Dynamic configuration of large-scale cortical networks accounts for heterogeneity in ADHD traits

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Introduction

How do specific **neural mechanisms** manifest at the behavioural level as **distinct ADHD traits** (inattention, hyperactivity/impulsivity)?

- Key objective in the dimensional approach to psychopathology outlined by the National Institute of Mental Health[1].

A primary cognitive deficit in those with ADHD is the ability to **execute and inhibit motor responses** [2], often operationalized through performance on inhibitory control tasks (i.e, Go/NoGo). Some evidence suggests individual differences in the neural mechanisms underlying this ability specifically account for **hyperactivity/impulsivity:**

1) Methylphenidate, known to **supress task-irrelevant connectivity,** is more effective at reducing hyperactive/impulsive than inattentive traits [3,4]

2) White matter tract abnormalities **connecting regions in the frontal and motor cortex** (involved in motor response execution/inhibition) are prominent in **ADHD-C**[5]

However, these mechanisms are not always **prominent sources** of ADHD heterogeneity:

1) **Regional neural activity** suggest **motor inhibition is intact** [6]

2) Cognitive measures of execution/inhibition often **fail** to **differentiate subtypes** [7, 8, 9]

Perhaps the ***dynamic changes*** **that large-scale cortical networks undergo during motor response/execution** differ between ADHD subtypes traits.

If this is the case, then graph-theoretical measures which capture how EEG functional networks dynamically organize during motor response execution/inhibition should reliably distinguish between ADHD traits (Inattention, Hyperactivity/Impulsivity).

Methods

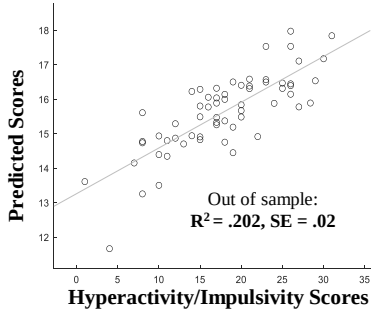
Participants
- 62 non-clinical participants (ages 18-24; 32 male)
- ADHD traits assessed using Conner's Adult ADHD Rating scales.

EEG
- Continuous 128-Channel EEG (500Hz Sampling rate).
- **Preprocessing:** 100Hz low pass, 60Hz notch, .5Hz high pass filter.
- **Ocular correction:** Gratton & Coles.
- **Artifact Rejection:** Trials with amplitude +/-200uV rejected.
- Signal filtered (1-3Hz; 4-7Hz; 8-13Hz; 14-29Hz; 30-90Hz), and phase time-series extracted using Hilbert transform.
- Across-trial Phase-lag Index (PLI) used to measure connectivity (synchronization between signals).
- **EEG Functional Networks constructed**: 'Edges' = PLI (connectivity); 'Nodes' = electrodes.
- **Dynamic Networks:** Sensor X Sensor adjacency matrices over time (2ms; temporally layered).
- **Static Networks:** Sensor X Sensor adjacency matrices averaged over 0-500ms

Task
- A-X Continuous performance task, Go/No-Go.
- Instructions: "Respond *quickly* and *accurately* to **X**, but only when it is preceded by **A.**"
- **Motor Response *Execution*** = Response trials: 42.18/subject.
- **Motor Response *Inhibition*** = No response trials: 44.35/subject.

LASSO Regression
- Least absolute shrinkage and selection operator (LASSO) regression used to predict ADHD traits.
- **Features:** Ten dynamic/static network measures (broadly capturing **modularity**, **small-worldness**, **integration** and **segregation**) for each frequency-band and both conditions (100 features per model).
- **Outcome Variables:** CAARS-Inattention, CAARS-Hyperactivity/Impulsivity
- **Overfitting prevented** by selecting hyperparameter *lambda* through repeated **10-fold cross validation.**

LASSO Model Predicting Hyp/Imp

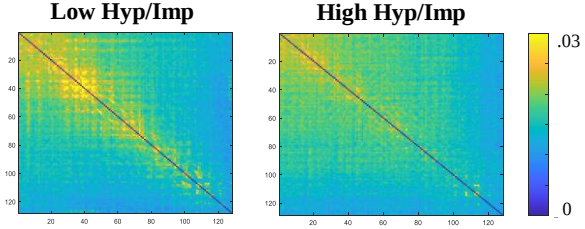


LASSO model predicting **Hyperactivity/Impulsivity** from the static and dynamic configuration of functional networks (all frequency bands) during both the execution and inhibition of motor responses

In LASSO models predicting **Inattention**, all **regression coefficients were driven to 0.**

Motor Response *Inhibition*

(Gamma: 30-90 Hz)



Adjacency matrices (Sensors = nodes, PLI = edges) showing the mean number of connections within each time period. The 10 participants with lowest//highest Hyperactivity/Impulsivity scores visualized.

Correlations with Hyperactivity/Impulsivity

Integration: r = .31, p = .01

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{l_{ij}}$$

N = Number of nodes.
l_{ij} = Length of shortest path between i and j.
High E = All nodes can communicate through a short number of connections.

Small-Worldness: r = .43, p = .0006

$$SWI_{stat} = \frac{E_r}{E} - \frac{C}{C_l}$$

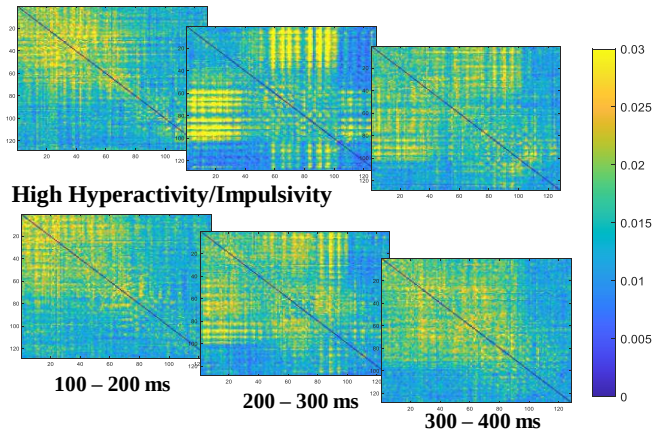
E = Global efficiency: integration.
C = Clustering coefficient: segregation.
r = Random network with equivalent degree.
l = Lattice network with equivalent degree
High SWI = Greater integration than expected based on the level of segregation.

Motor Response *Execution*

(Beta: 14-29 Hz)

Low Hyperactivity/Impulsivity

High Hyperactivity/Impulsivity



Adjacency matrices (Sensors = nodes, PLI = edges) showing the mean number of connections within each time period, 10 participants with low//high Hyp/Imp visualized.

Correlations with Hyperactivity/Impulsivity

Burstiness: r = -.32, p = .017

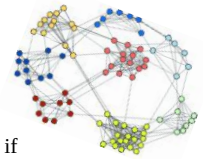
$$B = \frac{\sigma_\tau \mu_\tau - 1}{\sigma_\tau \mu_\tau + 1}$$

High B
Low B

τ = Distribution of inter-contact times between all node-pairs.
High B = Serially correlated communication (distinct on/off periods).
Low B = Periodic communication (regular intervals).

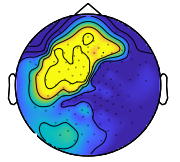
Modularity: r = .30, p = .018

$$Q = \frac{1}{2E} \sum_{ij} (A_{ij} - e_{ij}) \delta(m_i, m_j)$$



E = Number of edges.
e = Equivalent random network.
δ(mi, mj) = Kronecker delta function: equal to 1 if nodes *i* and *j* belong to the same module.
High Q = Easily divided into distinct 'subnetworks'.

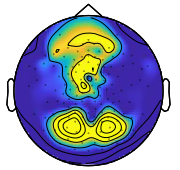
Topography of Effects



Motor Response Inhibition (Gamma)

Mean number of connections (degree) from 0-500ms (10% threshold, binarized), averaged across all participants.

Gamma: Frontal-left integration.



Motor Response Execution (Beta)

Mean degree from 200-300ms (10% threshold, binarized), averaged across all participants.

Beta: Mid-Frontal and mid posterior/central integration.

Conclusion

- The dynamic reconfiguration that large scale functional brain networks undergo during motor response execution/inhibition is altered in those with hyperactive/impulsive, but not inattentive, traits.

Hyperactivity/Impulsivity is associated with…
- During motor response execution:
  - A **modular** configuration, with **less burst-like** integration **between modules** in networks oscillating at a **beta** frequency.
  - Reflects **an altered integration between prefrontal and motor areas.**
- During motor response inhibition:
  - A more **small-world** like, **integrated** configuration in networks oscillating at a **gamma** frequency.
  - Reflects a **compensatory**, integrative mechanism used to overcome an **under-specialized functional network configuration**.
- The neural mechanisms underlying ADHD subtype heterogeneity can be measured by applying network measures to the EEG recorded during a Go/No-Go task, furthering EEG's use in clinical ADHD research.

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