Connectivity theory of Autism: Using connectivity measures in the assessment and treatment of autistic disorders

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Robert Coben, PhD
Neuroimaging findings in Autism

- PET – bilateral temporal hypoperfusion, superior temporal gyrus/sulcus (Boddaert et al., 2002)
- Social cognitive and language dysfunctions have been linked to neural substrates – amygdala, superior temporal sulcus, fusiform gyrus (Just et al., 2004; Pelphrey et al., 2004; Welchew et al, 2005)
Connectivity in Autistic disorders

- MRI reductions in white matter (McAlonan et al., 2004)
- fMRI underconnectivity in anterior-posterior connections (Cherkassky et al., 2006)
- fMRI hyperconnectivity across middle frontal regions (Mizuno et al., 2006)
- Theory of hyperconnected frontal cortices along with frontal to other hypoconnectivity (Courchesne & Pierce, 2005).
Connectivity findings in Autism

- Less white matter concentration in the genu, rostrum, splenium (Chung et al., 2004)
- Cell columns are more numerous, smaller and less compact in frontal and temporal regions (Casanova et al, 2002)
- Diminished connectivity in language areas during sentence comprehension (Just et al., 2004)
- 124 channel EEG – higher than normal neural connectivity and lower than normal connectivity between frontal and other brain regions (Murias, 2006)
fMRI coherence in Autism

Fig. 2 Examples of functional connectivity between LDLPFC and LIFG (Broca’s area) in individual participants, shown as the activation time series in the two brain regions, with vertical bars indicating boundaries between seven epochs of sentences of the same type. (A) Autistic participant with low functional connectivity, $r = 0.31$, where the two time series do not closely track each other. (B) Control participant with high functional connectivity, $r = 0.79$, where the activation time series in the two regions is highly similar.

Fig. 3 Functional connectivity for autistic and control participants in the 10 ROI pairs with a reliable ($P < 0.05$) difference between autistic and control participants (presented in descending order of mean connectivity). The pattern of functional connectivities across these 10 ROI pairs is very similar for the two groups ($r = 0.98$). Error bars represent the standard error of the mean. L = left; R = right; CALC = calcarine fissure; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; IES = inferior extrastriate; IFG = inferior frontal gyrus; IPL = inferior parietal lobe; IPS = intraparietal sulcus; IT = inferior temporal; TRIA = triangularis; OP = occipital pole; SMFP = superior medial frontal paracingulate.
White matter anomalies in Autism

Figure 1. Voxels that showed significant reduction in white matter fractional anisotropy in patients with autism compared with control subjects, mapped onto an average T1-weighted image of control and autism brains. (A, B, C) Sagittal view, significant clusters shown in the ventromedial prefrontal region (A, B), the anterior cingulate and subgenual area (C), the corpus callosum (B, C), the superior temporal gyrus (A), centrum semiovale (A), and temporoparietal junction (A). (D) Coronal view, significant clusters shown in the ventromedial prefrontal region bilaterally and along the middle frontal sulcus (D, E).

Figure 2. A three-dimensional representation of the aberrant white matter (dark gray) in relation to the corpus callosum (white), and the amygdala (checkered gray).
Connectivity theory of Autism

- Neural development and connectivity is stunted at an early developmental stage when the frontotemporal regions are undifferentiated.
- This lack of differentiation or independent development of brain regions leads to their hyperconnectivity and blocks coherence development with other critical brain regions.
- What is unknown is why this occurs, what can prevent it and what can be done about it.
- We are learning that NF can significantly alter this patterns in a more functional direction.
Classification Accuracy

- Coben, Chabot, Hirshberg (2007):
  - ASD vs. Normals vs. ADHD (N = 68, 250+)
  - Ages 5 – 18, matched for age and sex
  - ASD (90.1%) (88.7% replication) vs Normals (93.9%) (93% replication)
  - ASD (84.5%) (81.7% replication) vs. ADHD (84.3%) (83.6% replication)
Discriminant function critical variables

- Increased theta relative power
- Increased frontal/temporal beta coherence (ADHD)
- Decreased temporal coherence
- Central/Parietal decreased coherence (normals)

Coben, Clarke, Barry & Hudspeth (2006)

- 27 Autistics and 27 “Normals” matched for age, race, gender, medication usage (none).
- Normals had mean IQ = 103.2, mean age = 9 years, 8 months, screened for reading, spelling, behavior problems, head injury, ADHD, medication use, psychiatric diagnosis, learning problems.
- QEEG performed resting eyes closed.
- All EEG artifacting done by same person with over 30 years experience.
Mu rhythm and suppression in Autism: The Mirror Neuron System

Fig. 1. Mu suppression in control and ASD participants. Bars represent the mean log ratio of power in the mu frequency (8–13 Hz) during the watching balls condition (light gray), watching hand movement condition (medium gray), and moving own hand condition (dark gray) over the power in the baseline condition for scalp locations C3, Cz, and C4 for typically developing individuals (A) and individuals with ASD (B). Error bars represent the standard error of the mean. For all values, a mean log ratio greater than zero indicates mu enhancement; a mean log ratio less than zero indicates mu suppression. Significant suppression is indicated by asterisks, *P < 0.05, **P < 0.01, ***P < 0.005.
Mu rhythm oscillations

Fig. 3. Current source density maps for the grand average data for three subtractions for both left and right hands using the mean mu frequency band of 10–12 Hz. Units are μV/m². C3 and C4 electrodes are marked with a circle. Note the high degree of congruence in the topographies across the three spectral subtractions and the hand observed.
The importance of Mu/MNS

Figure 3: Mirror neuron system activity and symptom severity. (a-c) Negative correlations were found in the ASD group between activity in the pars opercularis of the inferior frontal gyrus and scores on the social subscale of both ADOS-G (a,c) and ADI-R (b,c): $t > 1.83, P < 0.05$, corrected for multiple comparisons at the cluster level.

Example of Mu-like Rhythm Oscillations
Part 1: EEG Analyses

- Sampled 56 QEEG profiles diagnosed with ASD and not taking any medications.
- Selected for mu-like rhythm oscillations over C3, C4.
- Activity did not diminish upon eye opening (lack of mu suppression).

Part 1: EEG Analyses

- C3, C4.
- 9 – 12 Hz. Maximal
- 8 – 13 Hz. Range
- Spectral Sort
  - Median splits
- C3: p<.015
- C4: p<.021
- Sorted into high and low mu-like records
Patterns of EEG Connectivity anomalies in Autistic disorders

1. Frontotemporal hyperconnectivity
2. Frontal (orbitofrontal) hypoconnectivity
3. Mu rhythm complex – mixed sensorimotor hypoconnectivity with frontal hyperconnectivity
4. Right posterior (occipital/parietal-temporal) hypoconnectivity
5. Frontal – posterior hypoconnectivity
6. Left hemisphere intrahemispheric hypoconnectivity
7. Left hemisphere intrahemispheric hyperconnectivity
Frontotemporal hyperconnectivity
Frontotemporal hyperconnectivity

- 37 Autistics seen in our practice for at least 20 sessions of EEG Biofeedback. During this time frame, only one patient dropped out.
- Compared to 12 WLC.
- Parental Judgment.
- Pre and Post ATEC, GADS, BRIEF, PIC-2.
- Pre and Post Neuropsychological testing and QEEG.
- Pre and Post Infrared Imaging surrounding each session.
Frontotemporal hyperconnectivity

Autistic Diagnoses

- Autism: 7
- PDD: 21
- Aspergers: 5
- CDD: 4
Neurofeedback Protocols

- 89% Interhemishperic, bipolar.
- 94% Frontotemporal electrode sites.
- 100% high beta inhibit (18-30 hz).
- 92% has low inhibits down to 1-2 hz.
- 68% had a third inhibit in the 7-14 hz region
- Reward bands setup for maximal hyperconnectivity – 5-16 hz.
Frontotemporal hyperconnectivity

Results: Parental Judgment

Benefit: Harm Ratio = 89
Frontotemporal hyperconnectivity

Results: Parent Ratings

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<th>Mean</th>
<th>SD</th>
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<td>46.100</td>
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Difference between means
95% CI
18.367
12.986 to 23.747

$t$ statistic
6.98
2-tailed $p$ <0.0001

40% reduction in symptoms

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<td>9.810</td>
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Difference between means
95% CI
11.333
7.453 to 15.214

$t$ statistic
8.00
2-tailed $p$ <0.0001

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Difference between means
95% CI
5.933
4.122 to 9.745

$t$ statistic
5.04
2-tailed $p$ <0.0001

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<td>Pre PIC-2 TOT-C</td>
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<td>10.252</td>
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<td>64.250</td>
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<td>7.000</td>
<td>6.304</td>
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Difference between means
95% CI
7.000
4.727 to 9.273

$t$ statistic
6.28
2-tailed $p$ <0.0001
Frontotemporal hyperconnectivity
Frontal (orbitofrontal) hypoconnectivity

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<th>Horizontal</th>
<th>Sagittal</th>
<th>Coronal</th>
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<th>Alpha</th>
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Frontal (orbitofrontal) hypoconnectivity
Frontal (orbitofrontal) hypoconnectivity
Coben (2006). HEG for ASD.

- 28 Autistics seen in our practice for at least 20 sessions of HEG (nir or pirHEG).
- All patients had already received 20 sessions of EEG Biofeedback.
- This was assessment guided HEG in that all patients were deemed to have frontal system dysfunction based on NP, IR and QEEG data.
- Pre and Post ATEC, GADS, BRIEF, PIC-2.
- Pre and Post NP testing.
- Pre and Post Infrared Imaging surrounding each session.
- Pre and Post QEEG.
HEG Procedures

• nirHEG or pirHEG – therapy remained the same over the entire course of 20 sessions.
• Sessions were 15 – 25 minutes depending on tolerance.
• Done twice weekly.
• Therapy was done with DVD and/or Gamecube video games.
Control Sample

• 12 subjects in wait list control group.
• Matched for gender, age, race, handedness, other treatments, initial ATEC score.
• No new treatment during study design.
• Pre-post testing showed no significant changes on any measure.
Frontal (orbitofrontal) hypoconnectivity

Results: ATEC ratings

• Total – p<.0001 – 42% reduction
• Communication – p<.017 - 47% reduction
• Socialization – p<.022 – 43% reduction
• Sensory/Cognition – p<.004 – 44% reduction
• Behavior – p<.0001 – 39% reduction
Frontal (orbitofrontal) hypoconnectivity

nirHEG/pirHEG Comparisons

- No significant difference for ATEC scores, GADS ADQ, BRIEF Working Memory, PIC-2 ADH, Deliquency, Family relations, Psychological discomfort, or any Neuropsychological index.
Frontal (orbitofrontal) hypoconnectivity

nirHEG/pirHEG Comparisons – Relative Power
Mu rhythm complex
Mu rhythm complex
Mu rhythm complex
Part 2: Neurofeedback Outcome Study

- 14 patients underwent 20 sessions EEGBF.
- Pre-post NP tests, NB rating scales, IR imaging, QEEG.
- Two comparison groups:
  - Coherence training
  - Interhemispheric, bipolar training
Part 2: Neurofeedback Outcome Study

- Total NF group (14 patients) had significant changes in:
  - GADS Pragmatics – p<.006
  - GADS Social Interaction – p<.027
  - GADS ADQ – p<.014
  - Executive Functioning – p<.0001
  - Visuospatial Skills – p<.004
  - Attention – p<.005
  - IR enduring change – min value – p<.033
  - IR enduring change – range – p<.05
Part 2: Neurofeedback Outcome Study: Comparative Analyses

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<td>Pragmatics</td>
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<td>Attention (sd)</td>
<td>0.4</td>
<td>1.2</td>
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<tr>
<td>IR min</td>
<td>1.17</td>
<td>0.37</td>
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<tr>
<td>Total Mu Change (x10)</td>
<td>1.06</td>
<td>0.2</td>
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Part 2: Neurofeedback Outcome Study: Comparative Analyses: QEEG changes

Mu rhythm complex
Mu rhythm complex
Mu rhythm complex

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<tr>
<th>EigenImages</th>
<th>Delta</th>
<th>Theta</th>
<th>Alpha</th>
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<tr>
<td>Horizontal</td>
<td>$r^2 = 93.0%$</td>
<td>$r^2 = 91.1%$</td>
<td>$r^2 = 91.8%$</td>
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<td>$r^2 = 79.1%$</td>
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<td>Sagittal</td>
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<tr>
<td>Coronal</td>
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D4: 0 - 100%
Mu rhythm complex

CORRELATION

-0.9
-0.7
-0.4

Delta
Theta
Alpha
Beta
Total

SEVERITY

+0.7
0
-0.7

Delta
Theta
Alpha
Beta
Total
Mu rhythm complex
Right posterior (occipital/parietal – temporal) hypoconnectivity
Right posterior (occipital/parietal – temporal) hypoconnectivity
Right posterior (occipital/parietal – temporal) hypoconnectivity
Frontal – posterior hypoconnectivity
Frontal – posterior hypoconnectivity
Left hemisphere hypoconnectivity
Left hemisphere intrahemispheric hyperconnectivity

- Horizontal
  - Delta: $r^2 = 91.4\%$
  - Theta: $r^2 = 93.0\%$
  - Alpha: $r^2 = 87.7\%$
  - Beta: $r^2 = 80.6\%$
  - Total: $r^2 = 76.4\%$

- Sagittal

- Coronal