TD (*n* = 15) Mean ± SD	*P-value*
Age (years)	21.7 ± 4.0	23.3 ± 2.9	0.223[a]
Sex	All males	All males	
FIQ	107.9 ± 13.9	114.8 ± 12.8	0.160[a]
AQ	29.3 ± 8.2	12.8 ± 6.2	<0.001[a]
SRS – Total (self-report)	76.9 ± 24.2	43.6 ± 21.7	<0.001[a]
SRS *subscales*			
Social awareness	9.2 ± 3.1	6.8 ± 2.8	0.03[a]
Social cognition	14.5 ± 4.8	7.2 ± 4.8	<0.001[a]
Social communication	25 ± 6.9	14.4 ± 8.1	<0.001[a]
Social motivation	15 ± 4.8	7.9 ± 4.8	<0.001[a]
Autistic mannerisms	13.1 ± 5.1	7.1 ± 4.5	0.002[a]

Abbreviations*:* FIQ, Full scale IQ; AQ, Autism Quotient; SRS, Social Responsiveness Scale. Higher scores in AQ and SRS represent greater ASD symptom severity.
[a]Two-sample T-test.

Data preprocessing and Denoising

Functional data was analysed in the CONN toolbox 19.c (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). Preprocessing was performed using batch scripts in Matlab (see Appendix C for scripts). The first five volumes were discarded to allow for stabilization of the magnetic field. The functional images were: a) realigned to the first volume, b) unwarped to remove distortion-by movement interactions and to estimate and correct the field inhomogeneity inside the scanner, c) slice-timing corrected by temporal interpolation to the middle slice, d) co-registered with structural data, e) spatially normalised into standard Montreal Neurological Institute (MNI) space, f) segmented into white matter, grey matter and cerebrospinal fluid (CSF), and g) spatially smoothed with an isotropic 5mm full-width-at-half-maximum (FWHM) Gaussian kernel (Alaerts et al. 2014).

Motion correction was performed using the Artifact Detection Tool (ART, www.nitrc.org/projects/artifact_detect/) to identify outlier scans for scrubbing. In addition, physiological and other

sources of noise were identified using CompCor, a method that extracts principal components from the white matter and CSF time courses (Behzadi, Restom, Liau & Liu, 2007). In sum, outlier scans, components from CompCor correction and the six head motion parameters from spatial motion correction were included as confounds in a first-level regression model, followed by linear detrending, despiking and band-pass filtering (0.01-0.08 Hz) to remove low frequency drifts and high frequency noise related to cardiac and respiratory activity (Díez-Cirarda et al. 2018; Kaiser et al., 2016; Wylie, Tregellas, Bear and Legget, 2020).

Dynamic FC analysis (sliding-window approach)

Two seeds regions of interest (ROI) masks for the raTPJ and the rpTPJ (Figure 1) were obtained from Abu-Akel et al. (2016). 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 RSFC analysis was performed using a sliding-window approach (Allen et al. 2014; Hutchison et al. 2013). ROI-to-ROI dynamic FC analyses return connectivity matrices representing the temporal variability in dynamic FC between pairs of seeds. In this case, dynamic FC analysis is performed between one pair of ROIs, returning 2x2 matrices. To implement the sliding-window technique, temporal decomposition of the resting-state scan was selected in the *Setup* tab of the CONN toolbox. The window length was set to 22 TRs (37.4s) with a sliding window step of 1 TR (1.7s) to ensure smooth transitions between windows, producing 224 temporal windows in total (245 volumes – 22 TRs + 1). These parameters were selected in order to find a balance between the sensitivity and specificity of the window, i.e. to define a window short enough to capture rapidly shifting dynamics of FC but long enough to avoid spurious fluctuations (see recommendation by Leonardi & Van De Ville, 2015; Preti et al., 2017).

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

Dynamic FC was quantified by two metrics: strength (DFC-Str) and variability (DFC-SD), calculated as the average and standard deviation, respectively, of the correlation coefficients between the pair of seeds across all windows (Allen et al., 2014; Calhoun et al., 2014).

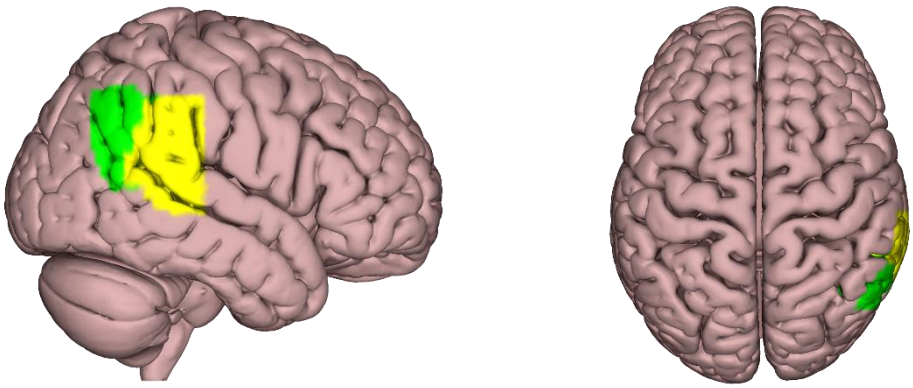

Figure 1. raTPJ (yellow) and rpTPJ (green) seed ROIs superimposed on the Oren-Nayer brain surface in Surf Ice viewer. Centre of gravity (in MNI space) for the rpTPJ: x = 54, y = -55, z = 26; and for the raTPJ: x = 59, y = -37, z = 30.

Functional connectivity state analysis

Dynamic FC indices were computed using in-house scripts (see Appendix D for scripts and output files) written in the Python programming language (Python Software Foundation, https://www.python.org/) and the open-source software Jupyter notebook (Project Jupyter, https://jupyter.org/).

Following Kaiser et al. (2016), FC patterns were estimated by classifying each subject's ROI-to-ROI connectivity values from each of the 224 windows into five states: high negative (z-scores < -0.50), moderate negative (-0.5 ≤ z-scores < -0.25), low-uncorrelated (-0.25 ≤ z-scores ≤ 0.25), moderate positive (0.25 < z-scores ≤ 0.50) and high positive (z-scores > 0.5). Then, the proportion of windows that fell into each particular range was calculated.

In addition, two more indices were computed to compare state configurations between groups:

- Mean Dwell Time (MDT), defined as the time participants remain in each FC state, was obtained by computing the average number of continuous windows attributed to the same state (Allen et al., 2014).
- Probability of transition (PT) from other states to a specific one was calculated as the number of transitions to each state (i.e. times a participant enters that specific state of connectivity) over the total number of state changes (Li et al., 2020).

Dynamic Independent Component Analysis (Dyn-ICA)

An ROI-to-ROI dyn-ICA was carried out in the CONN toolbox as an alternative pipeline to the traditional sliding-window approach in order to test, using a data-driven approach, if the variability of the dynamic FC is significantly different in the ASD group compared to healthy controls. Dyn-ICA returns spatial maps containing connectivity patterns that can be interpreted as building blocks of dynamic RSFC. In this case, because only two seeds are introduced in the analysis, we obtain one component/circuit timeseries that explains most of the variance across the 2x2 dynamic FC matrix (Nieto-Castanon, 2020).

A temporal window of 37.4s (temporal modulation smoothing kernel FWHM) was defined in the *Dyn-ICA* tab and the raTPJ and rpTPJ masks were introduced as seeds. 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, fastICA is used to obtain the dynamic, data-driven, independent component. Finally, generalised 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. The SD in these connectivity values (SD in z-scores) will be used as a measure of temporal variability for further statistical analysis involving dyn-ICA (Nieto-Castanon, 2020).

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 timeseries 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 $p_{uncorrected}<0.01$ and $p\text{-FDR}_{corrected}<0.05$.

Statistical analyses

All statistical analyses were conducted in IBM SPSS Statistics v.24. Group differences were assessed using independent samples *t*-tests for dyn-ICA, DFC-Str, DFC-SD and static FC, and three repeated measures ANOVAs for proportion of windows, MDT and PT with "group" as the independent

categorical variable and "states of connectivity" as the five-level (i.e. high negative, moderate negative, low uncorrelated, moderate positive and high positive) dependent variable (Rabany et al., 2019). In addition, Pearson's correlation analyses between dynamic RSFC (dyn-ICA) and connectivity states (MDT and PT) were performed in order to further explore the dynamic relationship between raTPJ and rpTPJ functional connectivity.

The association between ASD severity and dynamic FC indices was explored using multiple regression analysis in the ASD group (Kaiser et al., 2016). Proportion of windows and PT to each state were excluded from the model as they introduced high levels of collinearity. The final multiple regression model included the connectivity values from DFC-Str, DFC-SD and MDT in each state to predict ASD severity, quantified with SRS total scores. In addition, for the purpose of comparison, linear regression was used to assess if static FC can also predict ASD severity.

Results

Static functional connectivity

There was no significant difference between groups in static FC (t = 0.71, p = 0.48). Similarly, linear regression analysis did not return significant effects of static RSFC between raTPJ and rpTPJ on ASD severity, F(1, 13) = 0.55, p = 0.47.

Group differences in dynamic FC

Differences between the ASD and TD groups in DFC-Str, DFC-SD (Figure 2) and dyn-ICA (Figure 3) were estimated using t-tests. After FDR corrections, no significant results were obtained in DFC-Str (t = 0.738, p = 0.467) and DFC-SD (t = -0.204, p = 0.840). However, consistent with predictions, ASD individuals showed lower temporal variability in dyn-ICA compared to TD (t = -2.340, p = 0.027). Further Pearson's correlation analyses revealed that increased dynamic RSFC was related to decreased MDT in the low-uncorrelated state (r = -0.543, p = 0.041) and increased PT to this state (r = 0.59, p = 0.038).

On the other hand, repeated measures ANOVAs (Table 2) yielded a significant main effect of state across the three dynamic FC indices (MDT, PT and proportion of windows) across all participants. However, results failed to show effects of *group* or an interaction between *states of connectivity* and *group*, which was the primary expected outcome. Further pairwise comparisons (see Appendix E for results of pairwise comparison analyses) revealed that PT to high positive correlated and high

anticorrelated states were decreased (Figure 4b), as participants spent more time on these states and fluctuated more, but engaged less, in moderate and uncorrelated activity. In particular, both groups frequently entered low-uncorrelated connectivity states, as shown in Figure 4a, but once the state was entered, the time spent on it was significantly decreased compared to high connectivity states (Figure 4c).

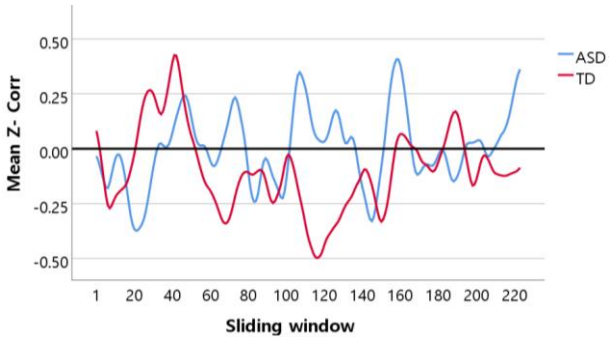

Figure 2. Dynamic RSFC pattern for each group, illustrated by the average Fisher's z-transformed correlation coefficient between raTPJ and rpTPJ in each sliding window.

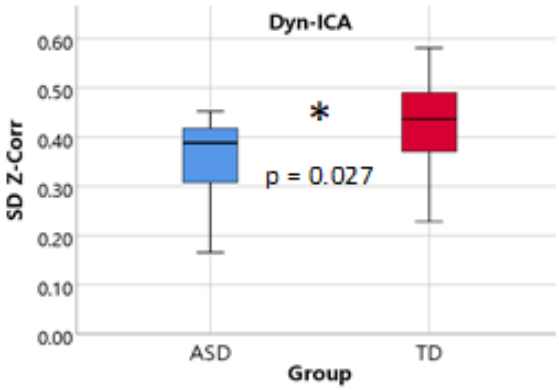

Figure 3. Dynamic ICA results for each group, illustrated by the SD in the Fisher's z-transformed correlation coefficient between raTPJ and rpTPJ in the data-driven temporal variability component.

Table 2. Repeated measures ANOVAs to assess between group differences in dynamic FC

Main effects	Proportion of windows	MDT	PT
State (within-subjects)	F(1.55, 41.81) = 10.00 p = 0.001[a]	F(1.46, 36.60) = 40.18 p < 0.001[a]	F(1.14, 30.89) = 24.22 p < 0.001[a]
Group (between-subjects)	F(1, 25) = 0.48 p = 0.473[a]	F(1, 25) = 0.35 p = 0.561[a]	F(1, 27) = 0.334 p = 0.568[a]
State * Group (interaction)	F(1.55, 41.81) = 0.99 p = 0.360[a]	F(1.46, 36.60) = 0.44 p = 0.585[a]	F(1.14, 30.89) = 1.558 p = 0.224[a]

[a] Greenhouse-Geiser was used, since Mauchly's test showed that the sphericity assumption was violated.

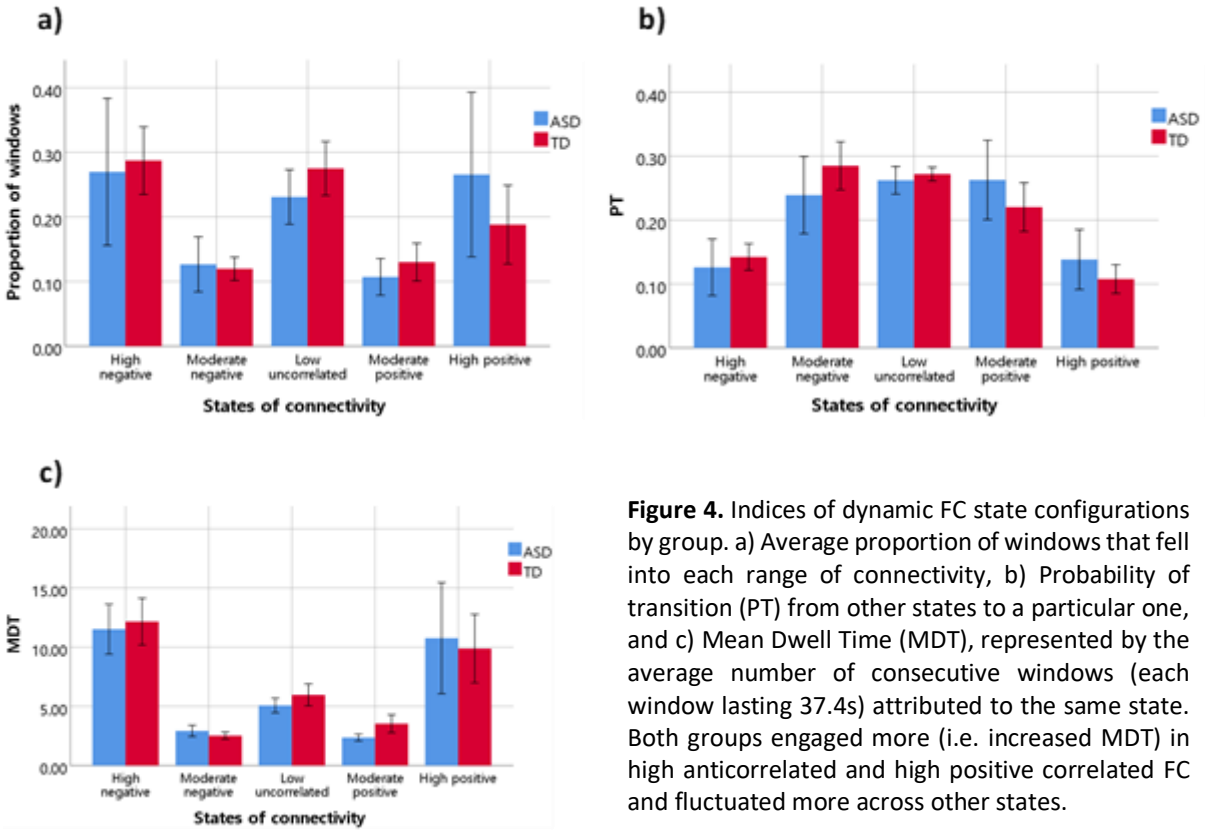

Figure 4. Indices of dynamic FC state configurations by group. a) Average proportion of windows that fell into each range of connectivity, b) Probability of transition (PT) from other states to a particular one, and c) Mean Dwell Time (MDT), represented by the average number of consecutive windows (each window lasting 37.4s) attributed to the same state. Both groups engaged more (i.e. increased MDT) in high anticorrelated and high positive correlated FC and fluctuated more across other states.

Association between ASD severity and dynamic FC

Multiple regression analysis revealed a significant association between dynamic FC metrics and ASD symptom severity, as measured by SRS total scores. Using the enter method, the dynamic FC indices were found to explain approximately 72% of the variance in the SRS values, $F(7, 6) = 5.69$, $p = 0.02$, $R^2 = 0.86$, $R^2_{Adjusted} = 0.72$. Specifically, DFC-Str, DFC-SD and MDT in the high positive state significantly predicted the severity of ASD (see Table 3). In line with anticipated results, increased strength and variability of dynamic RSFC between raTPJ and rpTPJ were associated with decreased ASD severity (Figure 5a and b), whereas longer patterns of high positive dynamic FC were associated with greater SRS scores (Figure 5c).

Table 3. Multiple regression using dynamic FC indices to predict ASD severity

Predictors	Standardised β	*t*	p-value
DFC-Str	-1.83	-3.53	0.012*
DFC-SD	-1.85	-5.51	0.001*
MDT high negative	0.76	2.04	0.088
MDT moderate negative	-0.56	-2.29	0.062
MDT low-uncorrelated	-0.20	-0.97	0.371
MDT moderate positive	-0.29	-1.42	0.205
MDT high positive	2.75	4.94	0.003*

Dependent variable: SRS total scores.

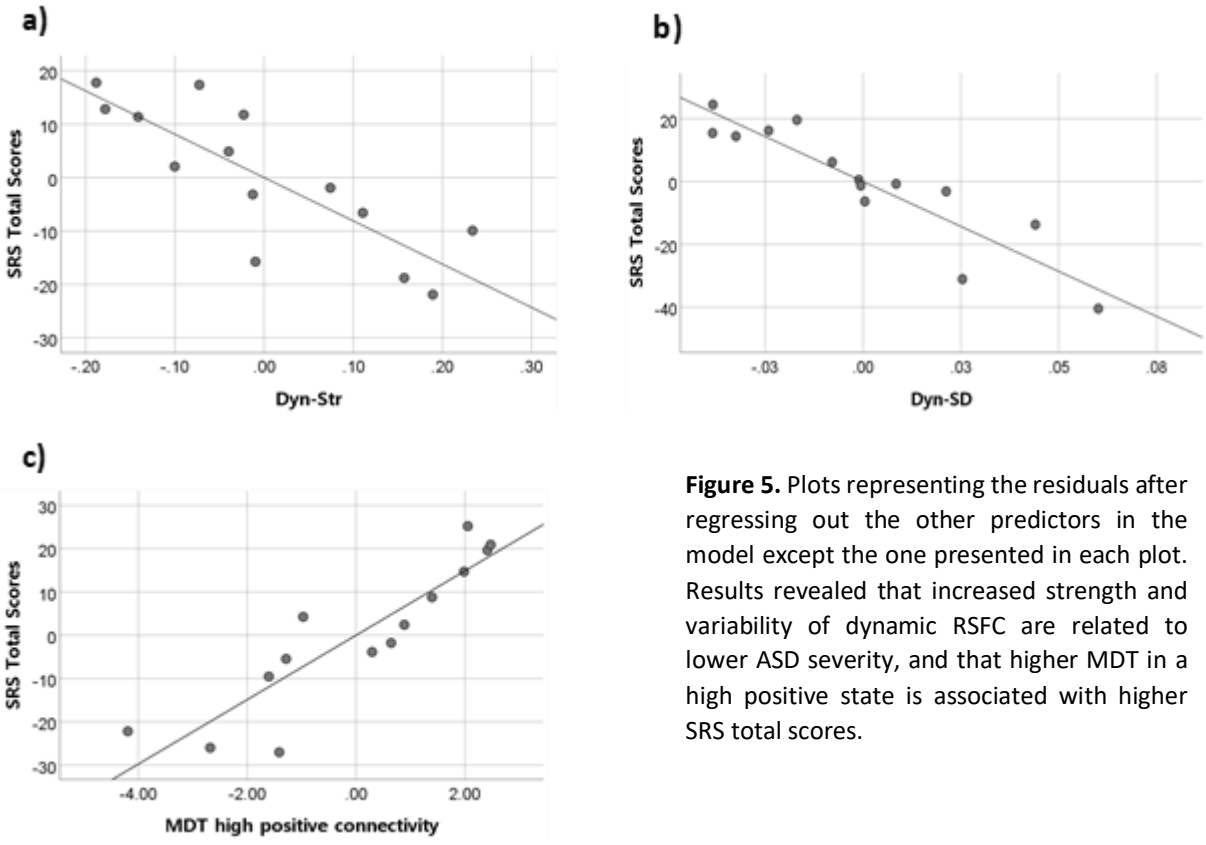

Figure 5. Plots representing the residuals after regressing out the other predictors in the model except the one presented in each plot. Results revealed that increased strength and variability of dynamic RSFC are related to lower ASD severity, and that higher MDT in a high positive state is associated with higher SRS total scores.

Discussion

The present study is the first to explore the dynamic FC between the anterior and posterior subregions of the rTPJ in high-functioning ASD and neurotypical adults to better understand the relationship between attention reorienting and mentalizing in this clinical population. For this purpose, the sliding-window (Allen et al., 2014, Calhoun et al., 2014) and dynamic ICA (Nieto-Castanon, 2020) approaches were used, and several dynamic FC indices were obtained to measure temporal variability (DFC-SD and dyn-ICA), connectivity strength (DFC-Str), and connectivity patterns (proportion of windows, PT and MDT in different states of connectivity). Consistent with predictions, the results indicated a decreased dynamic FC between raTPJ and rpTPJ in the ASD group, which was additionally found to be related to higher MDT in an uncorrelated state and lower PT to this state. However, there were no significant differences between ASD and TD in the dynamics of the connectivity patterns. Both groups spent more time in a state of high negative and high positive connectivity, and frequently entered, but spent less time, in the low-uncorrelated state. In addition, increased severity of ASD was associated with decreased dynamic FC and prolonged dwell time in a high positive state of connectivity.

Decreased dynamic FC in ASD

Compared to TD individuals, the high-functioning ASD group showed a decreased temporal variability in RSFC (dyn-ICA approach) between the raTPJ and rpTPJ. Similar findings have been reported in previous literature on dynamic FC in this population, although a whole-brain analysis has been the most common approach. Yao et al. (2016) performed time-varying FC analyses in ASD and found a reduced connectivity between precuneus/posterior cingulate gyrus and medial superior frontal gyrus, two hubs of the default mode network, which was additionally associated with social difficulties in this cohort. Considering previous evidence of a more variable connectivity between brain regions involved in integrative functions (Shine et al., 2016), the decreased dynamic FC shown by the ASD group suggests that the facilitative role that attention reorienting is thought to have on mentalizing is impaired in this population. Future research should look at the dynamic FC between anterior and posterior rTPJ in task-based fMRI data. If these findings are replicated, they could contribute to a better conceptualisation of ASD, and further development of earlier and more tailored interventions since, for example, an impairment in attention reorienting could anticipate social interaction difficulties (Kubit & Jack, 2013).

Connectivity states in ASD and TD individuals

Primarily two findings from previous research were considered to formulate the initially proposed hypotheses regarding state configurations: first, there is evidence from the literature on dynamic FC indicating greater time spent in a weak FC state in ASD compared to TD individuals (Chen et al., 2017; Yao et al., 2016); and second, there appears to be an antagonistic relationship between attention and mentalizing networks (Fox et al., 2005) and between the raTPJ and rpTPJ specifically (Bzdok et al., 2013), which would translate into an increased dwell time in a high negative connectivity state in the TD group. The findings of the present study did not support these hypotheses, as no significant differences were found between ASD and TD groups in the three indices of dynamic FC states (proportion of windows, MDT and PT). Despite this, it should be noted that a greater proportion of windows in the high positive connectivity state was seen in the ASD group (although not statistically significant; see Figure 4a), which fits with the association between dwell time in this state and ASD symptom severity that was identified by subsequent analysis. Moreover, this study suggests a more complex relationship between raTPJ and rpTPJ that is not only characterised by an anticorrelated state as shown by previous research on TD individuals assuming a stationary FC between these brain regions (Bzdok et al., 2013). Contrastingly, the present results showed that individuals spent significantly more time in both high negative and high positive connectivity states (see Figure 4c and Table 1E for pairwise comparisons).

Correlation between dynamic FC and the low-uncorrelated state

Correlation analyses revealed that increased dynamic FC was associated with a higher probability of transition to a low-uncorrelated connectivity state, but with a shorter time spent in this state. These findings could indicate an indirect route of transition between high negative and high positive FC states, since the MDT in these two was higher (Figure 4c). Similar results were obtained by Watanabe and Rees (2016), who studied whole-brain dynamics using an energy-landscape analysis and found that ASD participants had a decreased frequency of indirect transitions (through an intermediate state) between major connectivity states. In addition, the results from these correlation analyses imply that a reduced temporal variability might reflect an abnormal pattern of weak FC between raTPJ and rpTPJ. Rabany and colleagues (2019) compared the temporal variability and connectivity patterns between 56 independent components in individuals with ASD, schizophrenia and healthy controls. The authors reported a generally decreased dynamic FC in the ASD population due to an abnormally increased dwell time in a state of underconnectivity. Nevertheless, since the present study failed to show significant differences between the groups in the various connectivity

patterns, this possibility remains speculative. Future research should aim to increase the statistical power of the present model by increasing the sample size and better controlling for outliers to reduce measures variability.

Association between dynamic FC indices and ASD symptom severity

ASD symptom severity was assessed with the SRS total scores (Constantino & Gruber, 2005), which includes measures of social awareness, social cognition, social communication, social motivation and autistic mannerisms. Multiple regression analysis revealed that a decreased time-varying connectivity between raTPJ and rpTPJ was associated with higher severity of ASD symptoms. In a previous neuroimaging study, Allen et al. (2014) found that enhanced cognitive processing is related to more dynamic connections between brain networks. Similarly, Nguyen and colleagues (2017) reported an association between decreased FC variability and deficits in processing speed and executive function of patients with bipolar disorder. This is consistent with the idea that a more variable connectivity between regions would offer greater flexibility to neural networks to jointly function when a task is presented (Nguyen et al., 2017). Therefore, this rigid pattern of connectivity between raTPJ and rpTPJ appears to be related to the difficulties in responding effectively to social demands that characterise ASD. In addition, an increased dwell time in a high positive state also predicted greater symptom severity, which further supports the possibility of an aberrant high positive connectivity pattern within the rTPJ in ASD.

Strengths and Limitations

Some limitations should be acknowledged. 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). This decision was also motivated by the small sample size, as an opportunity to maximise power (Nguyen et al., 2017). 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. Moreover, although the field of dynamic FC is rapidly growing, much remains unknown about the methodology and neurocognitive implications of this analysis (Chen, Rubinov & Chang, 2017). The lack of a grounded theory regarding the parameters for the sliding window technique (especially window length and sliding step) could explain the incongruency found between the DFC-SD and dyn-ICA metrics, since they both represent a measure of temporal variability and therefore should return similar results. In spite of this, the present study also confirmed the importance of investigating the FC between interrelated neural networks from a time-varying

perspective. Thus, for example, previous static FC research indicated an anticorrelated connectivity between raTPJ and rpTPJ (Bzdok et al., 2013), but dynamic FC analyses have revealed that the relationship between these regions is not so straightforward and that high positive and uncorrelated states also play an important role. Therefore, inconsistencies in previous research looking at FC in ASD have probably been related to the inability of the static approach to capture the different connectivity patterns present throughout the scan.

Conclusion

In conclusion, this study suggests that the difficulties of ASD individuals to shift attention and perform social cognition tasks are related to a decreased dynamic connectivity between raTPJ and rpTPJ, which could be characterised by an aberrant high positive connectivity and less indirect transitions between the two major states (high negative and high positive) through an intermediate low-uncorrelated state. Although no conclusive inferences can yet be made about the presence of these atypical connectivity patterns in ASD, these findings opened the door to a new line of research investigating RSFC from a dynamic perspective to study attention reorienting and mentalizing impairments in clinical population.

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Appendix A

Student's Dissertation Report

This form should be added to the dissertation to provide the marker information to aid their evaluation of the final product.

Student ID: 2113504

Supervisor Name: Dr Carmel Mevorach

Features	Proposing research	Final dissertation
Title	*Inhibiting the right posterior temporo-parietal junction triggers diametric effects of autism and psychosis traits on mentalizing.*	*Resting-state dynamic functional connectivity of the right temporoparietal junction in Autism Spectrum Disorder.*
Research question	Does TMS over the rpTPJ disrupt the mentalizing process? If so, is this impairment exclusive to psychosis but not autism, as the diametric model proposes?	Are there atypicalities in the dynamic RSFC between raTPJ and rpTPJ (two regions involved in attention and mentalizing respectively) in ASD participants compared to healthy controls? If so, are these atypicalities associated with ASD severity?
Data (type, source and numbers)	Recruitment of approximately 30 participants, 15 with high ASD and low psychosis trait expressions and 15 with low ASD and high psychosis traits. Collection of anatomical MRI scans for neuronavigation during TMS over the rpTPJ, and mentalizing task (behavioural) before and after the brain stimulation.	Open-access anatomical and resting-state fMRI data from the Autism Brain Imaging Data Exchange repository. 25 Participants, 14 with ASD and 15 typically developed.
Analyses	Analysis of AQ and CAPE questionnaires for screening. Processing of structural images to add rvpTPJ mask to each participant's brain (native space). Statistical analyses of behavioural task from before and after the brain stimulation (Repeated measures ANOVA).	Preprocessing, first-level and group-level dynamic functional connectivity analysis of resting-state fMRI data using the sliding window and dynamic ICA approaches. Statistical analyses to assess between group differences in dynamic FC (t-tests and repeated measures ANOVAs) and its association with ASD severity (Multiple regression).

Please explain the rationale for each change made:

Due to the outbreak of COVID-19, I was unable to collect data. Therefore, I had to change the original project completely, but maintaining the interest in the rTPJ and its involvement in mentalizing and attentional processes in autism population.

Other comments:

Some difficulties were encountered, which may have added to the project's limitations:

- Due to COVID-19 and the University being closed I had to use my personal computer to do the analyses. The output files from the fMRI data analyses were considerably large and the sample size had to be reduced (29 subjects in total) which had a negative impact on the statistical power of the model.

- The nature of this project was mainly exploratory since this is the first study looking at dynamic functional connectivity within the right temporoparietal junction in general, not only in ASD. Therefore, there is a lack of previous research to support and help explain some of the main findings.

- There is still not a grounded theory for dynamic functional connectivity methodology and the accuracy of the different dynamic FC approaches remains slightly unknown. This made it challenging to thoroughly justify the significant differences found between groups when using the dynamic-ICA method but not the sliding-window approach (DFC-SD metric).

Appendix B

Student-supervisor contract/s

Instructions: Please complete this form in a meeting(s) with your Project Supervisor. Once completed, please upload the form to the Proposing Research page on Canvas by **26th November 2019, 12 noon**.

Student's Details:

Name: Laura Bravo Student ID number: 2113504

Programme: MSc BICN Start year: 2019

Status: Full-time

Supervisor's Details:

MSc Research Project Supervisor(s): Dr Carmel Mevorach

PhD/Post-doc RA:

Details of project alterations required by COVID-19, to be completed with the Project Supervisor:

Supervision meetings

Set out a general schedule here (e.g., group-based or individual; with supervisor or PhD/Post-doc; frequency, timing). Meetings could take into account the timing of assessments and feedback. In addition specify the mode of virtual communication that was set up.

- Individual weekly meetings via Skype with supervisor

Has the project changed due to COVID-19?

☐ No, the project has not changed

☐ Yes, a bit - the topic is similar but the source of data has change

☒ Yes, completely - The project has completely changed (theory and data)

If the project changed, please provide details of the change (below):

Brief project topic description detailing project after modification for COVID-19:

We will be analysing fMRI data of participants with autism (from the ABIDE project) to study the connectivity between the subregions of the right temporoparietal junction, commonly associated with the attention and social cognition processes.

The project will:

☐ Involve analysis of existing data from my lab

☒ Involve analysis of existing data from a public domain source or archive (data source _http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html_) ☐ Conduct and systematic review or meta-analysis ☐ Data have already been collected ☐ Other solution – specify below:
Do you anticipate any change to financial support? No
Are there any other additional new requirements or changes? We are shifting to analysing fMRI data instead of behavioural data as it was originally planned.
Specify the target journal(s) for the research project, with a brief explanation as to why it has been chosen (e.g., does project fit within the scope of the journal?) Autism Research

Seed references

Recommend 4 – 6 sources

- Abu-Akel, A., Apperly, I., Wood, S. J., Hansen, P. C. (2016). Autism and psychosis expressions diametrically modulate the right temporoparietal junction. *Social Neuroscience, 12,* 506– 518. http://dx.doi.org/10.1080/17470919.2016.1190786
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Student's signature and date signature	**Supervisor's digital**
Laura Bravo Balsa	**Carmel Mevorach**
29/05/2020	**29/05/2020**

Please indicate:

☒This contract has been completed **with** my supervisor who has read and approved its content.

Appendix C

Preprocessing and Denoising batch scripts for the CONN toolbox. Retrieved and adapted from https://web.conn-toolbox.org/resources/conn_batch

```
%%Preprocessing:

cd C:\fMRI_Data\Leuven_1
NSUBJECTS=29;
cwd=pwd;
FUNCTIONAL_FILE=cellstr(conn_dir('rest.nii.gz'));
STRUCTURAL_FILE=cellstr(conn_dir('mprage.nii.gz'));
if rem(length(FUNCTIONAL_FILE),NSUBJECTS),error('mismatch number of
functional files %n', length(FUNCTIONAL_FILE));end
if rem(length(STRUCTURAL_FILE),NSUBJECTS),error('mismatch number of
anatomical files %n', length(FUNCTIONAL_FILE));end
nsessions=length(FUNCTIONAL_FILE)/NSUBJECTS;
FUNCTIONAL_FILE=reshape(FUNCTIONAL_FILE,[NSUBJECTS,nsessions]);
STRUCTURAL_FILE=STRUCTURAL_FILE(1:NSUBJECTS);
disp([num2str(size(FUNCTIONAL_FILE,1)),' subjects']);
disp([num2str(size(FUNCTIONAL_FILE,2)),' sessions']);
TR=1.7; % Repetition time

%% Prepares batch structure
clear batch;
batch.filename=fullfile(cwd,'asd_Leuven2.mat');


% CONN Setup.preprocessing
(realignment/coregistration/segmentation/normalization/smoothing)
batch.Setup.isnew=1;
batch.Setup.nsubjects=NSUBJECTS;
batch.Setup.RT=TR;                                  % UI TR (seconds)
batch.Setup.functionals=repmat({{}},[NSUBJECTS,1]);       % Point to
functional volumes for each subject/session
for nsub=1:NSUBJECTS
    for nses=1:nsessions
        batch.Setup.functionals{nsub}{nses}{1}=FUNCTIONAL_FILE{nsub,nses};
    end
end %note: each subject's data is defined by three sessions and one single
(4d) file per session
batch.Setup.structurals=STRUCTURAL_FILE;                  % Point to
anatomical volumes for each subject
nconditions=nsessions;                                 % treats each
session as a different condition (comment the following three lines and
lines 84-86 below if you do not wish to analyze between-session
differences)
if nconditions==1
    batch.Setup.conditions.names={'rest'};
    for ncond=1,for nsub=1:NSUBJECTS,for nses=1:nsessions,
batch.Setup.conditions.onsets{ncond}{nsub}{nses}=0;
batch.Setup.conditions.durations{ncond}{nsub}{nses}=inf;end;end;end     %
rest condition (all sessions)
```

```
else
    batch.Setup.conditions.names=[{'rest'},
arrayfun(@(n)sprintf('Session%d',n),1:nconditions,'uni',0)];
    for ncond=1,for nsub=1:1,for nses=1:nsessions,
batch.Setup.conditions.onsets{ncond}{nsub}{nses}=0;
batch.Setup.conditions.durations{ncond}{nsub}{nses}=inf;end;end;end     %
rest condition (all sessions)
    for ncond=1:nconditions,for nsub=1:1,for nses=1:nsessions,
batch.Setup.conditions.onsets{1+ncond}{nsub}{nses}=[];batch.Setup.condition
s.durations{1+ncond}{nsub}{nses}=[]; end;end;end
    for ncond=1:nconditions,for nsub=1:1,for nses=ncond,
batch.Setup.conditions.onsets{1+ncond}{nsub}{nses}=0;
batch.Setup.conditions.durations{1+ncond}{nsub}{nses}=inf;end;end;end %
session-specific conditions
end
batch.Setup.preprocessing.steps='default_mni';
batch.Setup.preprocessing.sliceorder='ascending';
batch.Setup.preprocessing.fwhm=5; % UI, smoothing kernel
batch.Setup.preprocessing.art_thresholds=[5,0.9]; % outlier detector, set
to default
batch.Setup.outputfiles=[0,1,0]; % writing of denoised data as nifti
batch.Setup.done=1;
batch.Setup.overwrite='Yes';
batch.Setup.rois.files{1}= 'C:\Users\Laura\Dropbox\Modules BICN\Research
Project\MarsTPJParcellation\MarsTPJParcellation\TPJ_thr25_2mm.nii';
batch.Setup.rois.files{2}= 'C:\conn19c\conn\rois\atlas.nii';
batch.Setup.rois.files{3}= 'C:\conn19c\conn\rois\networks.nii';
% uncomment the following 3 lines if you prefer to run one step at a time:
conn_batch(batch); % runs Preprocessing and Setup steps only



%% DENOISING step
% CONN Denoising
% Default options (uses White Matter+CSF+realignment+scrubbing+conditions
as confound regressors); see conn_batch for additional options

batch.Denoising.filter=[0.009, 0.08];                 % frequency filter
(band-pass values, in Hz)
batch.Denoising.done=1;
batch.Denoising.overwrite='Yes';
```

Appendix D

Python script used to obtain dynamic FC indices (DFC-Str, DFC-SD, proportion of windows MDT and PT of connectivity states), including the outputs for each one of these analyses.

Available on GitHub repository:
https://github.com/laurabravo97/dynamic_functional_connectivity_analysis

Appendix E

SPSS outputs of Pairwise comparisons for the three repeated measures ANOVAs

State 1 = high-negative
State 2 = moderate negative
State 3 = low-uncorrelated
State 4 = moderate positive
State 5 = high positive

Table 1E. Pairwise Comparisons between the five different state configurations in MDT

					95% Confidence Interval for Difference[b]	
(I) State	(J) State	Mean Difference (I-J)	Std. Error	Sig.[b]	Lower Bound	Upper Bound
1	2	9.117*	.711	.000	7.653	10.581
	3	6.320*	.659	.000	4.962	7.678
	4	8.896*	.654	.000	7.549	10.243
	5	1.520	1.564	.340	-1.701	4.741
2	1	-9.117*	.711	.000	-10.581	-7.653
	3	-2.798*	.289	.000	-3.393	-2.202
	4	-.221	.255	.393	-.746	.303
	5	-7.598*	1.237	.000	-10.145	-5.050
3	1	-6.320*	.659	.000	-7.678	-4.962
	2	2.798*	.289	.000	2.202	3.393
	4	2.576*	.354	.000	1.848	3.305
	5	-4.800*	1.352	.002	-7.585	-2.015
4	1	-8.896*	.654	.000	-10.243	-7.549
	2	.221	.255	.393	-.303	.746
	3	-2.576*	.354	.000	-3.305	-1.848
	5	-7.376*	1.170	.000	-9.786	-4.967
5	1	-1.520	1.564	.340	-4.741	1.701
	2	7.598*	1.237	.000	5.050	10.145
	3	4.800*	1.352	.002	2.015	7.585
	4	7.376*	1.170	.000	4.967	9.786

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Table 2E. Pairwise Comparisons between the five different state configurations in proportion of windows

(I) State	(J) State	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	.155*	.026	.000	.102	.208
	3	.026	.032	.436	-.041	.092
	4	.160*	.035	.000	.088	.232
	5	.052	.057	.377	-.066	.169
2	1	-.155*	.026	.000	-.208	-.102
	3	-.130*	.014	.000	-.158	-.102
	4	.005	.017	.794	-.031	.040
	5	-.104*	.040	.016	-.186	-.021
3	1	-.026	.032	.436	-.092	.041
	2	.130*	.014	.000	.102	.158
	4	.134*	.018	.000	.097	.171
	5	.026	.040	.523	-.057	.109
4	1	-.160*	.035	.000	-.232	-.088
	2	-.005	.017	.794	-.040	.031
	3	-.134*	.018	.000	-.171	-.097
	5	-.108*	.028	.001	-.167	-.050
5	1	-.052	.057	.377	-.169	.066
	2	.104*	.040	.016	.021	.186
	3	-.026	.040	.523	-.109	.057
	4	.108*	.028	.001	.050	.167

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Table 3E. Pairwise Comparisons between the five different state configurations in PT

(I) State	(J) State	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	-.128*	.008	.000	-.144	-.112
	3	-.133*	.013	.000	-.159	-.107
	4	-.107*	.027	.000	-.163	-.052
	5	.011	.022	.620	-.034	.056
2	1	.128*	.008	.000	.112	.144
	3	-.005	.016	.751	-.037	.027
	4	.021	.033	.537	-.047	.088
	5	.139*	.028	.000	.082	.196
3	1	.133*	.013	.000	.107	.159
	2	.005	.016	.751	-.027	.037
	4	.026	.019	.188	-.013	.064
	5	.144*	.015	.000	.113	.175
4	1	.107*	.027	.000	.052	.163
	2	-.021	.033	.537	-.088	.047
	3	-.026	.019	.188	-.064	.013
	5	.118*	.006	.000	.106	.131
5	1	-.011	.022	.620	-.056	.034
	2	-.139*	.028	.000	-.196	-.082
	3	-.144*	.015	.000	-.175	-.113
	4	-.118*	.006	.000	-.131	-.106

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).