

Supplemental Information

Altered Periodic Dynamics in the Default Mode Network in Autism and Attention-Deficit/Hyperactivity Disorder

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Clinical and IQ Assessments

Twins were assessed by a team of experienced clinicians, and clinical diagnoses were endorsed by results from standardized tools; the Autism Diagnostic Interview—Revised (ADI-R)(1) the Autism Diagnostic Observation Schedule-2 (ADOS-2)(2), the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS-PL)(3) or the Diagnostic Interview for ADHD in Adults (DIVA 2.0)(4).

IQ was assessed as the General Ability Index (GAI), calculated based on three verbal comprehension and three perceptual reasoning subtests the Wechsler Intelligence Scales for Children (<18 years) or Adults, fourth editions (WISC-IV/WAIS-IV) (Wechsler 2003, 2008).

Participant Characteristics

Functional magnetic resonance imaging (fMRI) data were collected from a total of 307 RATSS participants. Thirteen individuals were excluded because their scans could not be processed, and two individuals were excluded because RS data sets were incomplete. The 292 remaining participants included 52 ASD cases and 70 ADHD cases. Of these, 23 participants included in the analyses had both diagnoses. The remaining participants were NT, defined here as neither having an ADHD nor ASD diagnosis. The included sample contained 122 complete same-sex twin pairs with verified zygosity: 76 monozygotic (MZ) and 46 dizygotic (DZ) twins. For the majority of these twin pairs (109 pairs), zygosity was determined on a panel of 48 single nucleotide

polymorphisms(5). For the remaining 13 pairs, genetically determined zygosity information was not available and a 4-item zygosity questionnaire was used instead. The Regional Swedish Ethical Review Board approved the study protocols, and all participants or their legal caregivers provided informed consent for participation. Forty-eight participants were included where co-twin data were not available.

MRI Data Pre-processing

Data were preprocessed with the default *direct normalization to MNI-space* pipeline in CONN which includes motion estimation and correction, slice-timing correction, outlier detection (Artifact Detection Tools (ART)-based scrubbing), normalization to MNI (Montreal Neurological Institute) space and smoothing (8mm Gaussian kernel). Slice order was *interleaved bottom-up* and functional outlier detection settings were intermediate (97th percentile in normative sample). Next, linear regression was applied to denoise data by removing the effects of head motion, physiological effects, and other artifacts set by default parameters in CONN. Max and mean head motion measures derived from the preprocessing steps in CONN was further included in the overall modelling approach (see Statistical Analysis for description). The resulting signals were band-passed filtered (0.008- 0.09 Hz). DMN regions were defined by structural co-registration with MNI space using the Harvard-Oxford brain atlas(6-9) (see Figure 1).

Recurrence quantification analysis

The application of RQA involves three general stages of analysis, as outlined in Figure 2, which here were applied in the context of BOLD signals extracted from regions of the DMN. First, via the application of Takens Embedding Theorem, lag-delayed surrogate time series were generated from each BOLD time series in order to construct phase portraits, as depicted in Figure 2B; the organization of data in this space, wherein the BOLD time series is plotted against a lag-delayed surrogate, is used to visualize the temporal organization of the system. This process involves the specification of two parameters, τ and m , which determine the lag interval and number of dimensions used in the reconstruction. The lag parameter, τ , was selected through the application of a mutual information algorithm, following the procedure outlined by Roulston(10); that is, lag-delayed surrogates of increasing τ were generated, and the smallest value of τ which minimized mutual information was selected. Similarly, per the method of Kennel et al(11), the number of embedding dimensions (m) was determined through the application of a false nearest-neighbors algorithm, such that phase portraits of increasing dimension were constructed, and the smallest value of m which minimized the number of false nearest neighbors was selected.

Resulting phase portraits were then used in the construction of a recurrence plot through the iterative application of a threshold function, ϵ , to each point in the phase portrait. A recurrence is defined as a moment where the system revisits a given coordinate space (of volume ϵ) occupied previously by another point. In a recurrence plot, as illustrated in Figure 2C, the timing of recurrences is given, with black points indicating the temporal interval of a given recurrence; for example, a recurrence

indicated at 20 time points on the x-axis and 40 time points on the y-axis would indicate that at time point 40 the system has revisited the coordinates it was in at time point 20. For this study, as in prior studies(12-15), the ϵ parameter was set via a dynamic filter to yield a fixed recurrence rate (that is, the total number of recurrence points in a recurrence plot) of 0.10.

The utility of this representation is in decomposing periodic, persistent, and transient dynamics in a given time-series, which in a recurrence plot will manifest as diagonal lines, laminar (vertical/horizontal) lines, or isolated points, respectively; white space, likewise, indicates the absence of recurrence, either due to unique events (e.g., a spike) or underlying trends, e.g., a linear slope. The magnification box in Figure 2C highlights examples of these structures. The focus of RQA is in quantifying these features. In this study, which focused on periodicity and synchronization, our application of RQA focused on three metrics which quantify aspects of periodicity in BOLD signals.

Determinism describes the relative prevalence of periodic processes in the BOLD signal and is measured as the ratio of diagonal lines to other types of recurrence, which include laminar structures (indicate of periods of stability or minimal variability) or isolated recurrences (indicative of transient repetition, likely at random). *Mean Diagonal Length* quantifies the duration of periodic processes via the simple mean of the distribution of diagonal line lengths. *Entropy* is a measure (Shannon Entropy) derived from Information Theory to quantify the predictability and variability in the distribution of diagonal line lengths; in practice, this is typically interpreted as a measure of complexity. In sum, these measures were used to quantify the prevalence, duration, and complexity of periodic processes in DMN BOLD signals. In all analysis of diagonal line distributions,

a diagonal structure had to be at least of length 3 (that is, a pattern of repetition that persisted across three successive measurements).

A key advantage of RQA is that this approach can be readily generalized to extend the analysis of individual signals to quantify cross-signal synchronization. In Figure 2E, we show the reconstruction of a phase portrait embodying signals; through the application of a threshold function, this can be used in the construction of a cross-recurrence plot (Figure 2F), which captures the timing wherein one system visits a space previously occupied by the other system. As in RQA, our application of Cross-Recurrence Quantification Analysis (CRQA) focused on the measurement of cross signal Determinism, Mean Diagonal Length, and Entropy, capturing the prevalence, duration, and complexity of synchronization between BOLD signals from varying ROIs. As in RQA, analysis of diagonal line distributions required a minimum length of 3. In all cases where distance metrics are estimated, simple Euclidean distance was used as the distance metric.

All C/RQA analyses were performed with the Dynamical Systems library (<https://juliadynamics.github.io/DynamicalSystems.jl/latest/>) in Julia(16).

All C/RQA visualizations were created with the Cross-Recurrence Toolbox v5.16 (<http://tocsy.pik-potsdam.de/CRPtoolbox/>) in Matlab v2019b (Mathworks)(17-20).

Data availability

Data sets generated and analyzed in the current study are not publicly available because they contain potentially sensitive and/or identifying patient health information but may be available upon request to Sven Bölte (sven.bolte@ki.se).

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