# **Appendix**

# Appendix 1. Main admission criteria

Main exclusion criteria comprised intellectual disability (estimated full-scale IQ <80), current substance use/abuse, assessed by detailed clinical interview and urine drug screen prior to MRI scan, clinical instability and MRI contraindications (e.g. in-body metal). Clinical diagnoses were ascertained using the Autism Diagnostic Observation Schedule (ADOS; [1]) module 4 for ASD, and the Structured Clinical Interview for DSM-IV (SCID; [2]) for SZ (including schizoaffective disorder, SZA). HC status entailed no current DSM-IV Axis I diagnosis, as determined by the SCID and ADOS as well as a detailed health questionnaire, no history of psychiatric hospitalization or pharmacological treatment, or reported first degree relative diagnosed with ASD, SZ, psychosis or bipolar disorder. All procedures were approved by Hartford Hospital's and Yale University's institutional review boards, and participants gave written informed consent prior to participation.

# Appendix 2. List of ICs by network

| Network  | brain region                | Xa  | У <sup>а</sup> | Z <sup>a</sup> |
|----------|-----------------------------|-----|----------------|----------------|
| Visual   | B. lateral occipital cortex | -30 | -97            | -8             |
|          | B. pericalcarine sulcus     | -9  | -67            | 7              |
|          | L. lingual gyrus            | -12 | -46            | -5             |
|          | B. pericalcarine sulcus     | 0   | -91            | 4              |
|          | L. lingual gyrus            | -21 | -70            | -14            |
|          | R. fusiform gyrus           | 21  | -70            | -14            |
|          | B. fusiform gyrus           | 42  | -64            | -20            |
|          | B. lingual gyrus            | 12  | -94            | -17            |
|          | B. superior parietal lobule | 24  | -67            | 58             |
|          | B. cuneus                   | 0   | -79            | 43             |
| Sensory- | B. paracentral cortex       | 0   | -19            | 73             |
| motor    | R. postcentral gyrus        | 39  | -19            | 64             |
|          | L. postcentral gyrus        | -42 | -34            | 61             |
|          | B. precentral gyrus         | -54 | -7             | 28             |
|          | B. posterior insula         | -42 | -22            | 10             |
|          | B. SMA                      | 0   | 11             | 49             |
|          | B. STS                      | 57  | -28            | -5             |
| Control  | B. mid ACC                  | 0   | -7             | 31             |
|          | L. anterior insula          | -39 | 11             | -5             |
|          | R. anterior insula          | 36  | 17             | -11            |
|          | B. IPL                      | 63  | -25            | 25             |
|          | B. VLPFC                    | -48 | 17             | 25             |
|          | B. dorsal ACC               | 0   | 29             | 31             |

| Default     | B. MPFC                                | 0   | 56  | 28  |
|-------------|--|-----|-----|-----|
| mode        | R. Fronto-parietal cortex <sup>^</sup> | 48  | -52 | 52  |
|             | L. Fronto-parietal cortex <sup>^</sup> | -42 | -64 | 49  |
|             | R. post. STS- MTS                      | 57  | -55 | 7   |
|             | B. Rostral ACC                         | 0   | 44  | -8  |
|             | B. PCC                                 | 0   | -49 | 25  |
|             | B. precuneus                           | 0   | -58 | 61  |
|             | L. STS- MTS                            | -57 | -40 | -2  |
| Amygdala-   | L. amygdala                            | -24 | 2   | -14 |
| temporal    | R. temporal pole                       | 33  | 8   | -26 |
| pole        | L. temporal pole                       | -33 | 5   | -26 |
|             | R. amygdala                            | 24  | -7  | -23 |
|             | L. amygdala                            | -24 | -10 | -20 |
| Subcortical | R. pallidum                            | 24  | -4  | 1   |
|             | R. putamen (anterior)                  | 18  | 8   | -8  |
|             | L. putamen (anterior)                  | -18 | 5   | -2  |
|             | R. putamen (posterior)                 | 30  | -16 | -2  |
|             | L. putamen                             | -18 | 14  | -8  |
|             | L. thalamus                            | -15 | -13 | 13  |
|             | R. thalamus                            | 12  | -13 | 16  |
|             | L. thalamus                            | -12 | -22 | 1   |
|             | R. thalamus                            | 12  | -19 | 1   |
|             | R. thalamus                            | 18  | -34 | 10  |
|             | R. hippocampus- parahippocampus        | 27  | -34 | -14 |
|             | L. hippocampus                         | -24 | -22 | -17 |
| Cerebellum  | Cerebellum 1                           | 0   | -55 | -5  |
|             | Cerebellum 2                           | 18  | -40 | -23 |
|             | Cerebellum 3                           | 21  | -49 | -47 |
|             | Cerebellum 4                           | -15 | -49 | -17 |
|             | Cerebellum 5                           | -36 | -67 | -44 |
|             | Cerebellum 6                           | -18 | -43 | -47 |
|             | Cerebellum 7                           | -27 | -40 | -17 |
|             | Cerebellum 8                           | -3  | -43 | -14 |

<sup>a</sup> MNI coordinates at peak activation.

L.– Left; R.- right; B- bilateral.

IC abbreviations (alphabetically ordered): ACC- anterior cingulate cortex; IPL- inferior parietal lobule; MTS- medial temporal sulcus; PCC- posterior cingulate cortex, SMA- supplementary motor area; STS- superior temporal sulcus; VLPFC- ventrolateral prefrontal cortex

**^** fronto-parietal cortex ICs include IPL and DLPFC.

# Appendix 3. No correlation between motion and dFNC parameters

To further test an association between head motion (mean framewise-displacement, root mean square) and dFNC parameters, Spearman's correlation was conducted. No correlation was found between any of the dFNC parameters to extent of motion.

# Appendix 4. Number of states estimation

The cluster validity index (computed as the ratio of within-cluster distances to between-cluster distance) was used to select the optimal number of distinct states. The elbow criterion indicated four as the optimal number of states.



#### Appendix 5. Associations between dFNC parameters to medication intake and IQ score

A) To test for the effect of medication intake, sensitivity analyses were conducted. For antipsychotic treatment we examined bivariate correlations between dFNC measures to clorpromazine (CPZ) equivalent dose within each one of the clinical groups.

#### Correlations between CPZ equivalent dose and dFNC parameters

|     |      | NS     | NT     | FT1    | FT2   | FT3    | DT1    | DT2   | DT3    |
|-----|------|--------|--------|--------|-------|--------|--------|-------|--------|
| SZ  | R    | -0.115 | -0.373 | -0.093 | 0.281 | -0.165 | 0.473  | 0.196 | 0.375  |
|     | Sig. | 0.583  | 0.066  | 0.658  | 0.174 | 0.432  | 0.686  | 0.347 | 0.138  |
|     | Ν    | 25     | 25     | 25     | 25    | 25     | 3      | 25    | 17     |
| ASD | r    | -0.614 | -0.352 | -0.078 | 0.314 | -0.329 | a<br>• | 0.697 | -0.342 |
|     | Sig. | 0.271  | 0.561  | 0.901  | 0.606 | 0.589  |        | 0.191 | 0.658  |
|     | N    | 5      | 5      | 5      | 5     | 5      | 1      | 4     | 5      |

<sup>a</sup>. correlation cannot be computed because at least one of the variables is constant

B) Additionally, within each of the clinical groups, we used Welch's ANOVA to compare dFNC values of participants treated vs. not-treated with antipsychotic and antidepressant medications.

# Comparisons of dFNC parameters between participants taking <u>antipsychotic</u> medications and those who are not

| Takin | g anti- |    |         | ASD        |                            |       | SZ |         |            |                           |         |
|-------|---------|----|---------|------------|----------------------------|-------|----|---------|------------|---------------------------|---------|
| psych | otics?  | N  | Mean    | Std. Error | ANOVA                      | Sig.  | Ν  | Mean    | Std. Error | ANOVA                     | Sig.    |
| NS    | Yes     | 6  | 2.000   | 0.258      | F( <sub>1, 6810</sub> ) =  | 0 500 | 29 | 1.900   | 0.103      | F(1,3.396) =              | 0 0 20  |
|       | No      | 26 | 2.150   | 0.107      | 0.303                      | 0.399 | 4  | 2.000   | 0.408      | 0.060                     | 0.820   |
| NT    | Yes     | 6  | 4.00    | 1.390      | F( <sub>1,8.776</sub> ) =  | 0 002 | 29 | 3.210   | 0.482      | F( <sub>1,3.887</sub> ) = | 0 000   |
|       | No      | 26 | 7.150   | 0.811      | 3.839                      | 0.085 | 4  | 3.000   | 1.291      | 0.023                     | 0.000   |
| FT1   | Yes     | 6  | 0.005   | 0.005      | F( <sub>1,26.007</sub> ) = | 0 050 | 29 | 0.004   | 0.003      | $F(_{1,3.344}) =$         | 0 5 2 7 |
|       | No      | 26 | 0.074   | 0.035      | 3.894                      | 0.039 | 4  | 0.013   | 0.013      | 0.471                     | 0.357   |
| FT2   | Yes     | 6  | 0.821   | 0.071      | F(1, 10.559) =             | 0.006 | 29 | 0.870   | 0.032      | $F(_{1,4.264}) =$         | 0.065   |
|       | No      | 26 | 0.661   | 0.050      | 3.348                      | 0.090 | 4  | 0.867   | 0.072      | 0.002                     | 0.905   |
| FT3   | Yes     | 6  | 0.174   | 0.067      | F( <sub>1,7.722</sub> ) =  | 0.264 | 29 | 0.098   | 0.021      | $F(_{1,3.508}) =$         | 0 777   |
|       | No      | 26 | 0.265   | 0.034      | 1.449                      | 0.264 | 4  | 0.121   | 0.073      | 0.093                     | 0.777   |
| DT1   | Yes     | 1  | 26.000  | -          |                            |       | 3  | 18.833  | 9.338      |                           |         |
|       | No      | 6  | 101.126 | 23.036     | -                          | -     | 1  | 44.000  | -          | -                         | -       |
| DT2   | Yes     | 6  | 381.755 | 108.230    | F( <sub>1,7.128</sub> ) =  | 0 257 | 29 | 441.681 | 51.201     | F( <sub>1,3.712</sub> ) = | 0 0 2 0 |
|       | No      | 26 | 235.878 | 48.241     | 1.516                      | 0.257 | 4  | 426.668 | 152.202    | 0.009                     | 0.930   |
| DT3   | Yes     | 5  | 67.207  | 10.560     | F(1,5.113) =               | 0 474 | 21 | 46.125  | 4.405      | F(1,2.063) =              | 0 5 2 7 |
|       | No      | 24 | 58.529  | 3.841      | 0.596                      | 0.474 | 3  | 72.222  | 35.246     | 0.540                     | 0.537   |

ASD SZ Taking anti-Ν Mean Std. Error ANOVA) Sig. Ν Mean Std. Error ANOVA Sig. depressants? NS Yes 12 2.000 0.213 11 1.820 0.182  $F(_{1,15.152}) =$  $F(_{1, 19.277}) =$ 0.402 0.541 0.724 22 0.387 20 2.200 0.092 1.950 0.123 No NT Yes 12 5.080 1.097 11 2.090 0.563  $F(_{1, 25.131}) =$  $F(_{1, 27.582}) =$ 0.113 0.052 2.693 4.110 20 0.936 22 0.578 7.450 3.730 No FT1 Yes 12 11 0.008 0.008 0.018 0.012  $F(_{1, 21.625}) =$  $F(_{1, 11.839}) =$ 0.145 0.589 2.288 0.309 No 20 0.087 0.044 22 0.003 0.002 11 FT2 Yes 12 0.780 0.059 0.900 0.045  $F(_{1, 27.615}) =$  $F(_{1, 23.588}) =$ 0.097 0.441 2.945 0.615 20 0.638 0.058 22 0.855 0.038 No FT3 Yes 12 0.202 0.051 0.045 11 0.092  $F(_{1, 22.238}) =$  $F(_{1, 14.096}) =$ 0.795 0.262 0.275 0.037 1.326 22 0.020 0.070 20 0.105 No DT1 Yes 3 34.111 4.244  $F(_{1, 3.317}) =$ 1 37.500 -0.010 132.605 27.492 3 No 4 18.299 21.000 11.504 11 520.682 DT2 Yes 12 361.718 91.274 82.191  $F(_{1, 15.824}) =$  $F(_{1, 20.084}) =$ 0.137 0.242 20 204.737 42.361 2.452 22 399.451 58.045 1.452 No 7 DT3 Yes 9 61.250 6.904 45.286 9.517  $F(_{1, 14.680}) =$  $F(_{1, 12.884}) =$ 0.831 0.633 0.047 0.240 20 59.474 4.363 17 51.076 7.024 No

Comparisons of dFNC parameters between participants taking <u>antidepressant</u> medications and those who are not

Bold- significant result

C) Similarly, since IQ average differed between the groups, bi-variate correlation were calculated between IQ score to each of the ordinal dFNC measures, within each one of the diagnostic groups.

# Correlations between full scale IQ score and dFNC parameters

|     |      | NS     | NT     | FT1    | FT2    | FT3    | DT1     | DT2    | DT3    |
|-----|------|--------|--------|--------|--------|--------|---------|--------|--------|
| HC  | r    | -0.200 | -0.336 | -0.068 | 0.189  | -0.311 | 0.017   | 0.354  | -0.111 |
|     | Sig. | 0.257  | 0.052  | 0.704  | 0.284  | 0.073  | 0.948   | 0.043  | 0.537  |
|     | Ν    | 34     | 34     | 34     | 34     | 34     | 18      | 33     | 33     |
| ASD | r    | 0.097  | 0.106  | -0.026 | -0.119 | 0.108  | 0.144   | -0.149 | -0.161 |
|     | Sig. | 0.599  | 0.565  | 0.888  | 0.517  | 0.554  | 0.758   | 0.416  | 0.404  |
|     | Ν    | 32     | 32     | 32     | 32     | 32     | 7       | 32     | 29     |
| SZ  | r    | 0.155  | 0.171  | -0.192 | -0.248 | 0.384  | -0.949^ | -0.248 | -0.154 |
|     | Sig. | 0.390  | 0.342  | 0.283  | 0.163  | 0.027  | 0.051   | 0.164  | 0.473  |
|     | Ν    | 33     | 33     | 33     | 33     | 33     | 4       | 33     | 24     |

Bold- significant result

#### Appendix 6. State plots k=5

In order to verify that the state decomposition generated by the k=4 reflects a true underlying pattern, a k=5 state decomposition was produces as well. K=5 resulted in four *reoccurring* states, and an additional state that occurred in 1% of the windows (similarly to the k=4 solution) which was thus excluded from analysis. As can be seen in the figure below, the overall structure of the results highly resembled that of the k=4 decomposition.



K=5 state plots: whole brain cross-correlation plots for each of the reoccurring\* FC states (black lines mark division into networks).

\* Four reoccurring states are presented. The fifth state occurred in 1% of the windows (as in the k=4 solution), and is thus excluded from analysis.

#### Appendix 7. Group differences in temporal dynamics- controlled for head motion

Repeating the group comparisons while controlling for head motion (framewise-displacement root mean square) showed similar results to the main ANOVA, and no significant effect for motion in any of the dFNC parameters

|     | dFNC sig. | dFNC   | Motion sig. |
|-----|-----------|--|-------------|
|     |           | Pairwise   |             |
|     |           | comparisons  |             |
| NS  | R<0.000   | SZ <hc (p<0.001)<="" th=""><th></th></hc>          |             |
|     | F<0.000   | ASD <hc (p="0.011)&lt;/th"><th>P-0.555</th></hc>   | P-0.555     |
| NT  | P<0.000   | SZ <hc (p<0.000)<="" th=""><th>D-0 220</th></hc>   | D-0 220     |
|     |           | SZ <asd (p<0.000)<="" td=""><td>P-0.220</td></asd> | P-0.220     |
| FT1 | D<0.000   | SZ <hc (p<0.001)<="" th=""><th></th></hc>          |             |
|     | P<0.000   | ASD <hc (p="0.002)&lt;/th"><th>P=0.505</th></hc>   | P=0.505     |
| FT2 |           | SZ>HC (p<0.001)                                    |             |
|     | P<0.000   | ASD>HC (p=0.003)                                   | P=0.464     |
|     |           | SZ>ASD (p=0.007)                                   |             |

| FT3 | D <0.000 | SZ <hc (p<0.001)<="" th=""><th>D = 0.644</th></hc> | D = 0.644 |
|-----|----------|--|-----------|
|     | P<0.000  | SZ <asd (p<0.001)<="" th=""><th>P=0.644</th></asd> | P=0.644   |
| DT1 | P-0.021  | SZ <hc (p="0.007)&lt;/th"><th>P-0.945</th></hc>    | P-0.945   |
|     | F=0.021  | SZ <asd (p="0.023)&lt;/th"><th>F=0.945</th></asd>  | F=0.945   |
| DT2 | P<0.000  | SZ>HC (p<0.001)                                    | D-0 882   |
|     | F<0.000  | SZ>ASD (p=0.006)                                   | F-0.082   |
| DT3 | P=0.258  | N.A.   | P=0.369   |

#### Appendix 8. Group differences in state engagement

When considering the particular states that participants occupied, far fewer patients from both groups entered the highly connected state, as compared to HC. Chi-square tests indicated that significantly fewer SZ and ASD participants entered state 1 as compared to HC (Fischer's exact test: p=0.001, p=0.012; respectively), and significantly fewer SZ participants entered state 3, as compared to HC (Fischer's exact test: p=0.013). No differences were found between the groups for state 2. **Appendix 9. Classification plot and structure matrix** 

Classification canonical discriminant functions plot



| C         | N / - +! |
|-----------|----------|
| Structure | iviatrix |

| Funct | ion |
|-------|-----|
| 1     | 2   |

| FT2        | 849  | .251 |
|------------|------|------|
| NT         | .818 | .193 |
| FT3        | .741 | .312 |
| FT1        | .655 | 547  |
| NS         | .603 | 356  |
| SE 1 (y/n) | .563 | 530  |
| SE 3 (y/n) | .412 | .119 |
| SE 2 (y/n) | 168  | .273 |

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions

# Appendix 10. Discriminant analysis cross-validation

To ensure stability of the results, the classification analysis was repeated using a leave-one out method. In cross validation, each case is classified by the functions derived from all cases other than that case. The results per-group are presented in the table below. Overall, 52.5% of cross-validated grouped cases correctly classified, while 57.6% of original grouped cases correctly classified (chance-level is 33%). These results re-iterate those of the original classification, thus attesting to their stability.

#### Leave-one-out cross validation

|                  |     | Pred                                 | Predicted Group Membership |            |  |  |  |  |
|------------------|-----|--------------------------------------|----------------------------|------------|--|--|--|--|
|                  |     | Assigned SZ Assigned ASD Assigned HC |                            |            |  |  |  |  |
| Diagnostic Group | SZ  | 75.8% (25)                           | 21.2% (7)                  | 3.0% (1)   |  |  |  |  |
|                  | ASD | 31.3% (10)                           | 43.8% (14)                 | 25.0% (8)  |  |  |  |  |
|                  | HC  | 29.4% (10)                           | 32.4% (11)                 | 38.2% (13) |  |  |  |  |

Gray- participants that were assigned to their diagnostic group

# Appendix 11.Single parameter classification results

When repeating the classification using number of transitions (NT) as a single independent variable an overall of 54.5% cases were correctly classified (with 54.5% in cross-validation as well), while 57.6% of

original grouped cases correctly classified (chance-level is 33%). The results per-group are presented in the table below.

|                         |     | Pred        | Predicted Group Membership |             |  |  |  |
|-------------------------|-----|-------------|----------------------------|-------------|--|--|--|
|                         |     | Assigned SZ | Assigned ASD               | Assigned HC |  |  |  |
| Diagnostic Group        | SZ  | 75.8% (25)  | 15.2% (5)                  | 9.1% (3)    |  |  |  |
|                         | ASD | 34.4% (11)  | 21.9% (7)                  | 43.8% (14)  |  |  |  |
|                         | HC  | 23.5% (8)   | 11.8% (4)                  | 64.7% (22)  |  |  |  |
| <b>Cross-Validation</b> | SZ  | 75.8% (25)  | 15.2% (5)                  | 9.1% (3)    |  |  |  |
|                         | ASD | 34.4% (11)  | 21.9% (7)                  | 43.8% (14)  |  |  |  |
|                         | HC  | 23.5% (8)   | 11.8% (4)                  | 64.7% (22)  |  |  |  |

Gray- participants that were assigned to their diagnostic group

#### Appendix 12. –QLS sensitivity analysis.

To test for the effect of overall clinical severity, a sensitivity analysis was conducted. The Quality of Life Scale (QLS; [3]), a 21-item scale based on a semi-structured interview was used, as a proxy of overall severity. We examined bivariate correlations between dFNC measures to QLS score within each one of the clinical groups. Results are presented in the table hereinafter.

Correlations of dFNC parameters with QLS Total Score (Spearman's Rho)

|     |      | NS    | NT     | FT1    | FT2    | FT3   | DT1    | DT2    | DT3    |
|-----|------|-------|--------|--------|--------|-------|--------|--------|--------|
| НС  | r    | 0.138 | -0.072 | -0.067 | 0.014  | 0.033 | -0.250 | 0.011  | 0.114  |
|     | Sig. | 0.443 | 0.689  | 0.713  | 0.937  | 0.856 | 0.318  | 0.953  | 0.535  |
|     | Ν    | 33    | 33     | 33     | 33     | 33    | 18     | 32     | 32     |
| ASD | r    | 0.276 | 0.284  | 0.270  | -0.359 | 0.297 | 0.571  | -0.273 | 0.021  |
|     | Sig. | 0.133 | 0.122  | 0.142  | 0.047  | 0.105 | 0.180  | 0.137  | 0.916  |
|     | Ν    | 31    | 31     | 31     | 31     | 31    | 7      | 31     | 28     |
| SZ  | r    | 0.198 | 0.134  | 0.040  | 0.011  | 0.011 | 0.400  | -0.035 | -0.362 |
|     | Sig. | 0.268 | 0.459  | 0.827  | 0.952  | 0.952 | 0.600  | 0.846  | 0.082^ |
|     | Ν    | 33    | 33     | 33     | 33     | 33    | 4      | 33     | 24     |

Bold- significant result

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