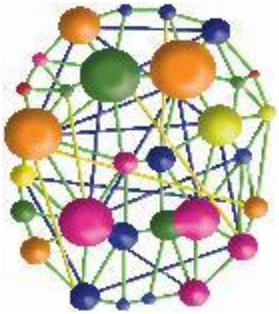
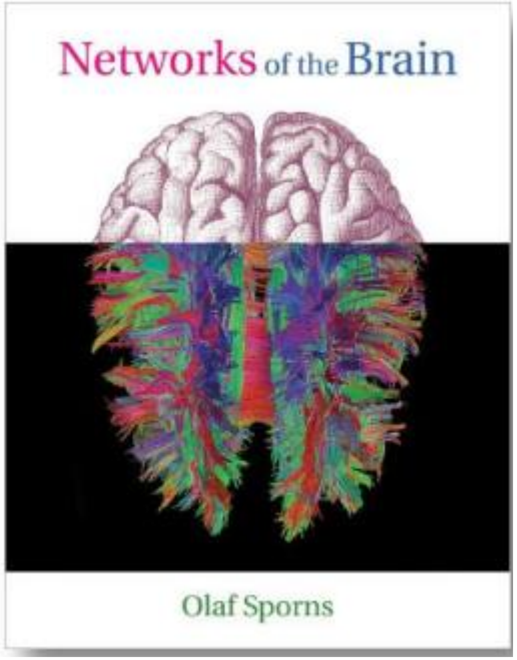
The Impact of Using Effective Connectivity Measures (Granger Causality) in Guiding Neurofeedback

Robert Coben, PhD & Anne W Stevens, PhD,
Integrated Neuroscience Services



Types of Neural Connectivity

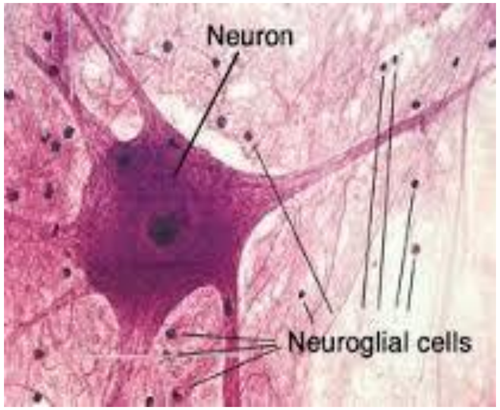
- **Structural Connectivity**
- **Functional Connectivity**
- **Effective Connectivity**

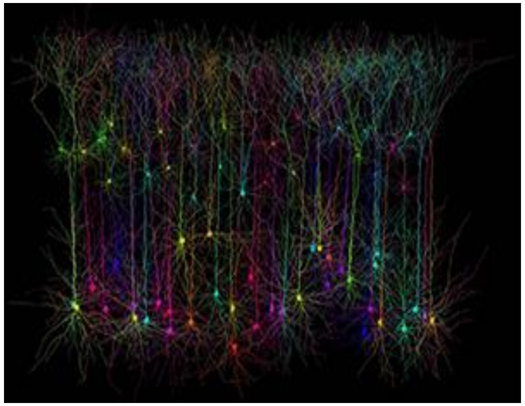


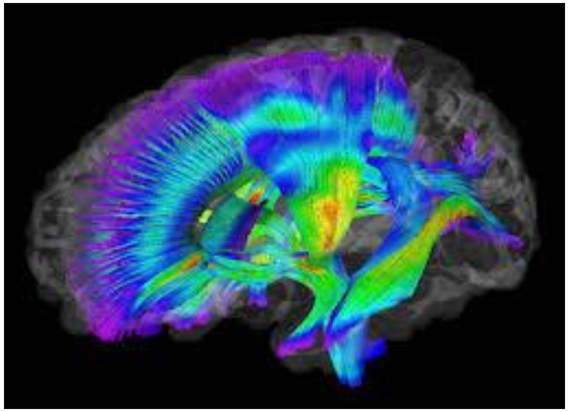
Sporns, O. (2010). *Networks of the Brain*. MIT press.

Structural Connectivity

◎A set of physical or anatomical connections linking neural elements.

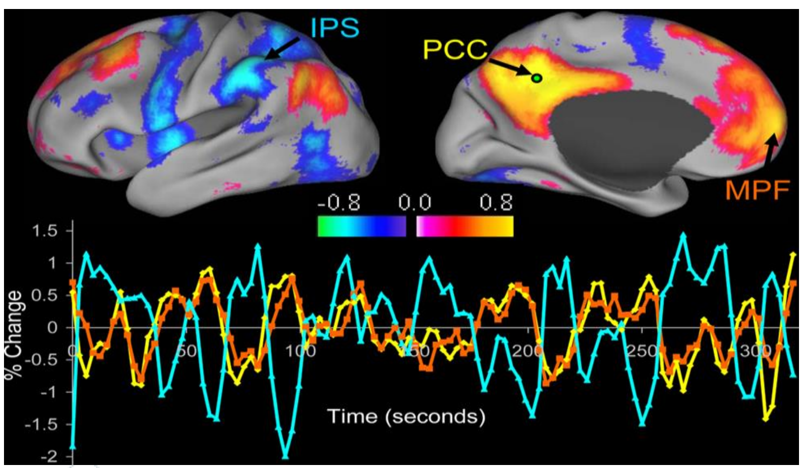


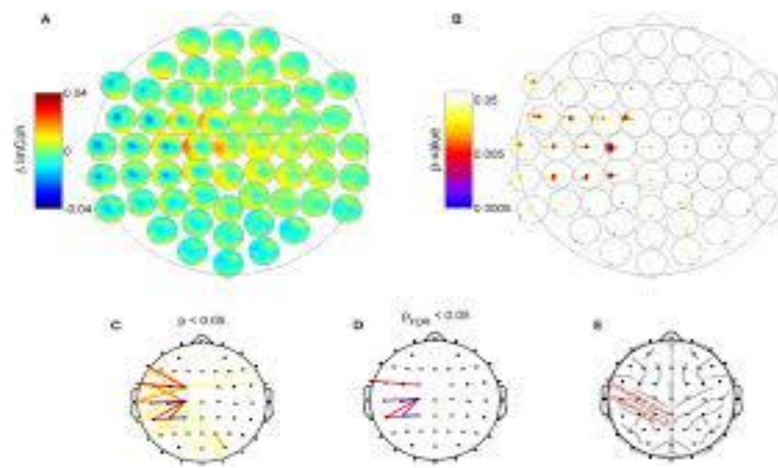




Functional Connectivity

◎Patterns of deviations from statistical independence between distributed and spatially remote neuronal units. The basis of this is time series data from neural recordings. Their relation is taken as neuronal coupling and often takes the form of correlation, coherence, phase locking or comodulation. There is no causal relationship, effect or interaction.



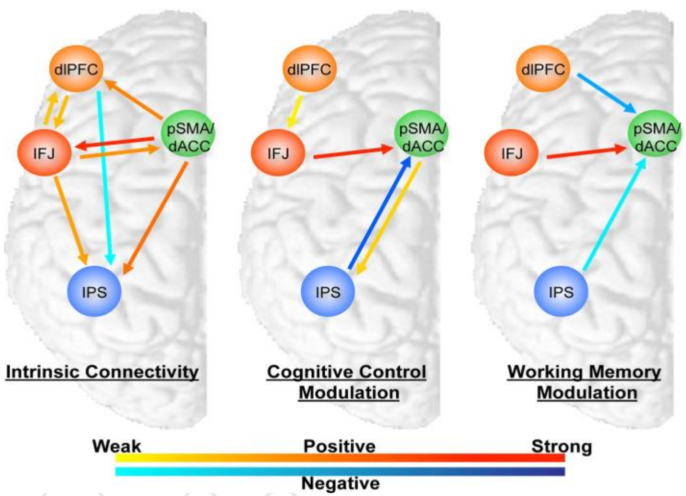


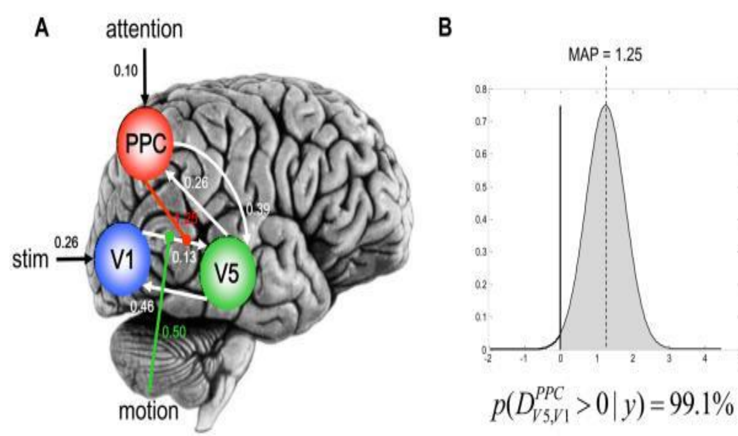
Effective Connectivity

◎Network and causal effects between neural elements.

◎Inferred through statistical techniques such as time series analyses and statistical modeling that assess causality and interaction.

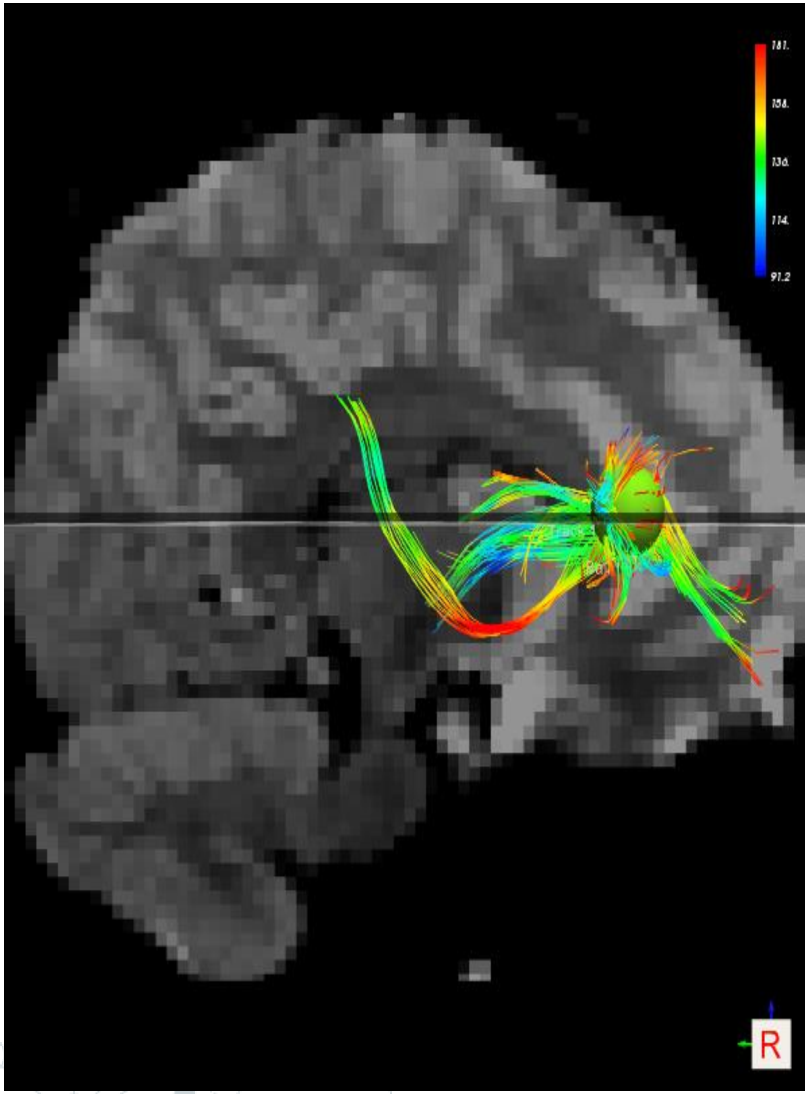
◎Requires complex data processing and modeling techniques such as ICA, Partial Directed Coherence and Granger Causality.

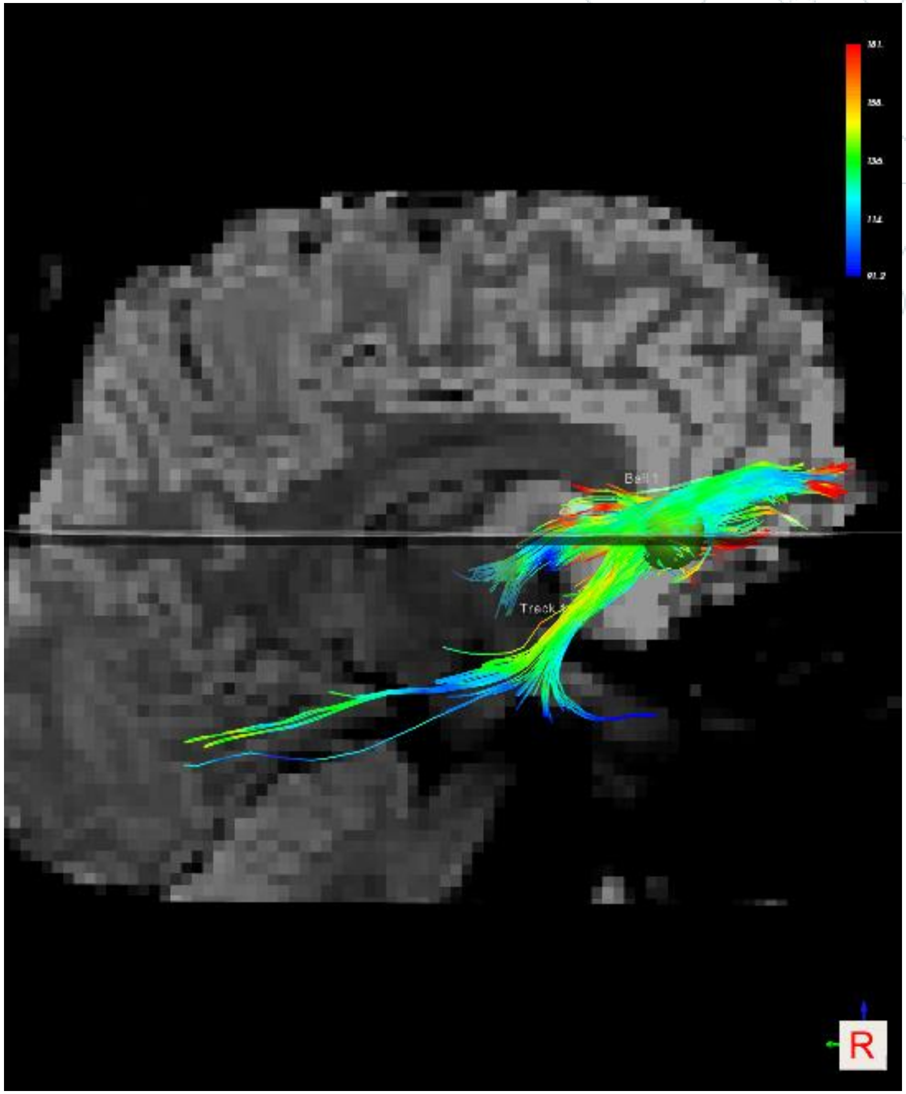


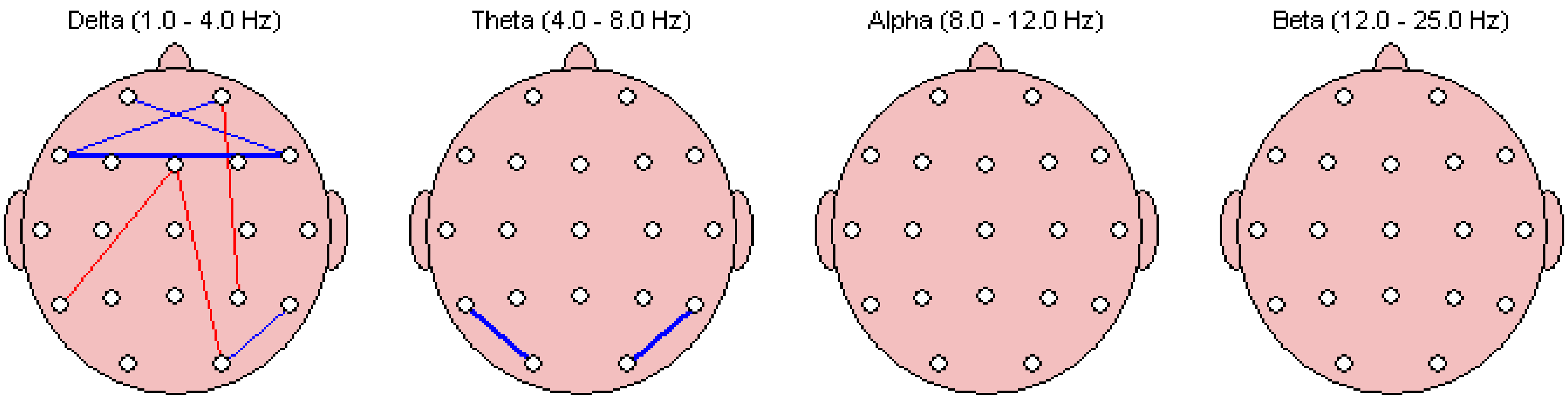


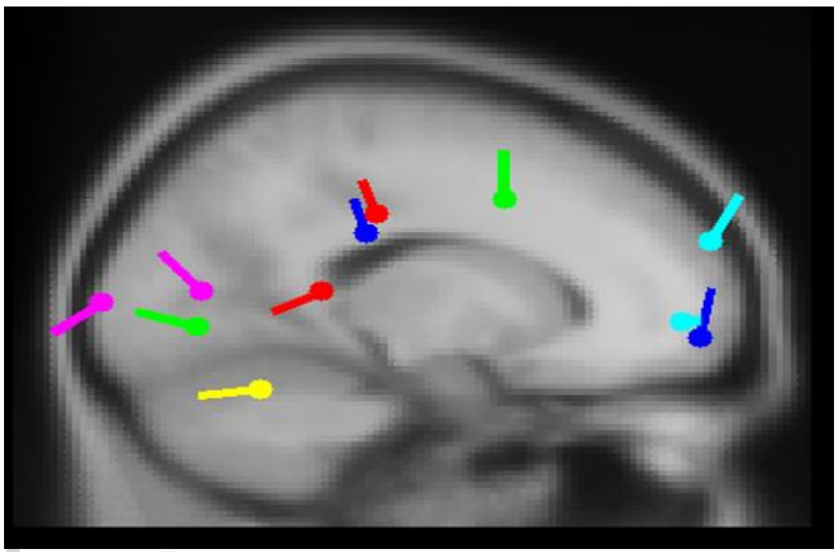
Multivariate Autoregressive Models (MVAR)

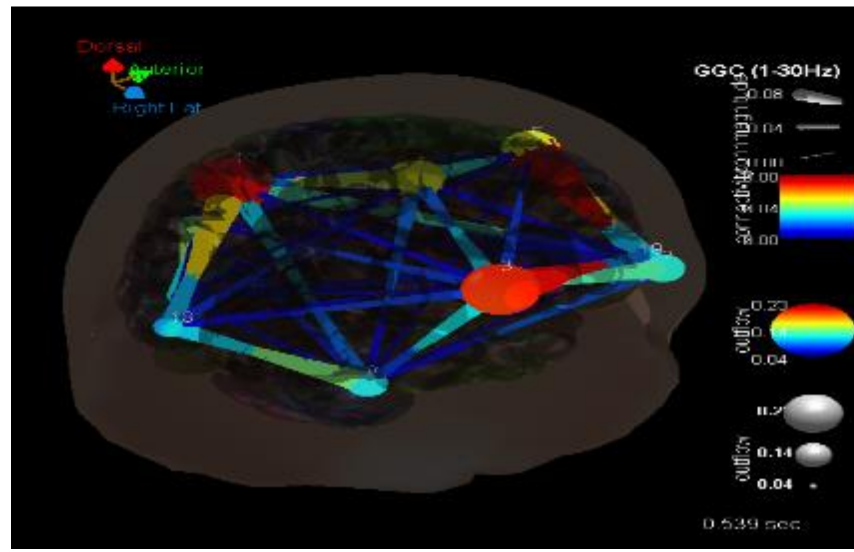
Comparing levels of connectivity






Delta (1.0 - 4.0 Hz)
Theta (4.0 - 8.0 Hz)
Alpha (8.0 - 12.0 Hz)
Beta (12.0 - 25.0 Hz)




Dorsal
Anterior
GGC (1-30Hz)
0.539 sec

Med Biol Eng Comput (2011) 49:521–529
DOI 10.1007/s11517-011-0739-x

SPECIAL ISSUE - REVIEW

Review of the methods of determination of directed connectivity from multichannel data

Katarzyna J. Blinowska

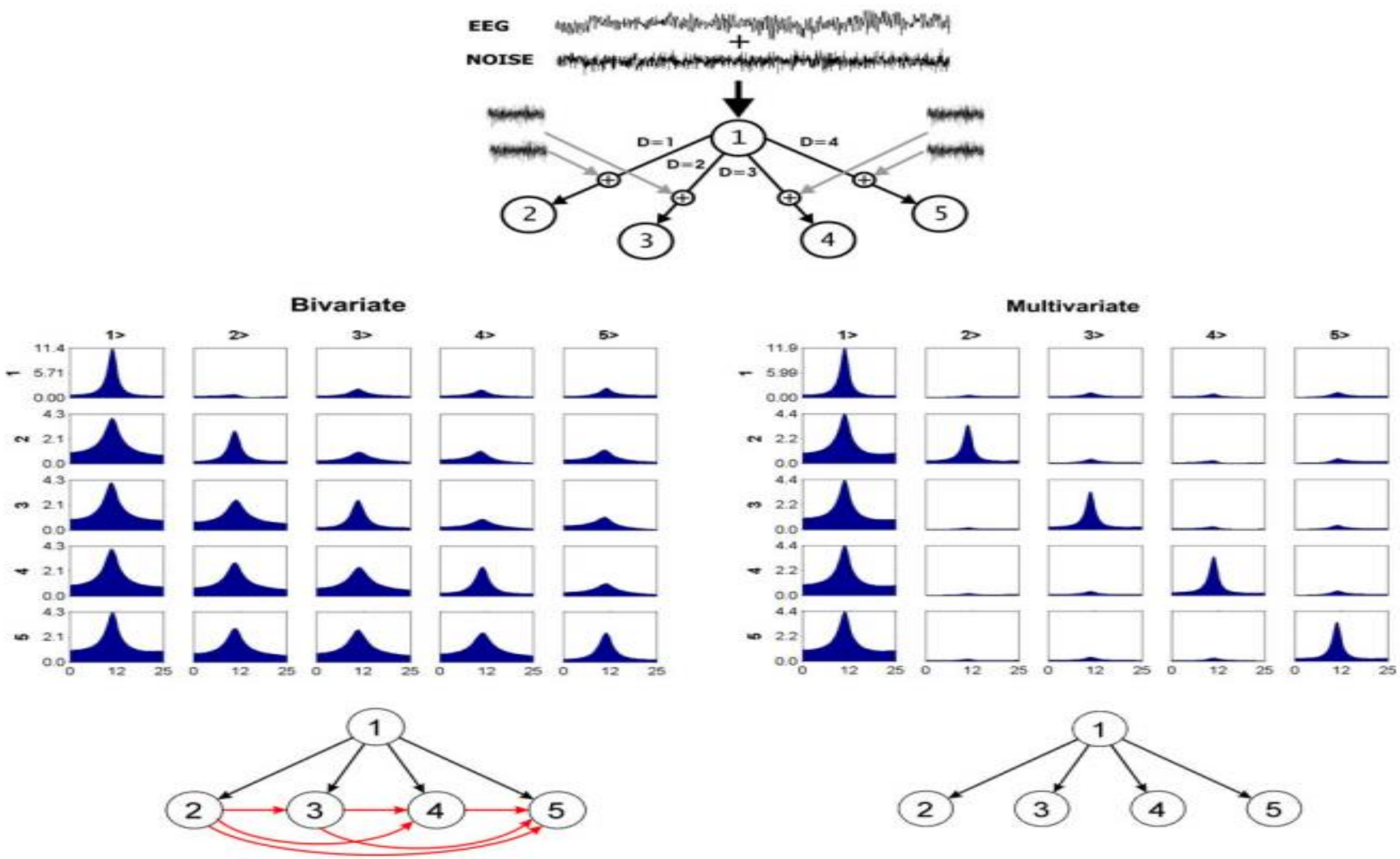


Fig. 1 Comparison of bivariate and multivariate methods of estimation of directed connectivity. *Top* simulation scheme (*D* delay value, at each step white noise is added). *Bottom* connectivity measures, at the *left* bivariate, at the *right* multivariate. Propagation from the channel marked above the column to the channel marked at *left*. In each *box* DTF is shown as a function of frequency. At the diagonal power spectra. At the very *bottom* obtained connections schemes

OPINION ARTICLE

Front. Neural Circuits, 26 September 2018 | https://doi.org/10.3389/fncir.2018.00076

Is Graph Theoretical Analysis a Useful Tool for Quantification of Connectivity Obtained by Means of EEG/MEG Techniques?

Maciej Kaminski[1*†] and Katarzyna J. Blinowska[1,2†]

[1]Department of Biomedical Physics, Faculty of Physics, University of Warsaw, Warsaw, Poland

[2]Institute of Biocybernetics and Biomedical Engineering of Polish Academy of Sciences, Warsaw, Poland

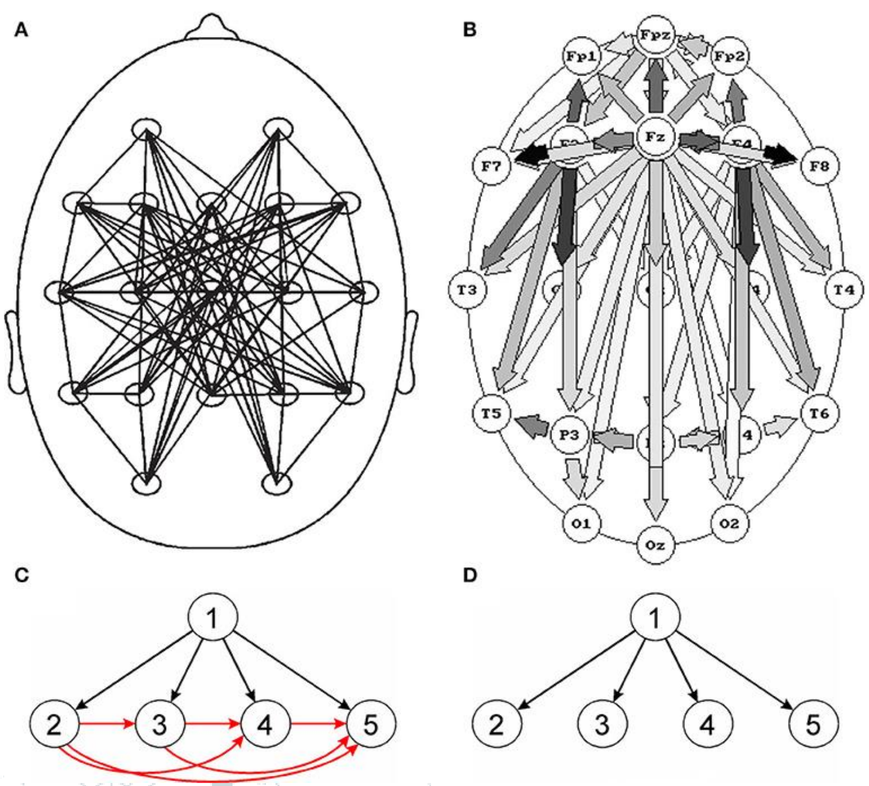


Figure 1. Comparison of bivariate and multivariate connectivity measures. Top images: connectivity patterns for slow wave sleep (stage 3/4), **(A)** obtained using the bivariate measure (SL), **(B)** obtained using the multivariate measure (DTF). Although in **(A)** undirected and in **(B)** directed connections are shown, however the main difference between the pictures are: disorganized pattern of connections in **(A)** and clear-cut pattern of connections compatible with physiological evidence in **(B)**. Bottom images—propagation patterns for a simulation which assumes a propagation of activity from electrode 1 to electrodes 2, 3, 4, and 5; **(C)**—pattern obtained for a bivariate measure (coherence) and **(D)**—for a multivariate measure (DTF). For the bivariate connectivity measure, false connections are created resulting from common driving. **(A)** Reproduced from Leistedt et al. (2009). **(B)** Reproduced from Kaminski et al. (1997) (with permission).

Using quantitative and analytic EEG methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over- and under-connectivity

Robert Coben[1,2]*, Iman Mohammad-Rezazadeh[3,4] and Rex L. Cannon[5]

[1] Neurorehabilitation and Neuropsychological Services, Massapequa Park, NY, USA
[2] Integrated Neuroscience Services, Fayetteville, AR, USA
[3] Center for Mind and Brain, University of California, Davis, CA, USA
[4] Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA
[5] Psychoeducational Network, Knoxville, TN, USA

Frontiers in Human Neuroscience www.frontiersin.org February 2014 | Volume 8 | Article 45 | 1

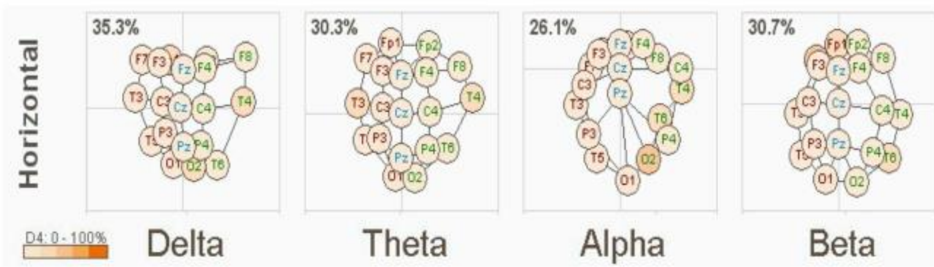


FIGURE 1 | NeuroRep Multivariate Connectivity analyses showing eigen images in the horizontal place across delta, theta, alpha, and beta frequencies. Observable features include; (1) right hemisphere (temporal) hypocoherences across all frequency bands, (2) hypercoherences in the alpha band over prefrontal regions, and (3) right parietal-posterior temporal hypercohences in the theta and alpha frequency bands.

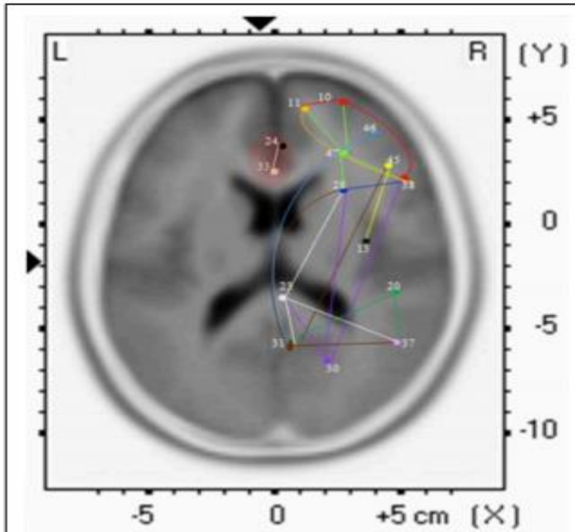


FIGURE 3 | Each of the 15 ROIs for this case study are represented in a different color. The lines indicate significant correlations between the colored ROI and other regions. The color of the line is the same as the ROI in relation to its functional connectivity with other ROIs.

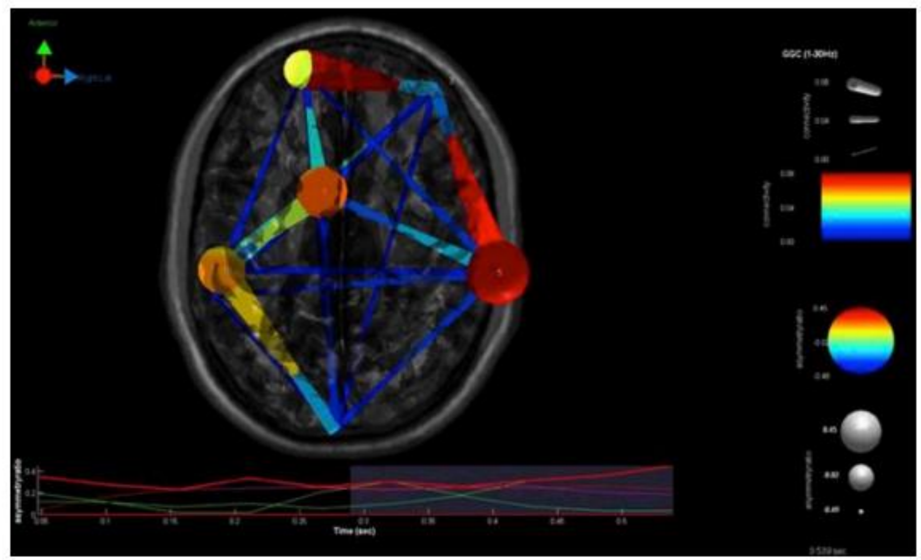
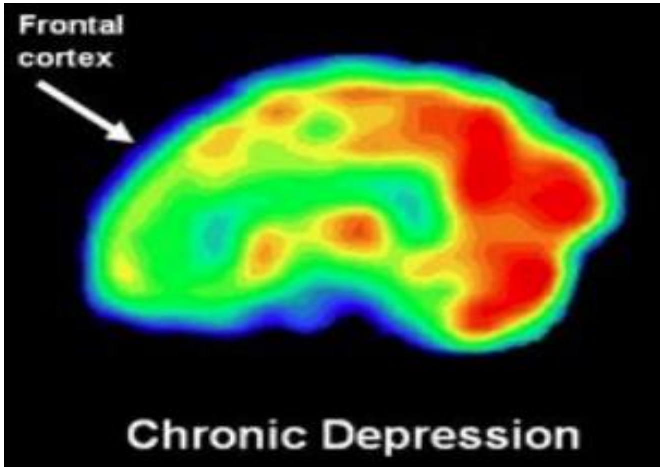
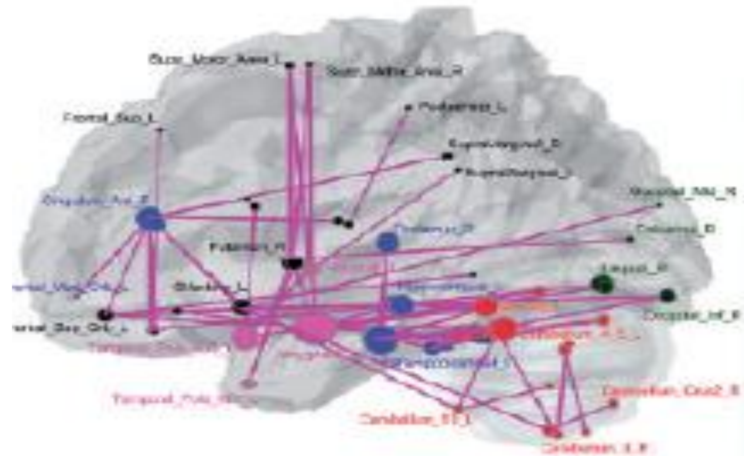
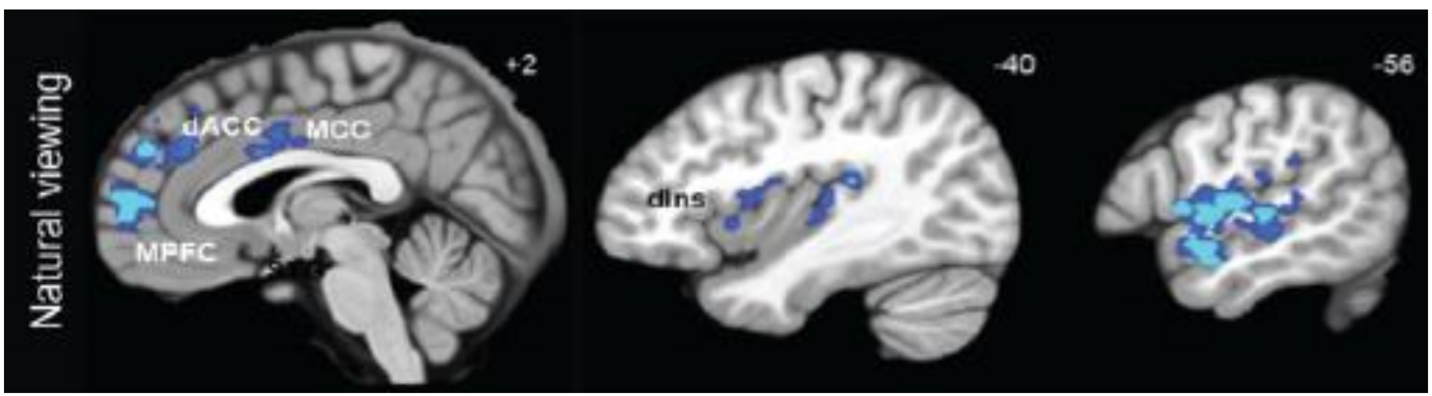


FIGURE 5 | SIFT/Granger (GGC) causality brain image. Levels of greater connectivity are shown with thicker lines and brighter colors. Direction of causality is indicated by the key in the upper left hand corner. ICs and their localization are listed as part of **Table 3**.

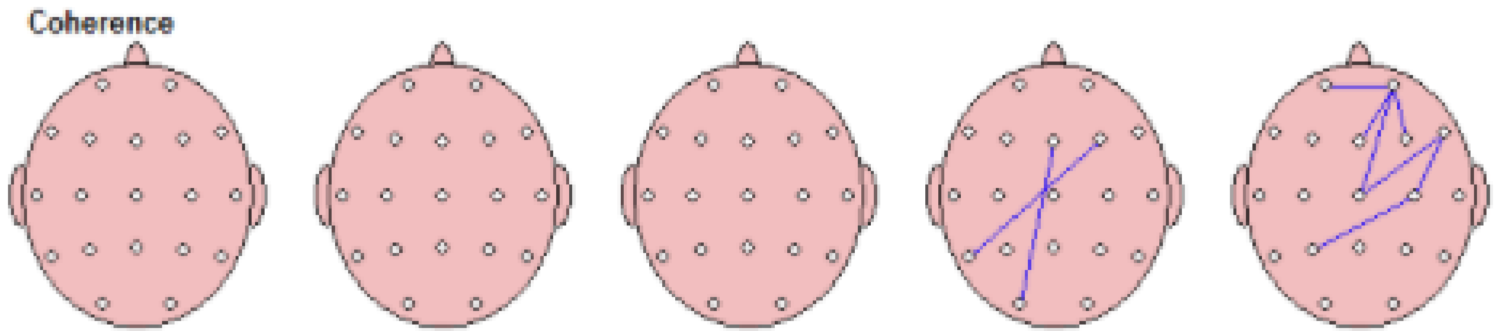
Exemplar: Major Depression

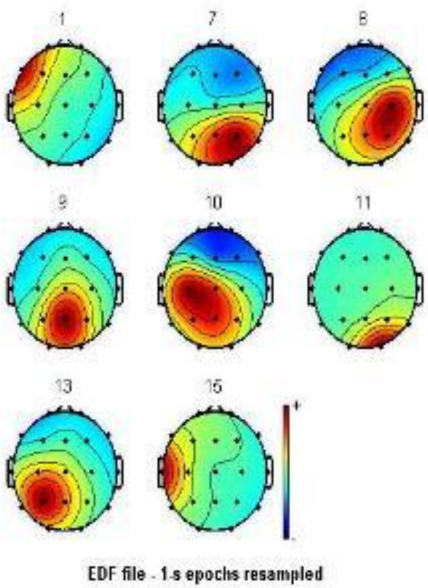


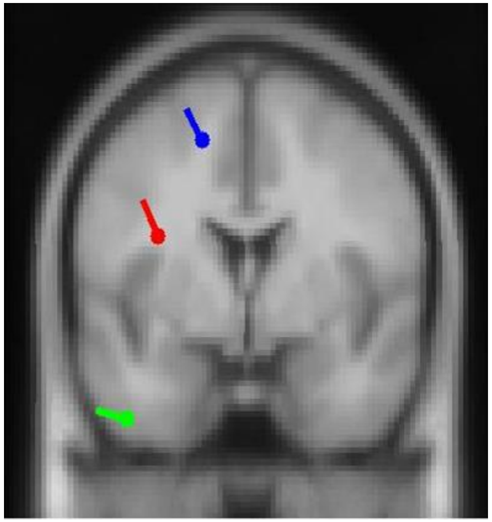


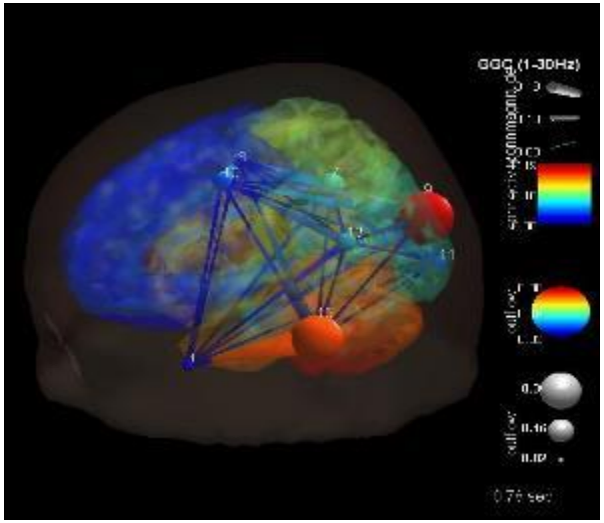


Exemplar: Major Depression

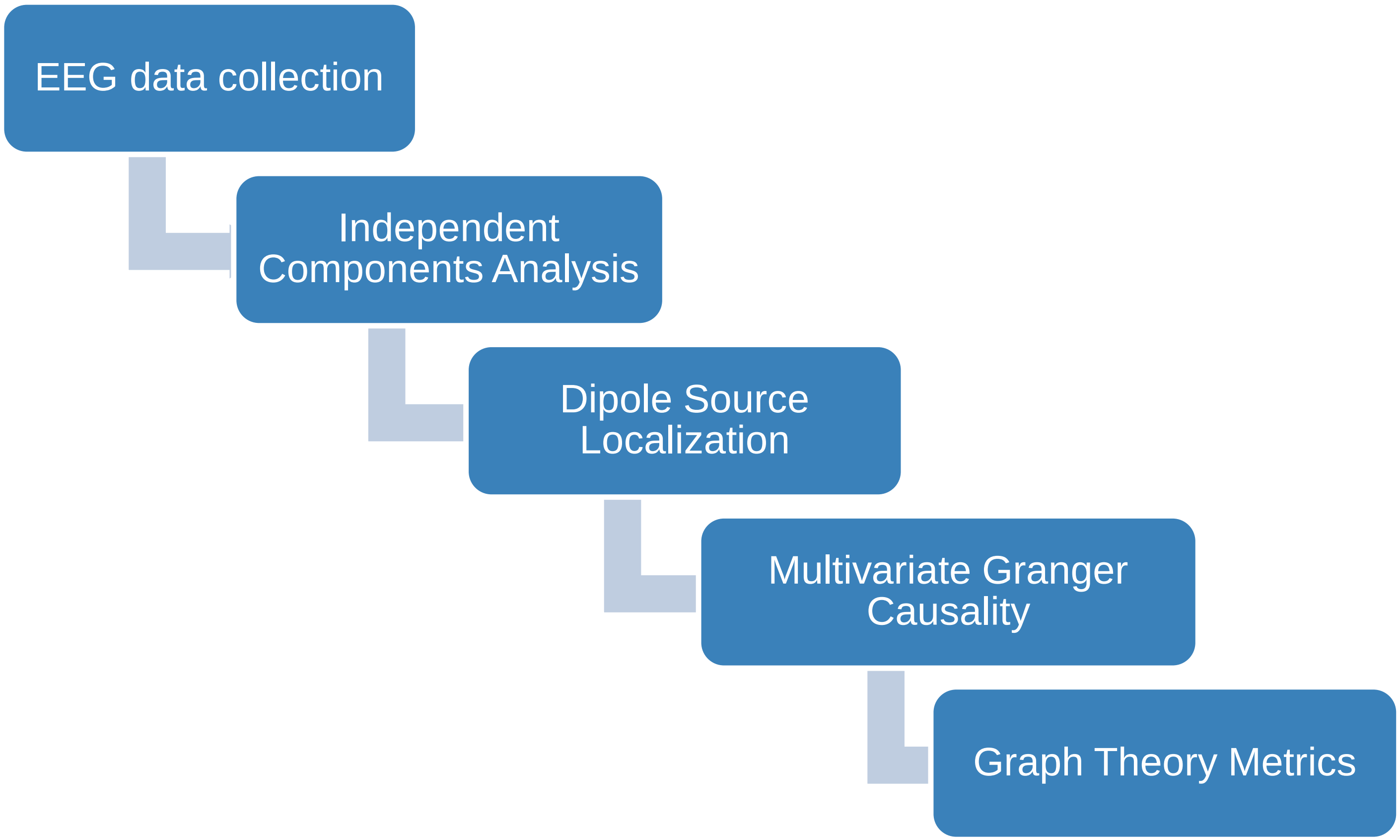








Novel EEG Analysis pipeline focused on effective connectivity assessment



ICA/EEGLAB Scientists and Journals

- Journal of Neuroscience Methods
- Plos One
- Computational Intelligence and Neuroscience
- NeuroImage
- Computational Intelligence and Neuroscience
- Frontiers in Neuroscience
- Frontiers in Neural Circuits

- UCSD Swartz Center for Computational Neuroscience
- University of Oxford
- UCLA Semmel Neuroscience Institute
- MGH/Harvard Medical School
- Georgetowwn University Medical Center
- University of Michigan Neuroscience Department

ELSEVIER

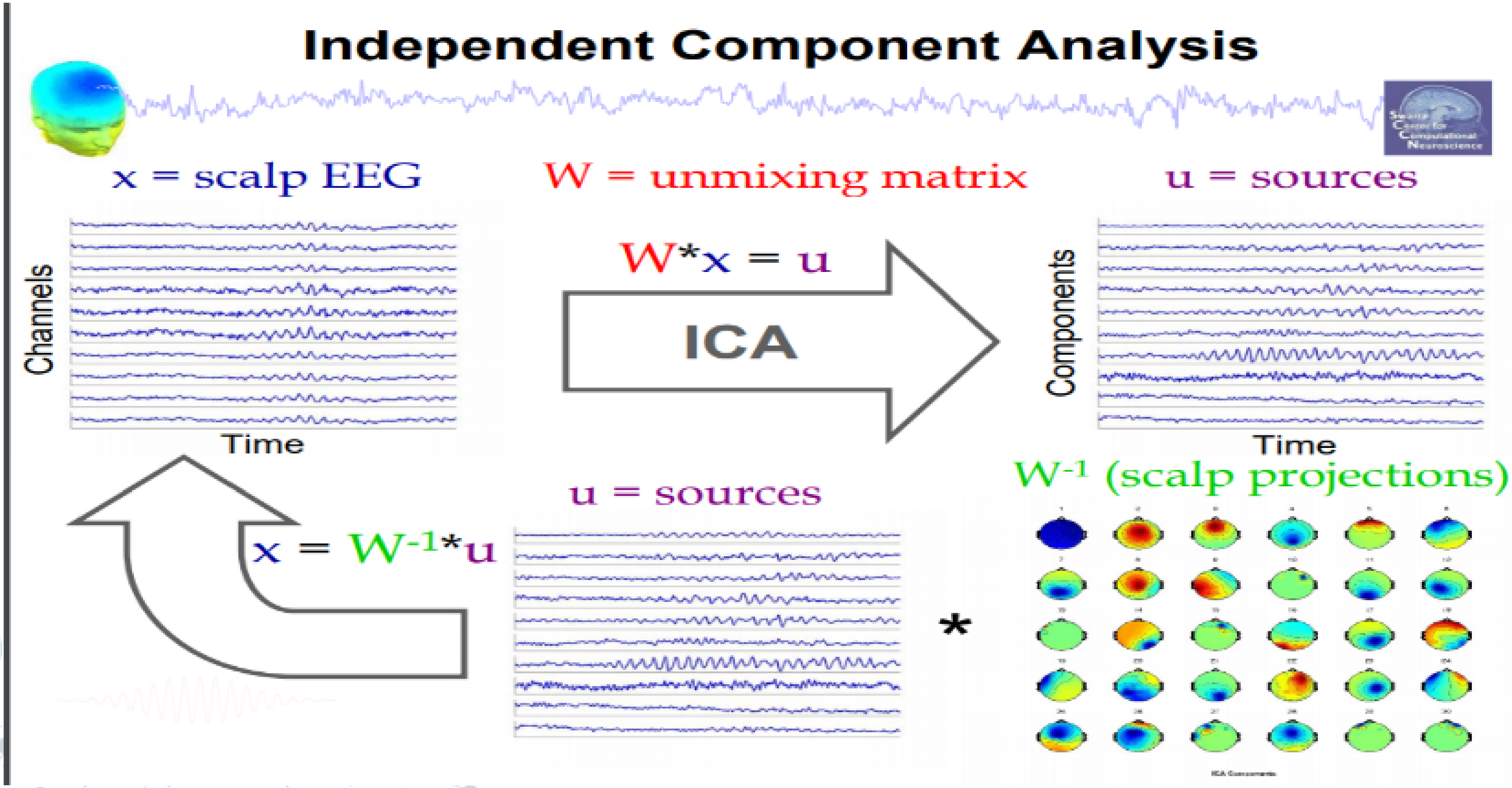
Journal of Neuroscience Methods
Volume 134, Issue 1, 15 March 2004, Pages 9-21

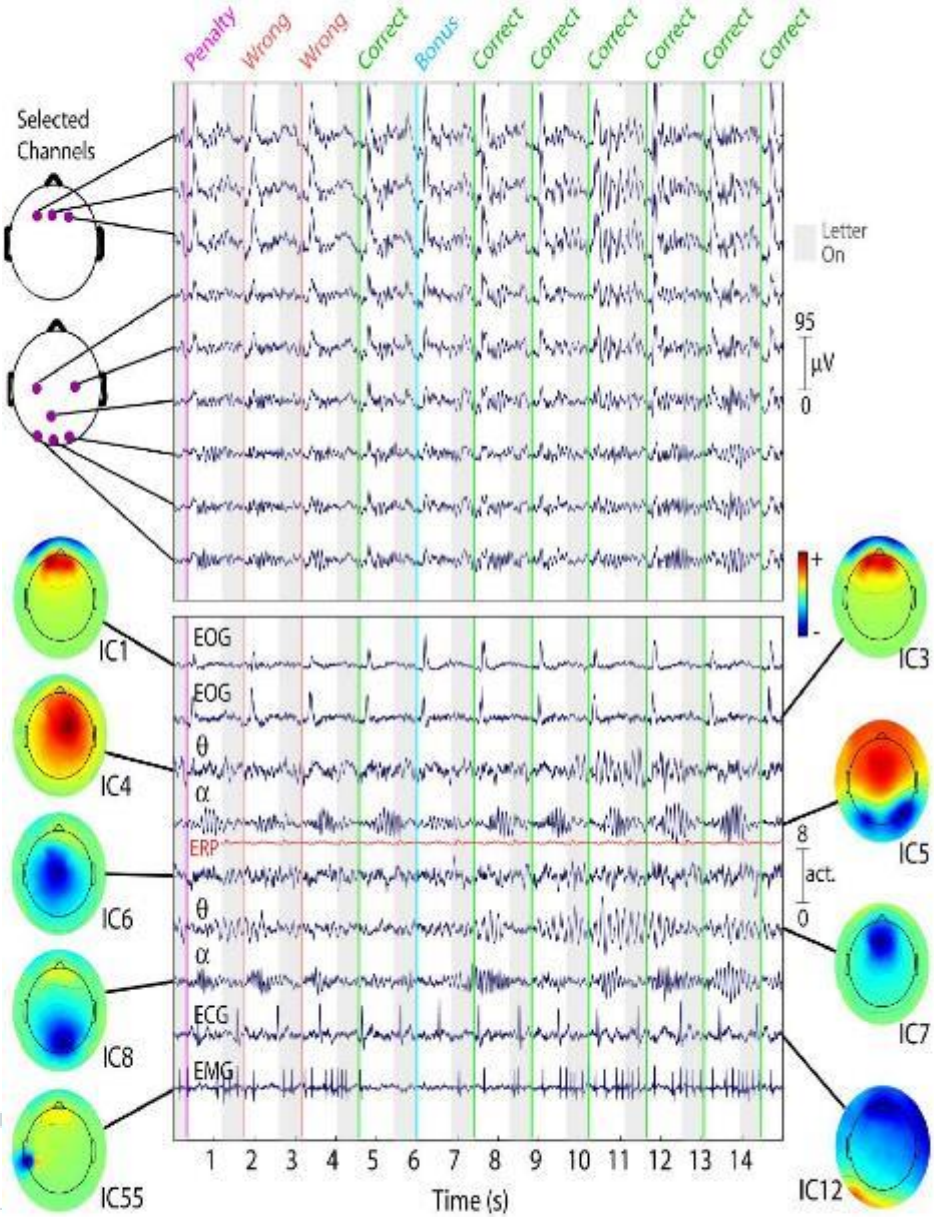
EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis

Arnaud Delorme, Scott Makeig

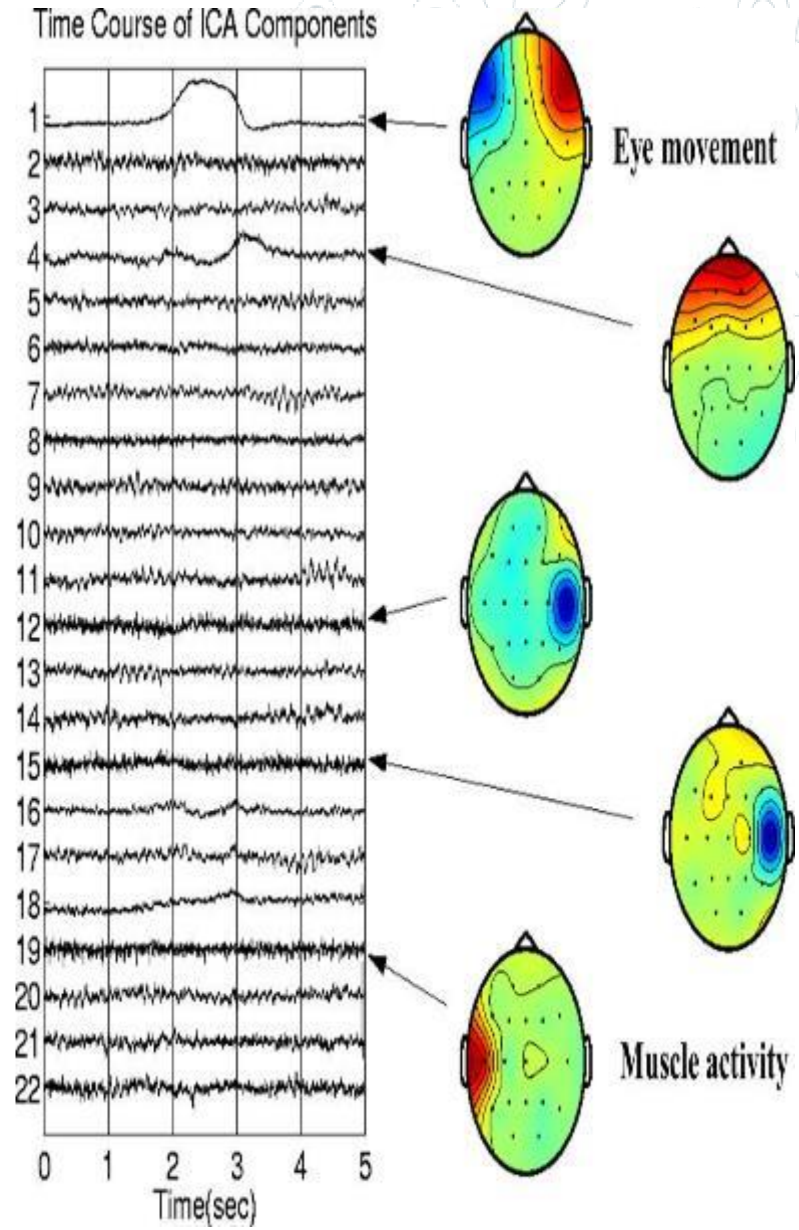
Show more

https://doi.org/10.1016/j.jneumeth.2003.10.009



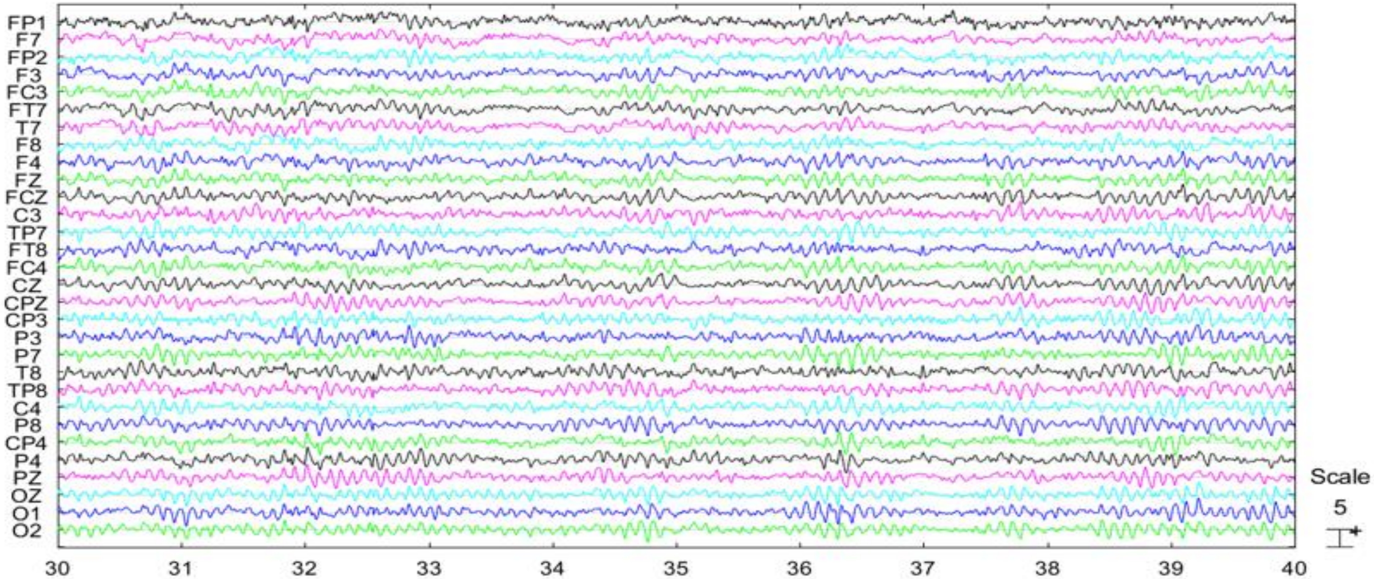


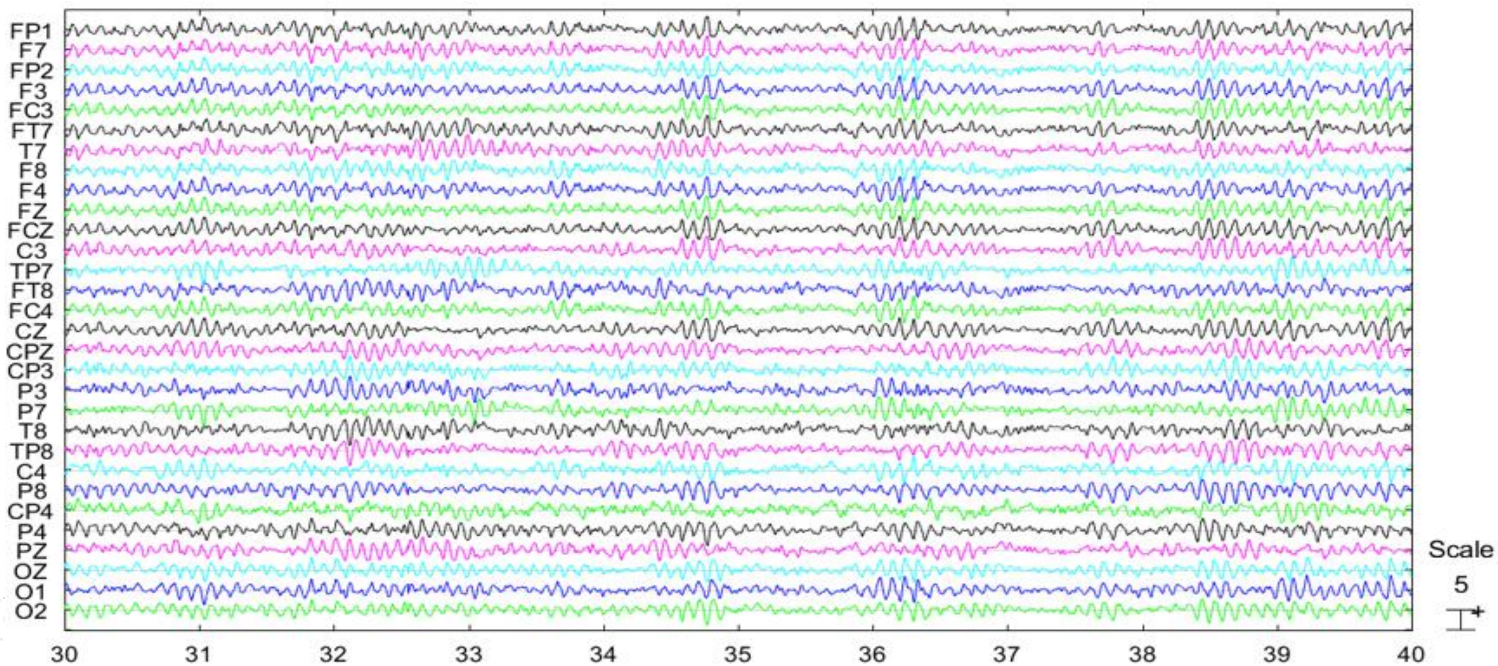
Penalty
Wrong
Wrong
Correct
Bonus
Correct
Correct
Correct
Correct
Correct
Correct
Selected Channels
Letter On
95
μV
0
EOG
EOG
θ
α
ERP
θ
α
ECG
EMG
8
act.
0
IC1
IC4
IC6
IC8
IC55
IC3
IC5
IC7
IC12
Time (s)

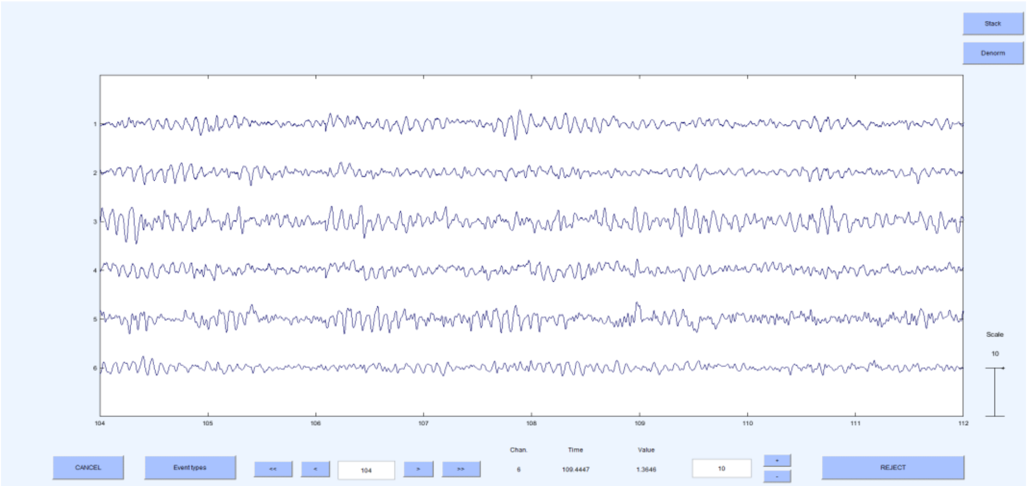


Time Course of ICA Components
Eye movement
Muscle activity
Time(sec)

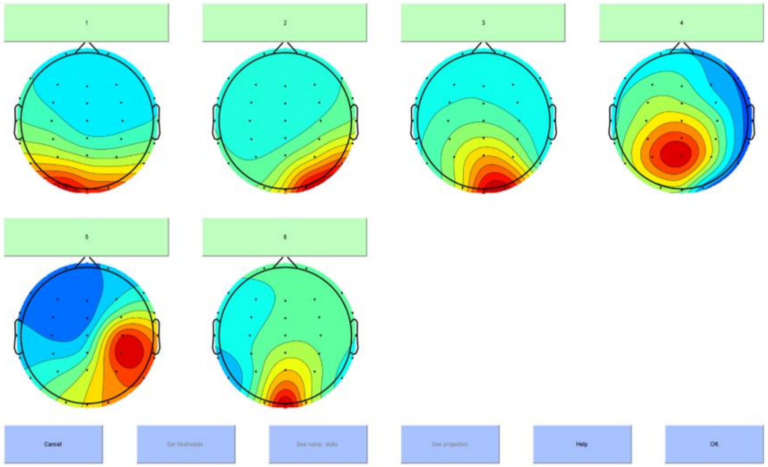
Example: 25 year old woman with a history of emotional abuse as a child and adult. Presents with anxiety, panic, nightmares and dissociation.



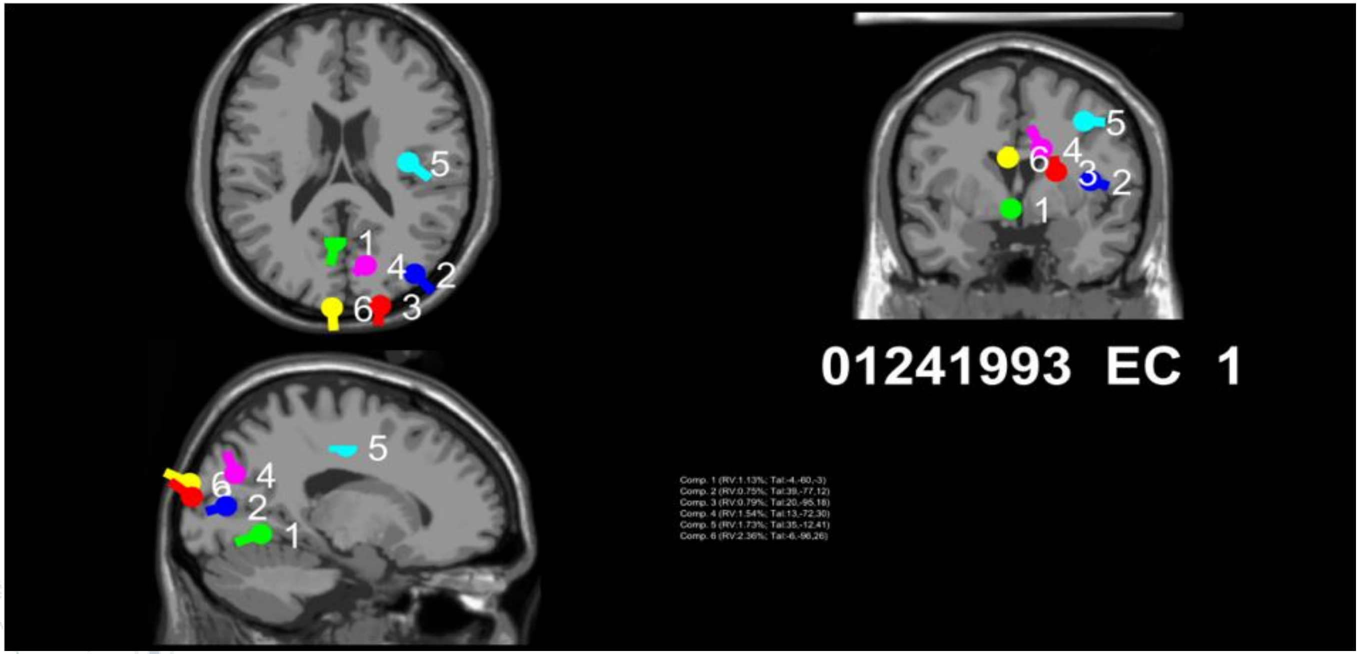




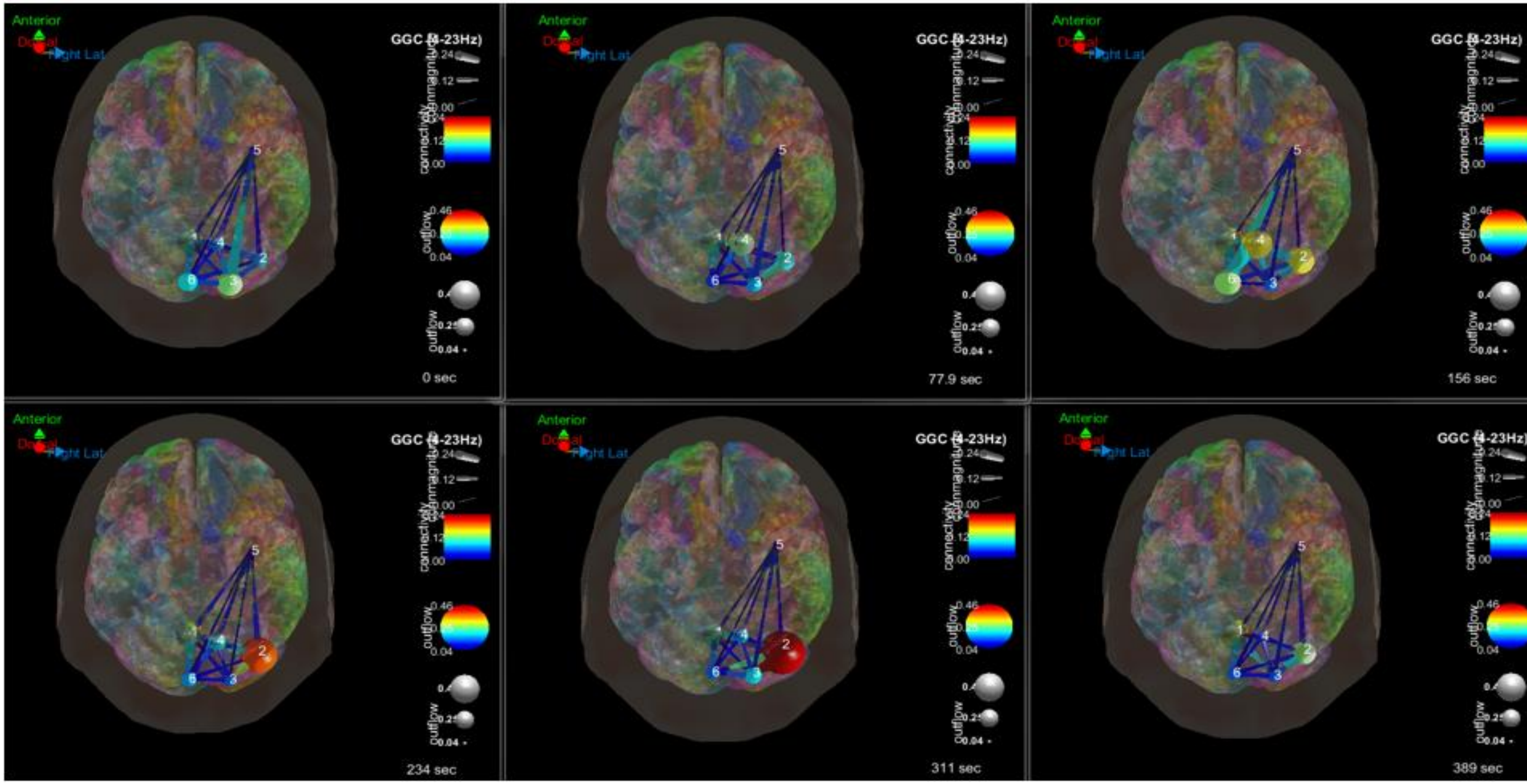
Stack
Denorm
Scale
10
CANCEL
Event types
104
Chan.
Time
Value
6
109.4447
1.3646
10
REJECT



1
2
3
4
5
6
Cancel
Help
OK



01241993 EC 1
Comp. 1 (RV:1.13%; Tal:-4,-60,-3)
Comp. 2 (RV:0.75%; Tal:39,-77,12)
Comp. 3 (RV:0.79%; Tal:20,-95,18)
Comp. 4 (RV:1.54%; Tal:13,-72,30)
Comp. 5 (RV:1.73%; Tal:35,-12,41)
Comp. 6 (RV:2.36%; Tal:-6,-96,26)



Graph Theory Metrics

Time Range	Freq Range	Clust Coeff	Path Length	Global Eff	Radius	Diameter
281-352s	4-23Hz	0.031157467	37.27736431	0.044989651	39.41305	91.9196607

Graph Theory: Network Dynamics

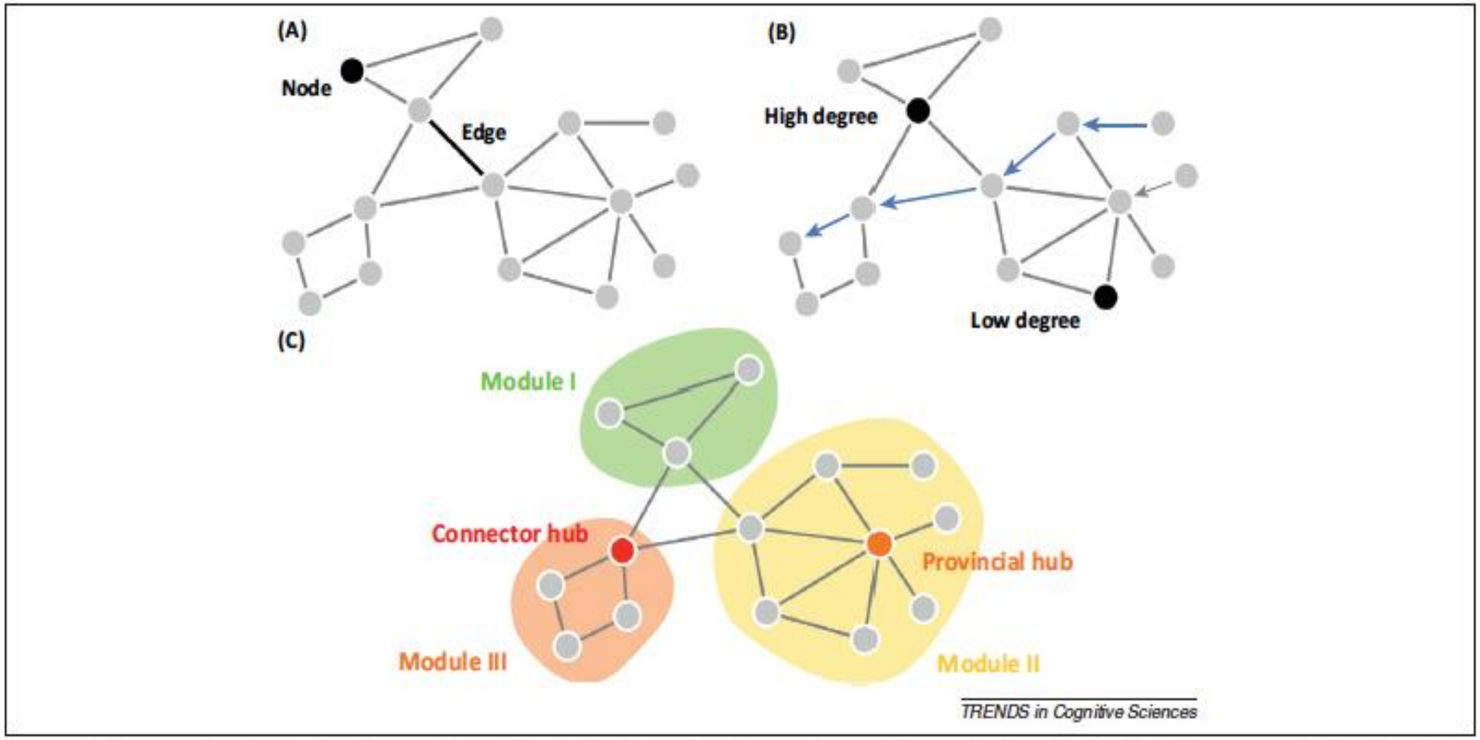
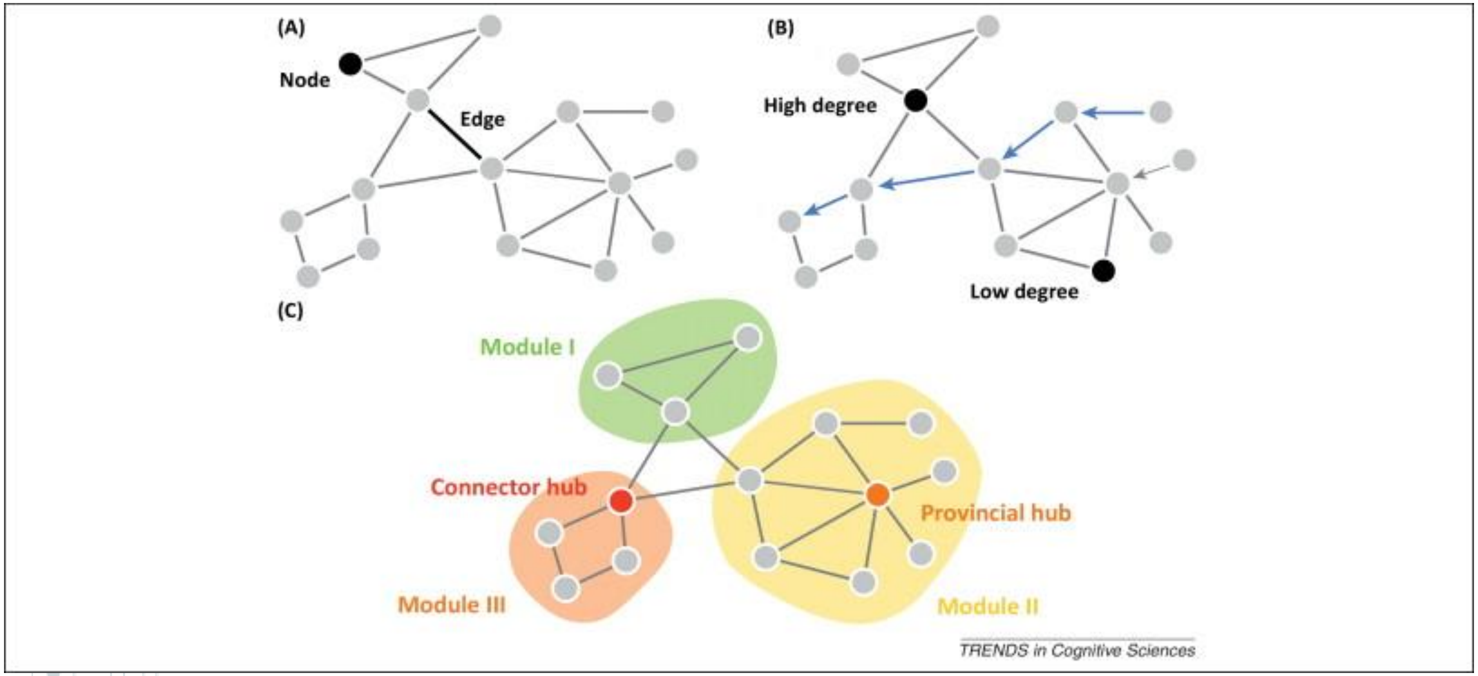
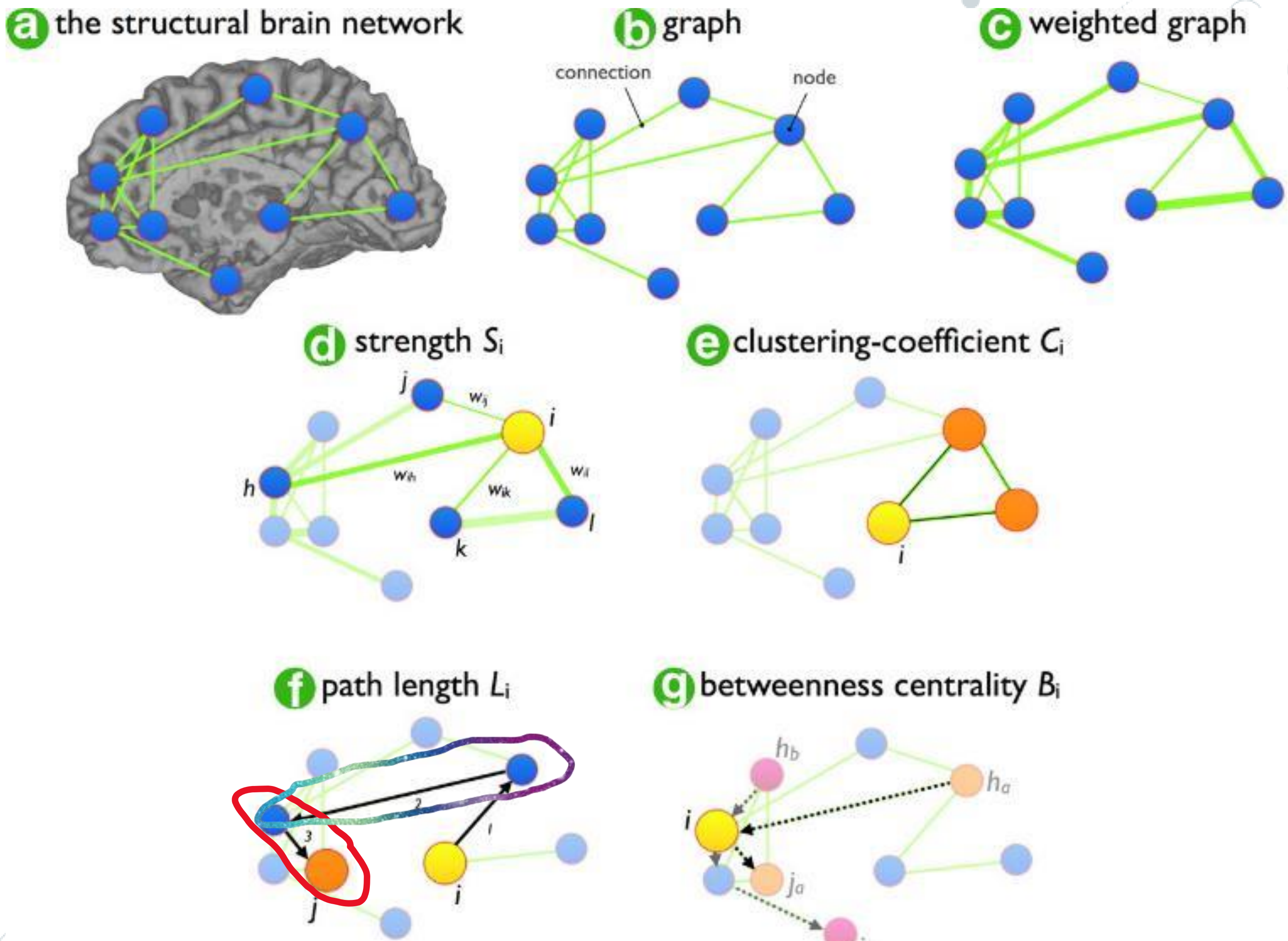


Figure 1. Basic network attributes. **(A)** Brain networks can be described and analyzed as graphs comprising a collection of nodes (describing neurons/brain regions) and a collection of edges (describing structural connections or functional relationships). The arrangement of nodes and edges defines the topological organization of the network. **(B)** A path corresponds to a sequence of unique edges that are crossed when traveling between two nodes in the network. Low-degree nodes are nodes that have a relatively low number of edges; high-degree nodes (often referred to as hubs) are nodes that have a relatively high number of edges. **(C)** A module includes a subset of nodes of the network that show a relatively high level of within-module connectivity and a relatively low level of intermodule connectivity. 'Provincial hubs' are high-degree nodes that primarily connect to nodes in the same module. 'Connector hubs' are high-degree nodes that show a diverse connectivity profile by connecting to several different modules within the network.

Graph Elements

- Hubs: A node with links that exceeds average.
- Low vs High Degree Hubs.
- Provincial Hubs.
- Modules.
- Connector Hubs.





Radius Diameter

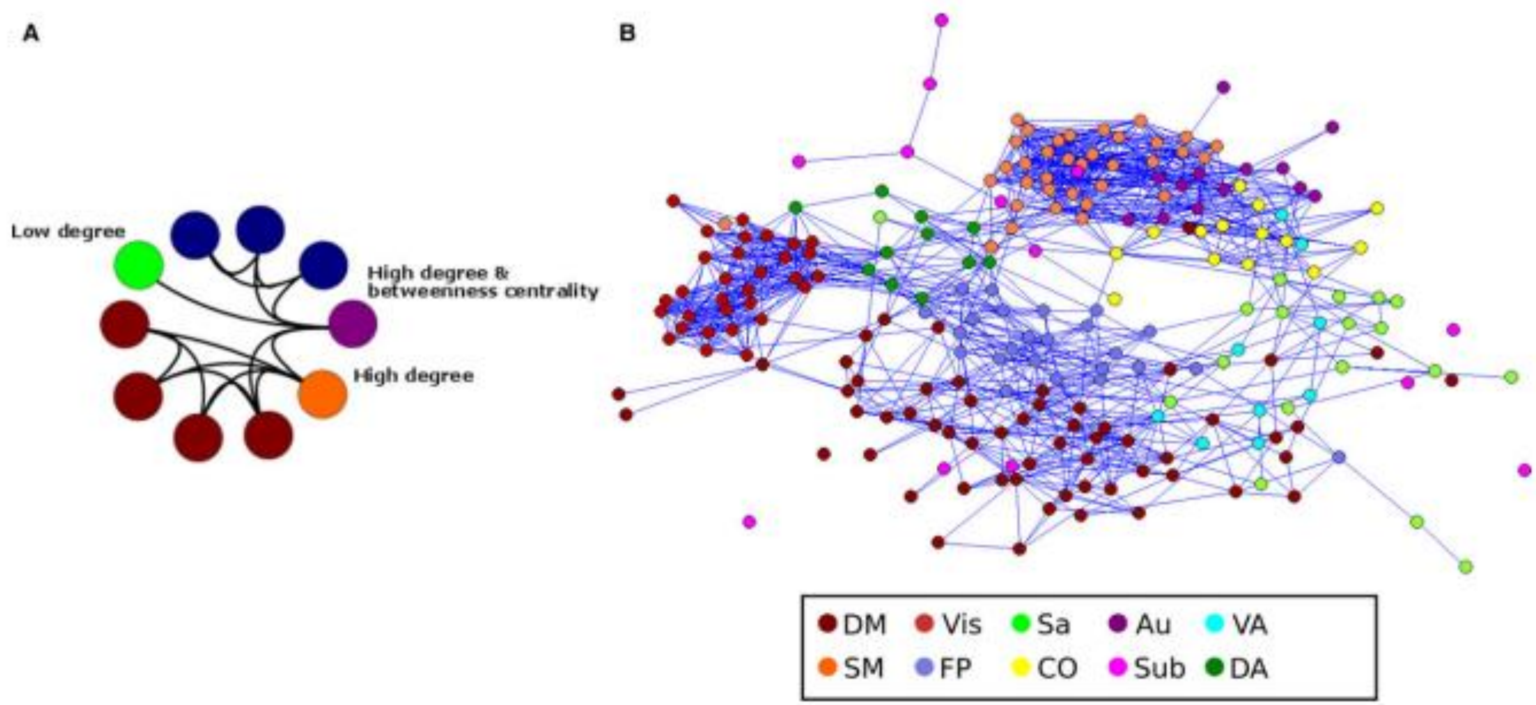
Acta Pædiatrica ISSN 0803-5253

REVIEW ARTICLE

The functional brain connectome of the child and autism spectrum disorders

Katell Mevel[1], Peter Fransson (Peter.Fransson@ki.se)[2]

1.Laboratory for the Psychology of Child Development and Education (LaPsyDÉ), CNRS UMR 8240, Sorbonne Paris Cité, GIP Cyceron, Université de Caen Normandie, Université Paris Descartes, Paris, France
2.Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden



frontiers
in Neuroscience | Neural Technology
Front. Neurosci., 11 October 2018 | https://doi.org/10.3389/fnins.2018.00729

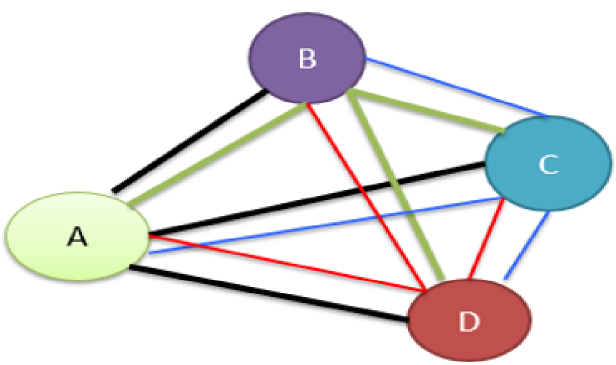
Four Channel Multivariate Coherence Training: Development and Evidence in Support of a New Form of Neurofeedback

Robert Coben[1]*, Morgan Middlebrooks[1], Howard Lightstone[2] and Madeleine Corbell[3]

[1]Integrated Neuroscience Services, Fayetteville, AR, United States
[2]EEG Software, LLC, Gainesville, FL, United States
[3]Department of Psychological Science, University of Arkansas, Fayetteville, AR, United States

QPS: Averaging coherences

- A method of combining averaged psync values.
  - 4 channels of EEG
  - Each pair has a running psync calculation
  - For each channel, the 3 pairs of psync values are computed, averaged and this is used as the output reward value
  - If a raw channel is in artifact condition, the channel is not used in the averaging calculation



A = (AB + AC + AD)/3
B = (BA + BC + BD)/3
C = (CA + CB + CD)/3
D = (DA + DB + DC)/3

QPS Ave = (A + B + C + D)/4

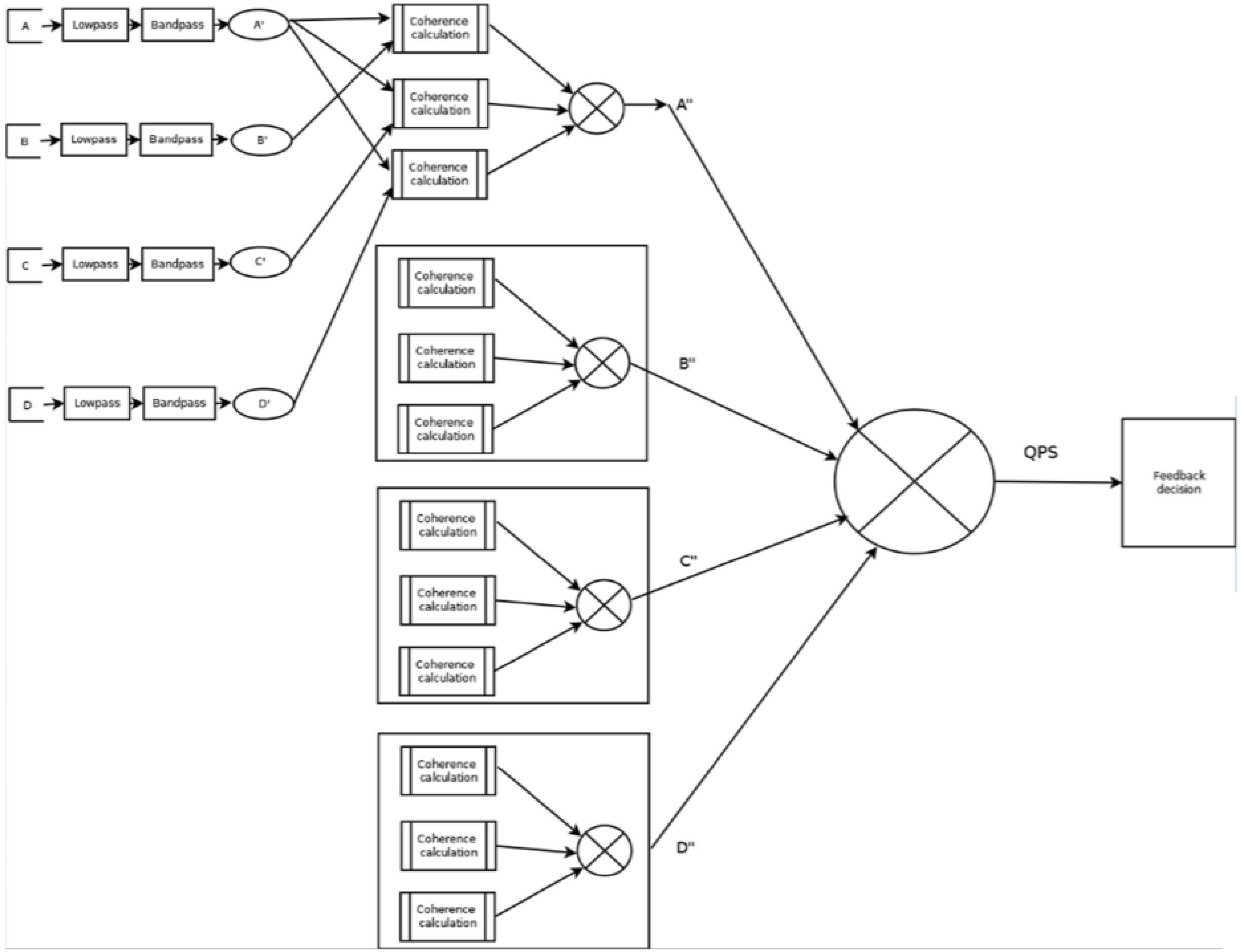


FIGURE 2 | Visual representation of A_Psync filter.

Efficacy Studies in Support of 4 channel MVCNF (N = 591)

Population	Sample	Design	Findings 1	Findings 2
General Population	N = 174	MVCNF v 2 Ch CNF	MVCNF > 2 Ch CNF	Enhanced coherence and reduced power
Traumatic Brain Injury	N = 20	Compared time since injury in 3 groups	Improvements in symptoms and NP testing	Changes associated with increases in coherence
Epilepsy	N = 52	MVCNF v 2 Ch CNF	MVCNF > 2 Ch CNF	81% reduction in seizures
Learning Disabilities	N = 63	MVCNF v 2 ch CNF v resource room	MVCNF > 2 ChCNF > RR	1.6 year increase in reading
Autism	N = 110	MVCNF v 2 Ch CNF	MVCNF > 2 Ch CNF	98% success rate
Autism MND	N = 78	MVCNF v 2 Ch CNF v Bipolar	MVCNF > 2 ChCNF > Bipolar	Mu suppression with coherence changes
Depression	N = 54	MVCNF Psychotherapy v WLC	MVCNF > both groups	94% success rate, crossover and 2 yr f/u
Developmental Trauma	N = 40	MVCNF v. Psychotherapy	Exp > controls on clinical ratings	Δ in power, sources and connectivity

Study Methodology

◎Subjects were assigned to one of three groups (N = 45).

◎These included an effective connectivity (15), functional connectivity within group (15) and a functional connectivity between group (15) comparison. Group 1 and 2 were the same subjects (within groups) that received different interventions at different time points (FC always first).

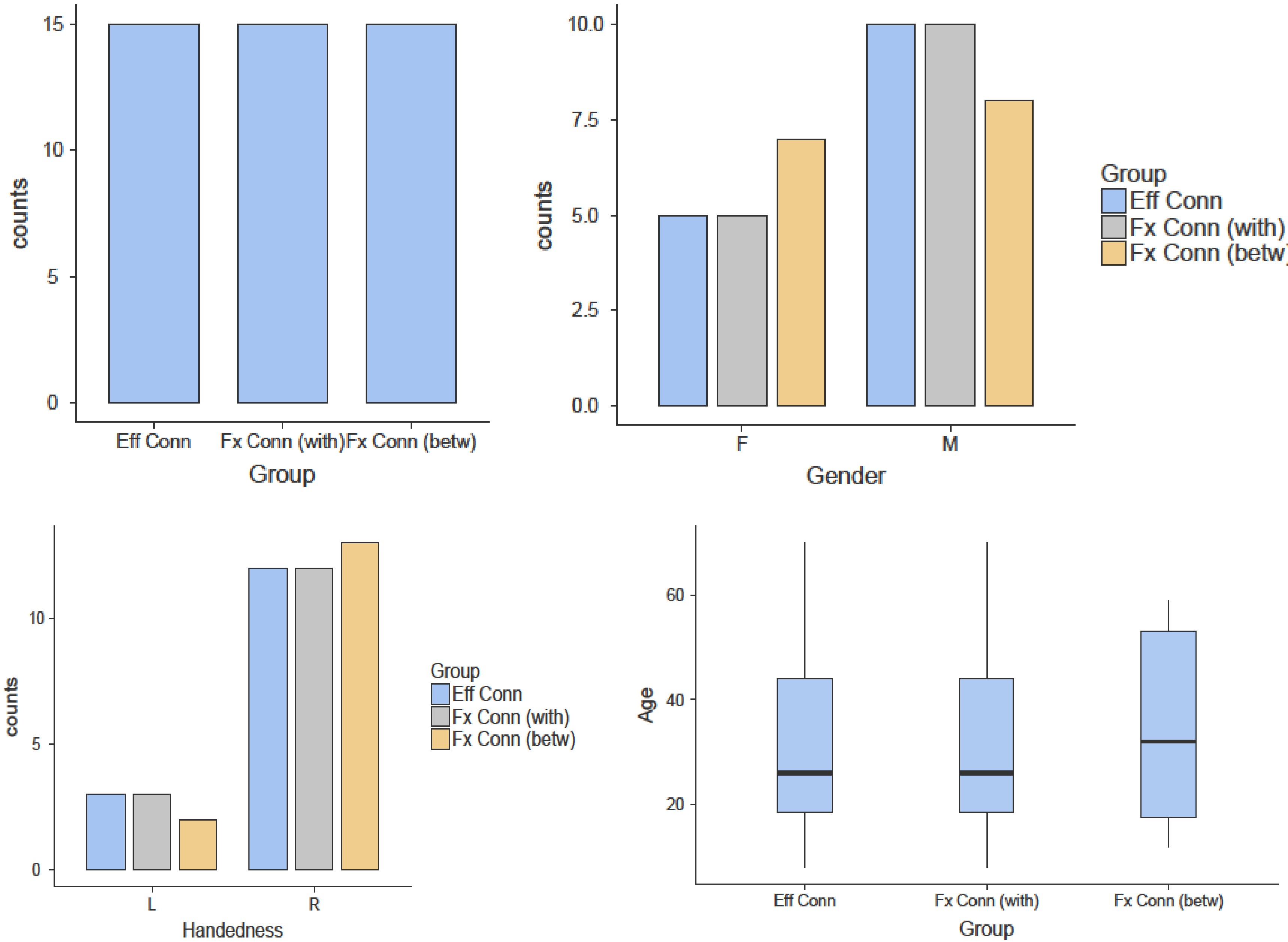
◎All subjects received four channel multivariate coherence training over 12-15 sessions.

◎Clinical ratings and therapist ratings (0-20) were derived at the completion of their treatment regimen.

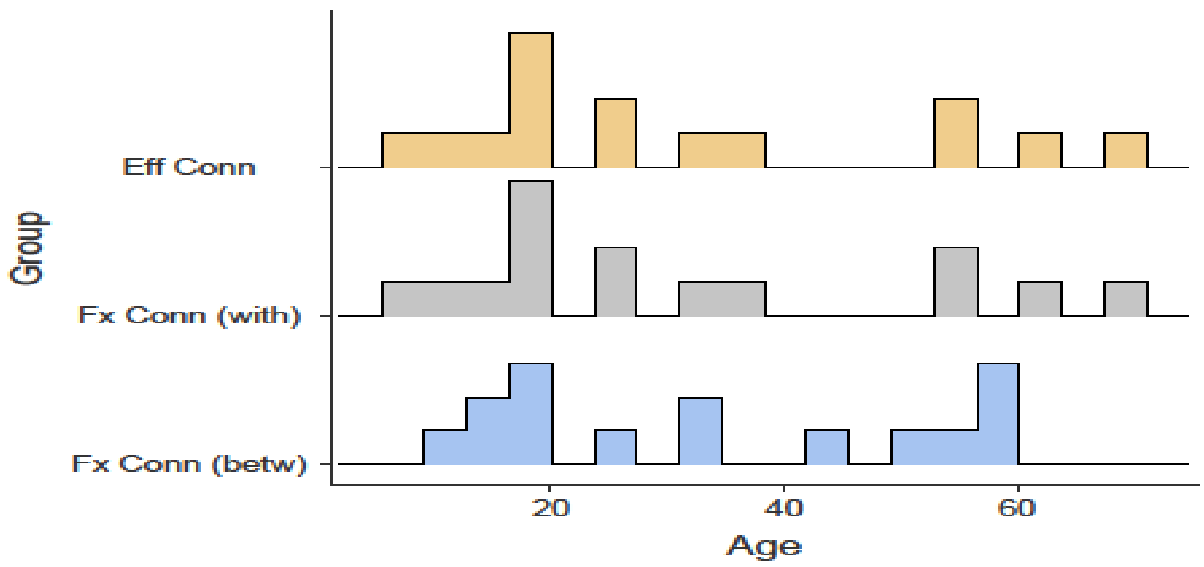
◎Client ratings were largely subjective and based on self-ratings only or parental ratings at the completion of training and during the process.

◎Therapist ratings were performed at the completion of training and were based on objective test findings including neuropsychological, behavioral and qeeg findings that reflected change over time.

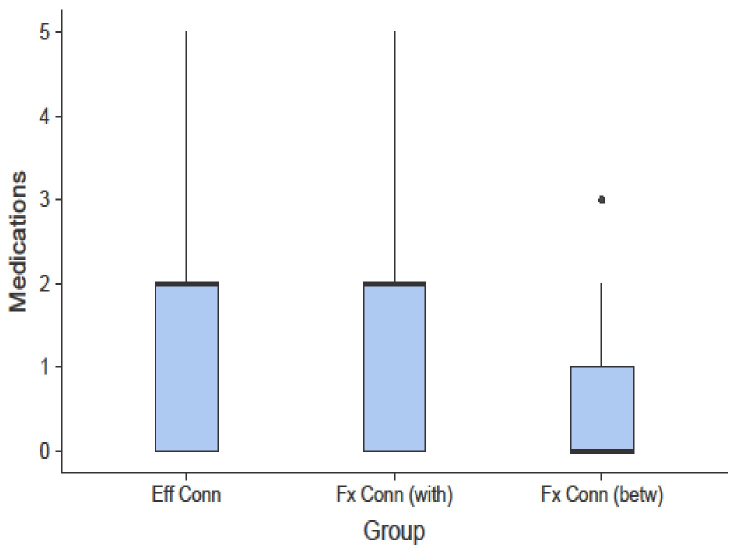
◎QEEG analysis of change included measures of power at the component level, dipole sources, spectral properties, and multiple measures of graph theory connectivity.



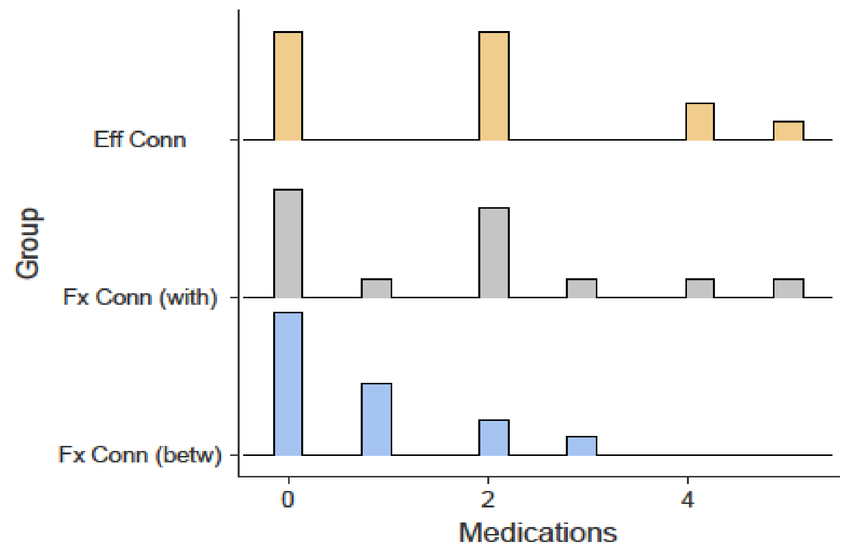
15
10
5
0
counts
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
10.0
7.5
5.0
2.5
0.0
counts
F
M
Gender
Group
Eff Conn
Fx Conn (with)
Fx Conn (betw)
10
5
0
counts
L
R
Handedness
Group
Eff Conn
Fx Conn (with)
Fx Conn (betw)
60
40
20
Age
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group



Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
20
40
60
Age



5
4
3
2
1
0
Medications
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group



Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
0
2
4
Medications

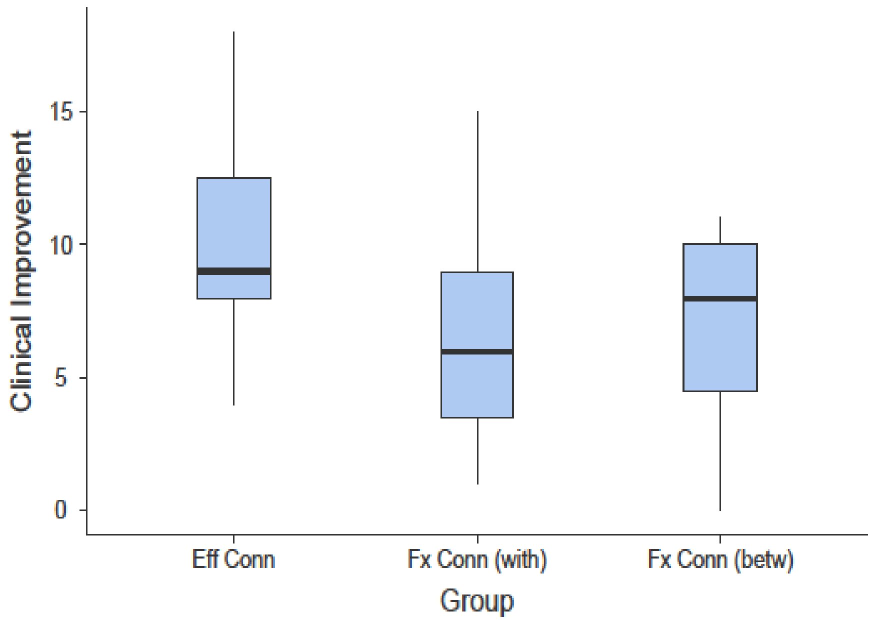
Statistical comparisons for demographics across groups

Age	Gender	Handedness	Medications
F = 0.123	$X^2 = 0.756$	$X^2 = 0.304$	F = 1.82
p = 0.884	p = 0.685	p = 0.859	p = 0.174

ANOVA

ANOVA

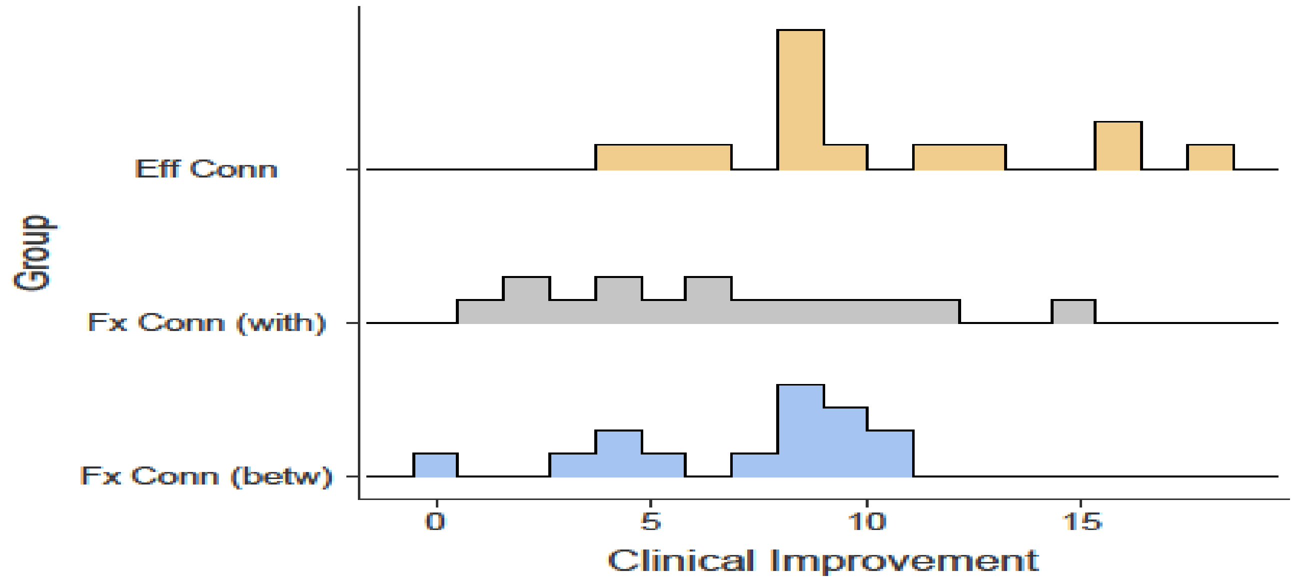
	Sum of Squares	df	Mean Square	F	p
Group	110	2	55.1	3.66	0.034
Residuals	631	42	15.0		



Contrasts

Contrasts - Group

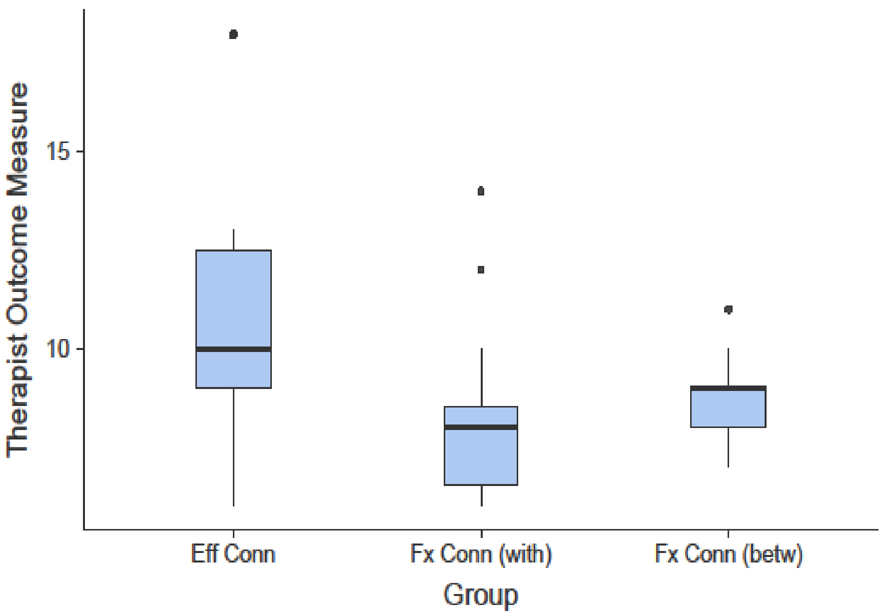
	Estimate	SE	t	p
Fx Conn (with) - Eff Conn	-3.67	1.42	-2.59	0.013
Fx Conn (betw) - Eff Conn	-2.80	1.42	-1.98	0.055



ANOVA

ANOVA

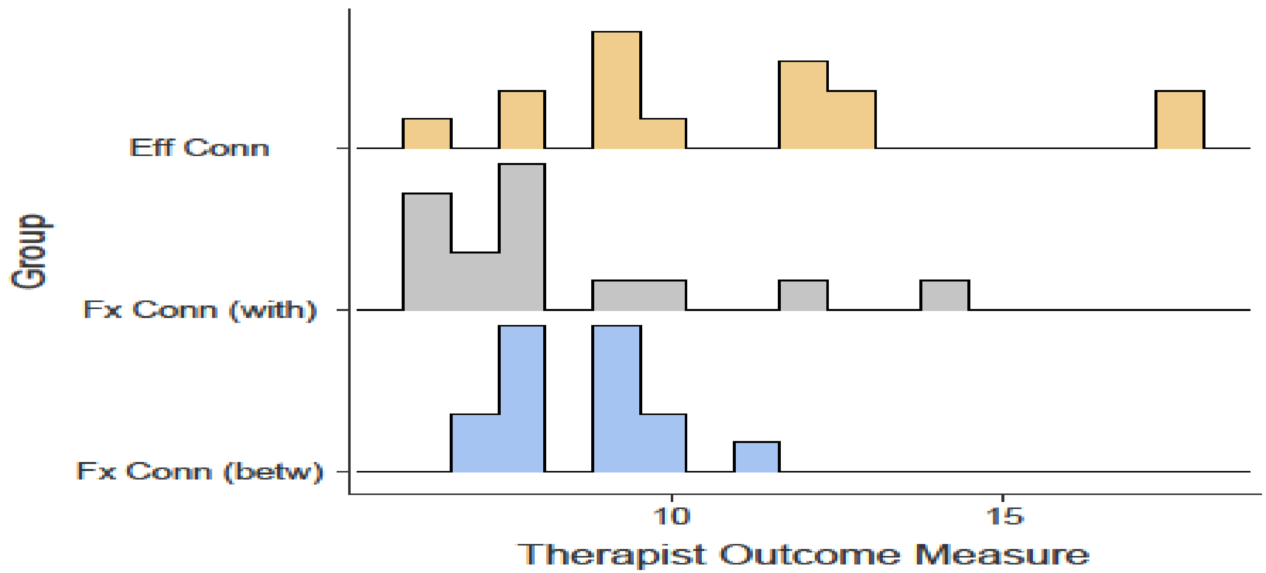
	Sum of Squares	df	Mean Square	F	p
Group	71.0	2	35.49	5.72	0.006
Residuals	260.7	42	6.21		

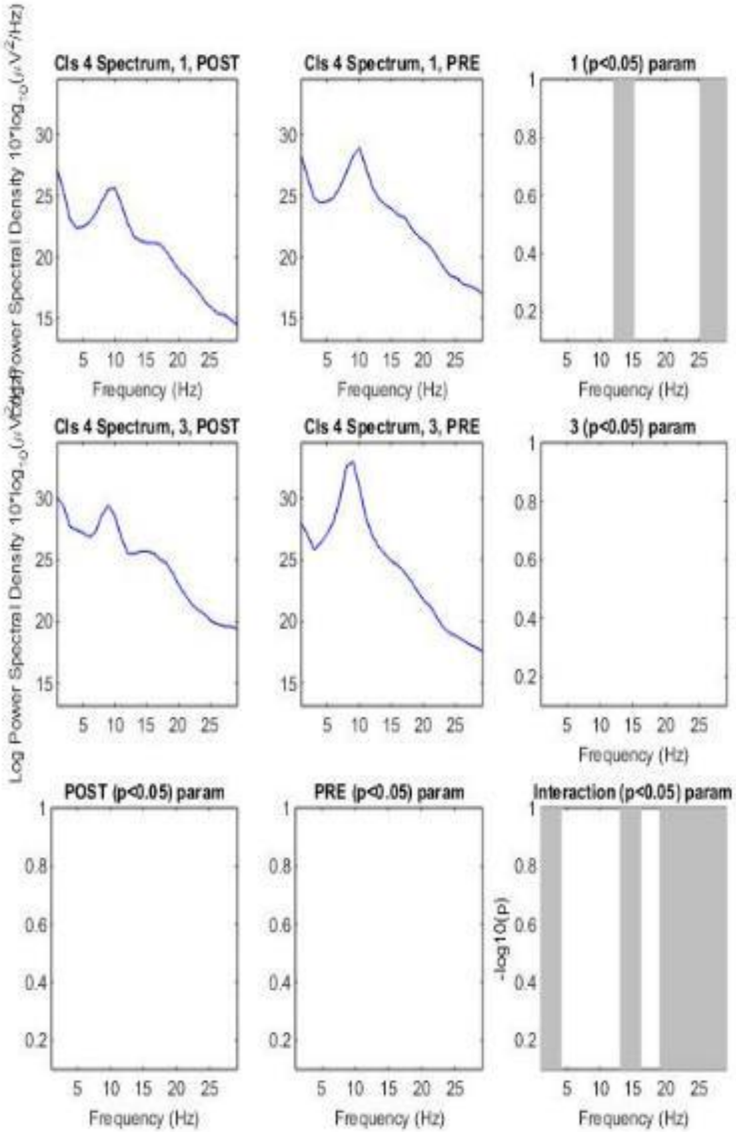


Contrasts

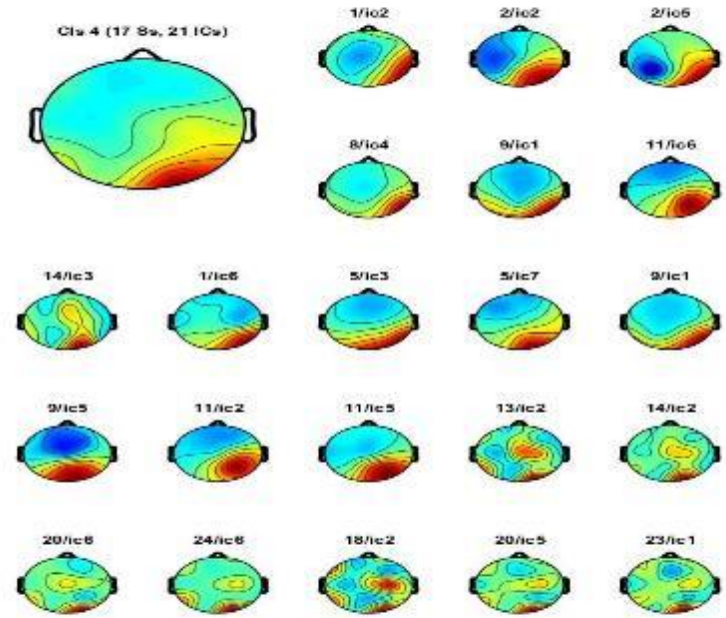
Contrasts - Group

	Estimate	SE	t	p
Fx Conn (with) - Eff Conn	-2.87	0.910	-3.15	0.003
Fx Conn (betw) - Eff Conn	-2.40	0.910	-2.64	0.012

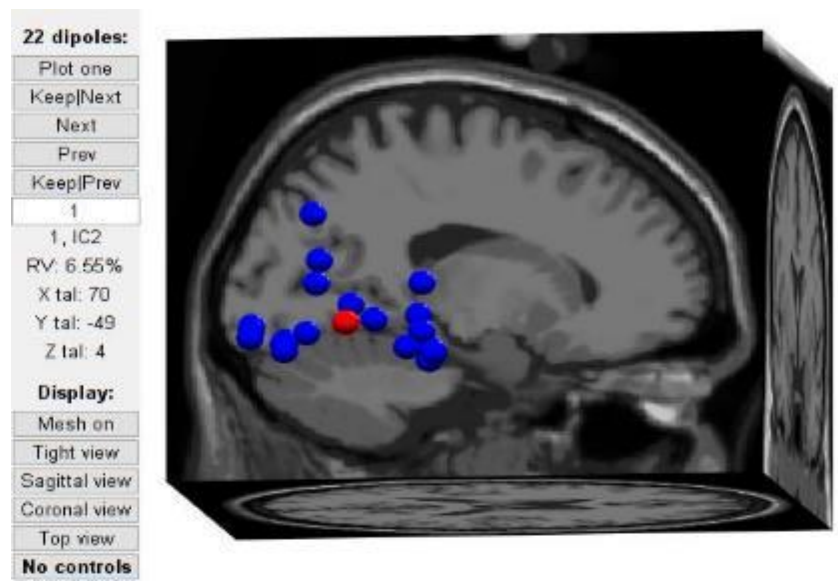




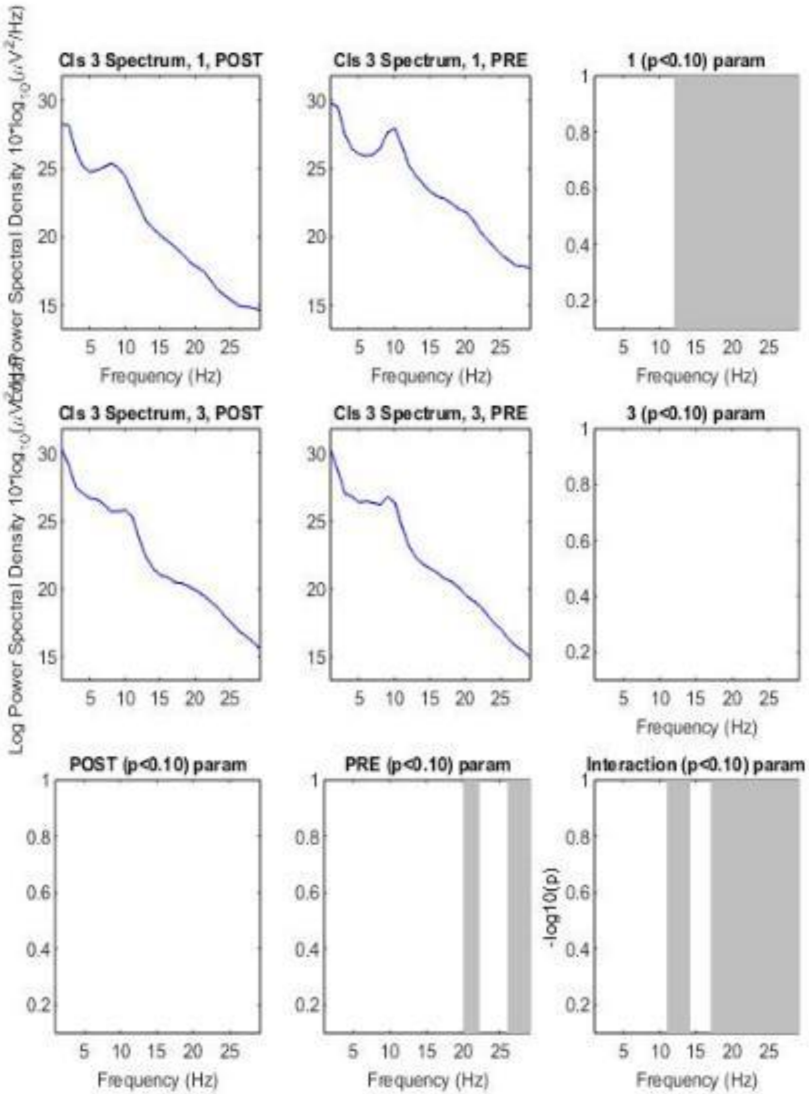
Cls 4 Spectrum, 1, POST
Cls 4 Spectrum, 1, PRE
1 (p<0.05) param
Cls 4 Spectrum, 3, POST
Cls 4 Spectrum, 3, PRE
3 (p<0.05) param
POST (p<0.05) param
PRE (p<0.05) param
Interaction (p<0.05) param
Frequency (Hz)
Log Power Spectral Density 10*log10(μV²/Hz)
-log10(p)

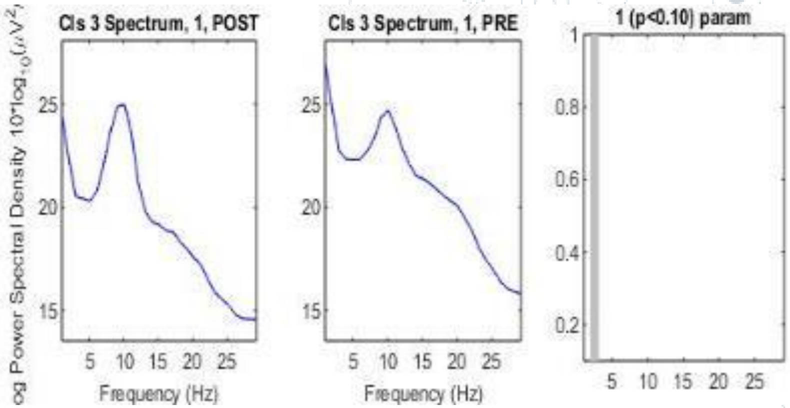


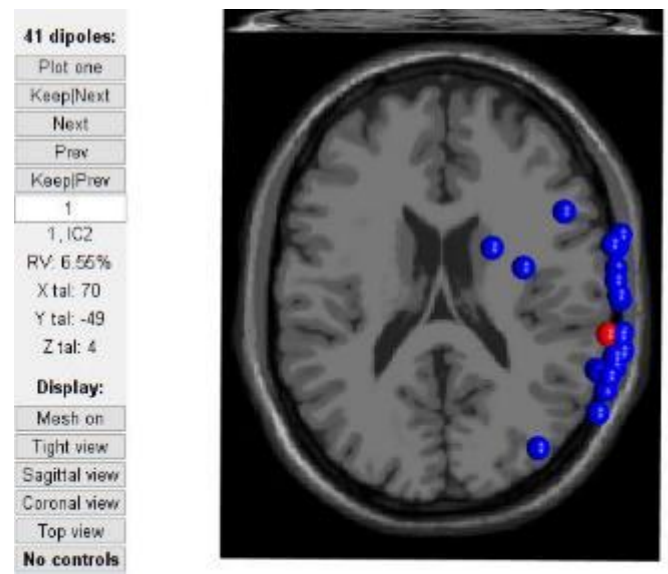
Cls 4 (17 Ss, 21 ICs)
1/ic2
2/ic2
2/ic6
8/ic4
9/ic1
11/ic6
14/ic3
1/ic6
5/ic3
5/ic7
9/ic1
9/ic5
11/ic2
11/ic5
13/ic2
14/ic2
20/ic6
24/ic6
18/ic2
20/ic5
23/ic1

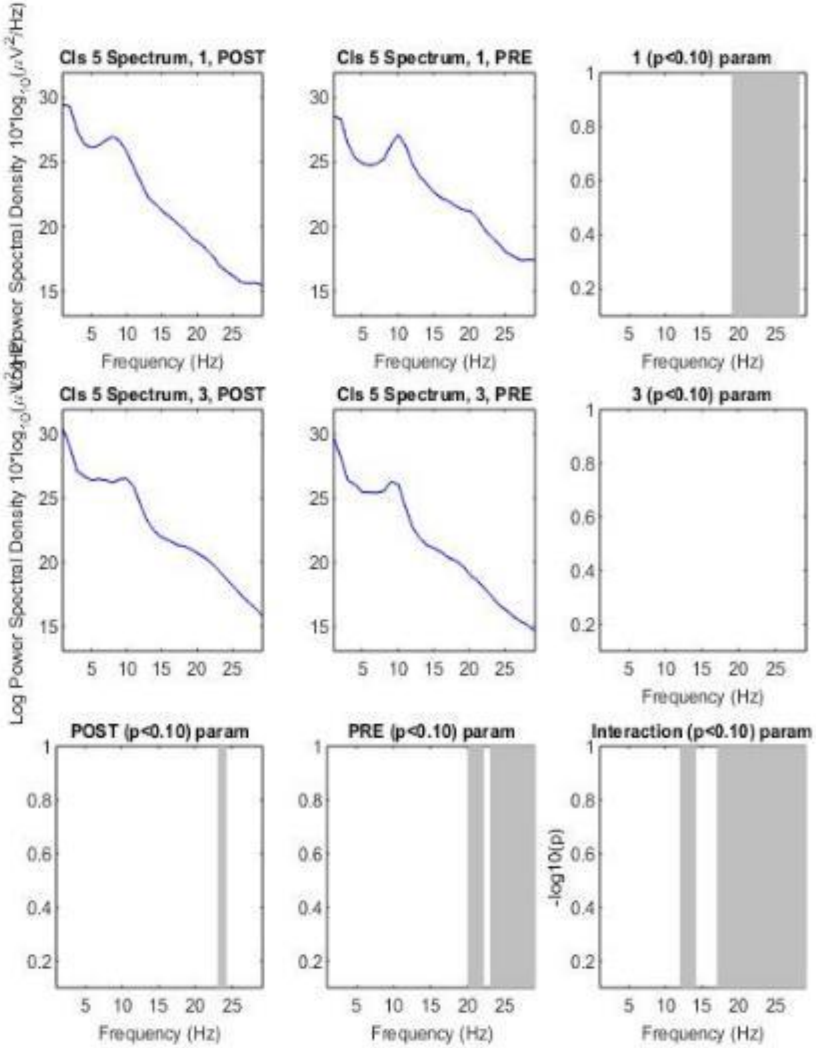


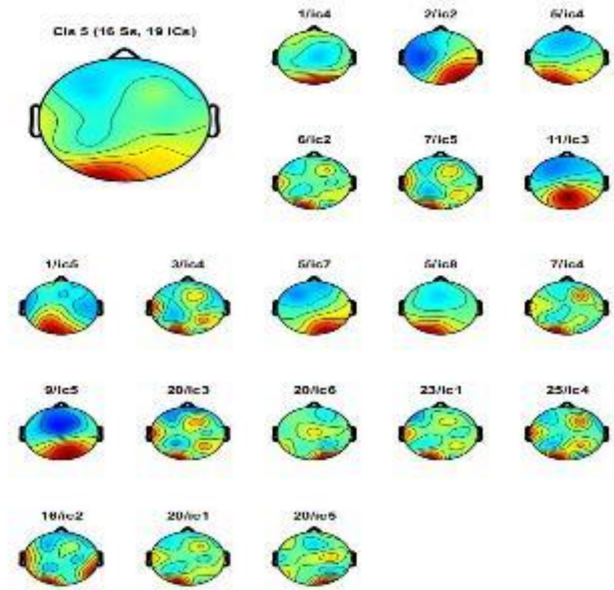
22 dipoles:
Plot one
Keep|Next
Next
Prev
Keep|Prev
1
1, IC2
RV: 6.55%
X tal: 70
Y tal: -49
Z tal: 4
Display:
Mesh on
Tight view
Sagittal view
Coronal view
Top view
No controls

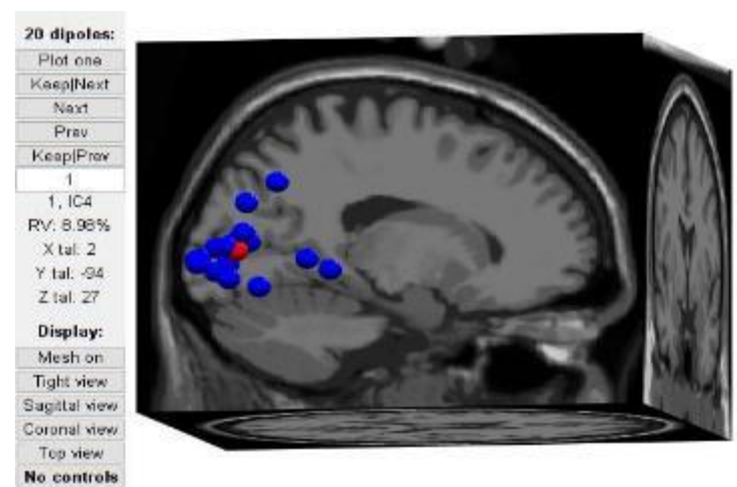

Cls 3 Spectrum, 1, POST
Cls 3 Spectrum, 1, PRE
1 (p<0.10) param
Cls 3 Spectrum, 3, POST
Cls 3 Spectrum, 3, PRE
3 (p<0.10) param
POST (p<0.10) param
PRE (p<0.10) param
Interaction (p<0.10) param
Log Power Spectral Density 10*log10(μV²/Hz)
Frequency (Hz)
-log10(p)

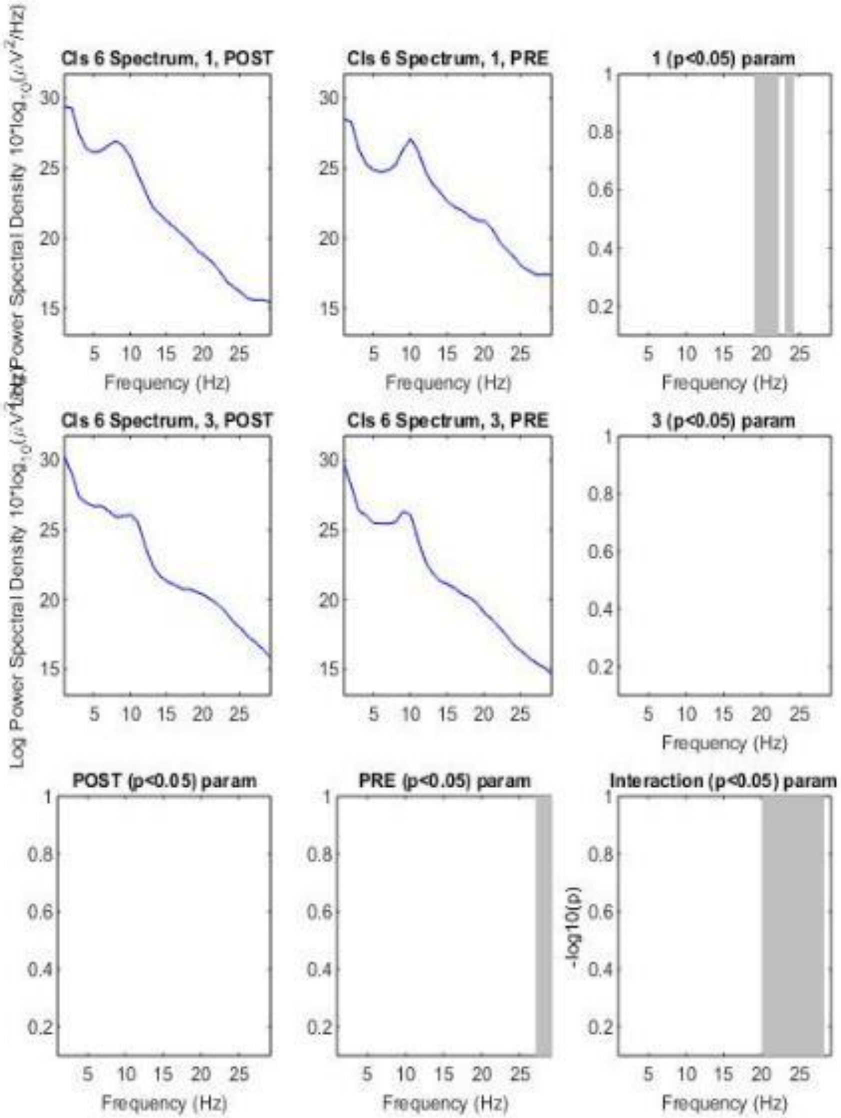

Cls 3 Spectrum, 1, POST
Cls 3 Spectrum, 1, PRE
1 (p<0.10) param
og Power Spectral Density 10*log10(μV²/
Frequency (Hz)


41 dipoles:
Plot one
Keep|Next
Next
Prev
Keep|Prev
1
1, IC2
RV: 6.55%
X tal: 70
Y tal: -49
Z tal: 4
Display:
Mesh on
Tight view
Sagittal view
Coronal view
Top view
No controls

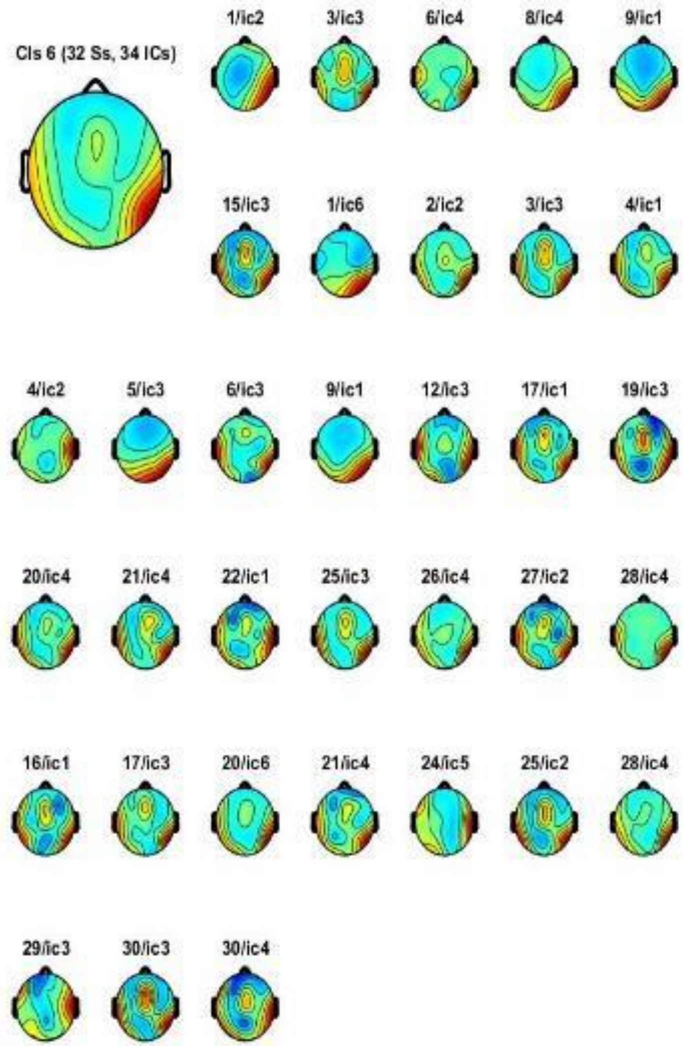

Cls 5 Spectrum, 1, POST
Cls 5 Spectrum, 1, PRE
1 (p<0.10) param
Cls 5 Spectrum, 3, POST
Cls 5 Spectrum, 3, PRE
3 (p<0.10) param
POST (p<0.10) param
PRE (p<0.10) param
Interaction (p<0.10) param
Log Power Spectral Density 10*log10(μV²/Hz)
Frequency (Hz)
-log10(p)


Cls 5 (16 Ss, 19 ICs)

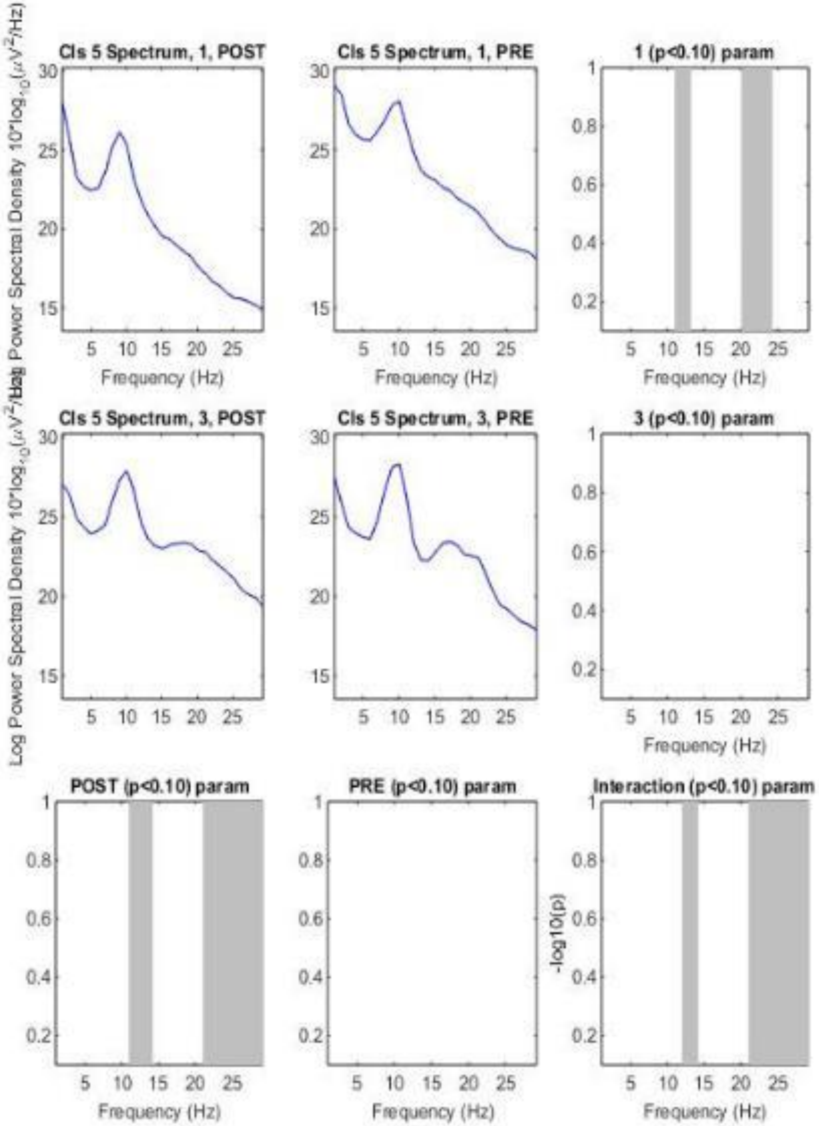

20 dipoles:
Plot one
Keep|Next
Next
Prev
Keep|Prev
1
1, IC4
RV: 8.98%
X tal: 2
Y tal: -94
Z tal: 27
Display:
Mesh on
Tight view
Sagittal view
Coronal view
Top view
No controls

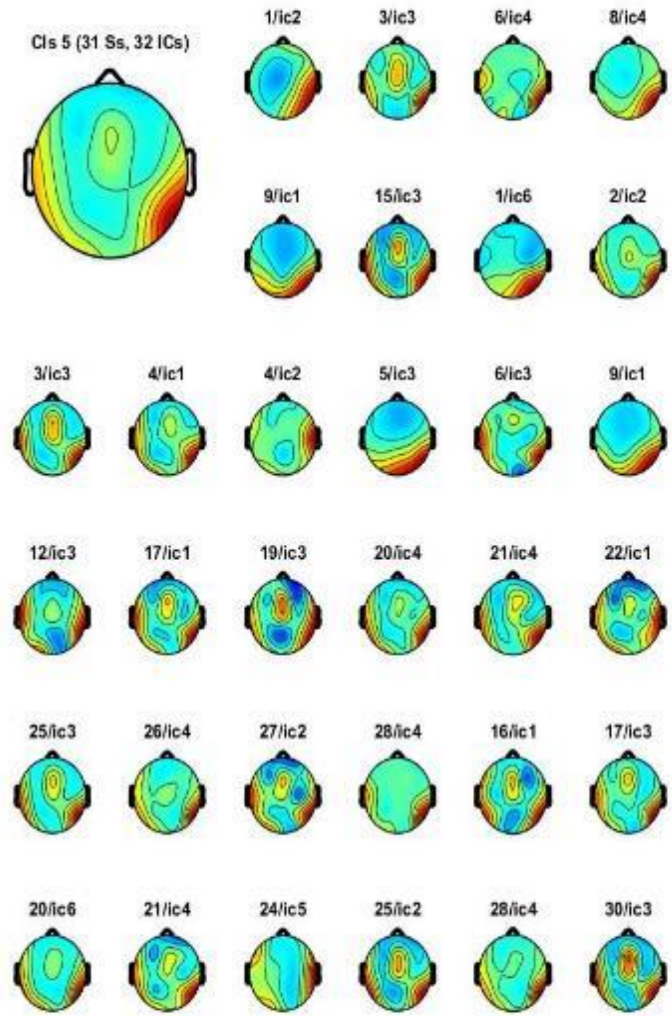


Cls 6 Spectrum, 1, POST
Cls 6 Spectrum, 1, PRE
1 (p<0.05) param
Cls 6 Spectrum, 3, POST
Cls 6 Spectrum, 3, PRE
3 (p<0.05) param
POST (p<0.05) param
PRE (p<0.05) param
Interaction (p<0.05) param
Log Power Spectral Density 10*log10(μV²/Hz)
Frequency (Hz)
-log10(p)



Cls 6 (32 Ss, 34 ICs)
1/ic2
3/ic3
6/ic4
8/ic4
9/ic1
15/ic3
1/ic6
2/ic2
3/ic3
4/ic1
4/ic2
5/ic3
6/ic3
9/ic1
12/ic3
17/ic1
19/ic3
20/ic4
21/ic4
22/ic1
25/ic3
26/ic4
27/ic2
28/ic4
16/ic1
17/ic3
20/ic6
21/ic4
24/ic5
25/ic2
28/ic4
29/ic3
30/ic3
30/ic4

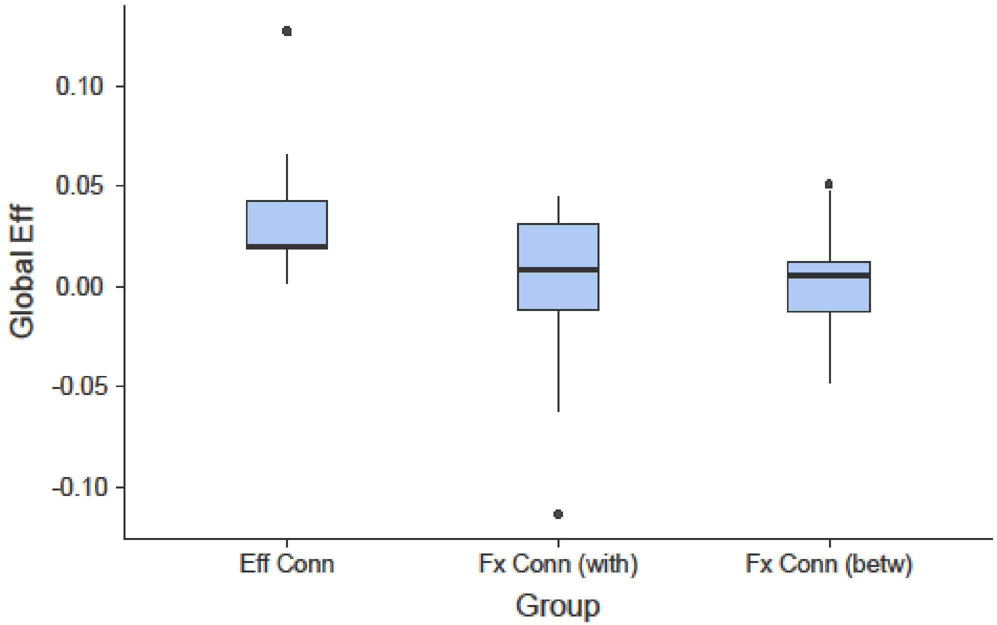

Cls 5 Spectrum, 1, POST
Cls 5 Spectrum, 1, PRE
1 (p<0.10) param
Cls 5 Spectrum, 3, POST
Cls 5 Spectrum, 3, PRE
3 (p<0.10) param
POST (p<0.10) param
PRE (p<0.10) param
Interaction (p<0.10) param
Log Power Spectral Density 10*log10(μV²/Hz)
Frequency (Hz)
-log10(p)


Cls 5 (31 Ss, 32 ICs)
1/ic2
3/ic3
6/ic4
8/ic4
9/ic1
15/ic3
1/ic6
2/ic2
3/ic3
4/ic1
4/ic2
5/ic3
6/ic3
9/ic1
12/ic3
17/ic1
19/ic3
20/ic4
21/ic4
22/ic1
25/ic3
26/ic4
27/ic2
28/ic4
16/ic1
17/ic3
20/ic6
21/ic4
24/ic5
25/ic2
28/ic4
30/ic3

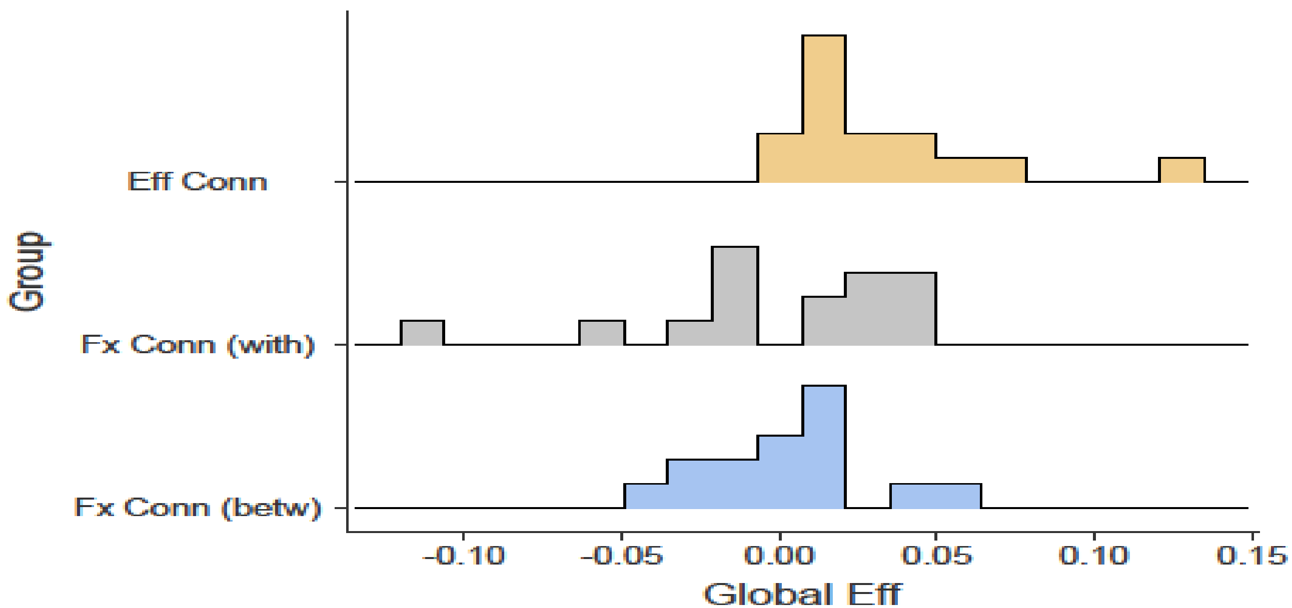
Statistical Analyses of Graph Theory Metrics (Connectivity)

Analysis of Variance

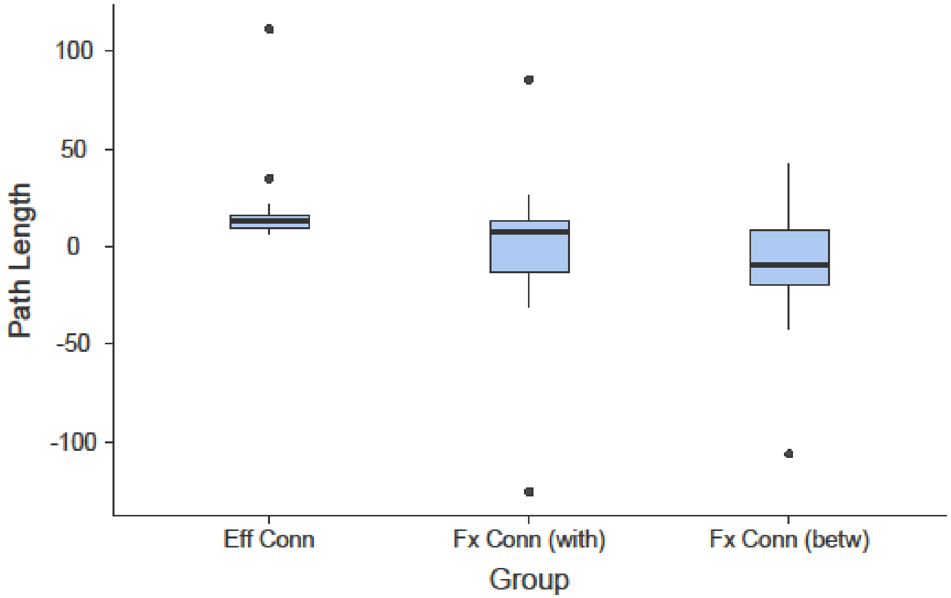
Cluster Coefficient	Global Efficiency	Path Length	Radius	Diameter
F = 0.429	F = 4.60	F = 2.93	F = 3.35	F = 3.70
p = 0.654	p = 0.016	p = 0.064	p = 0.045	p = 0.033

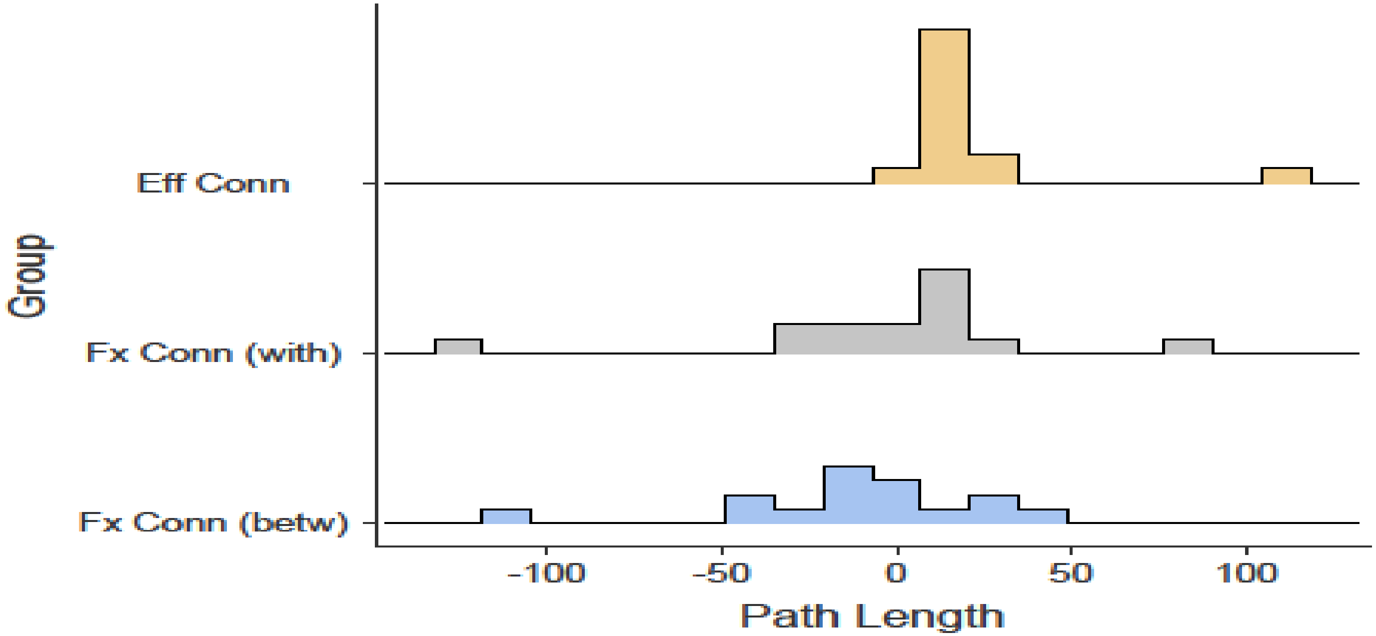


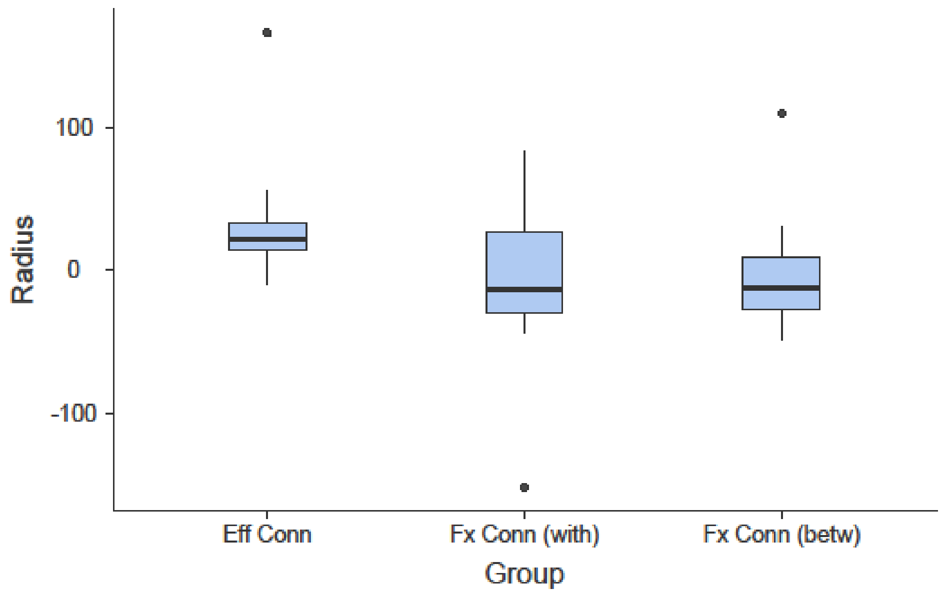
0.10
0.05
0.00
-0.05
-0.10
Global Eff
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group



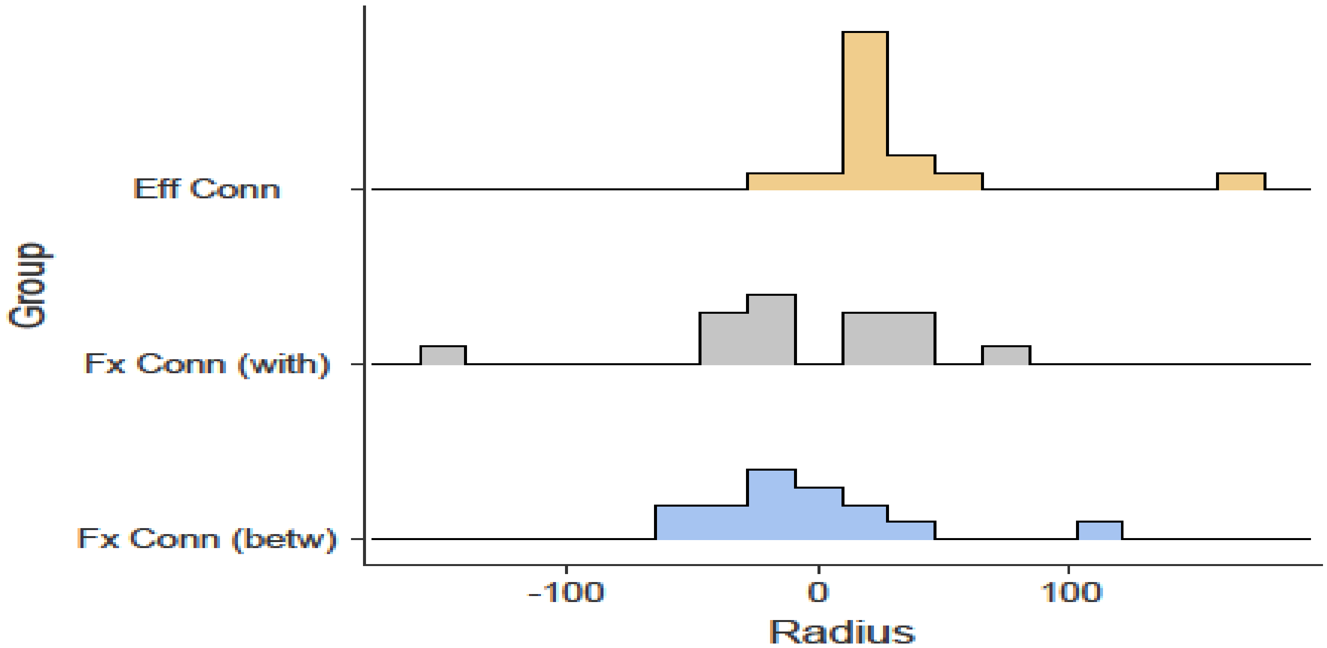
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
-0.10
-0.05
0.00
0.05
0.10
0.15
Global Eff


100
50
0
-50
-100
Path Length
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group

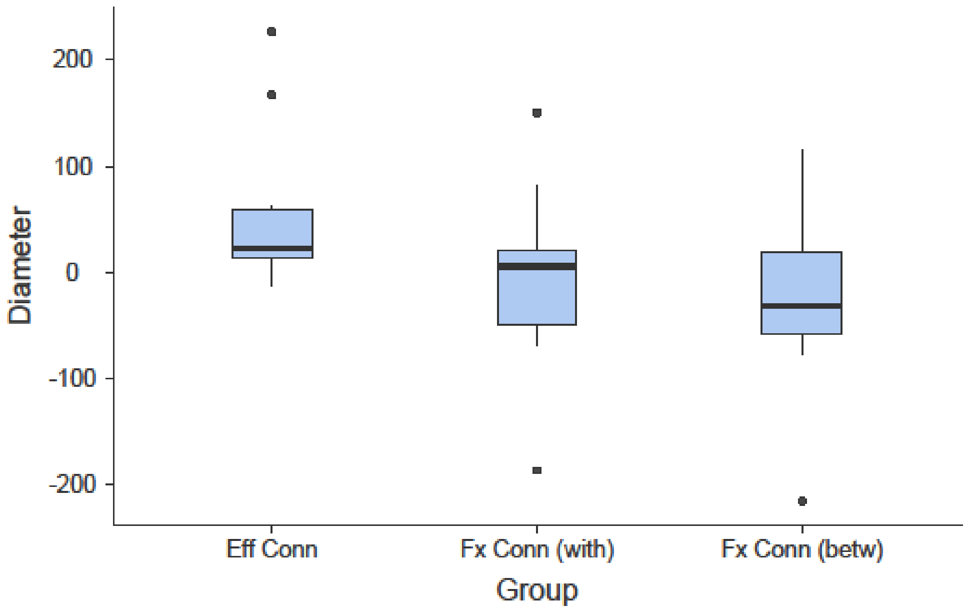

Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
-100
-50
0
50
100
Path Length

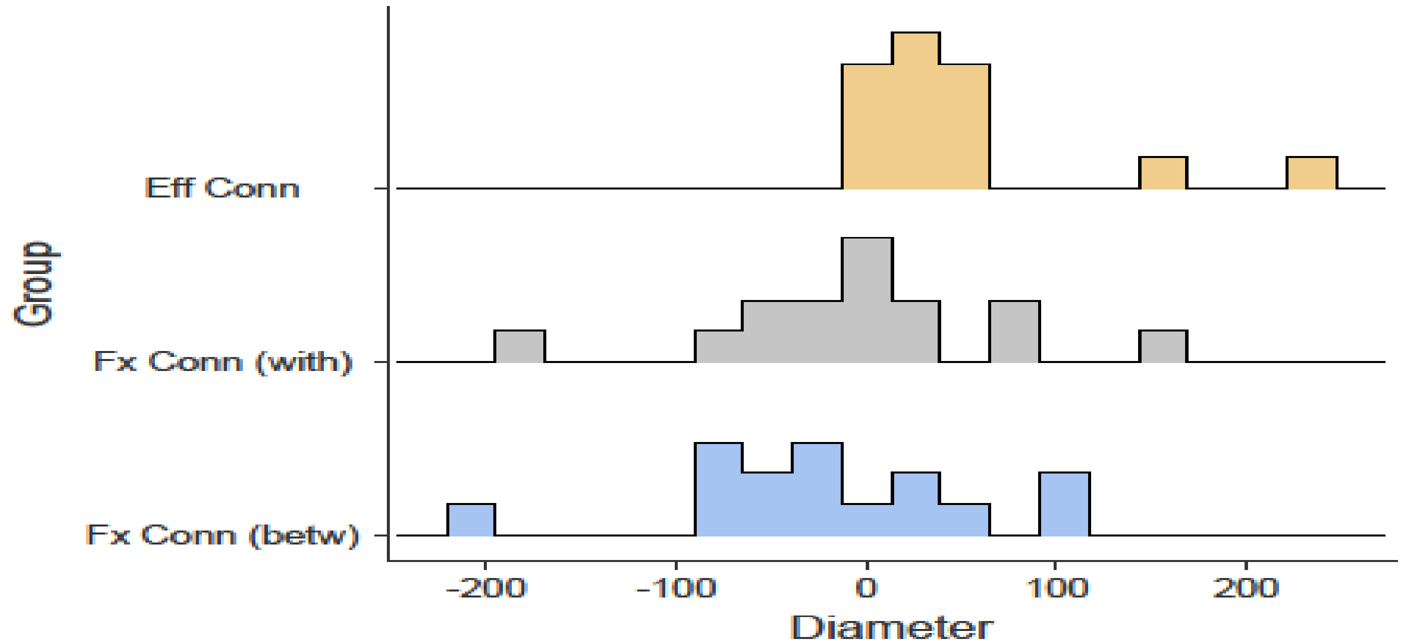


100
0
-100
Radius
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group



Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
-100
0
100
Radius


200
100
0
-100
-200
Diameter
Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group


Eff Conn
Fx Conn (with)
Fx Conn (betw)
Group
-200
-100
0
100
200
Diameter

Correlation Matrix

		Medications	Clinical Improvement	Therapist Outcome Measure	Diameter
Medications	Pearson's r	—	-0.142	-0.142	-0.027
	p-value	—	0.353	0.351	0.862
Clinical Improvement	Pearson's r		—	0.563	0.319
	p-value		—	< .001	0.033
Therapist Outcome Measure	Pearson's r			—	0.242
	p-value			—	0.109
Diameter	Pearson's r				—
	p-value				—

Conclusions

- Measures of effective connectivity can be gleaned from QEEG data.
- Effective connectivity guided multivariate coherence training led to enhanced client and therapist ratings of outcome.
- Therapist ratings are consistently higher than clients and show more significant differences.
- Both ratings show an increased likelihood of greater outcomes (> 10) in the effective connectivity group.
- Positive NF outcomes in this group showed greater reductions of delta/theta, alpha and beta frequencies. These were commonly seen over bilateral posterior brain regions including temporal locations and midline frontal locations as well.
- Positive NF outcomes were associated with greater changes in multivariate connectivity. This is especially true for long range connectivity (diameter).
- Use of effective connectivity leads to changes in connectivity and is more likely to prevent negative connectivity changes.

Thanks to our team:

Clark Thompson, PsyD
Carl Armes, BS
Melchizedek Ghandour, BS
Tarik Bel-Bahar, PhD