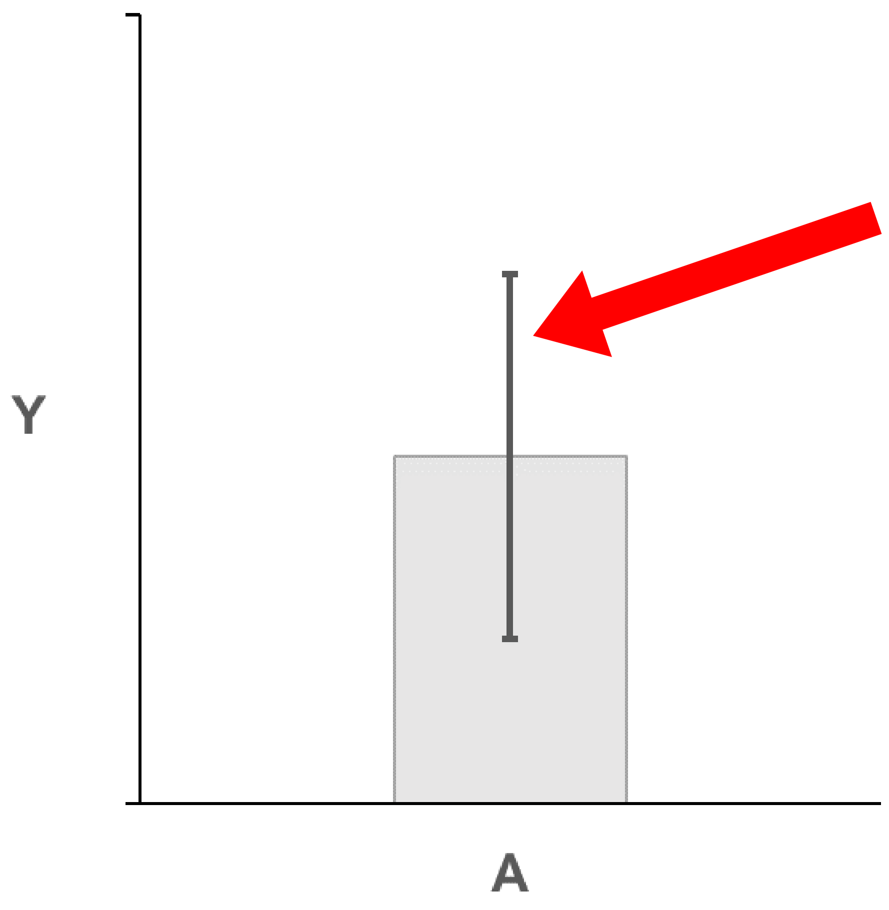
Independent Component Analysis (ICA) of MRI and PET: Unmixing addiction in the brain

Patrick D Worhunsky, PhD
Assistant Professor
Department of Psychiatry
Yale School of Medicine

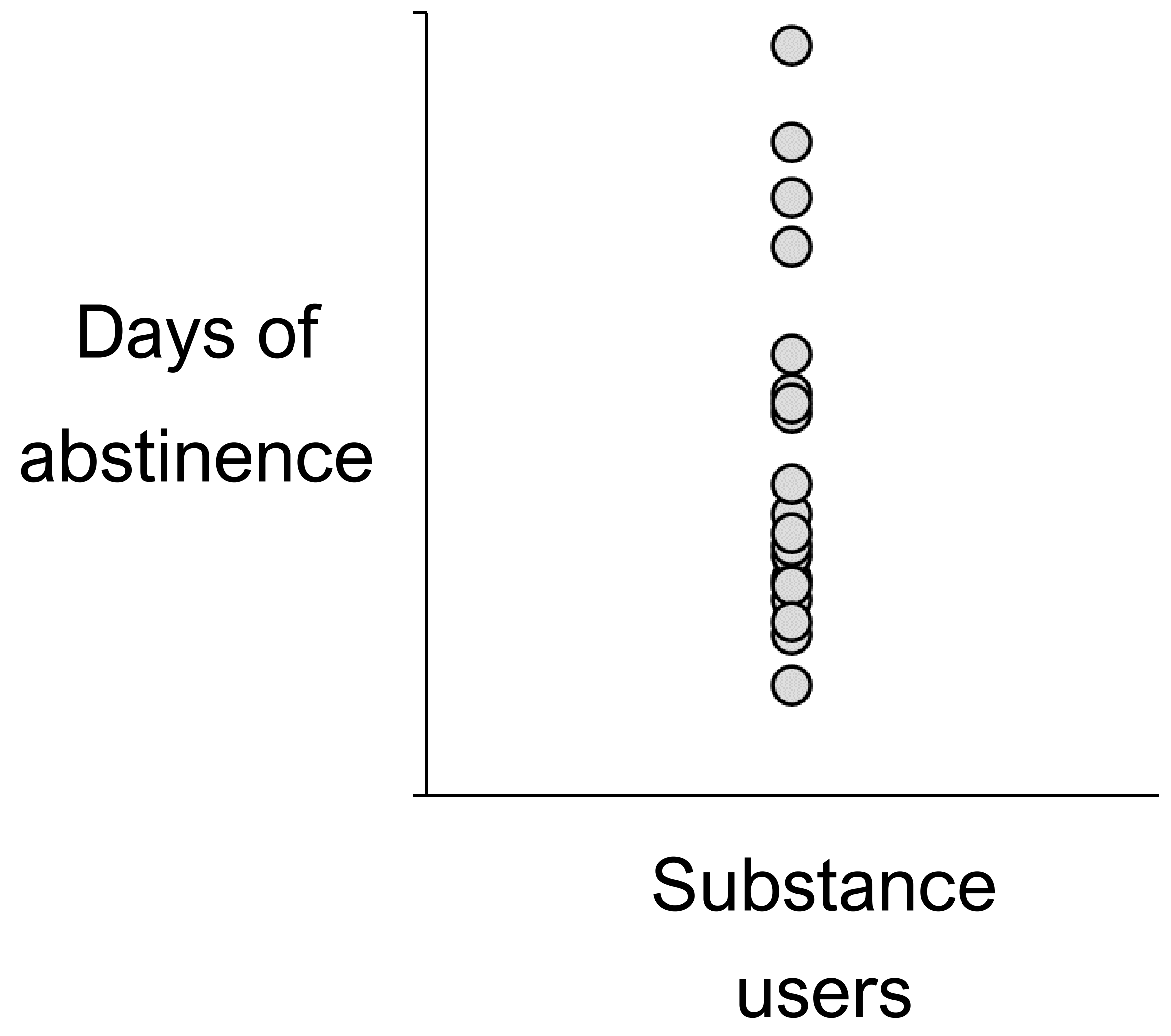
Independent component analysis, a brief primer

- **Variance**



Independent component analysis, a brief primer

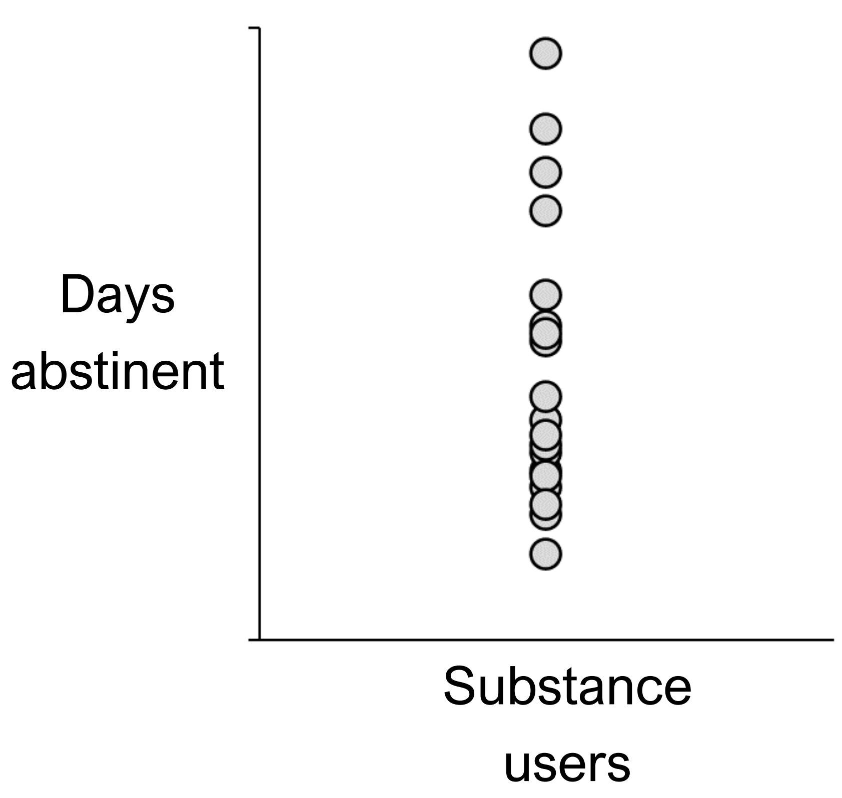
- **Variance**



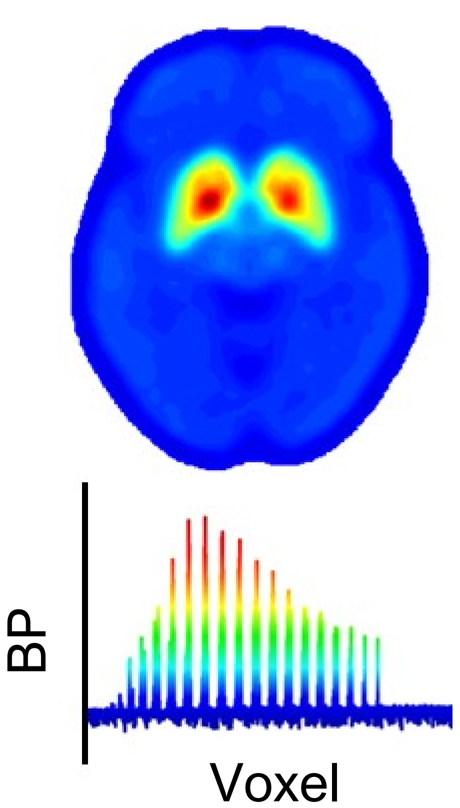
Independent component analysis, a brief primer

- **Variance**

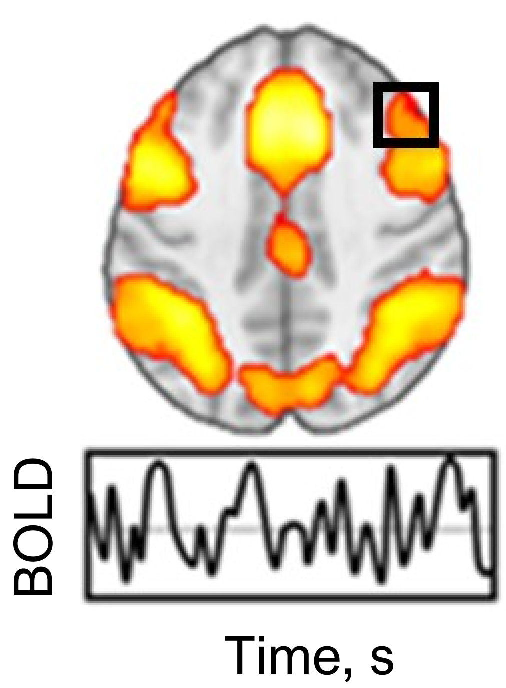
Between subjects



Across space

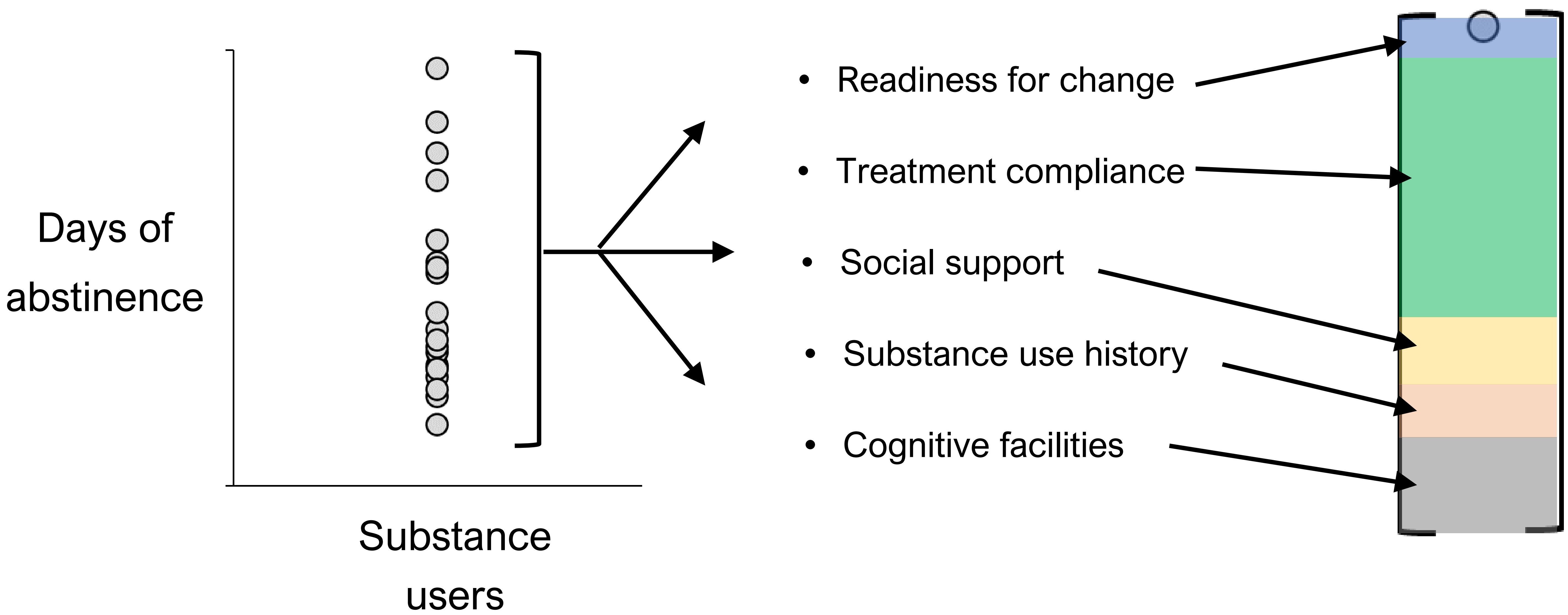


Across time



Independent component analysis, a brief primer

- **Sources** of variance
  - Where variance comes from:
    - True noise or measurement error/imprecision (random variance)
    - Underlying, non-random factors that influence the measurement

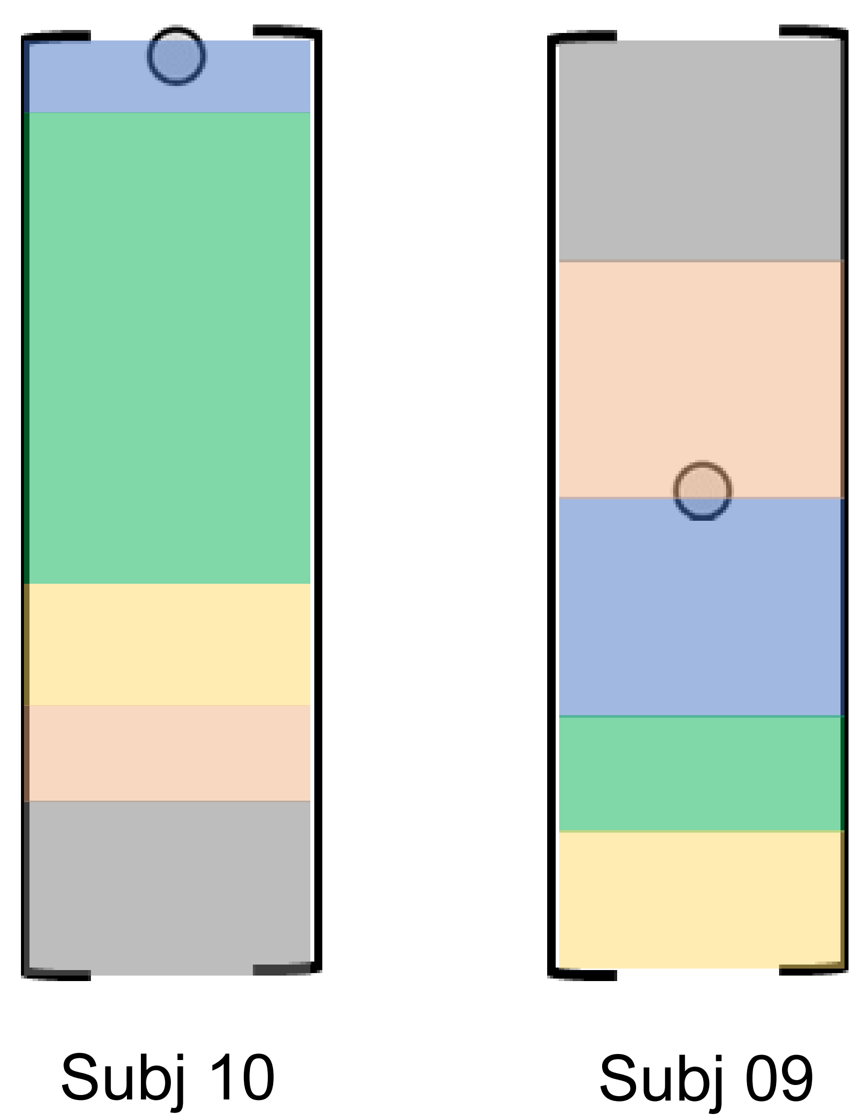


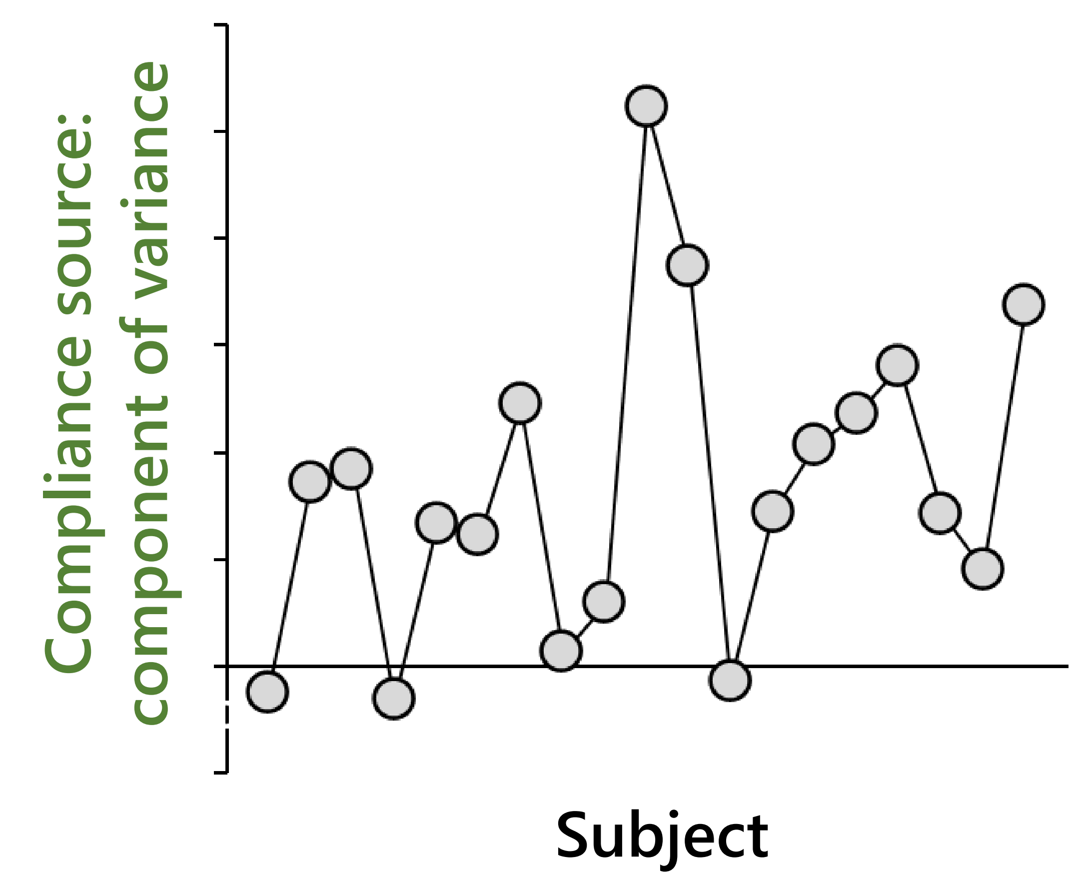
Independent component analysis, a brief primer

- **Components** of variance
  - How much variance is explained by each source:
    - It may not be the same amount for every measurement
    - The amount of variance attributed to each source

Sources of variance:

- Readiness for change
- Treatment compliance
- Social support
- Substance use history
- Cognitive facilities





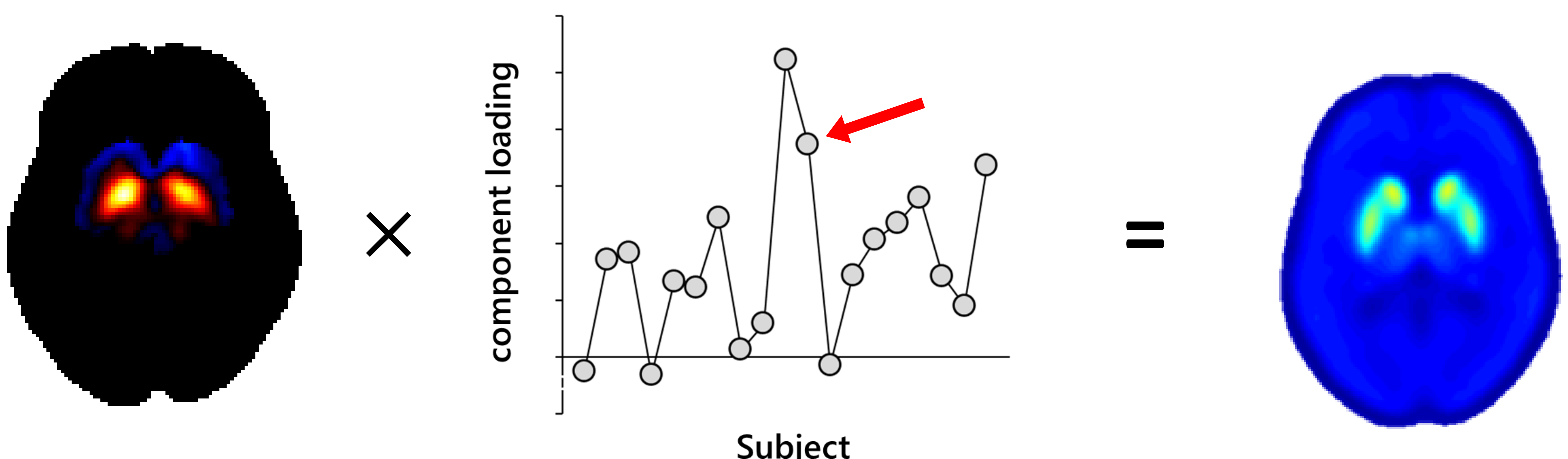
Independent component analysis, a brief primer

- **Loadings, source loadings and component loadings**
  - Source loading: how much of a component variance comes from each source
  - Component loading: how much variance that source contributes to each measurement
  - Loadings are just betas/coefficients of the variance mixture linear equation

	Readiness for change		+	Treatment compliance		+	Social support		=	Days Abstinent
	Source loading	Com loading		Source loading	Com loading		Source loading	Com loading		
S01:	**.30** *	**.25**		**.50** *	**1.51**		**.20** *	**.95**		**90**
S02:	**.30** *	**.90**		**.50** *	**.25**		**.20** *	**.10**		**12**

Independent component analysis, a brief primer

- **Loadings, source loadings and component loadings**
  - Source loading: how much of a component variance comes from each source
  - Component loading: how much variance that source contributes to each measurement
  - Loadings are just betas/coefficients of the variance mixture linear equation



Source loadings

Subject's component variance

Independent component analysis, a brief primer

- **Network:** source network and functional networks
  - Source network: set of regions that source a single component of variance (PET)
  - Functional networks: set of regions that source a coherent component time course (fMRI)

Independent component analysis, a brief primer

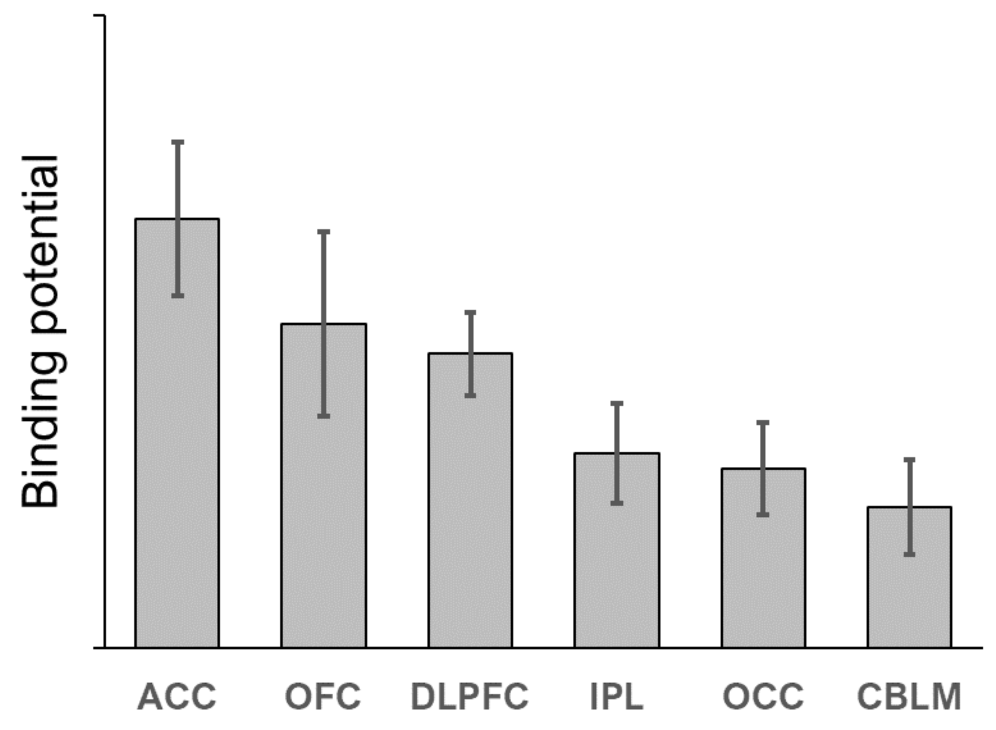
- The pursuit of **Independence**
  - Blind separation of non-random variance structures
  - Find maximally non-Gaussian variance
  - Minimize mutual information across components and sources
  - Different ICA algorithms pursue independence differently
- Limitations and restrictions
  - ICA does not work on truly random data (allowance for *a* random sources depends on algorithm)
  - User decides the number of sources/components to solve for
  - Restricted to linear mixtures of component variance
  - ‘True’ sources cannot be known

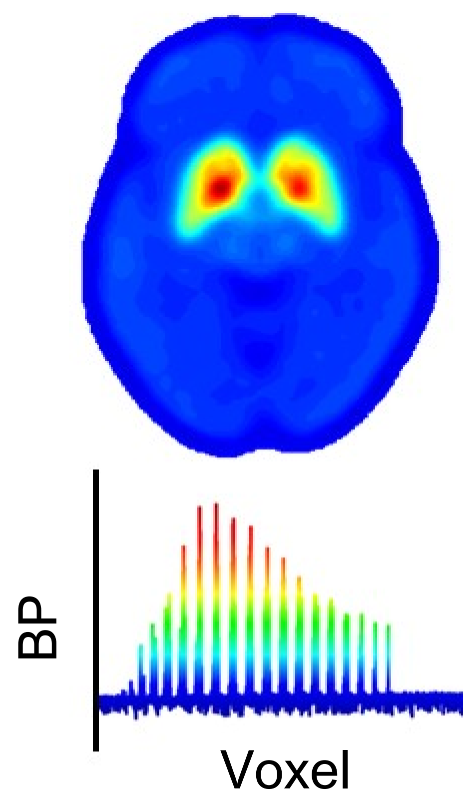
Independent component analysis, a brief primer

- To review:
  - We have some **variance** we would like to explain. Its not random variance, we think it has some structure and represents the sum-mixture of **underlying variance sources**
  - ICA can separate out the **components of variance** and identify their sources by pursuing maximal independence.
  - ICA will output **two sets of loadings:** how much of the component variance was found in each source (source loading), and how much each component explains the total variance of each measurement (component loading).
  - The sum of all source*component loadings will reconstruct an estimate of the original data

ICA of PET

- ICA of PET



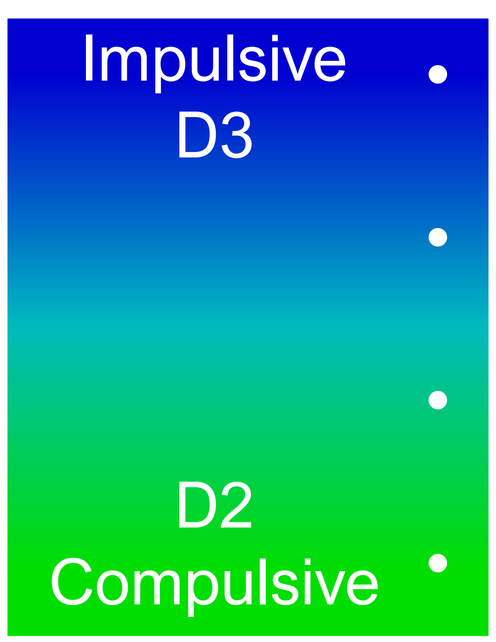


- Is PET regional variance totally random or might there be some underlying sources?
- ICA to analyze the patterns of regional covariances across subjects to look for independent sources of component variance
- $[^{11}C]$-(+)-PHNO, dopamine D2/D3 receptors

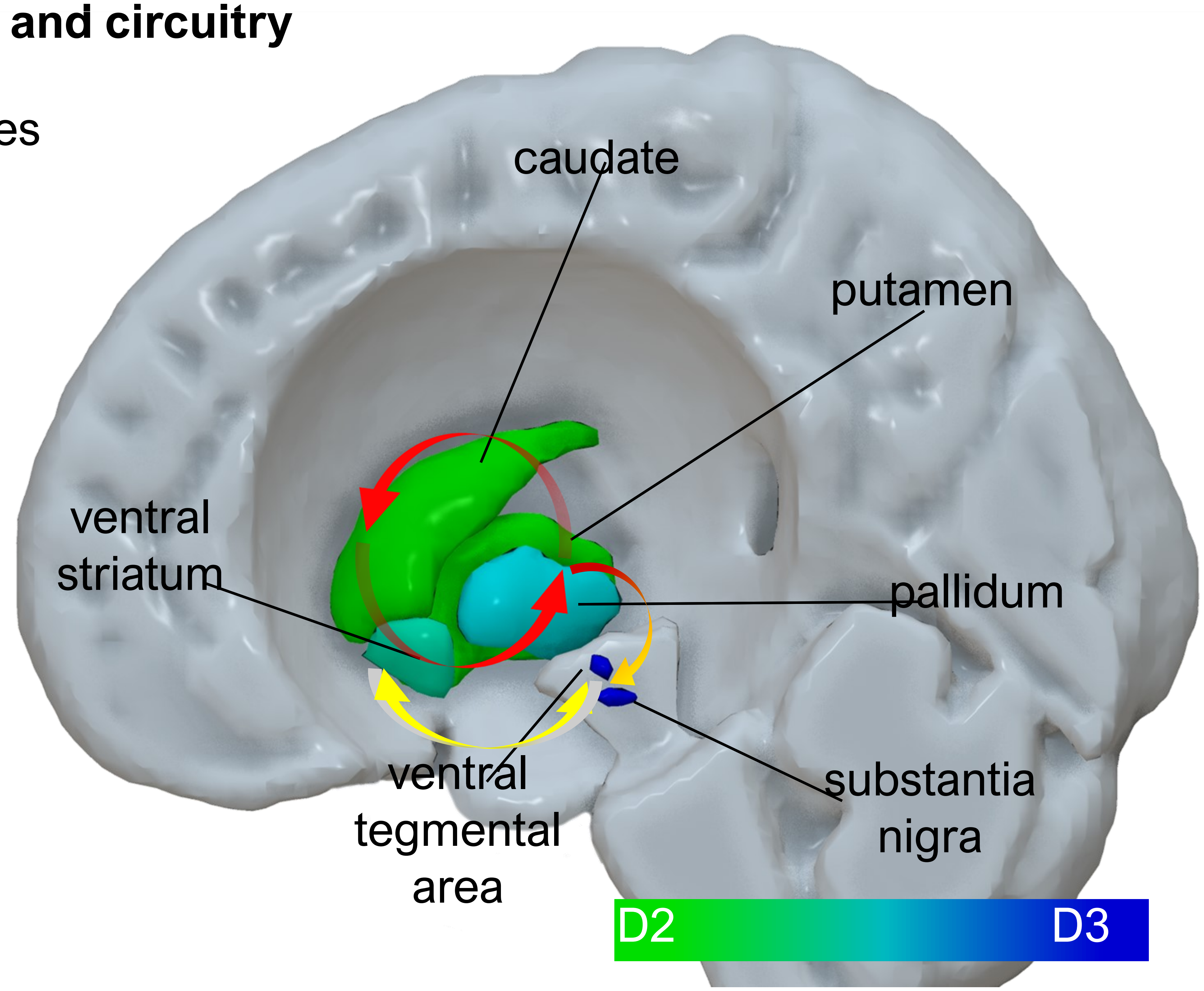
ICA of dopamine D2/D3 PET

- **D2 and D3 receptors**
  - Highly expressed in subcortical and midbrain structures central to addictive processes
  - Broadly implicated in impulsive and compulsive processes
    Berridge, 2003; Robinson et al, 2015

- **Distinct and overlapping D2/D3 distribution and circuitry**
  - Suggests unique and shared functional roles

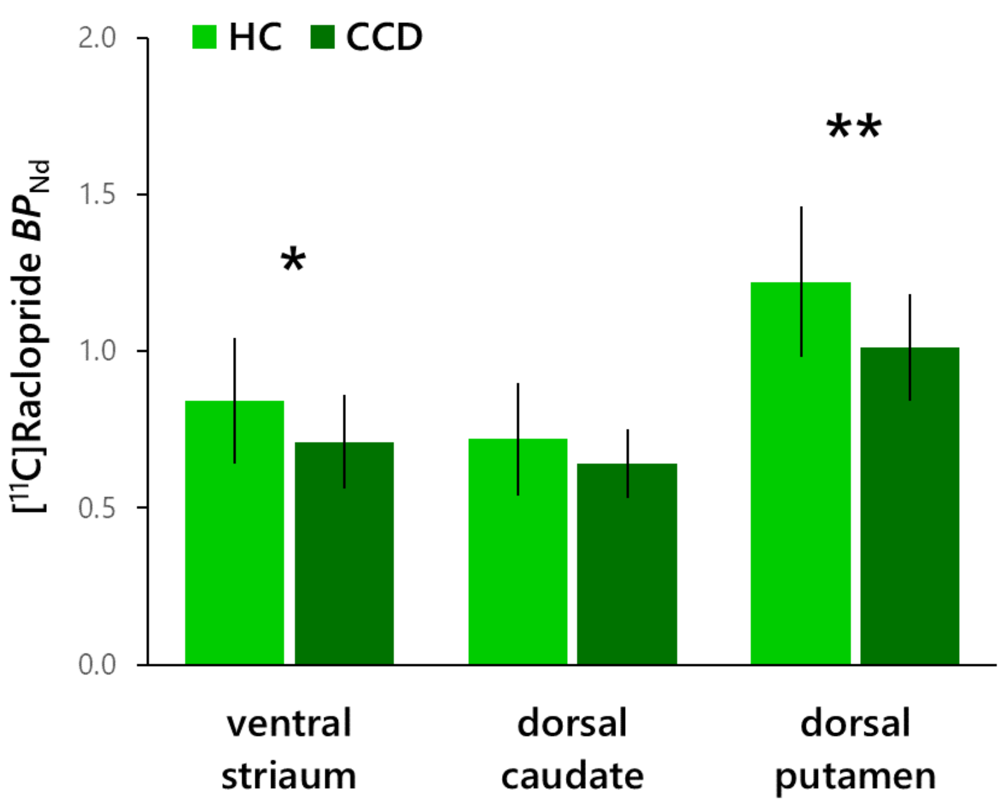


- Stimulus reactivity
- Reward sensitivity
- Reinforcement
- Habituation



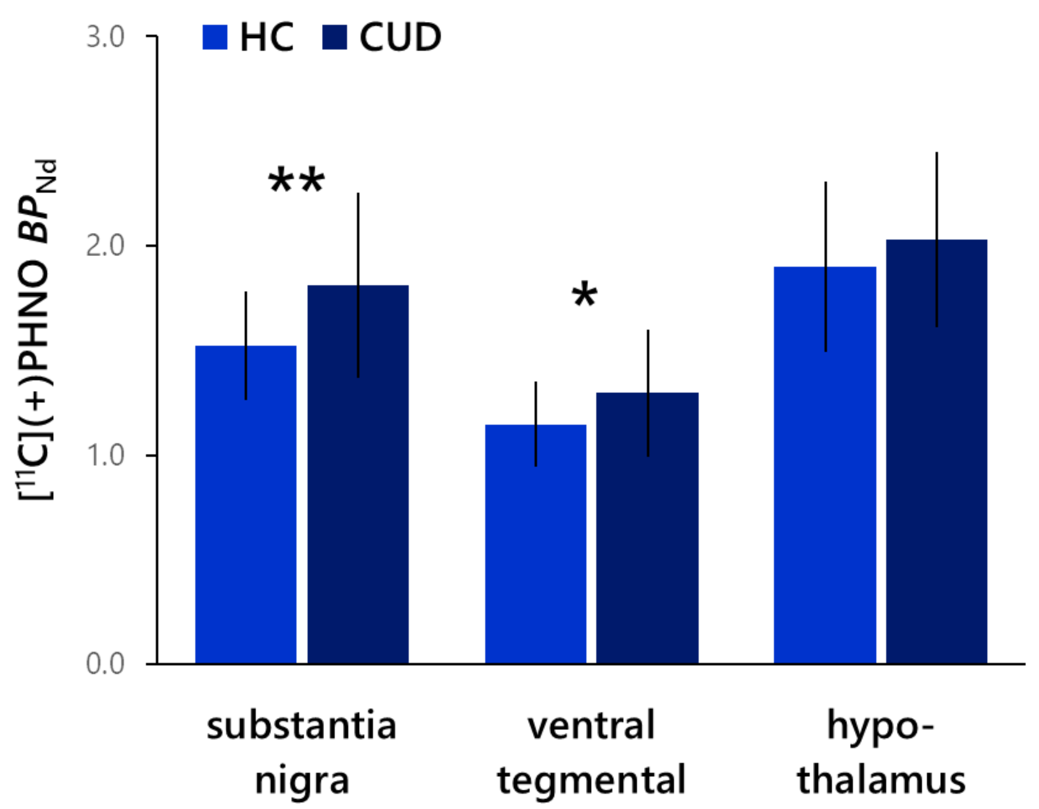
ICA of dopamine D2/D3 PET

- **D2 and D3 receptors in CUD**
  - **Lower striatal D2 availability** in CUD
    Volkow et al, 1990; Martinez et al, 2004
    - $[^{11}C]$-raclopride studies
      - Equal D2/D3 affinity
      - No CUD differences in midbrain



Data from: Martinez et al, 2004 *$P<0.05$, **$P<0.01$

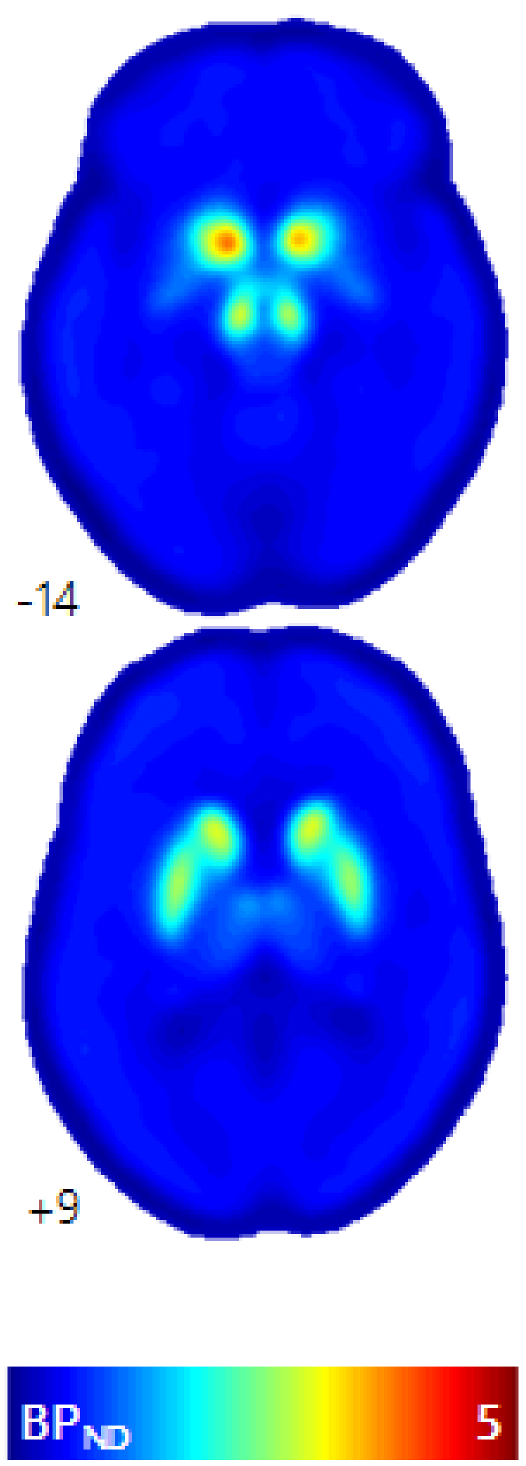
  - **Higher D3 availability** in CUD
    Payer et al, 2014 Matuskey et al, 2014
    - $[^{11}C]$-(+)-PHNO studies
      - 30:1 *in vivo* D3:D2 affinity
      - No CUD differences in striatum

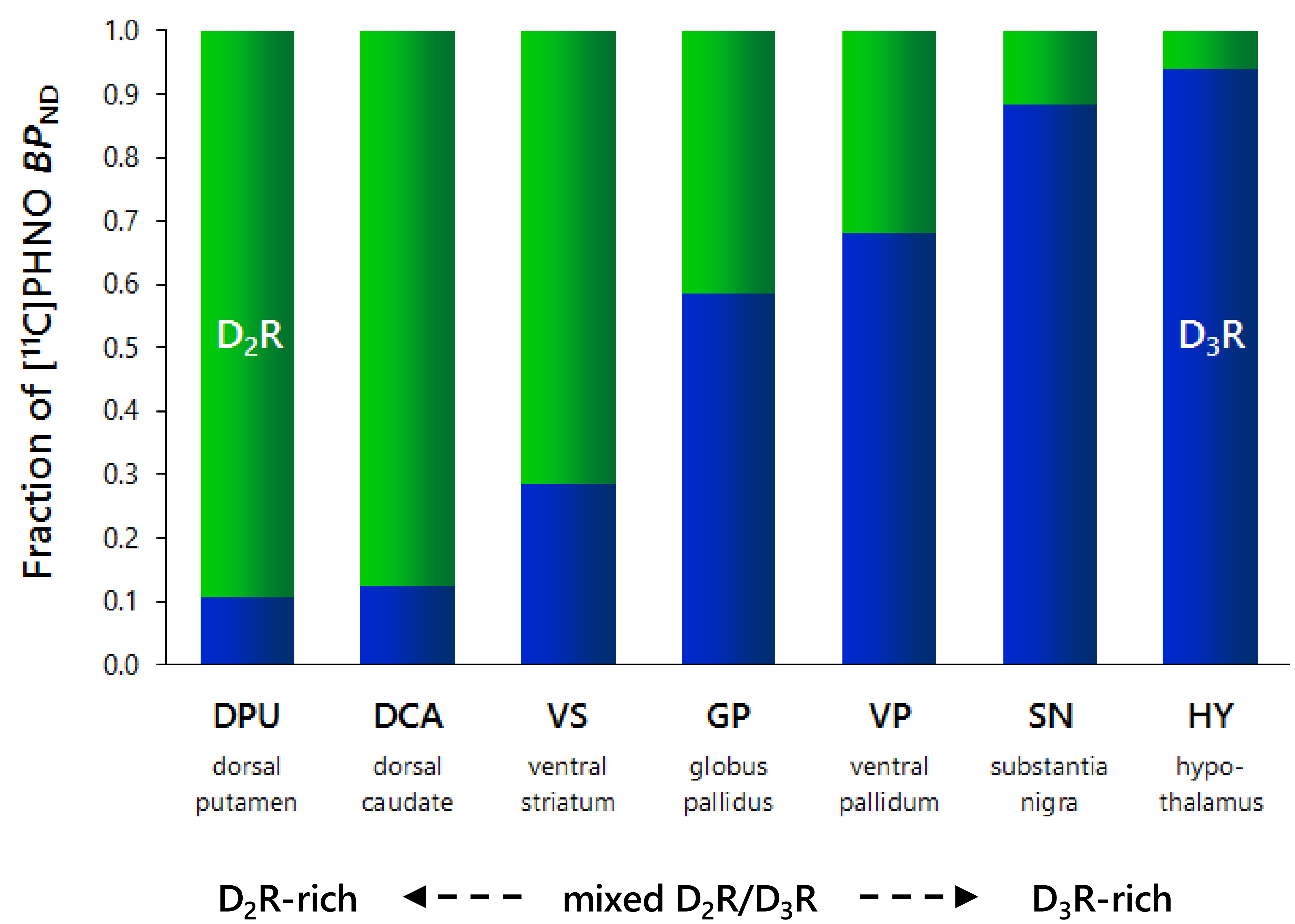


Data from: Worhunsky et al, 2017 *$P<0.05$, **$P<0.01$

ICA of dopamine D2/D3 PET

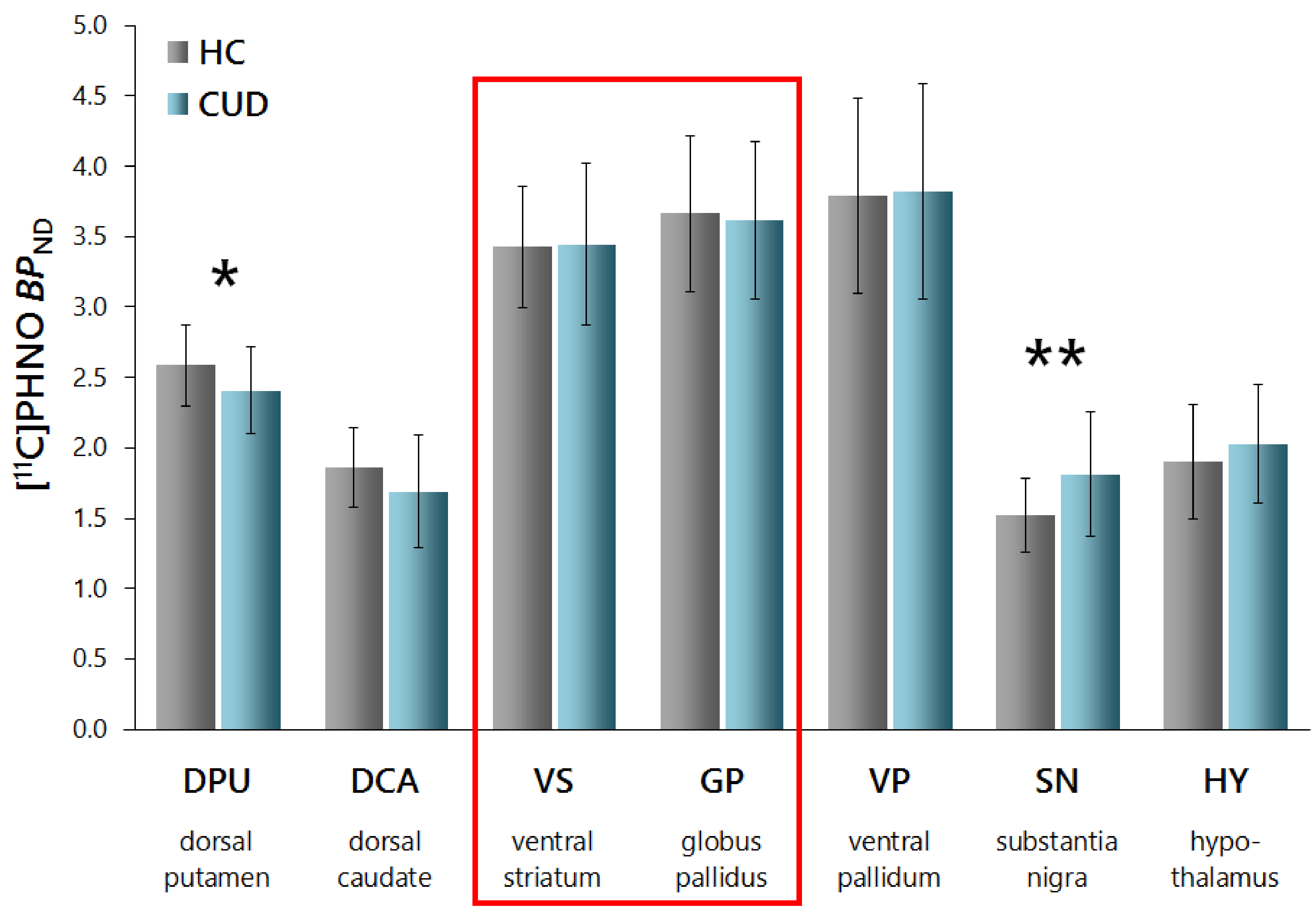
- Regional [^{11}C]-(+)-PHNO binding reflects local D2/D3 receptor concentration
  Searle et al, 2013; Tziortzi et al, 2011





ICA of dopamine D2/D3 PET

- N=52 (26 CUD, 26 HC)
- Replicated previous ROI methods (SRTM2, cerebellum)

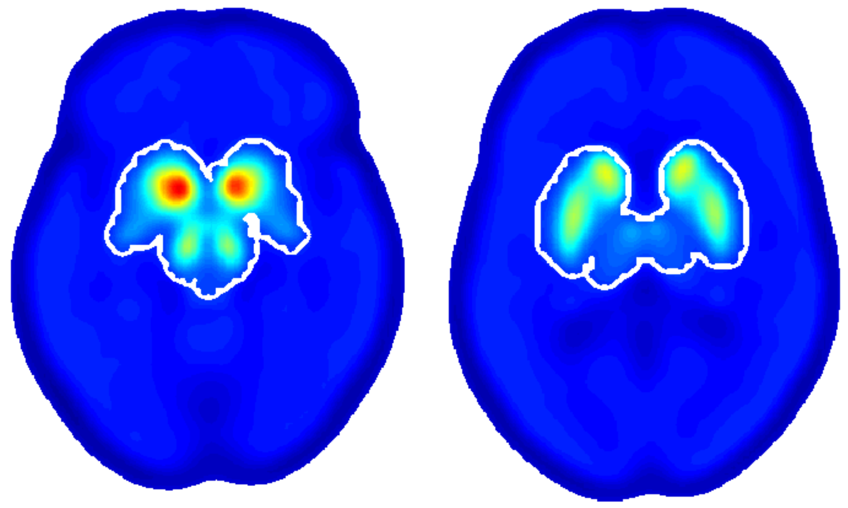


CUD relative to HC participants displayed lower BP_{ND} in the dorsal putamen (**DPU; ****P*=0.037) and greater BP_{ND} in the substantia nigra (**SN, *****P*=0.005). Error bars indicate SD.

- Can ICA separate D2 and D3 binding in mixed-signal regions?

ICA of dopamine D2/D3 PET

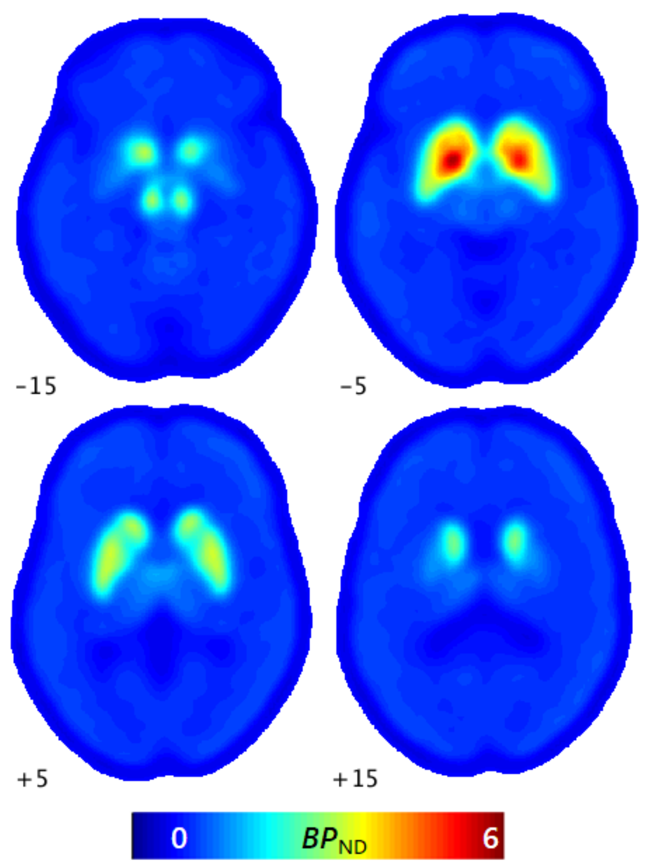
- **Image processing**
  - Parametric images (SRTM2) were registered to MNI152 space using SPM12 and smoothed with 4mm FWHM Gaussian kernel
  - Explicit masking to eliminate voxels of no-interest (BP_{ND}<0.25; not expected to have structure)



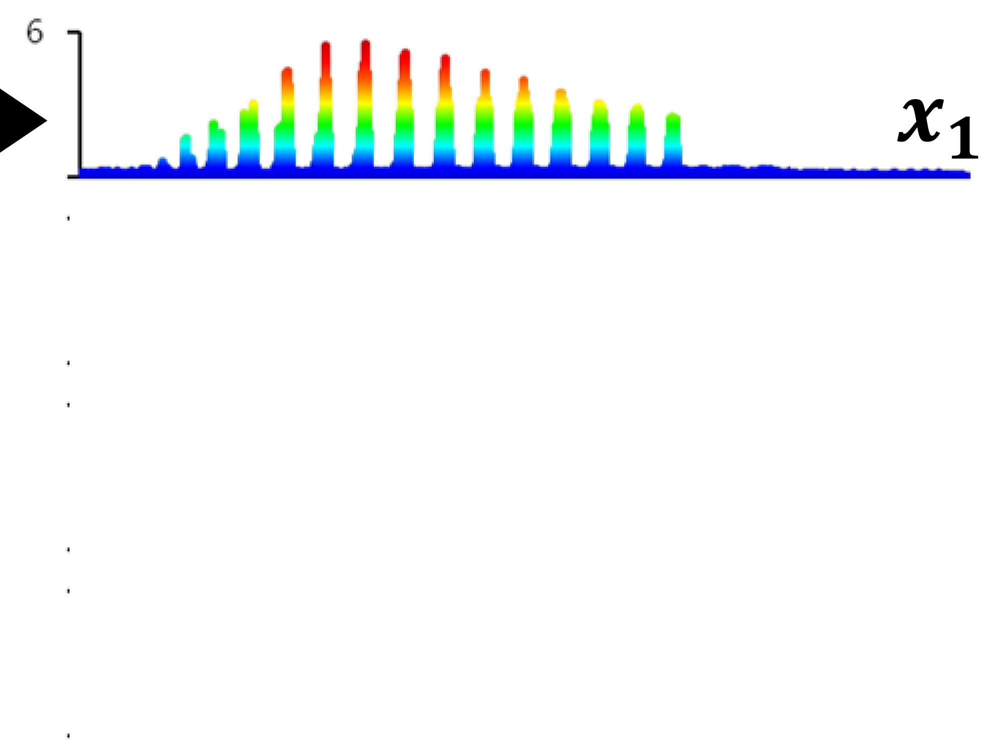
- **ICA analysis**
  - MDL criteria estimated 3 independent components optimally fit the data set
    Li et al, 2007
  - Components were extracted with InfoMax using the SBM module of the GIFT
    Bell and Sejnowski, 1995; Calhoun et al, 2001; Xu et al, 2009

ICA of parametric imaging data

- **ICA input**



Parametric PET image



Voxel-wise vector

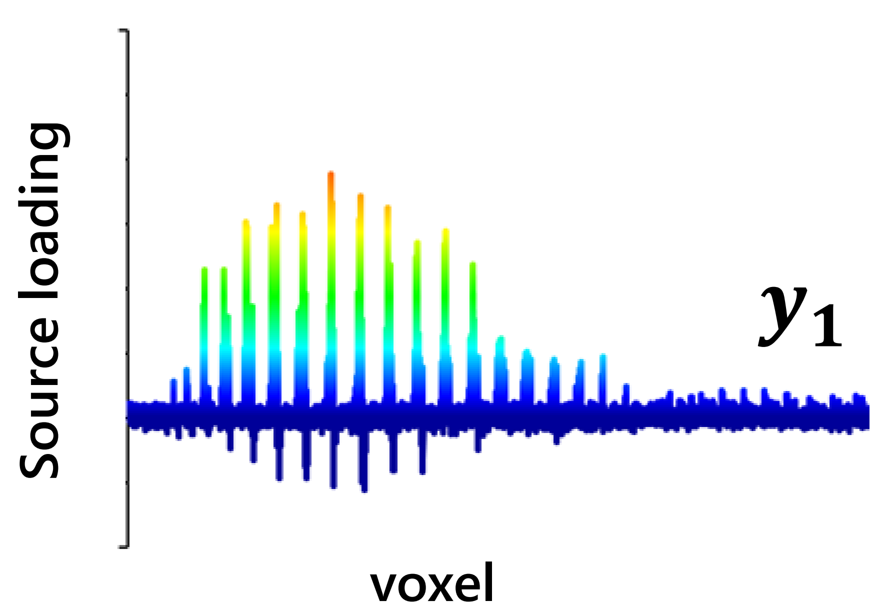
ICA

sources →

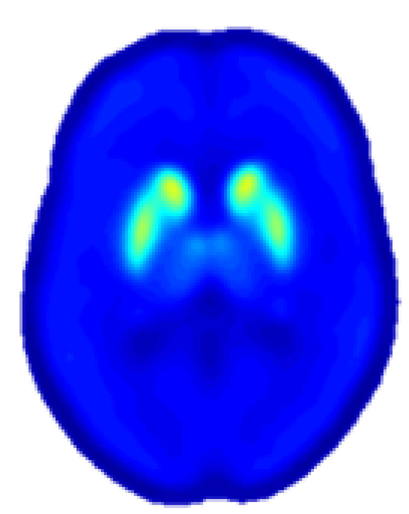
$$\begin{array}{c|ccc} & y_1 & y_2 & y_M \\ \hline \text{components} \downarrow & a_{1,1} & a_{1,2} & a_{1,M} \\ & a_{2,1} & a_{2,2} & a_{2,M} \\ & a_{3,1} & a_{3,2} & a_{3,M} \\ & a_{N,1} & a_{N,2} & a_{N,M} \end{array}$$

un-mixing matrix

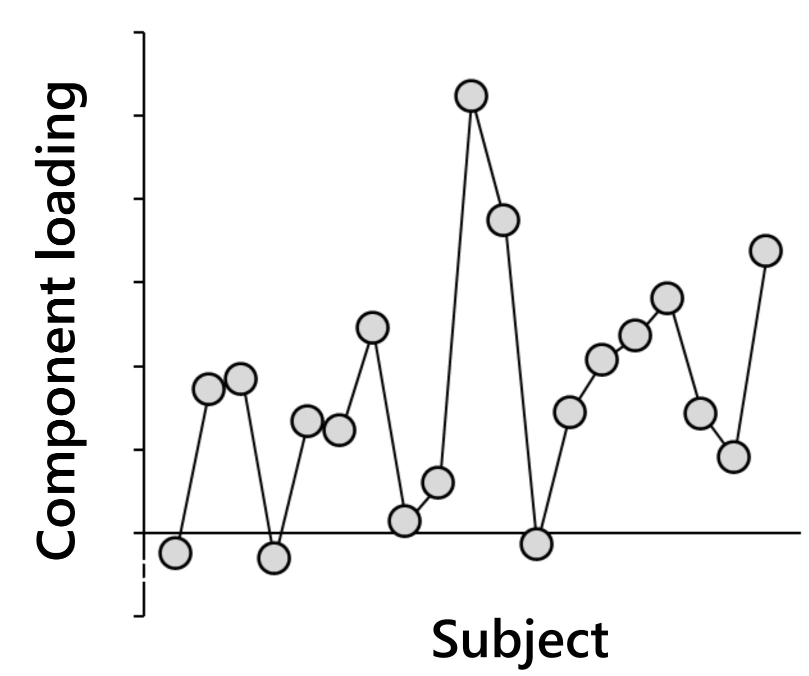
- **Unmixing matrix give us source and component loadings**



Source vector



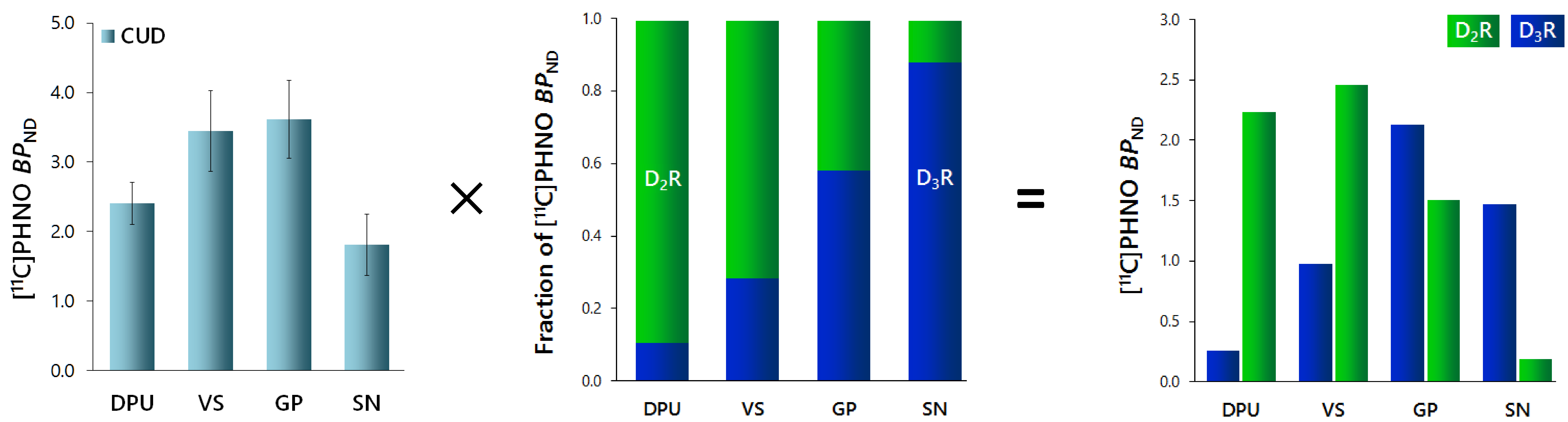
Source map



Subject component loading

ICA of parametric imaging data

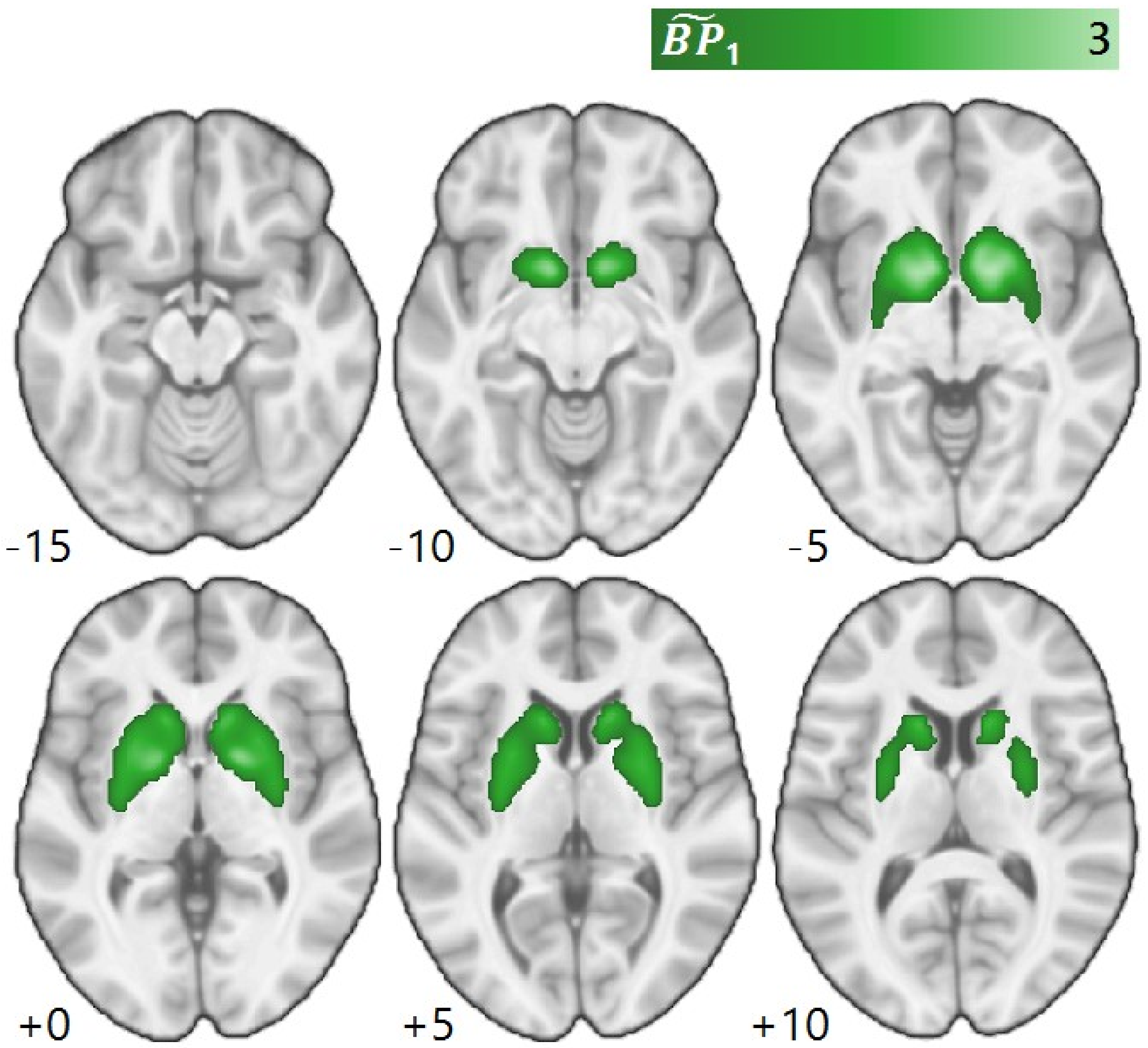
- **ICA post-processing**
  - Group source maps were scaled to estimated $\widetilde{BP}_{ND}$ units:
    Source loading map * average component loading = $\widetilde{BP}_{ND}$ contribution
  - Comparison to ROI-based D2/D3 BP_{ND}
    - $\widetilde{BP}_{ND}$ calculated for ROIs
    - Generate estimates of regional D2- and D3-related binding based on reported fractions from displacement studies
      Searle et al, 2013; Tziortzi et al, 2011



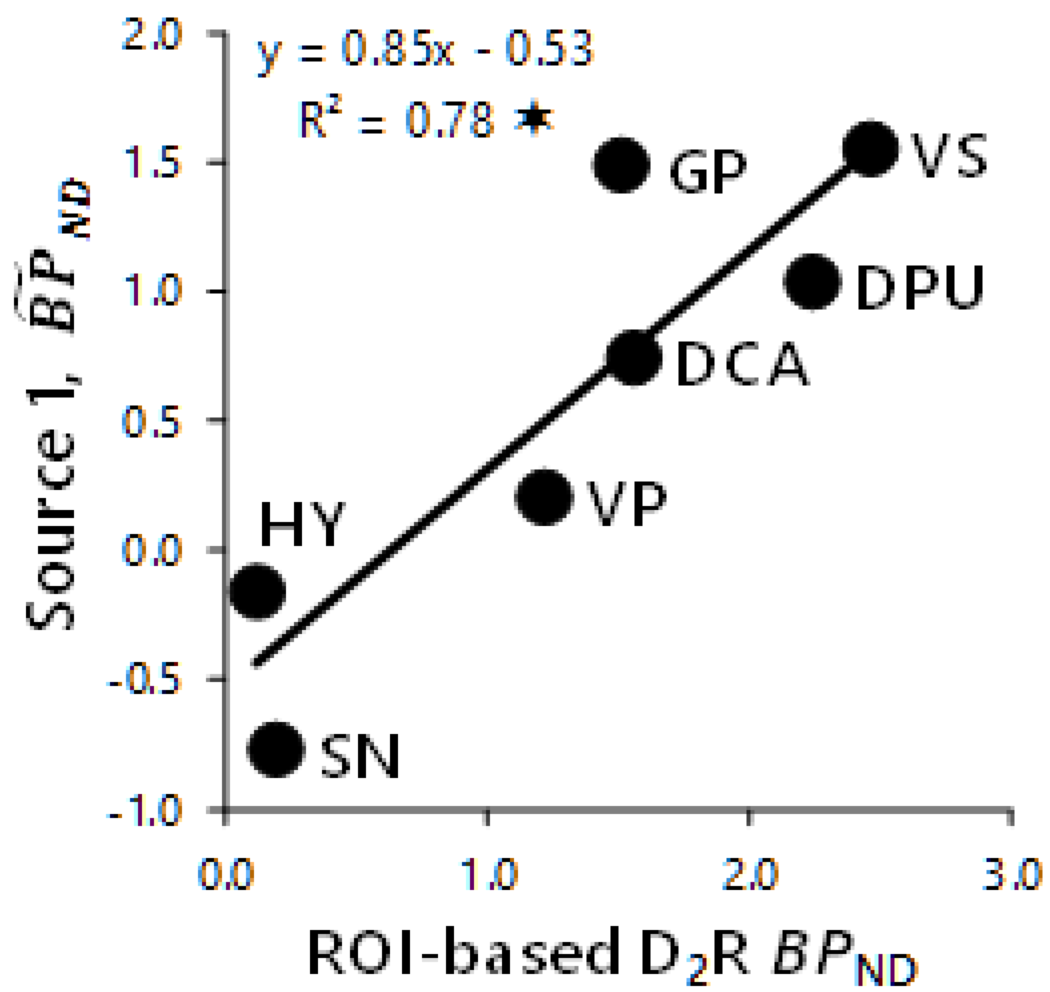
ICA of dopamine D2/D3 PET

- **Striatopallidal source network**

  - Source spatial map



- Regional $\widetilde{BP}_{ND}$ correlated with **D2-related** binding

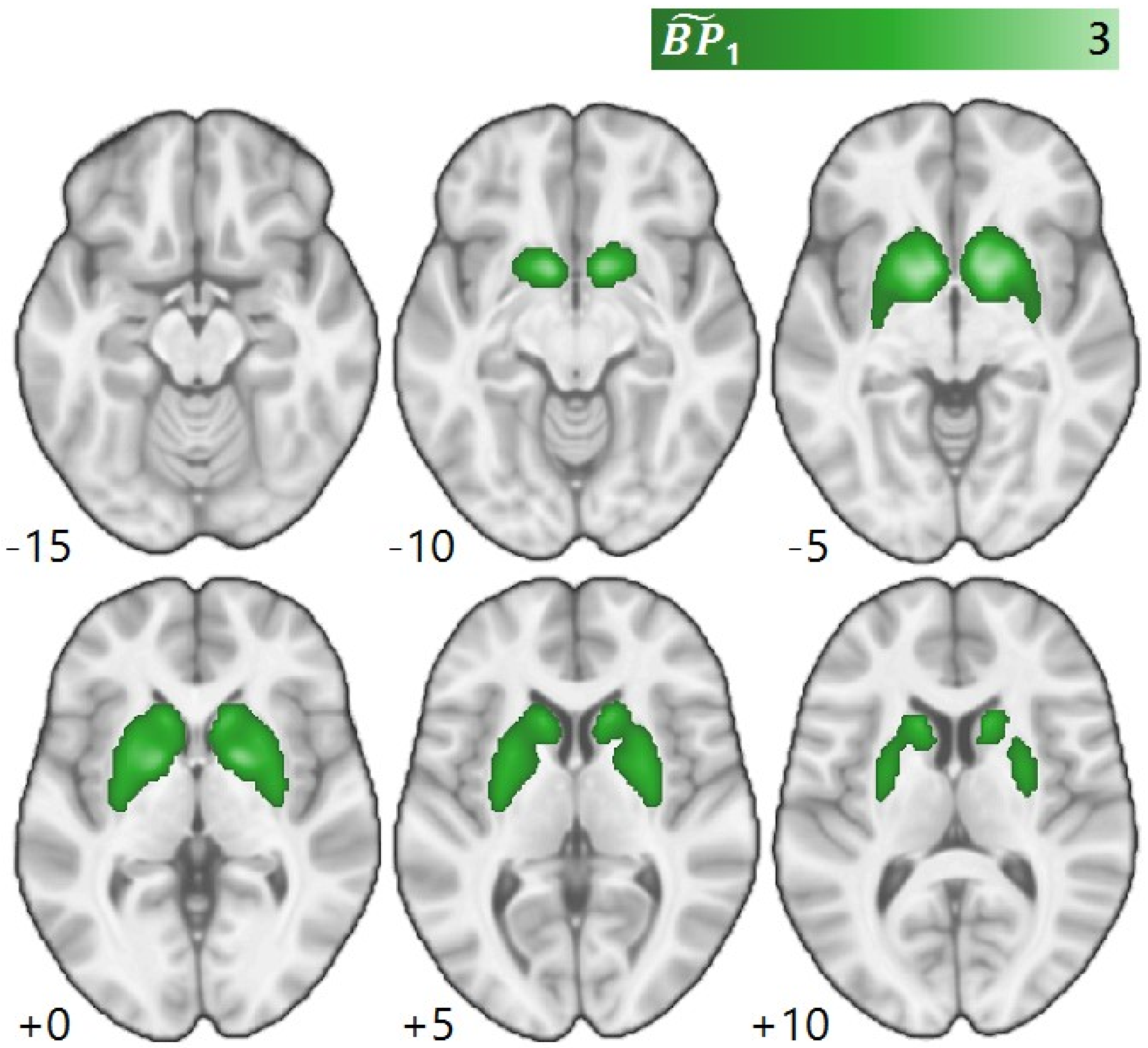


**P*=0.008

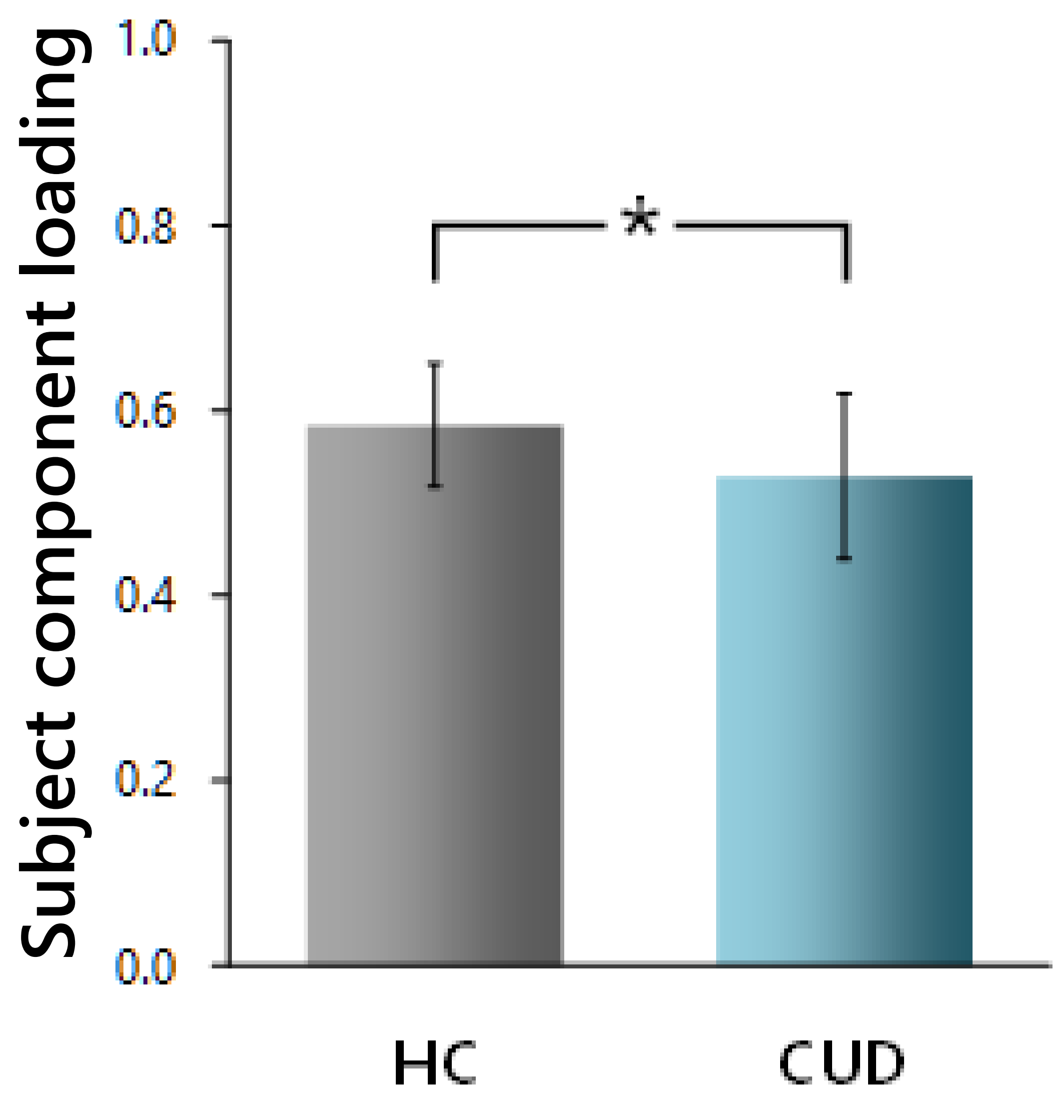
ICA of dopamine D2/D3 PET

- **Striatopallidal source network**

  - Source spatial map



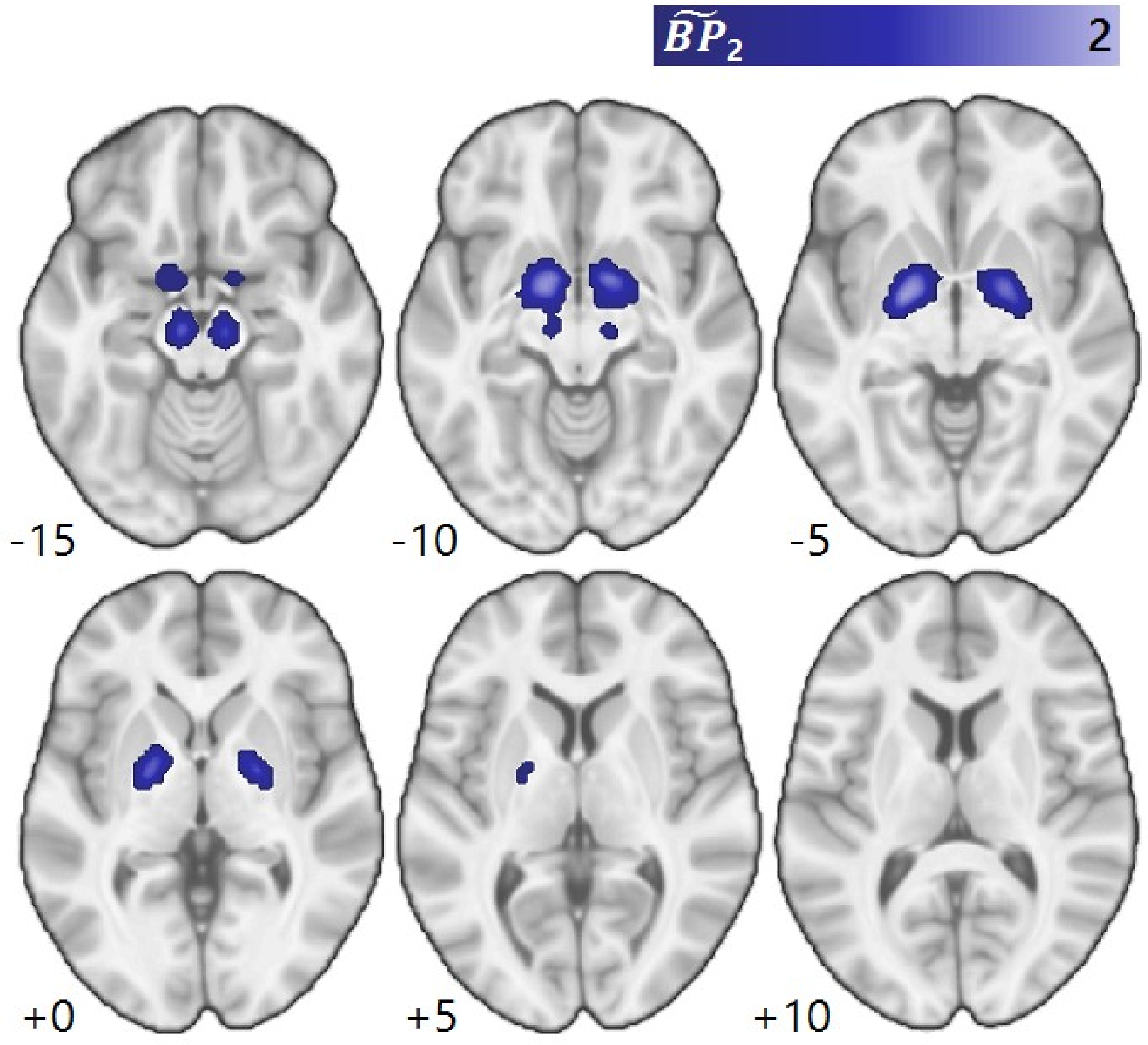
  - Lower component loadings in CUD



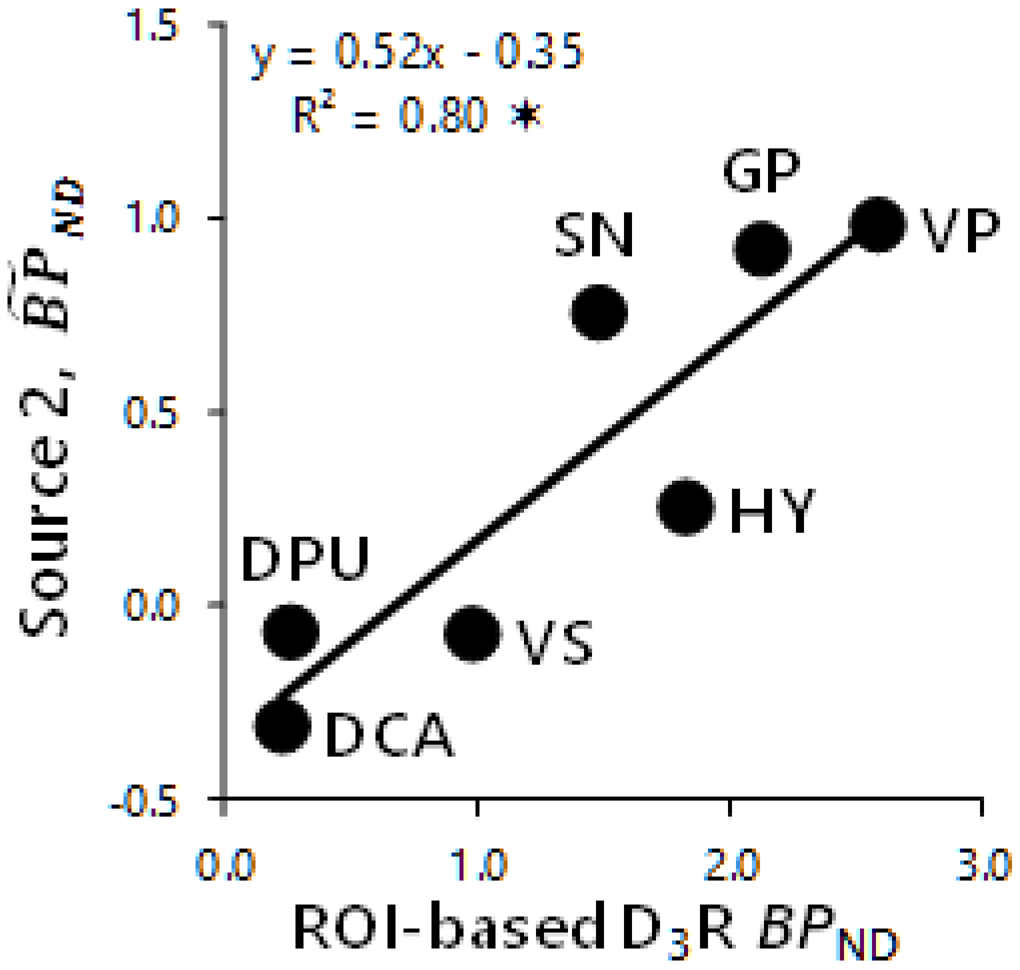
Error bars indicate SD. *P=0.013

ICA of dopamine D2/D3 PET

- **Pallidonigral source network**
  - Source spatial map



- Regional $\widetilde{BP}_{ND}$ correlated with **D3-related** binding

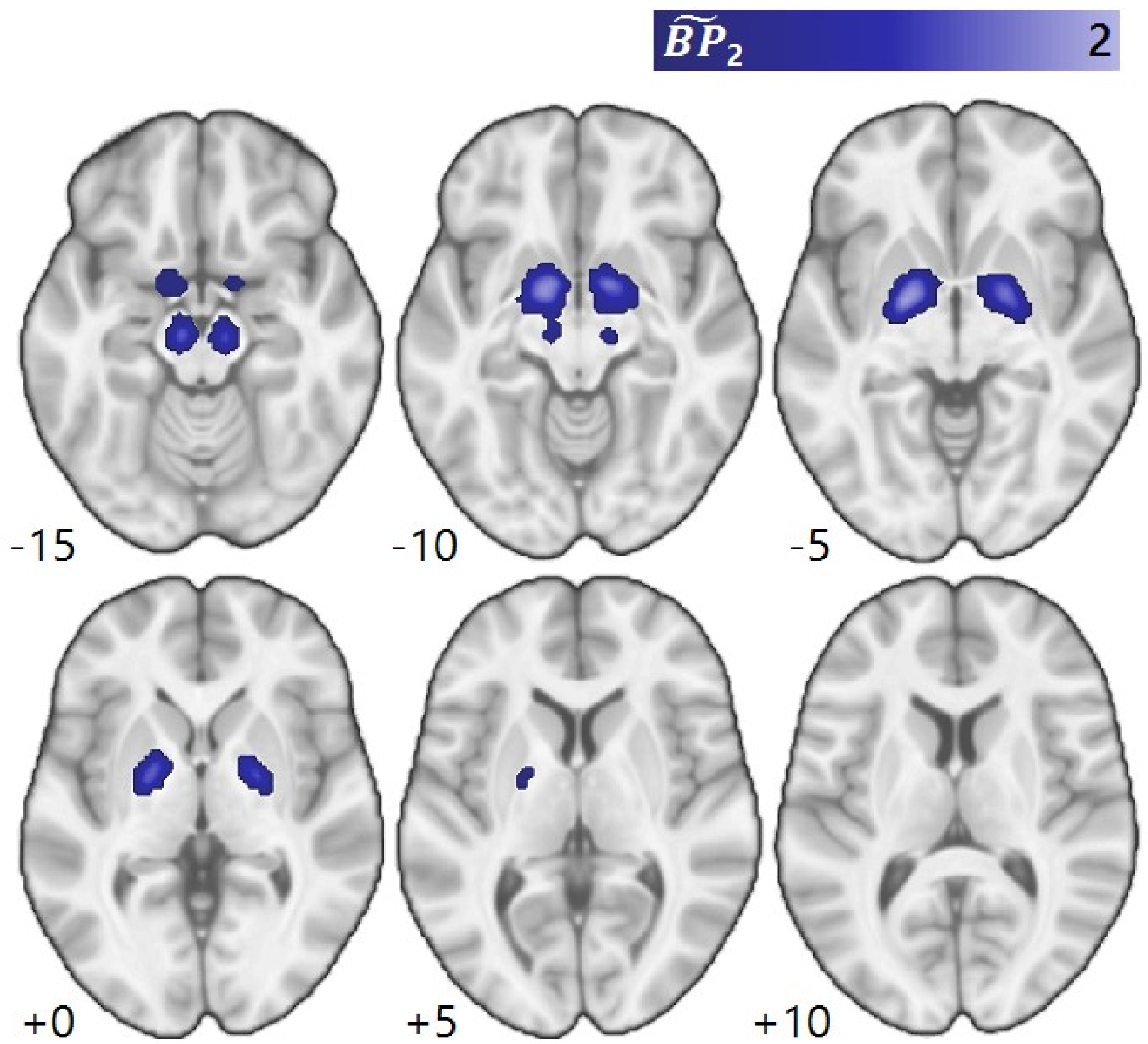


*P=0.007

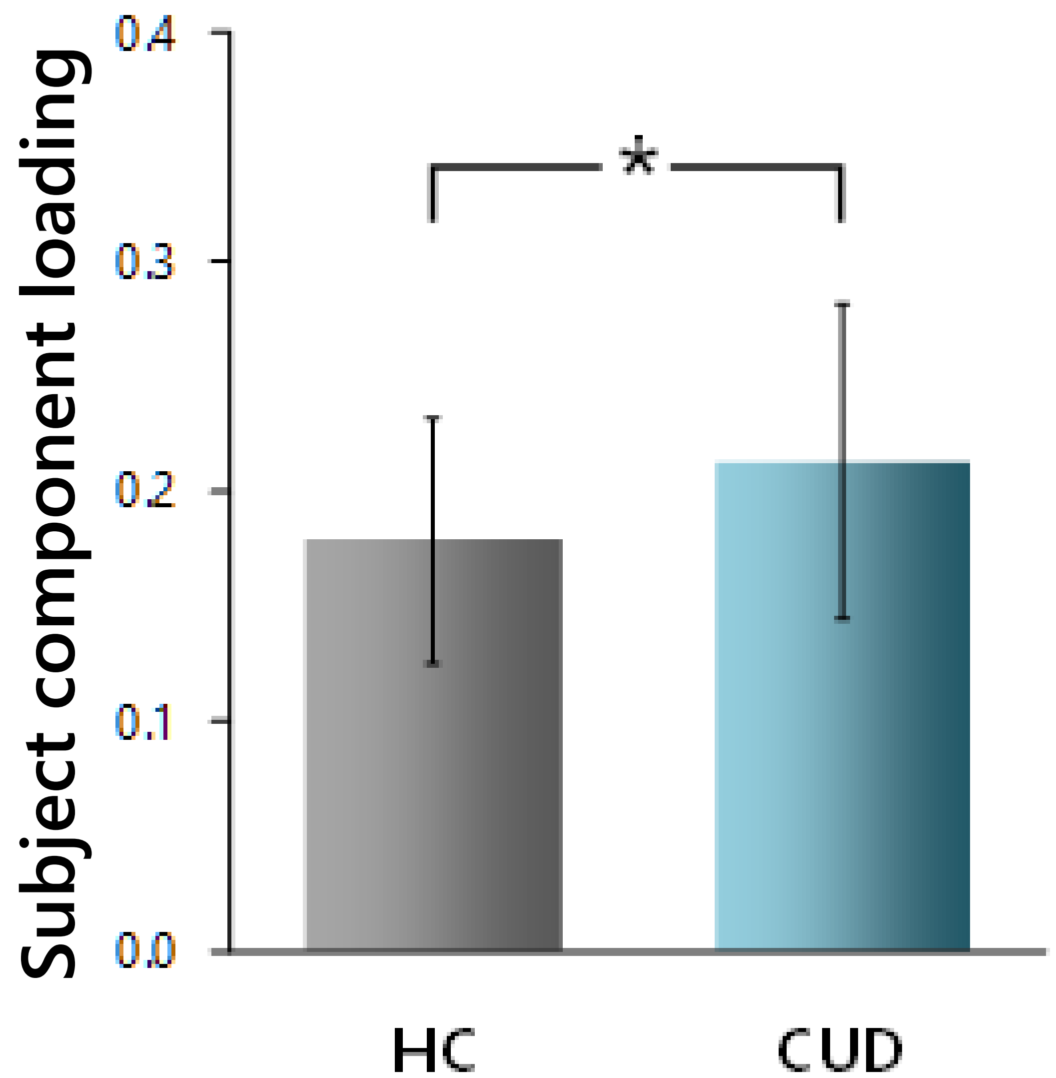
ICA of dopamine D2/D3 PET

- **Pallidonigral source network**

  - Source spatial map



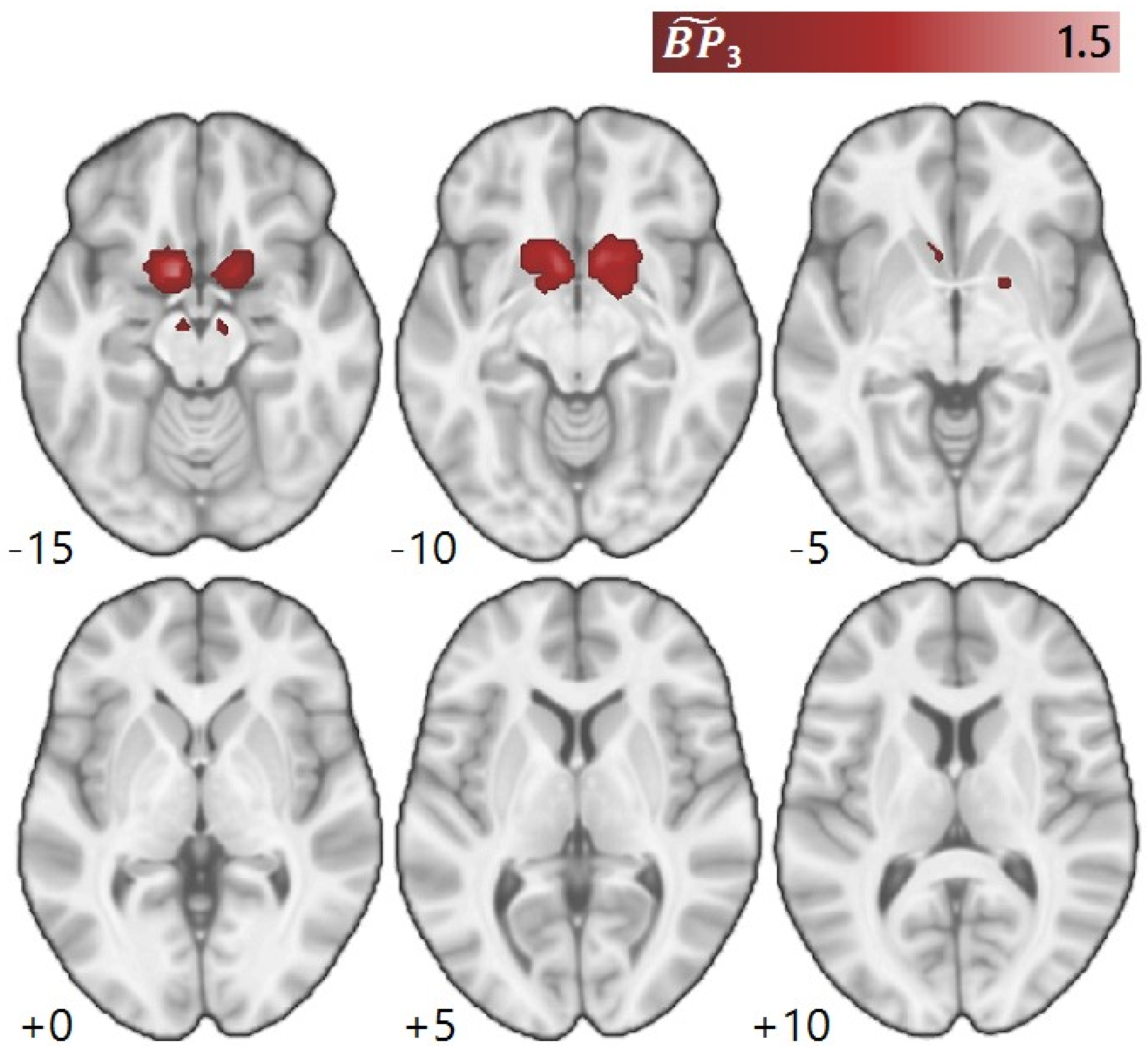
  - Higher component loadings in CUD



Error bars indicate SD. *P=0.047

ICA of dopamine D2/D3 PET

- **Mesoaccumens source network**
  - Source spatial map

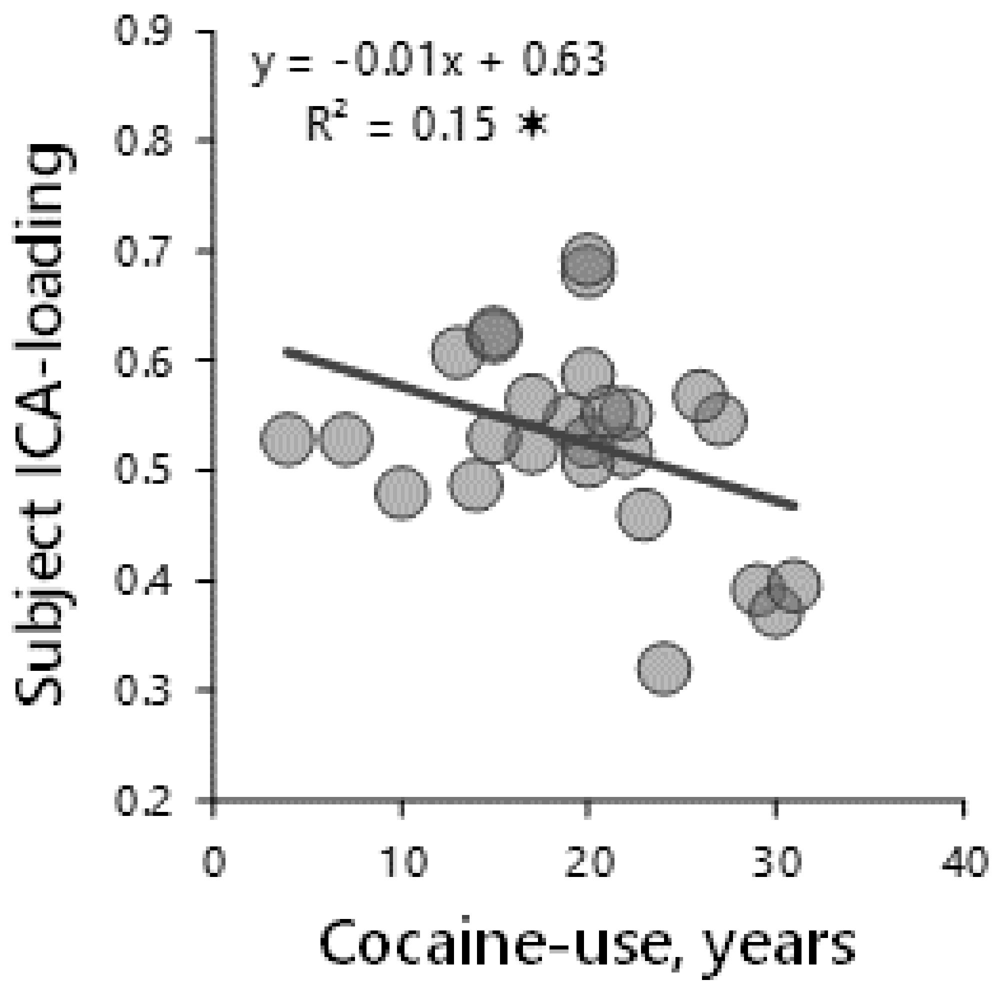


- Encompassed D_3R-rich regions, but not correlated with ROI-based D_3R BP_{ND}
- Relatively weak source of BP_{ND} across ROIs
- No group difference (P=0.11)

ICA of dopamine D2/D3 PET

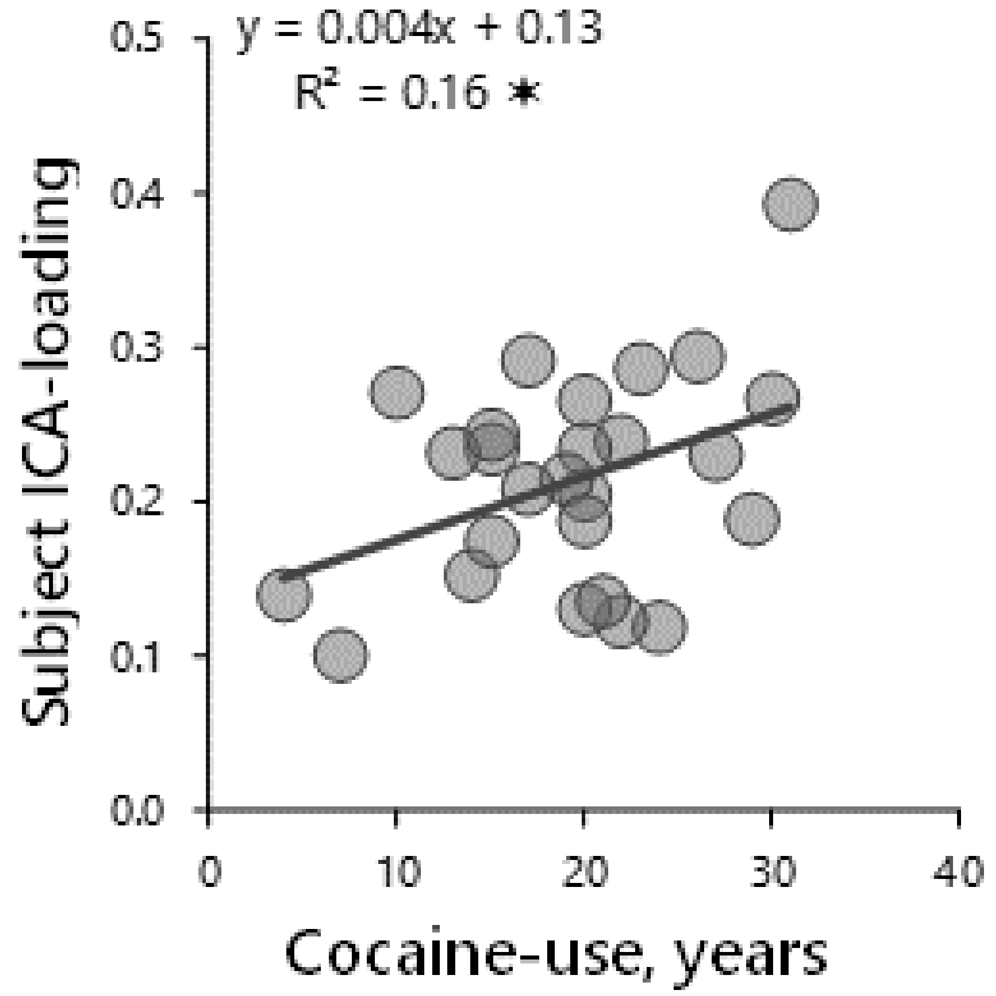
- Component loadings associated with years of cocaine use
- No associations with years of use with standard ROI-based BP_{ND} value

- Striatopallidal (D2)



*p=0.048

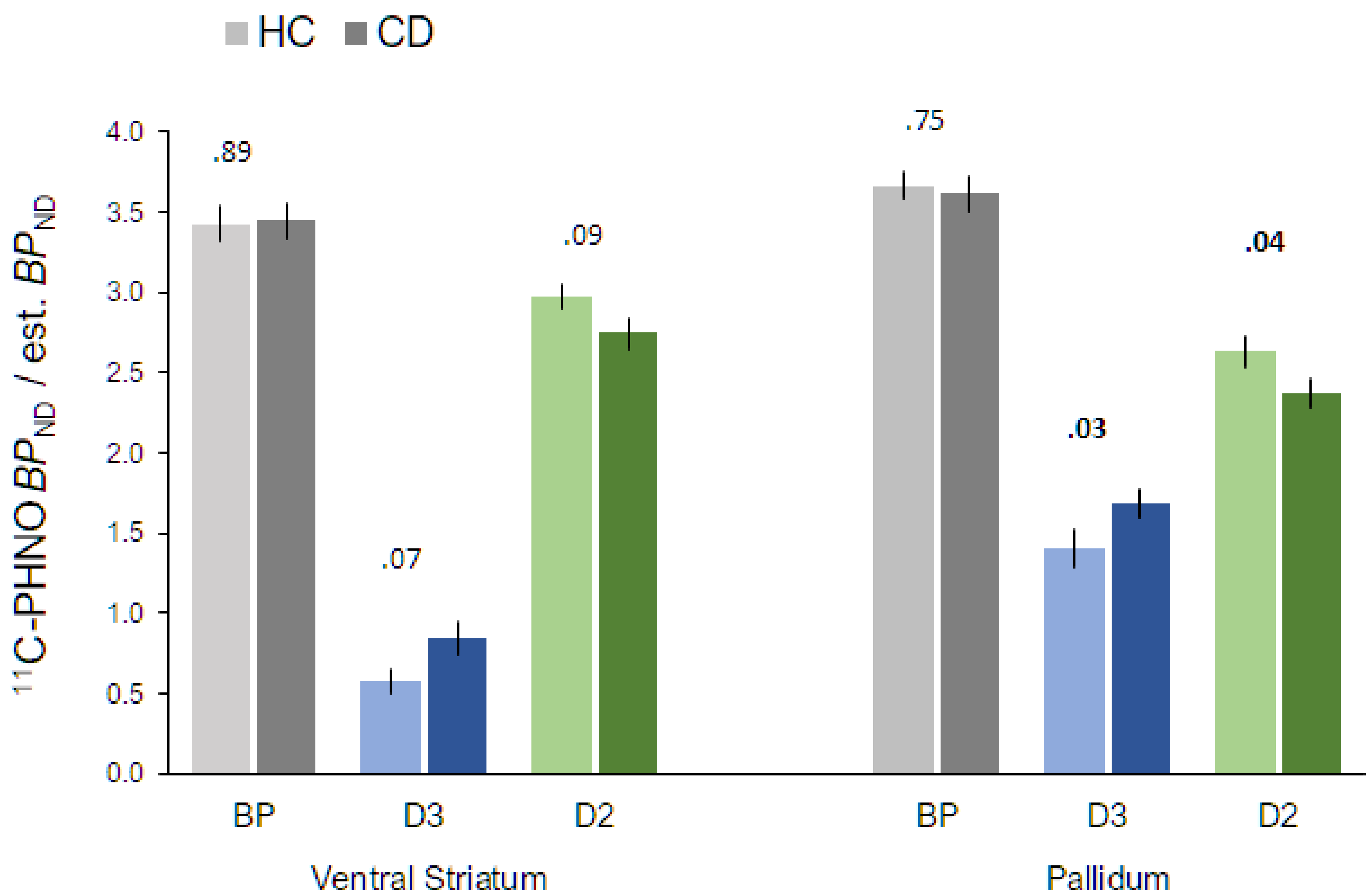
- Pallidonigral (D3)



*p=0.042

ICA of dopamine D2/D3 PET

- **D2/D3 in mixed-binding regions**
- Group differences in the ventral striatum did not achieve significance
- Differences of both lower D2- and higher D3-related binding in the pallidum in CUD



Standard BP_{ND} and ICA-estimated D2- and D3-related BP_{ND} in the ventral striatum and pallidum. Numbers above pairs are p-values of two-sample t-tests. Error bars are SE.

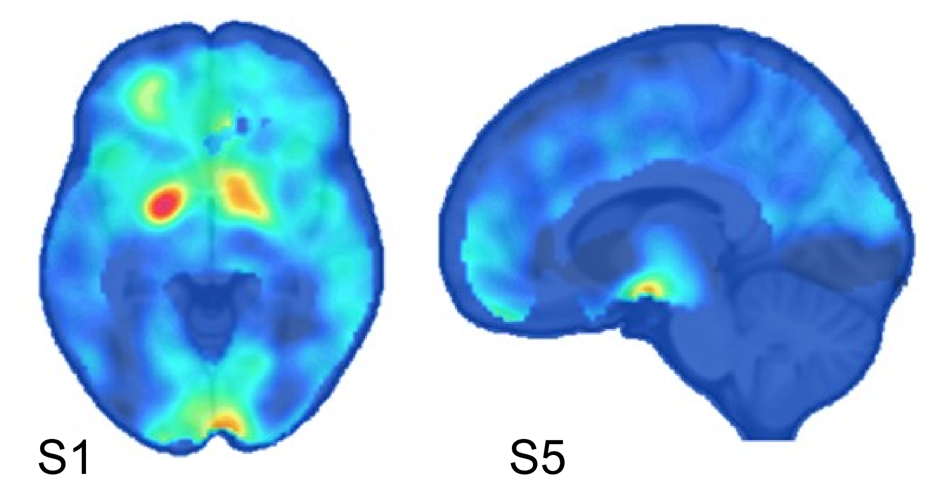
ICA of dopamine D2/D3 PET

- **Summary**
  - [^{11}C]-(+)-PHNO has unique binding profile to assess both D2 and D3 receptors
  - ICA blindly separated D2- and D3-related sources of BP_{ND}
  - ICA estimates were more sensitive to CUD chronicity than standard binding values
  - ICA estimates suggest bi-directional CUD-related alterations in D2 and D3 are present mixed-binding regions (i.e., GP)

ICA of PET

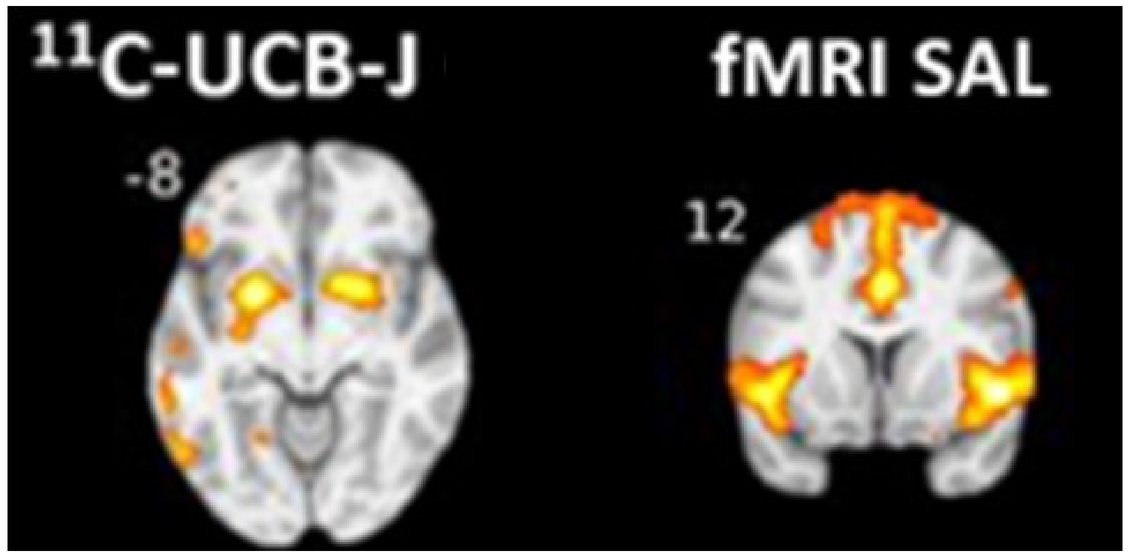
- **ICA of PET using not-mixed-binding-profile radiotracers**
  - ICA of [^{11}C]-P943 (serotonin 1B)
    - Lower 5-HT-1B sources in CUD relative to HC and GD

      Worhunsky et al, work in process



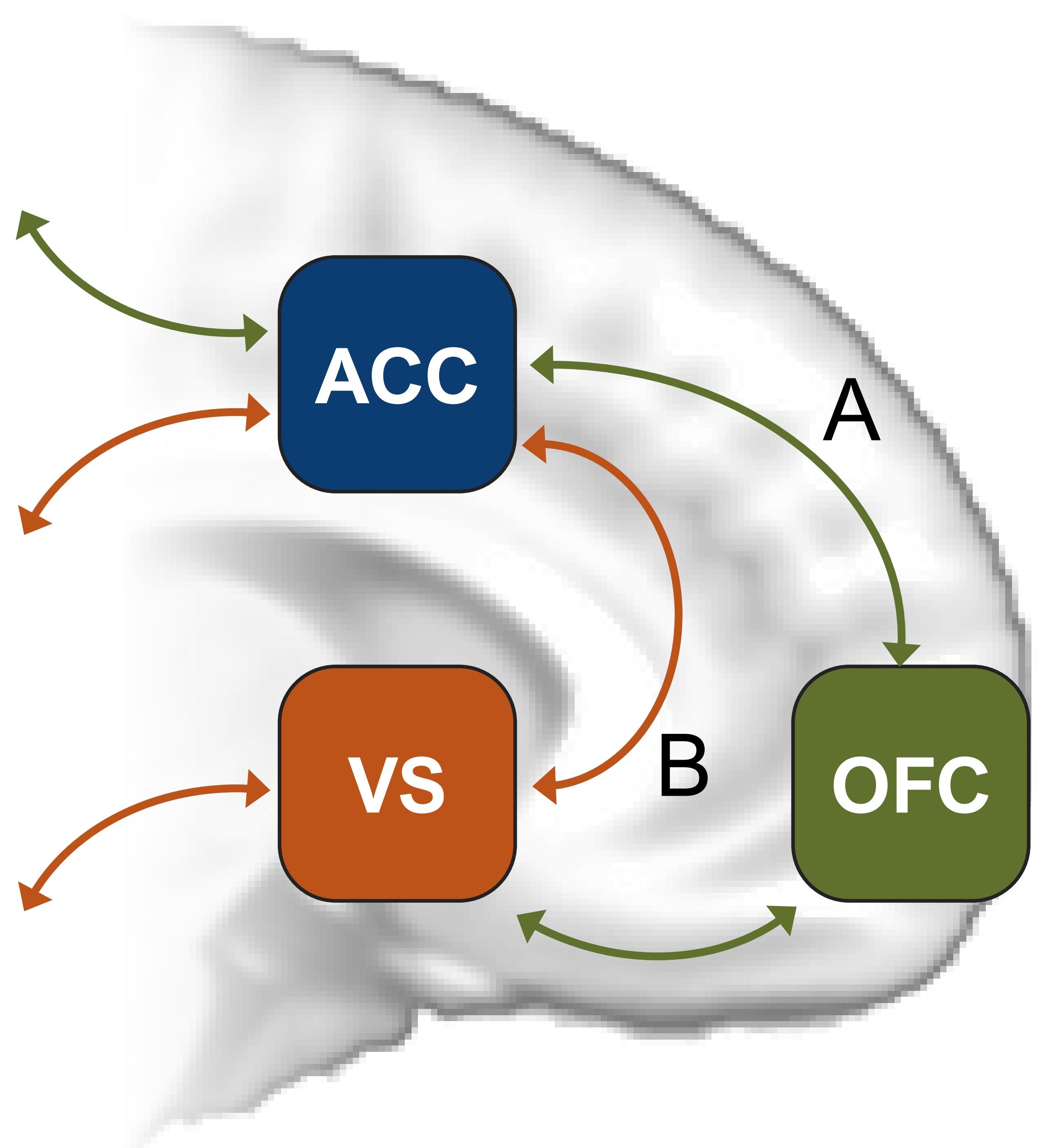
  - ICA of [^{11}C]-UCB-J (SV2A; synaptic density)
    - SV2A sources related to RSN activity in HC

      Fang et al, work in process



ICA of fMRI

- **ICA of fMRI – functional brain networks**
  - Distinct functions may be distributed across a distinct set regions

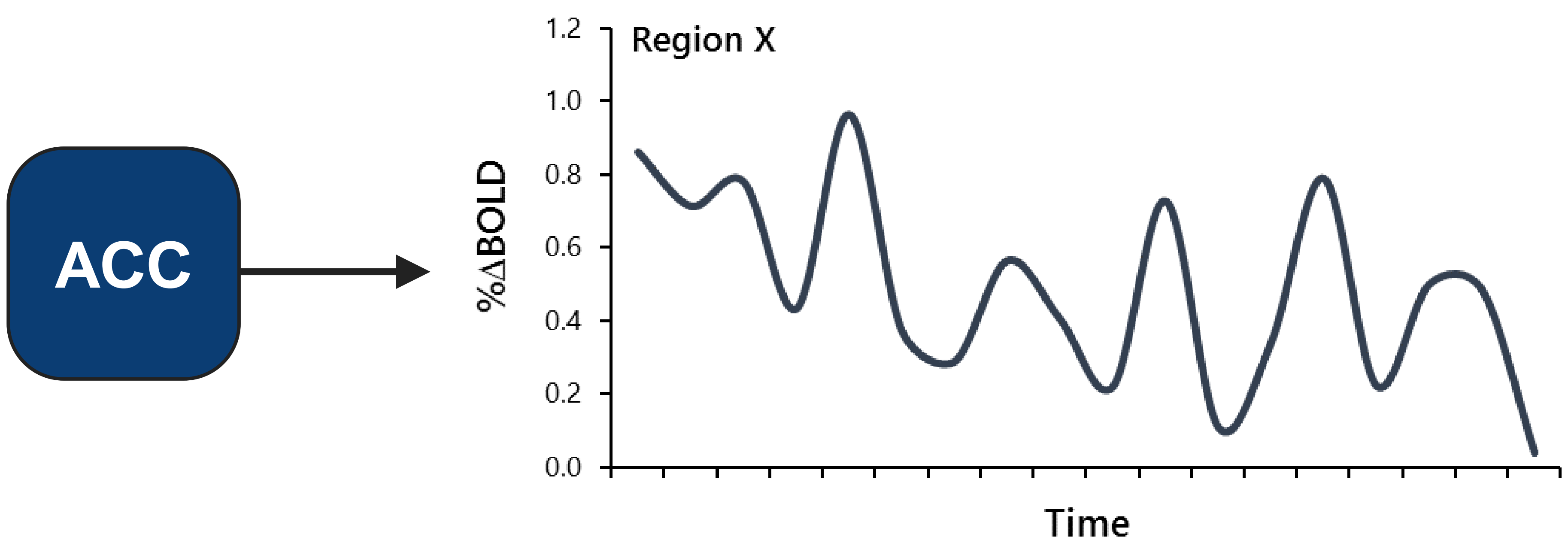


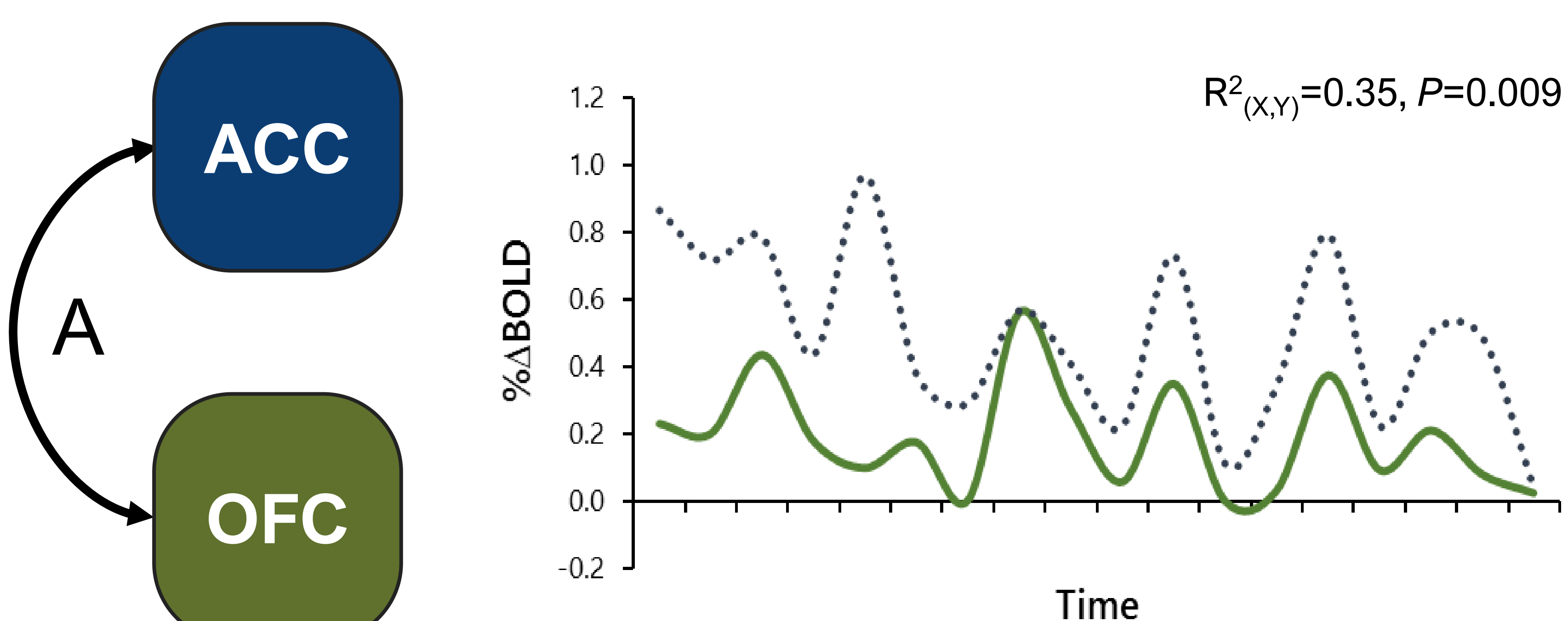
- function A involves the ACC and the OFC
- function B involves the ACC and the VS
- If we see lower ACC activity in addiction, understanding which other regions that activity is connected to can provide insight into which function is impaired

ICA of fMRI

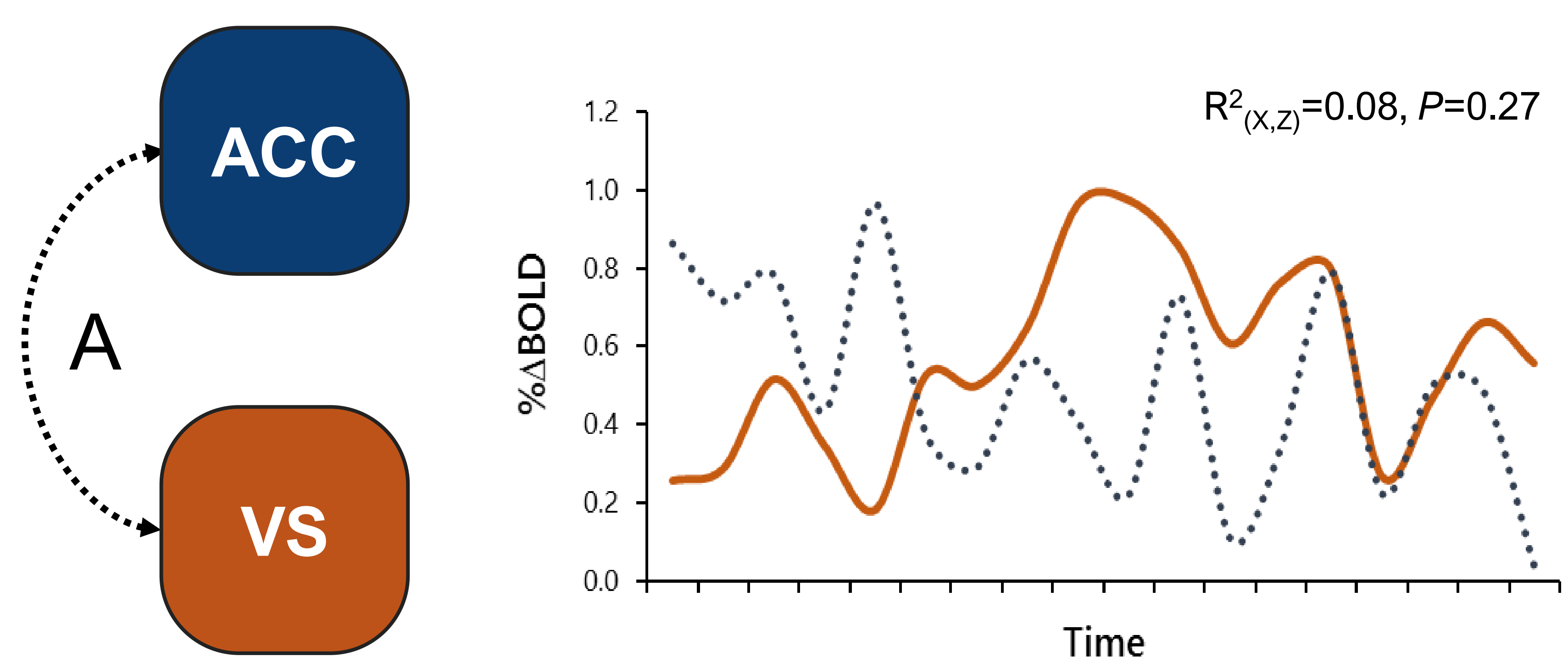
- **Connectivity as temporal correlation in fMRI**
  - e.g., seed-based connectivity

Activity in **ACC** while performing function **A**





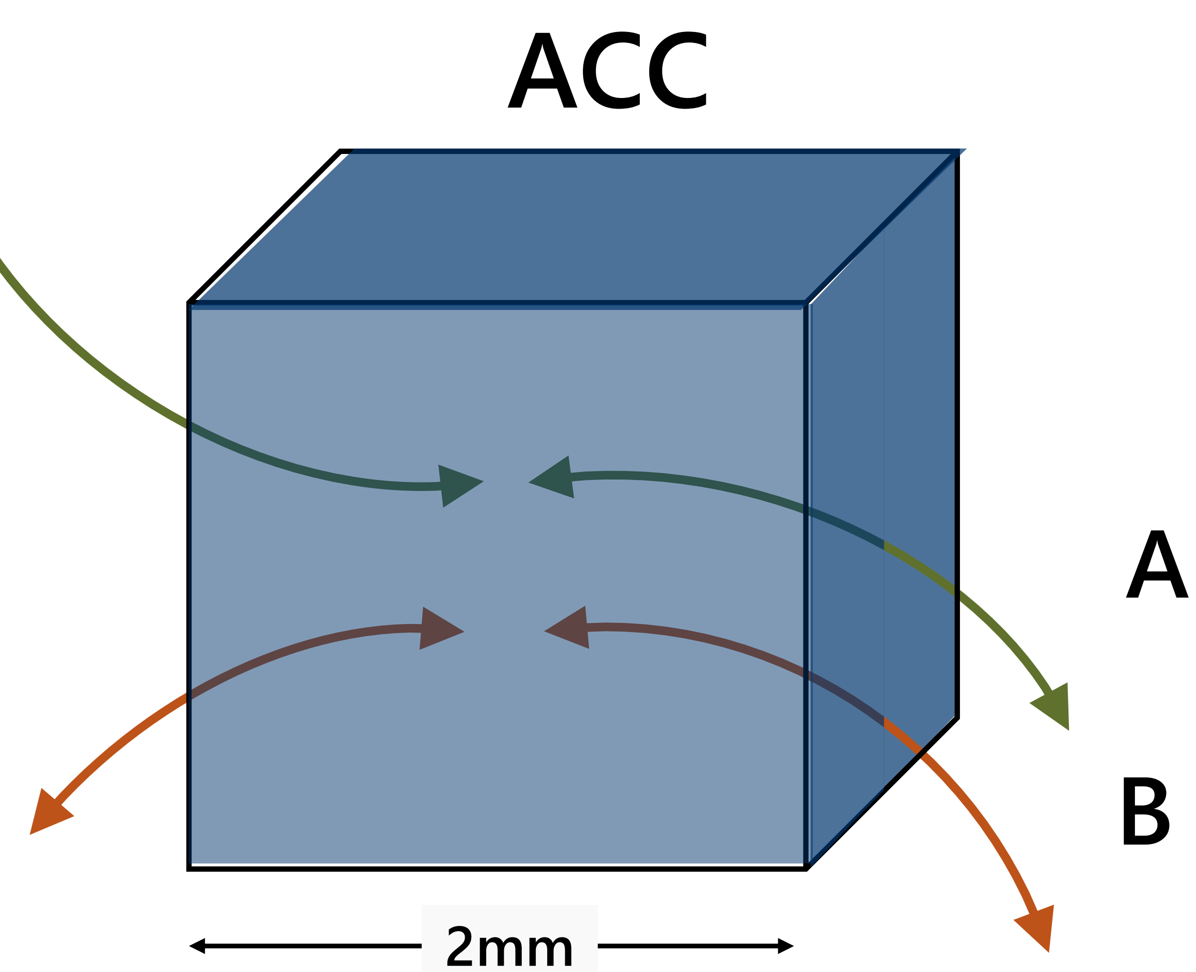
During A, ACC and OFC are connected

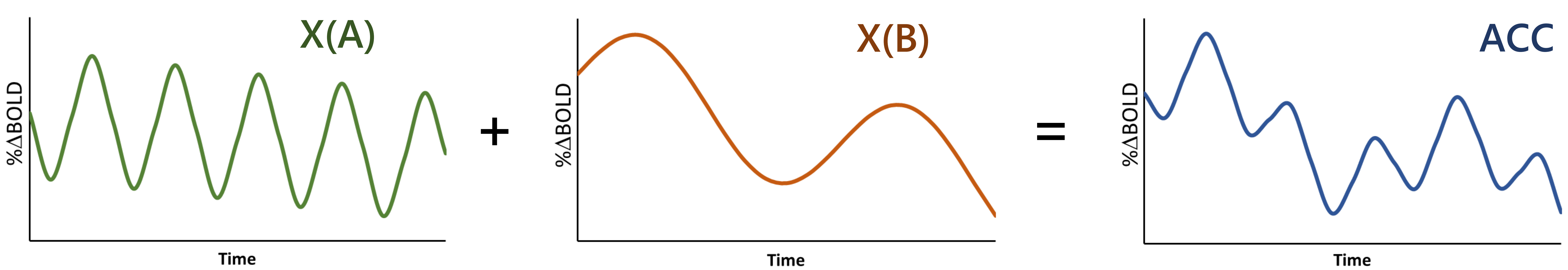


During A, ACC and VS are not connected

ICA of fMRI

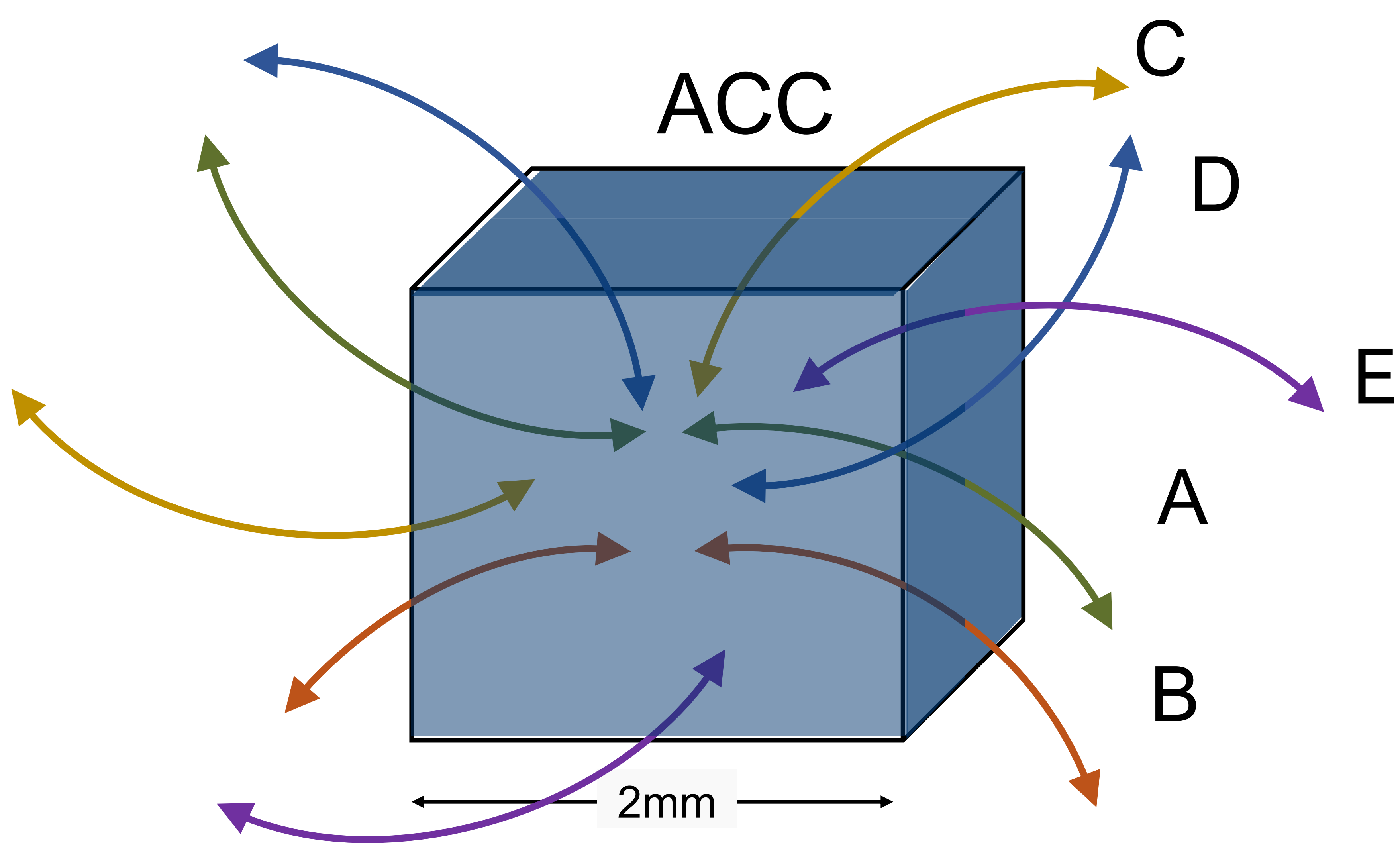
- **fMRI BOLD signal as a summation of local neural activity**
  - "Do A and B simultaneously"
  - BOLD in the ACC is the summation of A and B related signals





ICA of fMRI

- Challenging to isolate single discrete functions in fMRI task-design
- **fMRI BOLD as a mixture of 'functional components'**

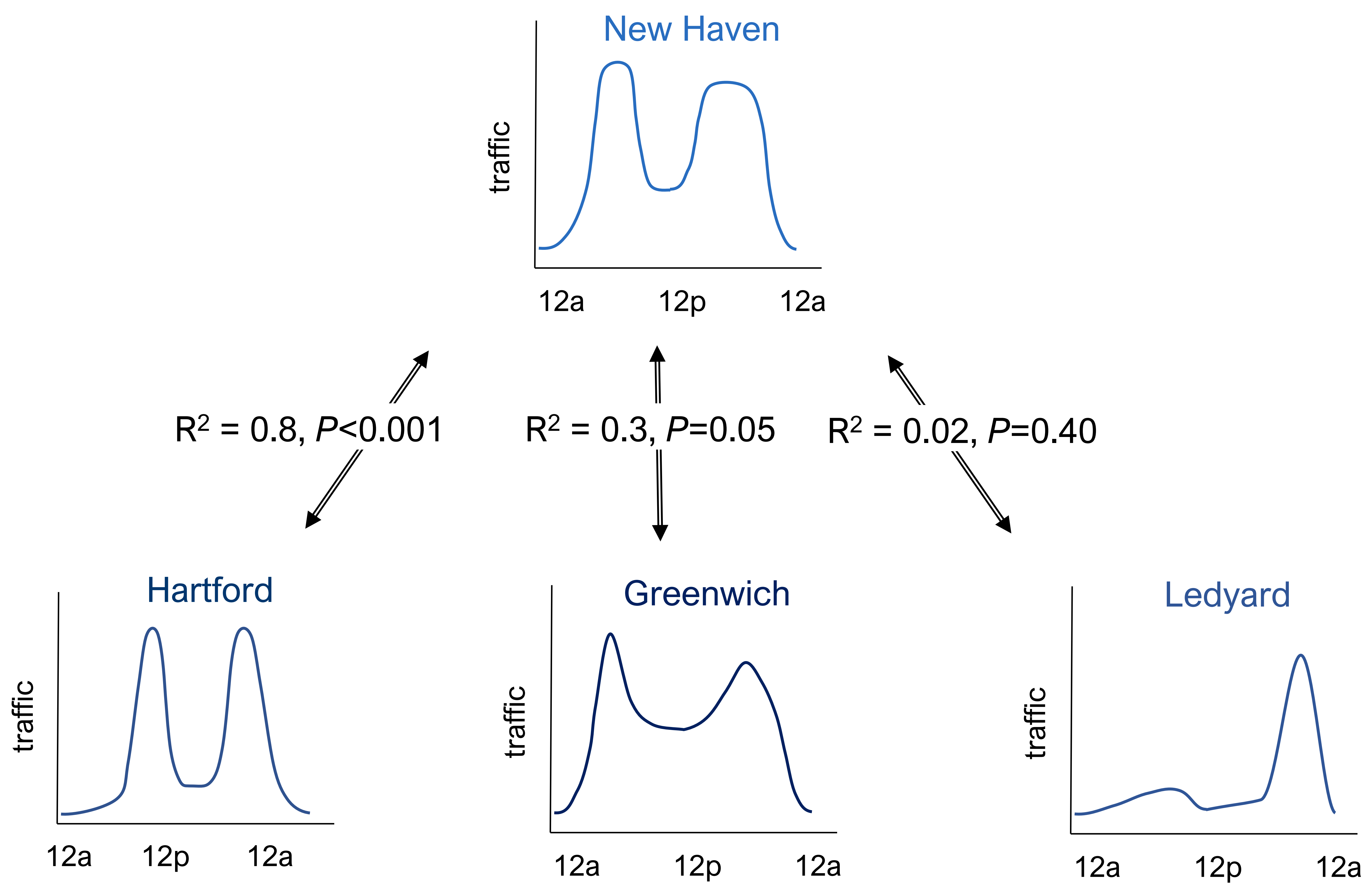


X(A) + X(B) + X(C) + X(D) + X(E) = ACC

Y(A) + Y(F) + Y(G) + Y(H) + Y(J) = OFC

functional components

- What is New Haven traffic related to?
  - Traffic in other Connecticut cities (connectivity)?



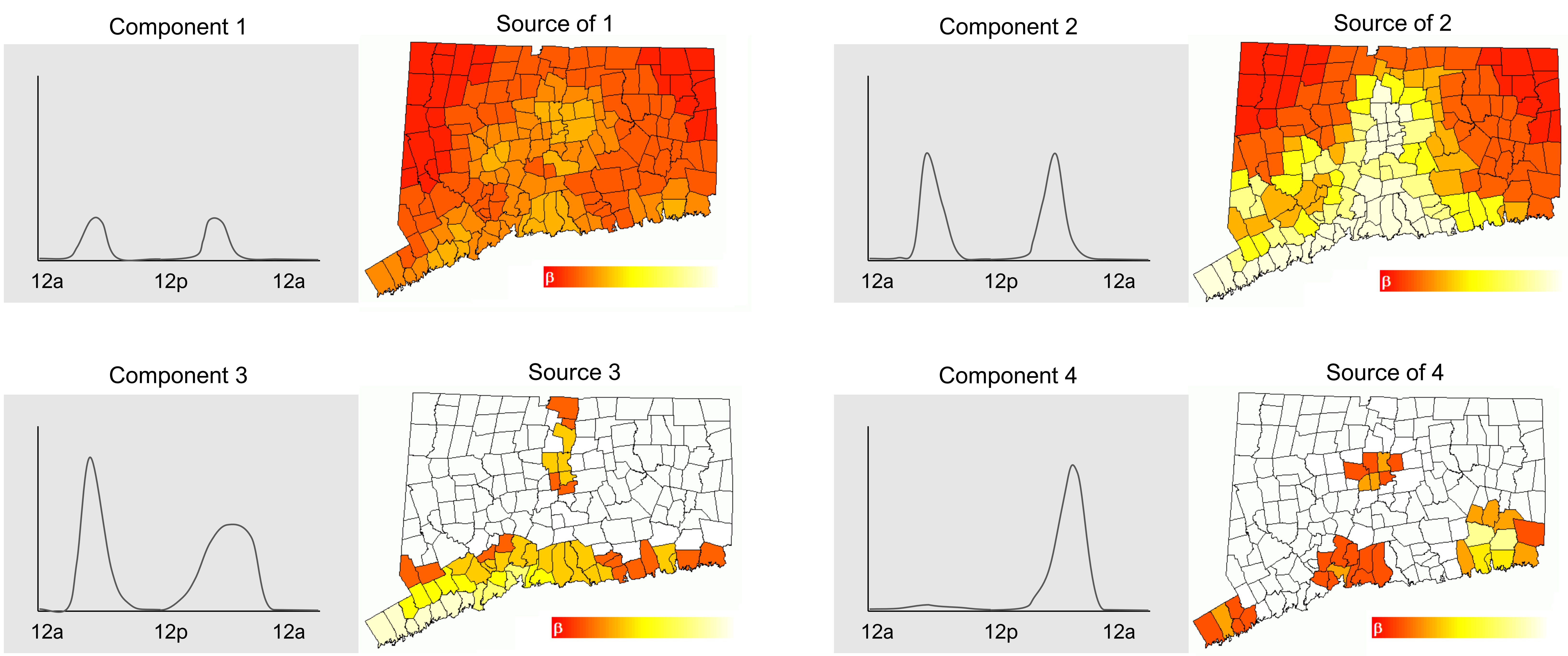
Yes! New Haven traffic is connected to Hartford

New Haven traffic may be connected to Greenwich

New Haven traffic is not connected to Ledyard

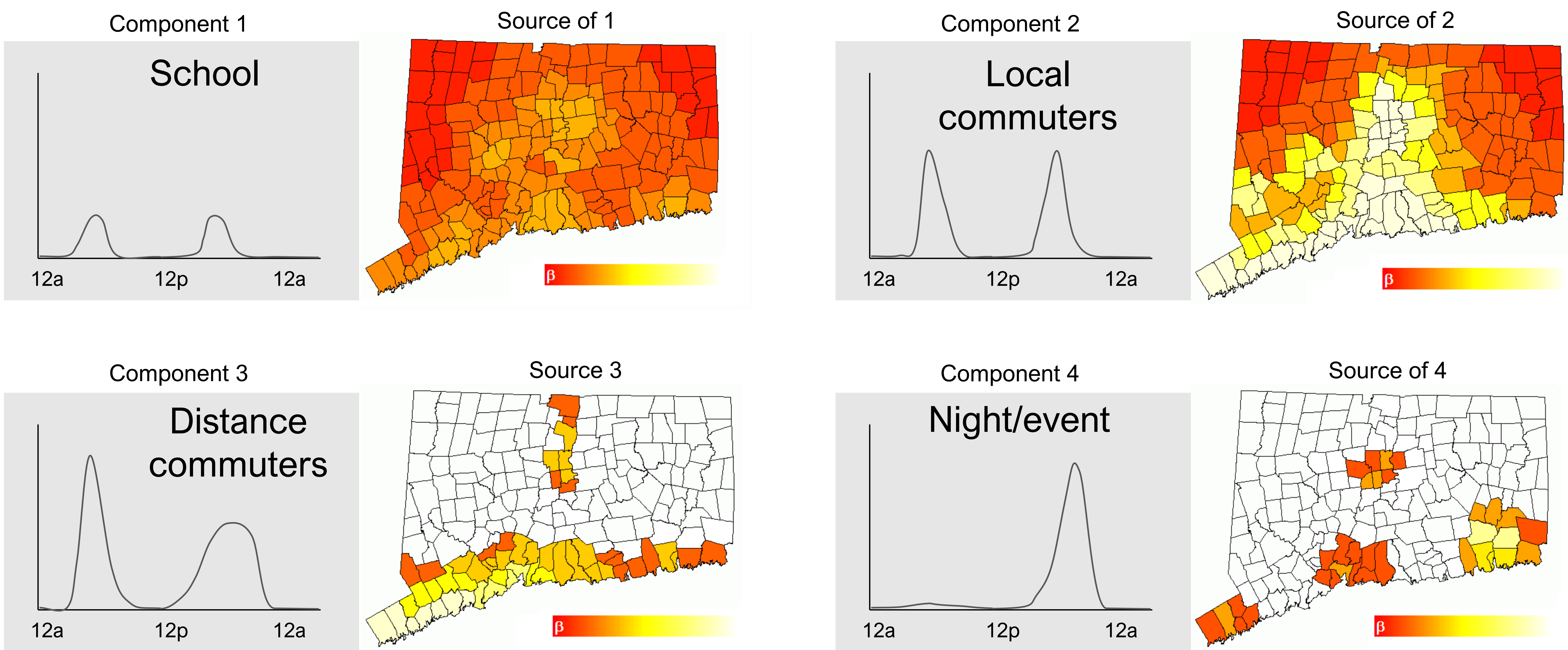
functional components

- What are the sources and components of traffic in Connecticut?



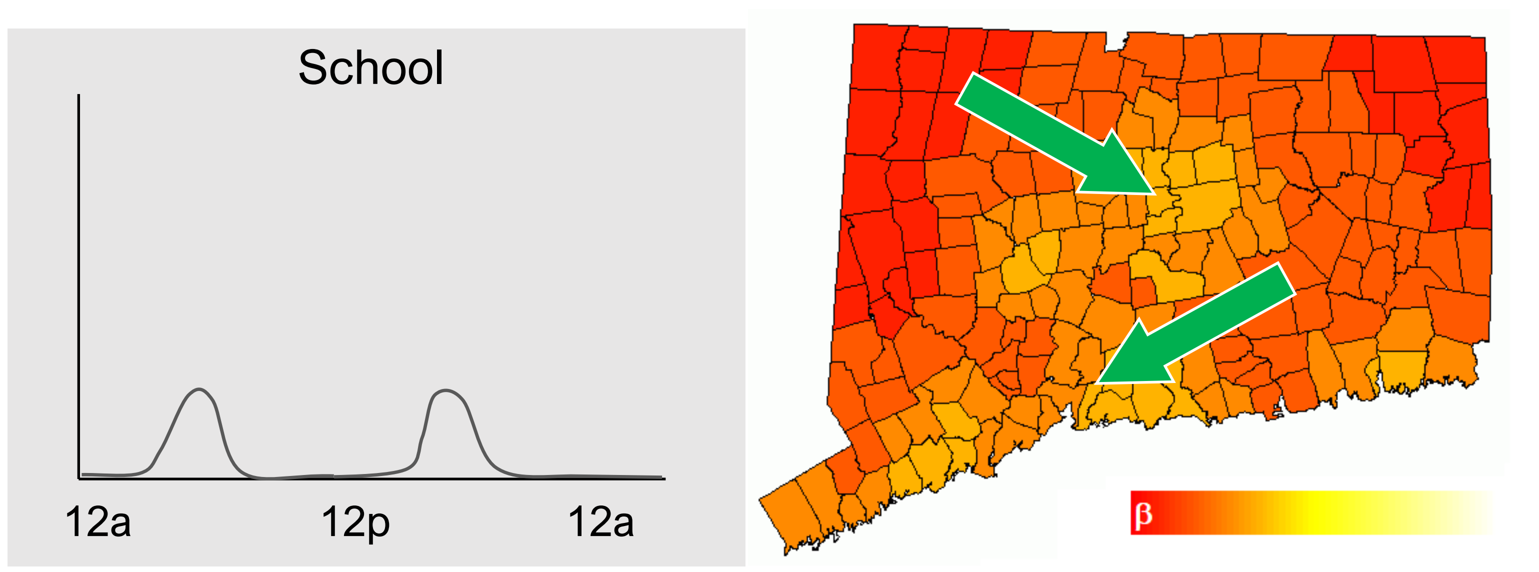
functional components

- Can test models (or make inferences) about types of traffic each source/component represents



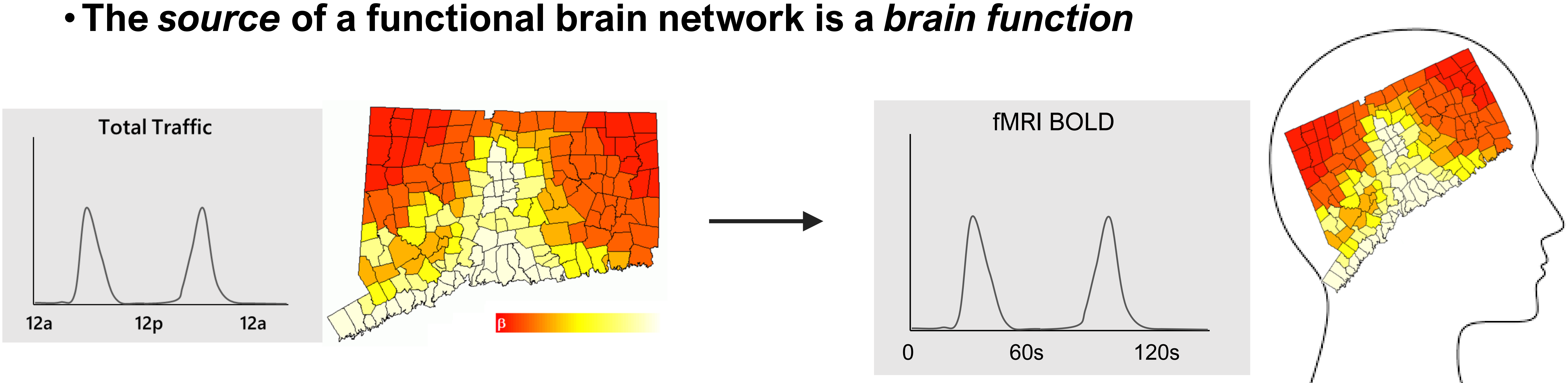
functional networks

- **Functional network (network of function)**
  - No assumption of connectivity/effectivity (functional network ≠ connectivity network)



Hartford school traffic does not cause or influence New Haven school traffic, but both ‘signals’ are processing school-related traffic

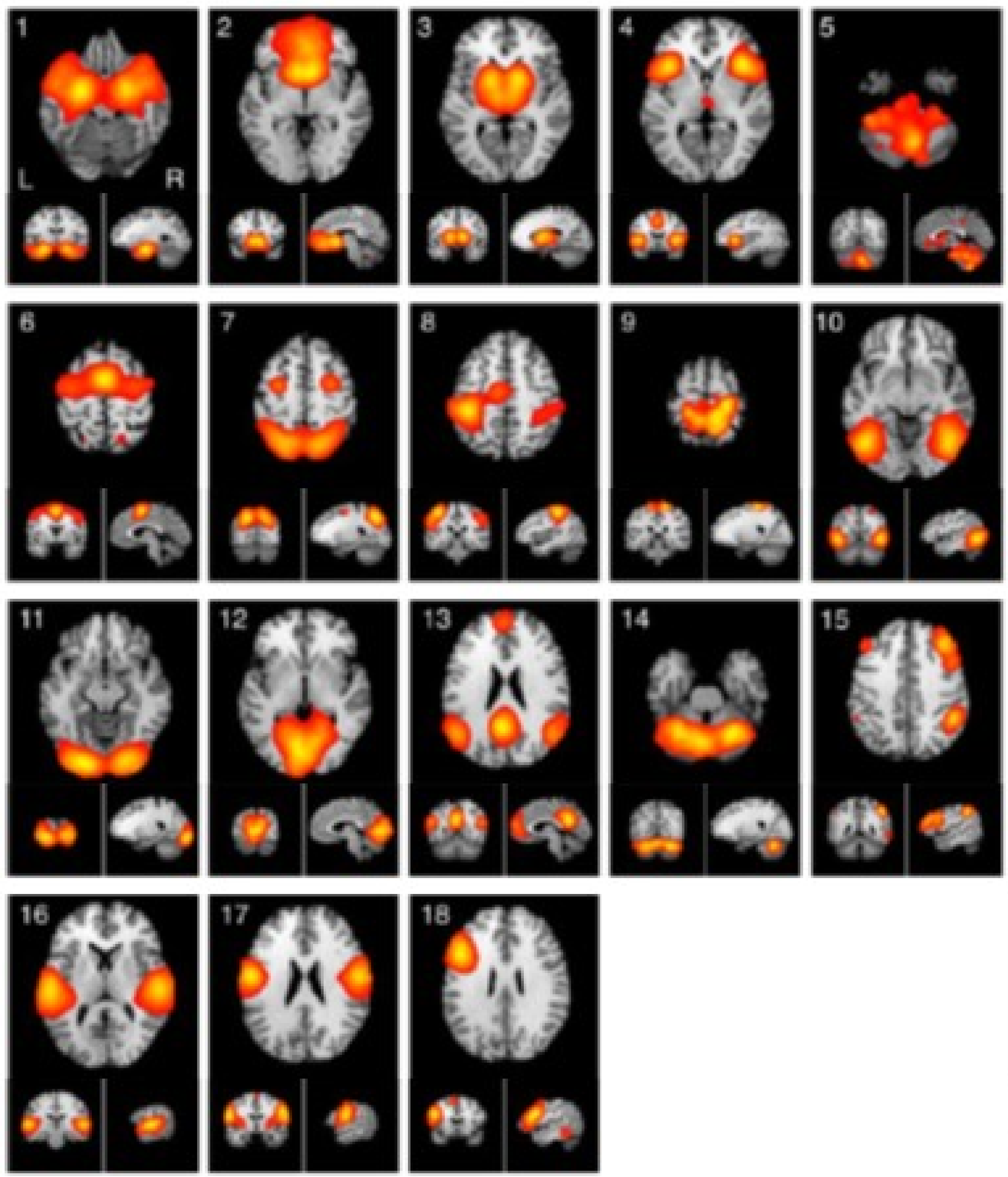
  - Networks of ‘types’ of cars (car-functions), not cars travelling place to place
  - Functional network: ‘*network of sources of a component function’*
  - fMRI: A set of regions that source a temporal component of the BOLD mixture ’
  - **The *source* of a functional brain network is a *brain function***



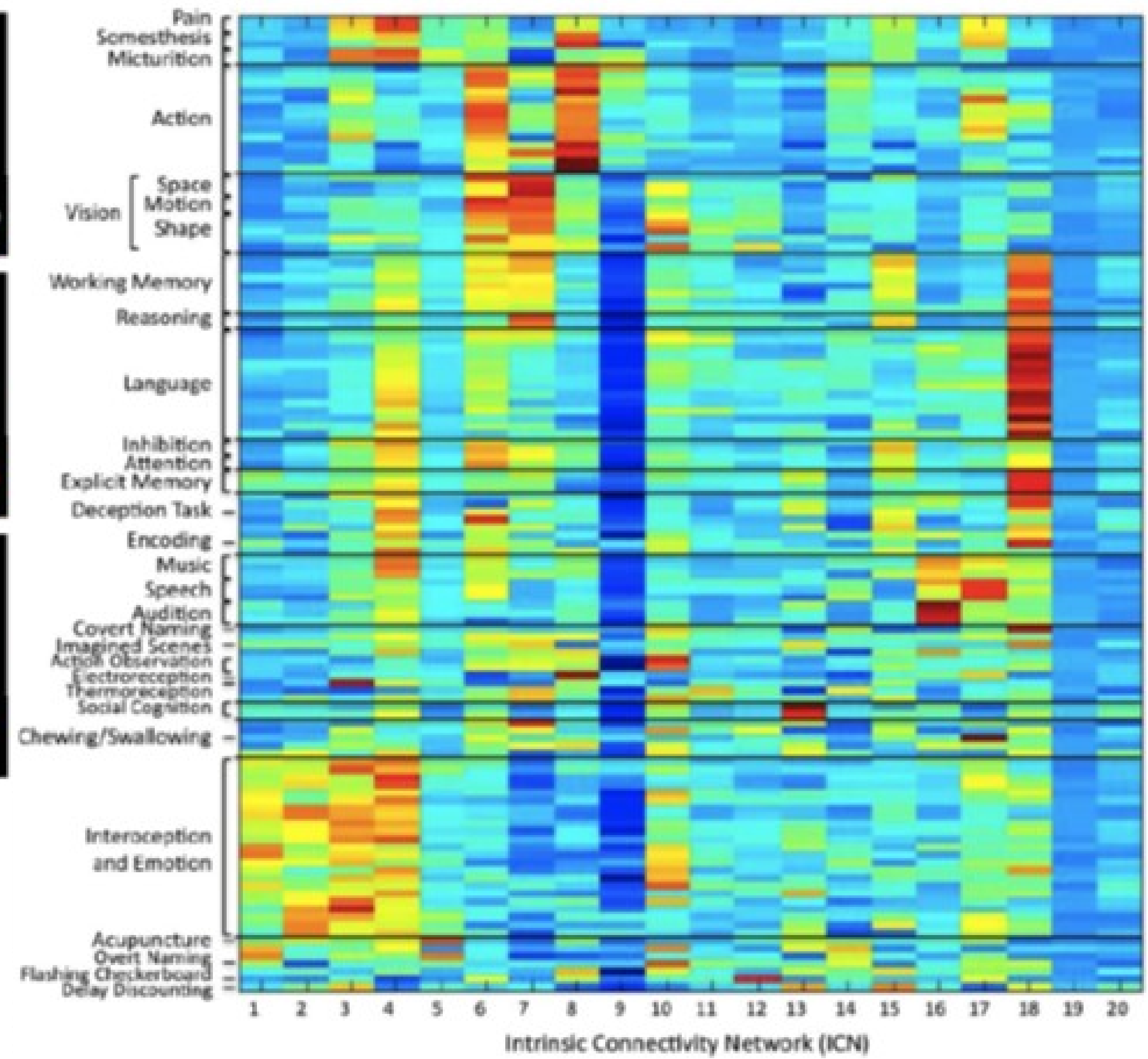
functions of functional networks

- Meta-analysis of component brain networks and associated functional domains

ICA of 8,637 peak-activation maps



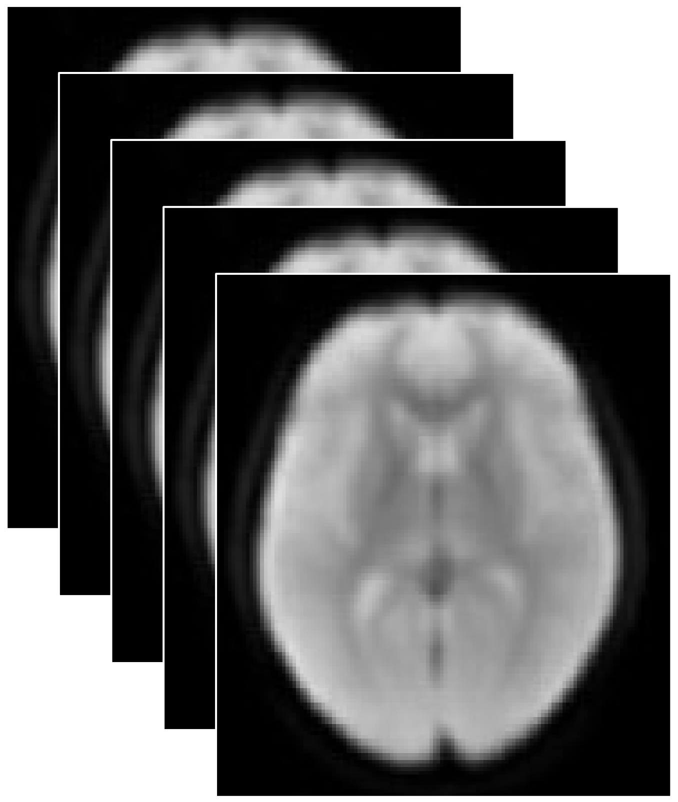
Regression with study functional domains



Laird, et al 2011

ICA of fMRI

- **ICA input**



BOLD timeseries

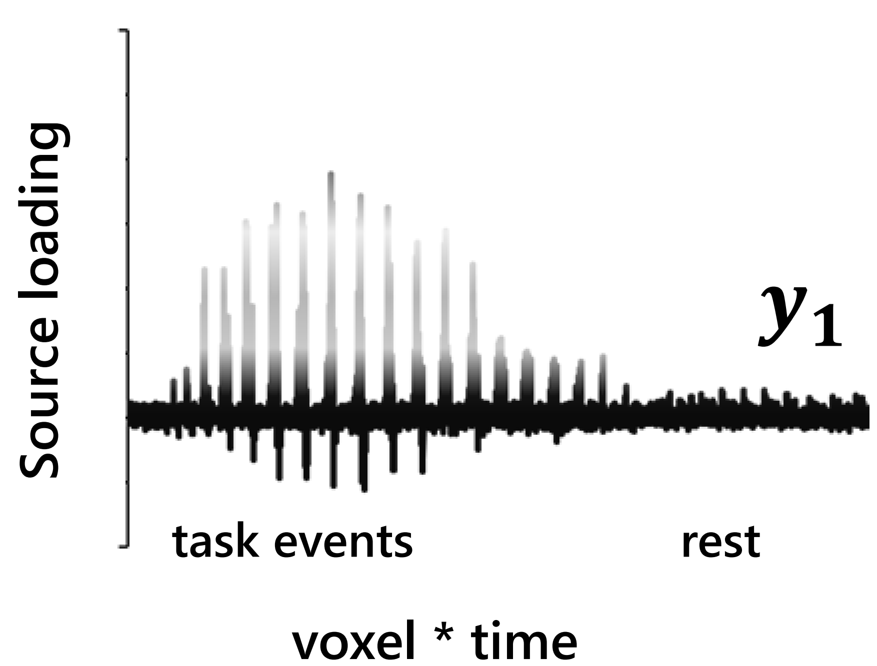
voxel * subject

PCA
ICA

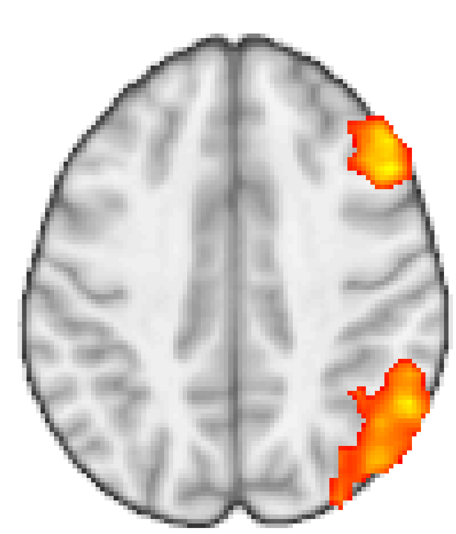
$$
\begin{array}{c|ccc}
 & \multicolumn{3}{c}{\text{sources} \longrightarrow} \\
 & y_1 & y_2 & y_M \\
\hline
\text{components} \downarrow & a_{1,1} & a_{1,2} & a_{1,M} \\
 & a_{2,1} & a_{2,2} & a_{2,M} \\
 & a_{3,1} & a_{3,2} & a_{3,M} \\
 & a_{N,1} & a_{N,2} & a_{N,M}
\end{array}
$$

un-mixing matrix

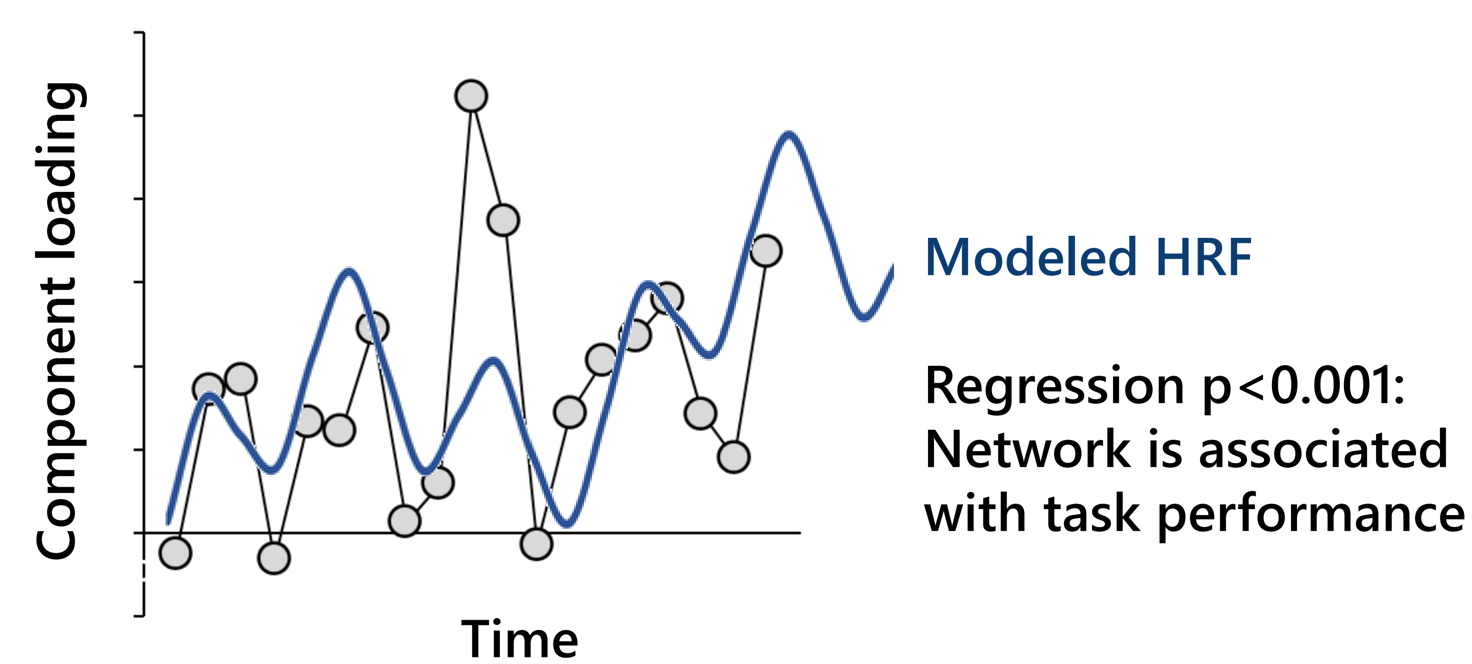
- Back-reconstruct subject-level data



Subject
source vector



Subject
source map



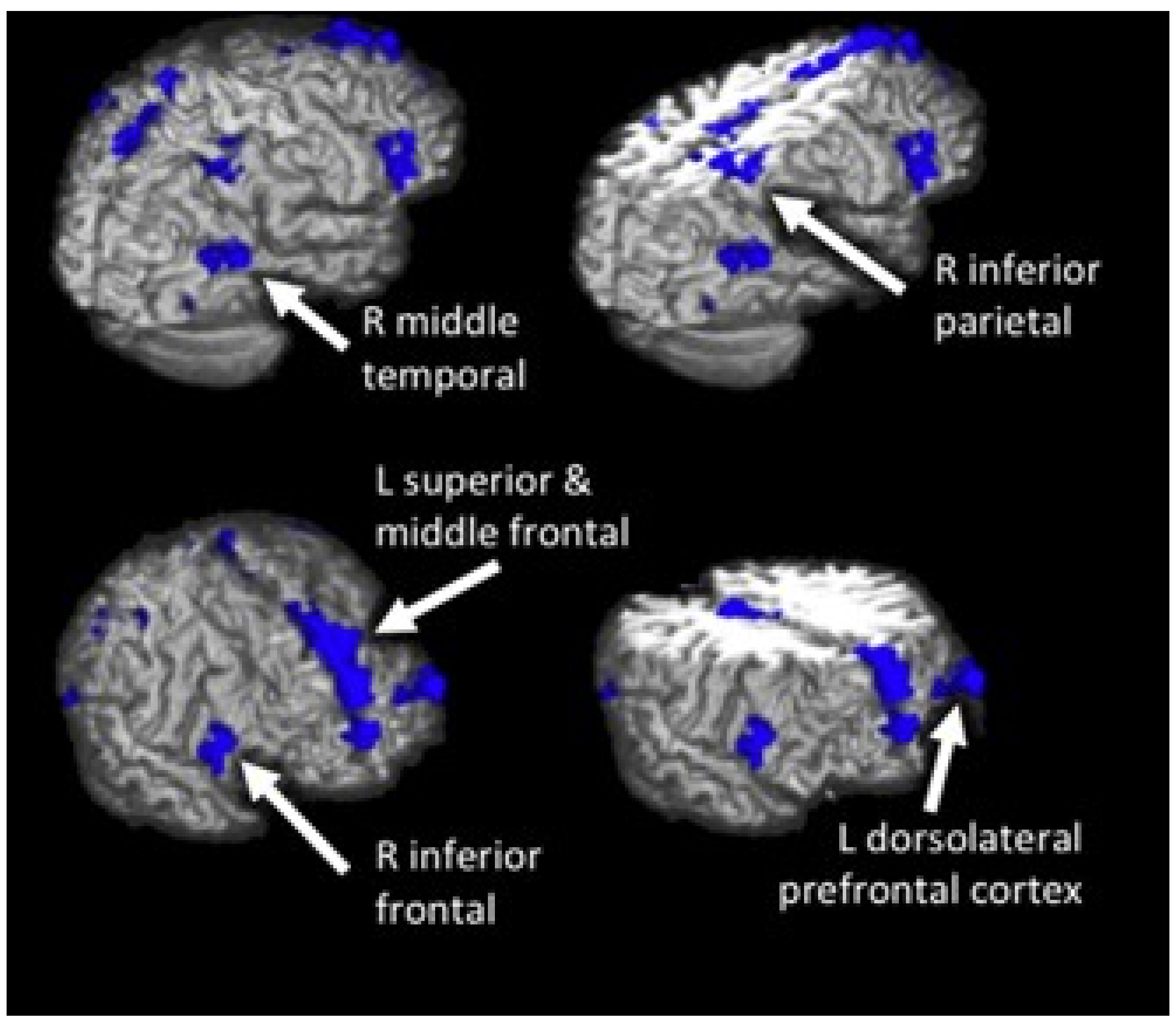
Subject component time course

functional networks in young adult drinkers

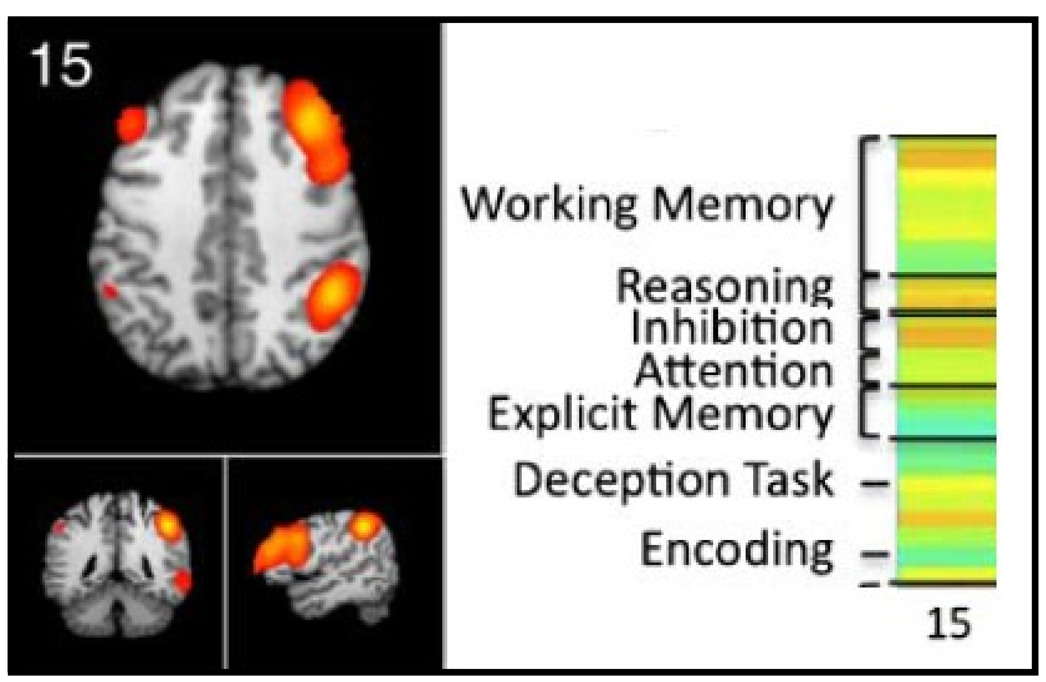
- Response inhibition (Go/NoGo) and college drinking trajectories

- Widespread reductions in inhibitory activity related to initiating drinking.
- Lots of regions with lots of functional implications

- Right frontoparietal network reduced on average in binge-drinkers
- Reduced frontoparietal in committing errors predicted 1-year escalation in binge drinking



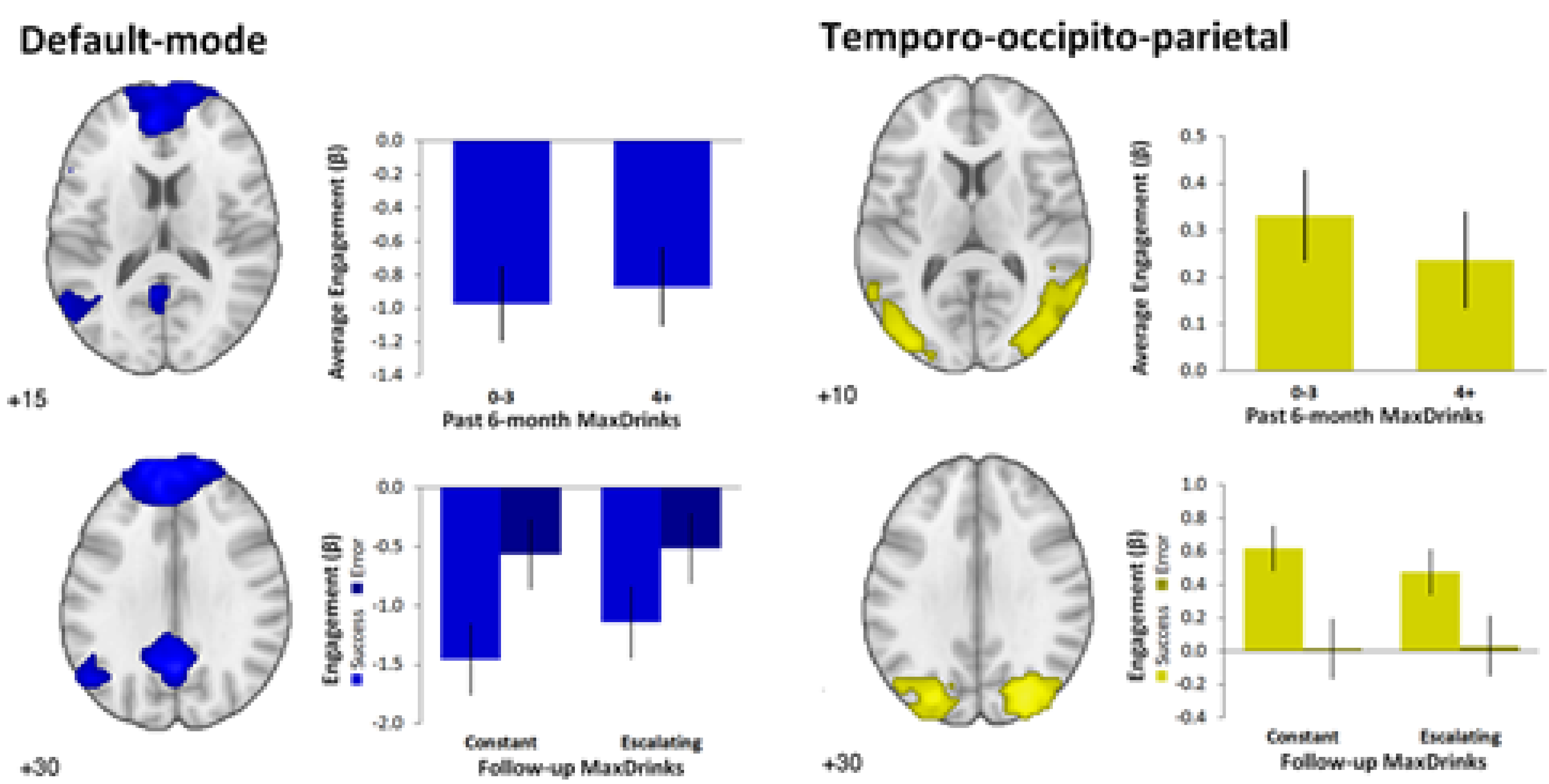
Adol. drinking initiators; Norman et al, 2011



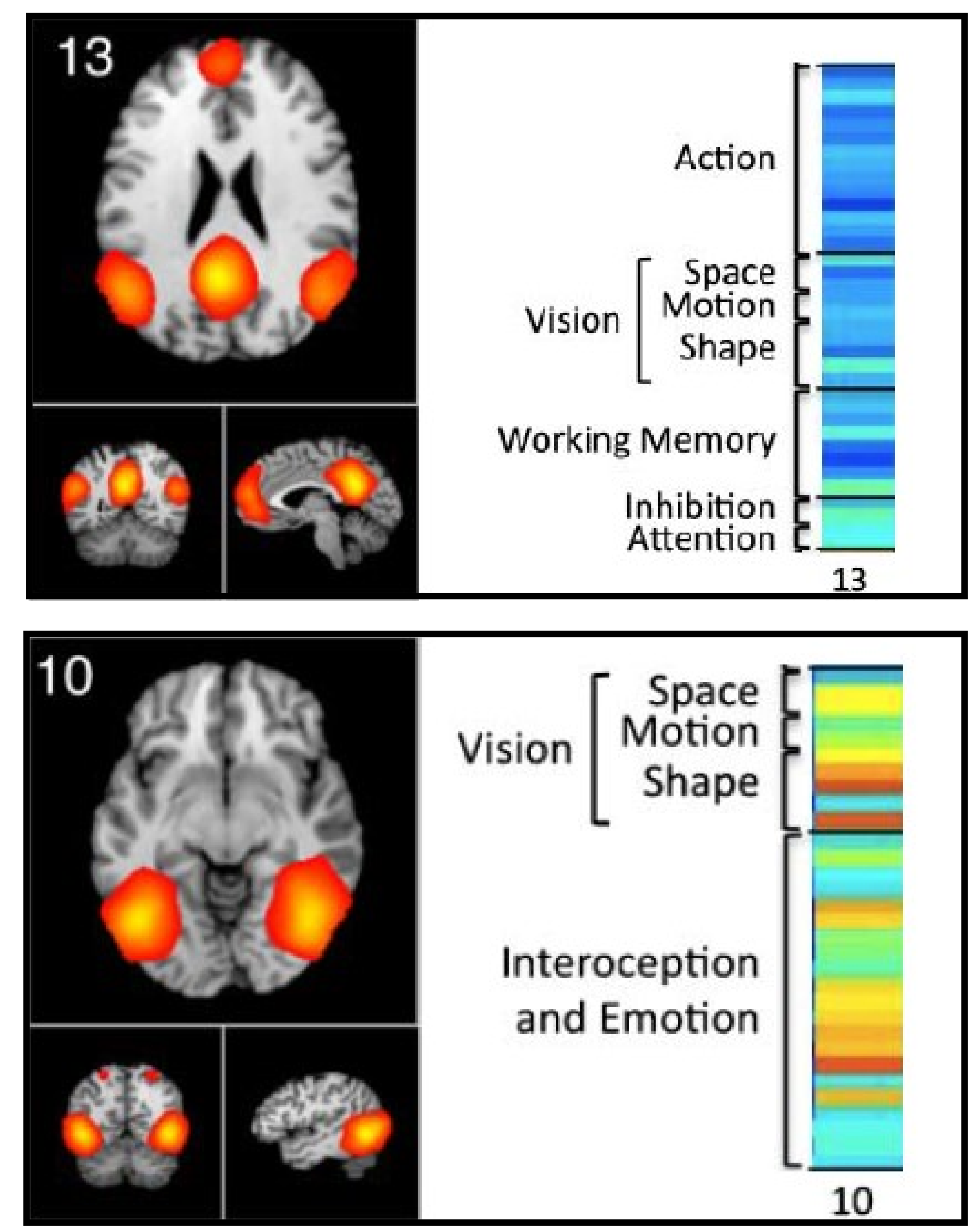
Worhunsky, et al 2015

functional networks in young adult drinkers

- Response inhibition (Go/NoGo) and college drinking trajectories
    - No differences in default mode network: i.e., not related to being more/less on-task
    - No difference in temporo-occipito-parietal network: i.e., not related to stimulus discrimination processing



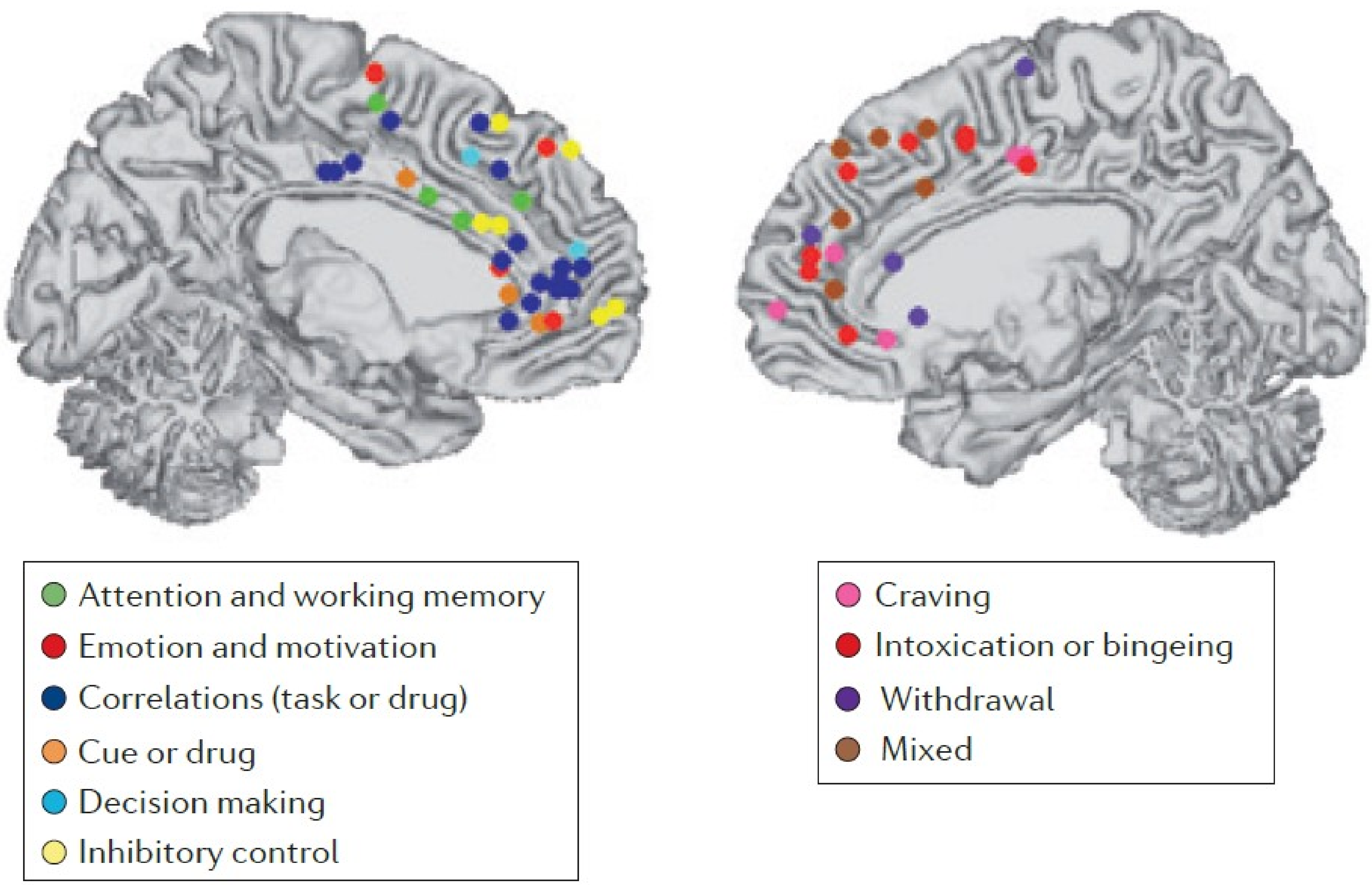
Worhunsky, et al 2015



- **ICA of fMRI allows an investigation of the component functions of complex (or simple) tasks**

functional networks in addiction

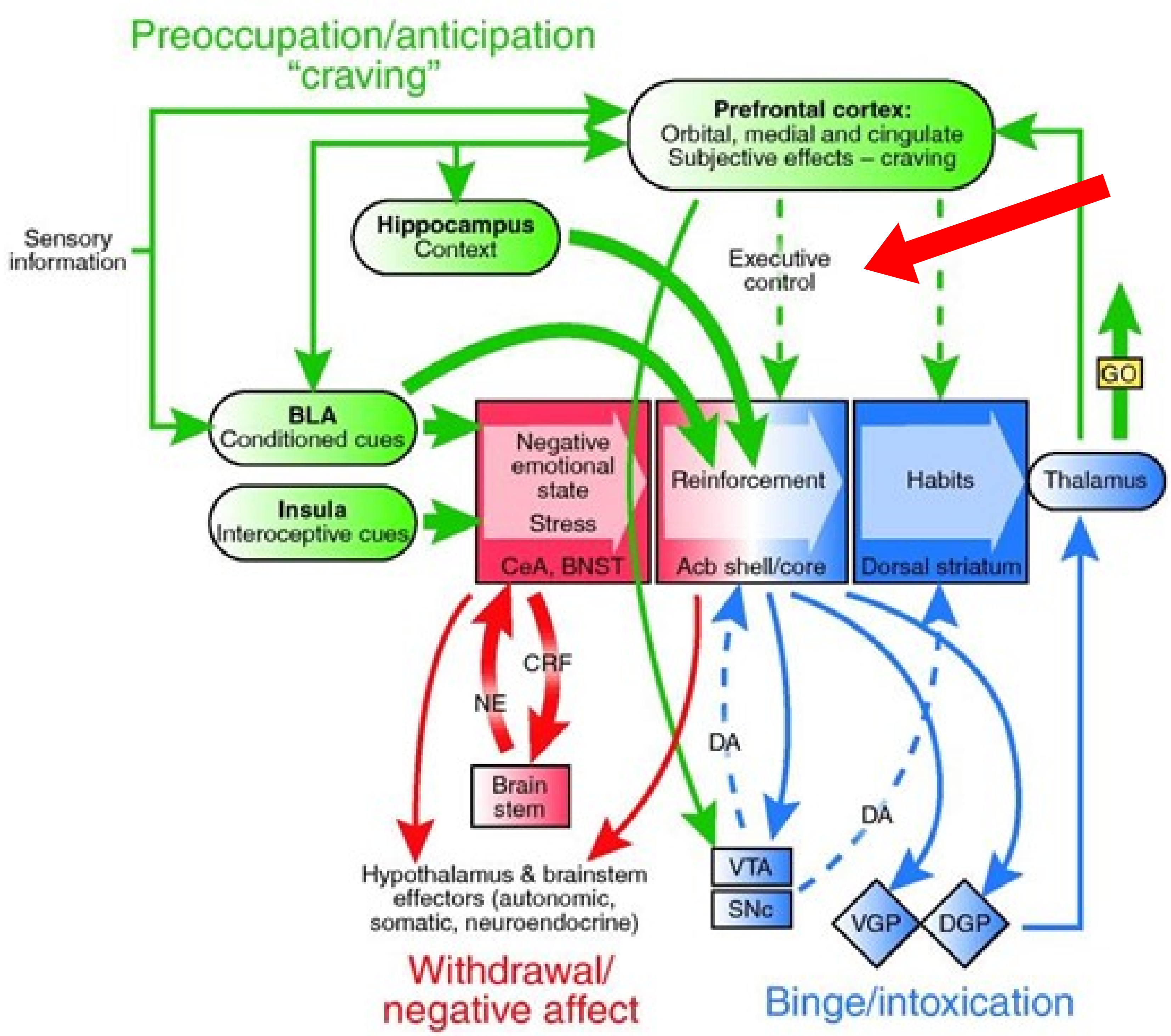
- Executive control alterations in substance use disorders



Goldstein, et al 2011

functional networks of executive control in cocaine use disorder

- 3-stage addiction model

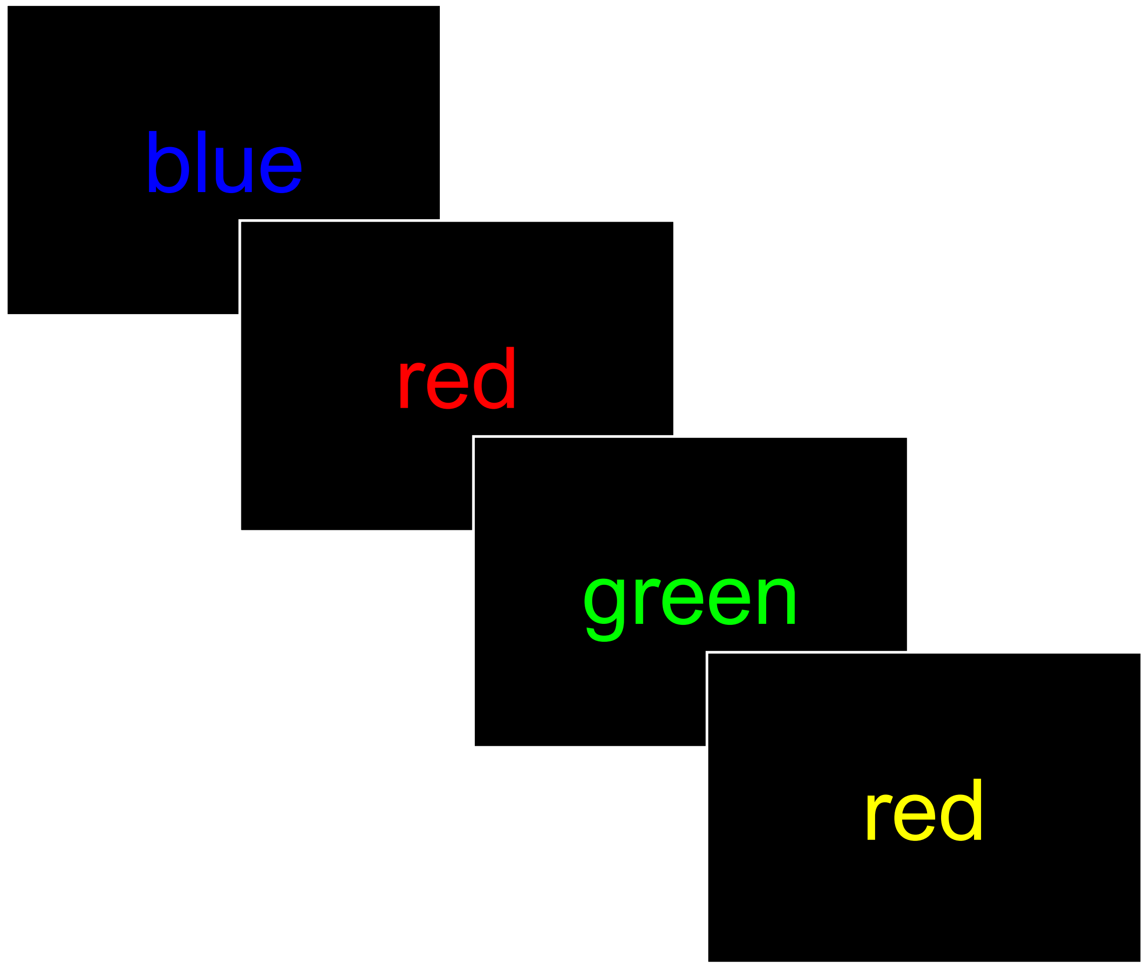


Koob & Volkow, 2010

- Blunted 'top-down' control in CUD looks like:
  - Lower cortical control networks:
    - Frontoparietal, medial frontal, salience
  - Lower default-mode suppression
    - Blunted global functioning
- Greater 'bottom-up' reactivity looks like:
  - Higher subcortical network

fMRI of executive control

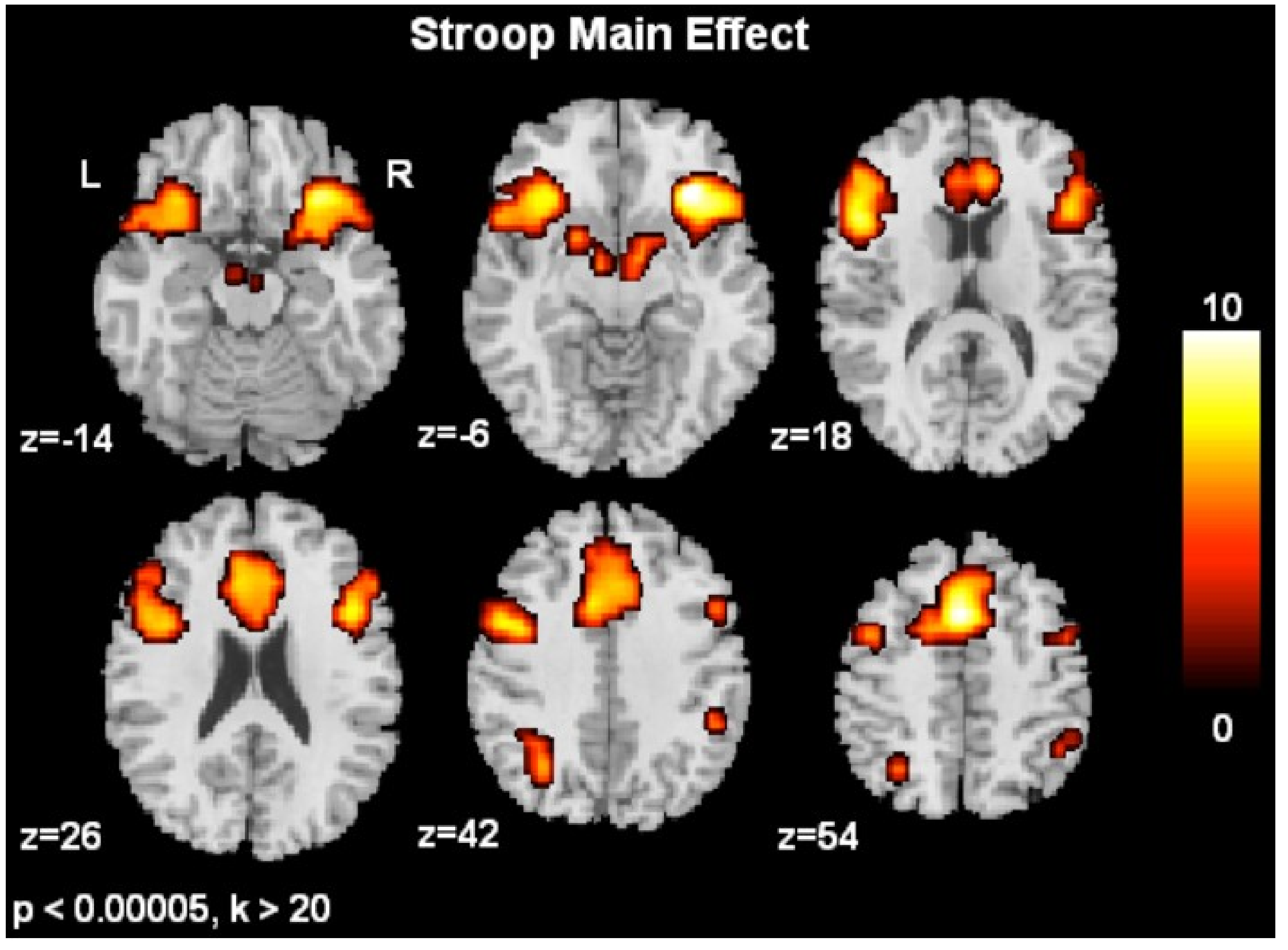
- **Event-related Stroop fMRI task**
  - Color-word Stroop
  - 1.3s stim, 350ms ISI
  - Pseudo-random (9-13:1 C:I)
  - 6, 3-min runs
  - 'Silent' performance in-scanner



- fMRI data spatially processed in SPM12
- ICA performed with Group ICA Toolbox (GIFT)
  - Components extracted using InfoMax
  - Spectral analysis to identify and exclude artifact/noise sources (LF:HF>4.0)
  - Temporal regression to select incongruent-related networks

Stroop-related brain activity

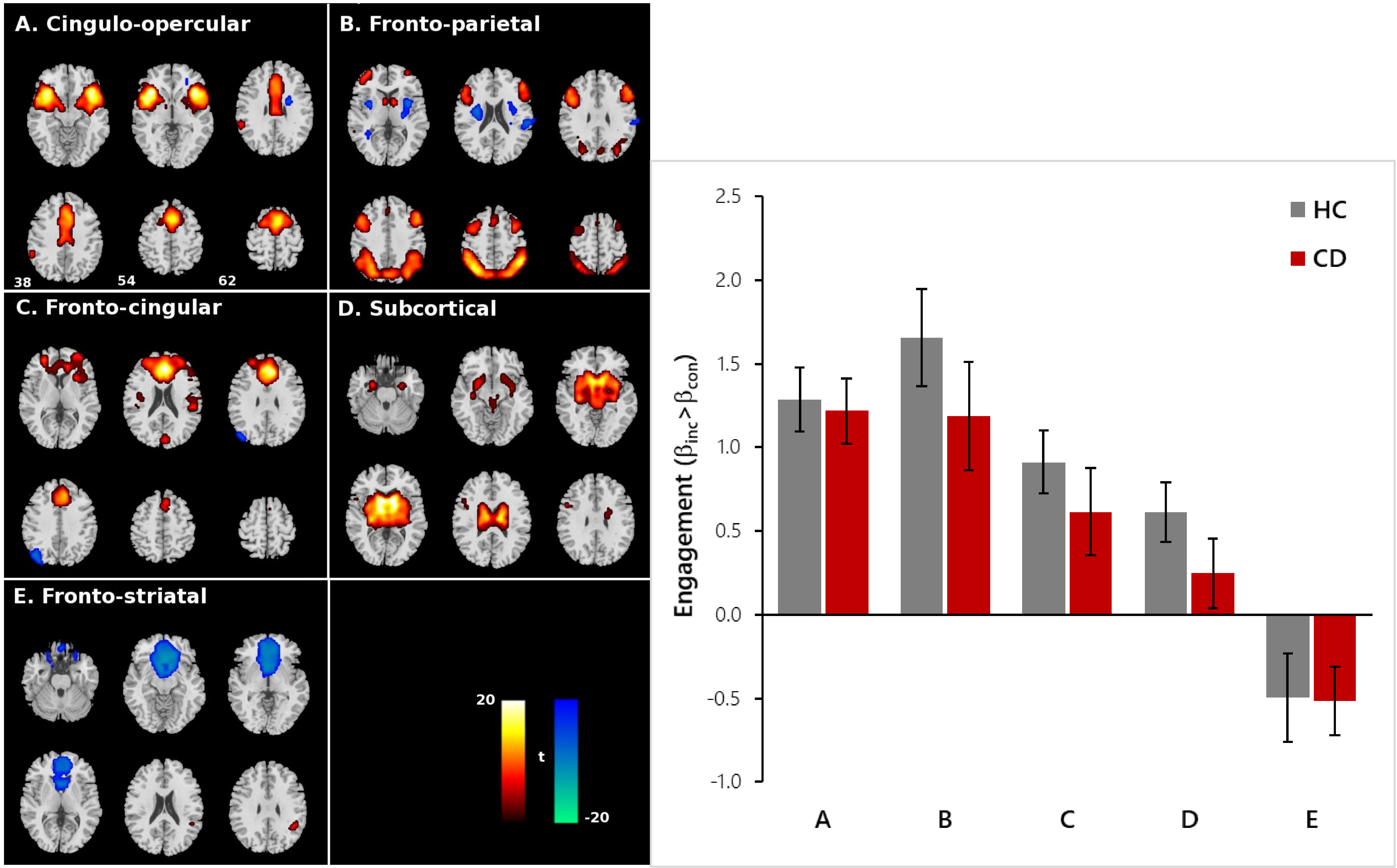
- Stroop interference-related brain activity in treatment-seeking CUD (N=20) and HC (N=20)
  - **Standard GLM-based analyses**
    - No regional differences in Stroop activity between CUD and HC
    - No difference in performance measures (reaction times, error rates)



Brewer, et al 2008

Stroop-related functional networks

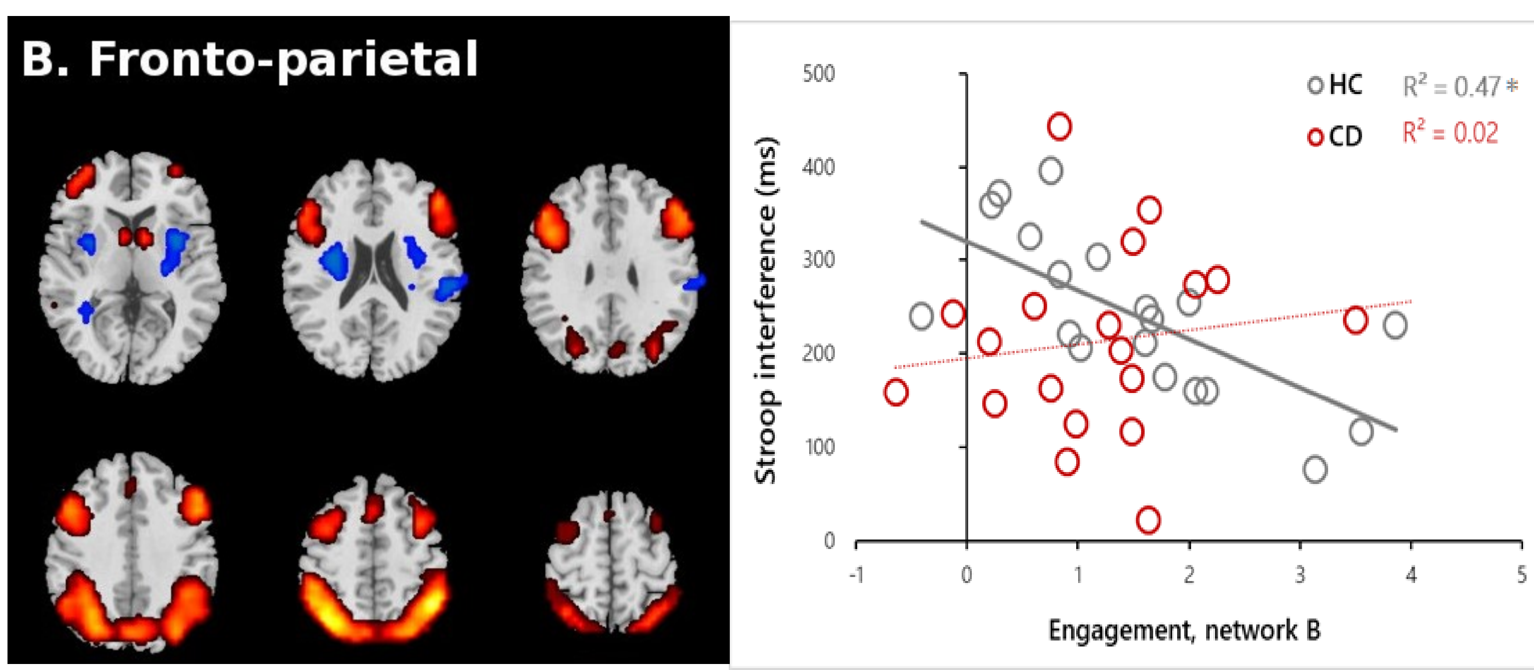
- **Functional networks of Stroop performance**
  - No group difference in any executive-control-related network
  - No group difference in striatal network engagement

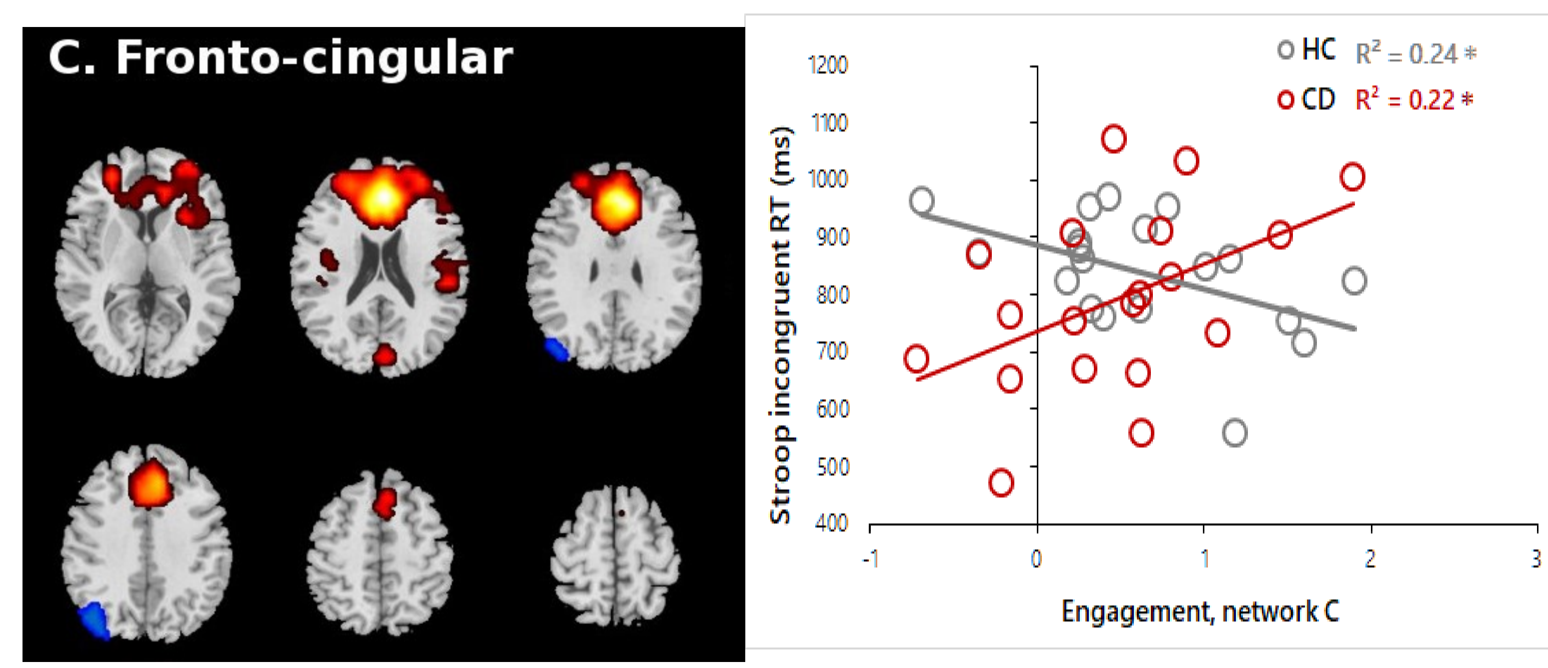


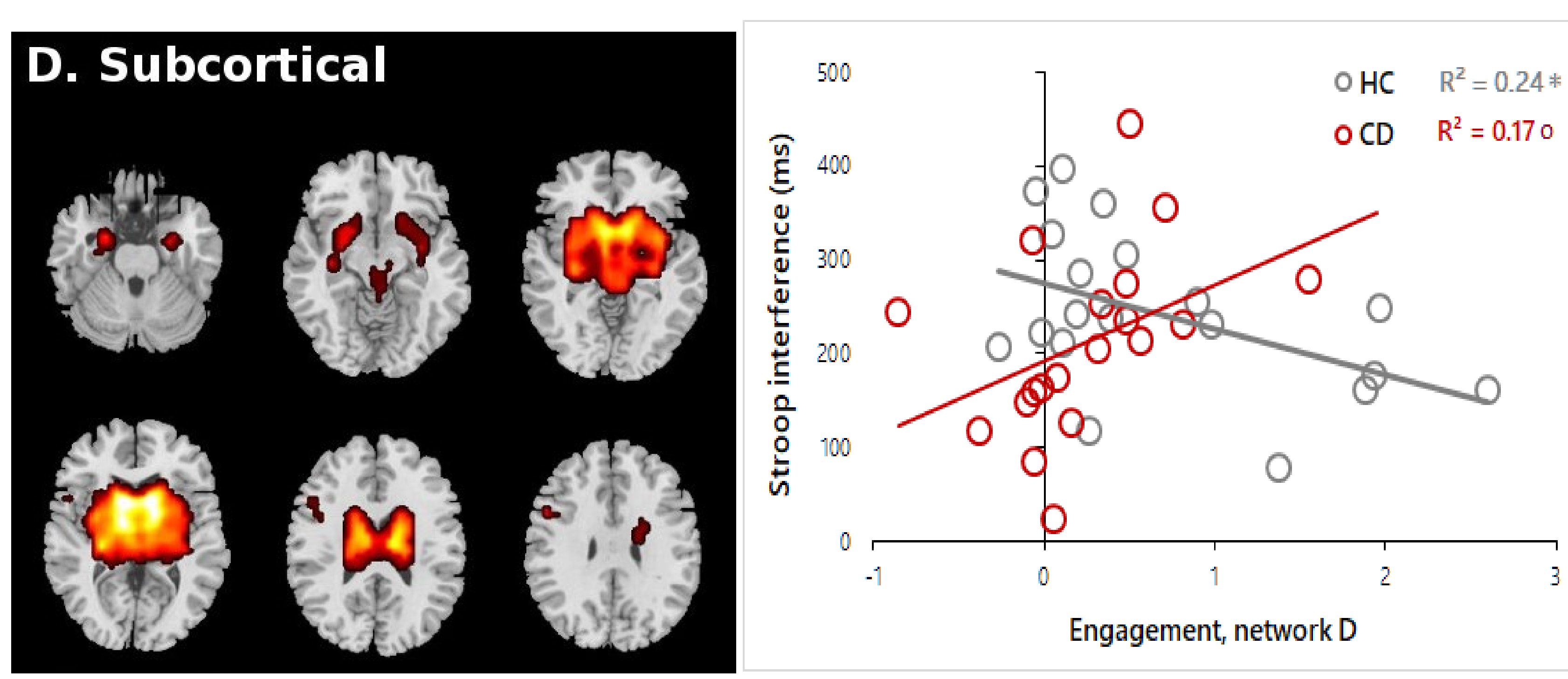
Worhunsky, et al 2013

Stroop-related functional networks

- **Differential relationship between functional networks and behavior**
  - In HC, greater engagement (B, C, D) associated with *faster* interference processing
  - In CUD, greater engagement (C, D) associated with *slower* interference processing
  - In CUD, greater activity is more reactive/interruptive, in HCs activity is resolution-based?



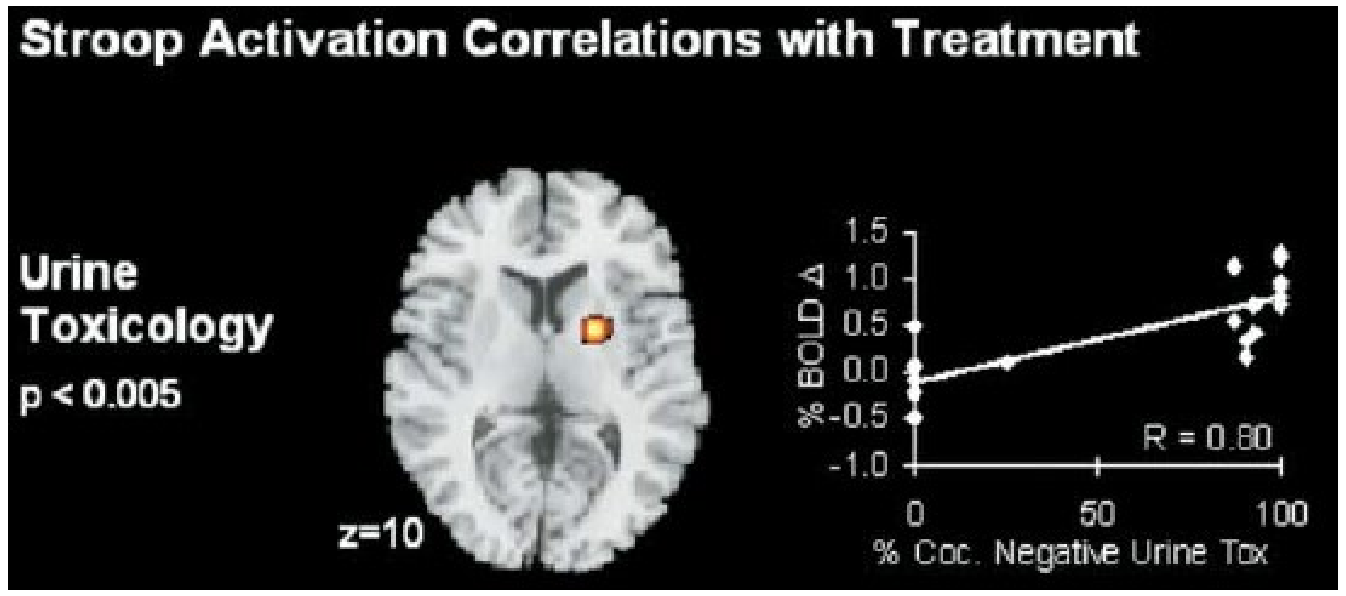




Worhunsky, et al 2013

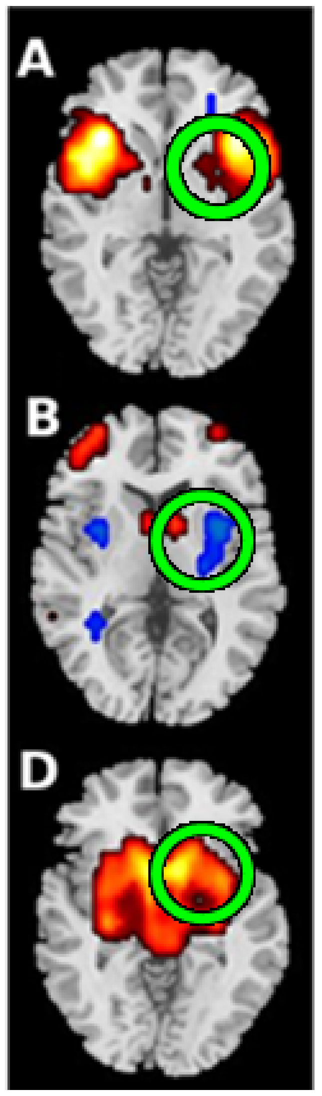
Stroop-related functional networks

- Stroop control by treatment response
  - GLM: Right dorsal striatum predicts abstinence during treatment
  - Which functional process is this related to?



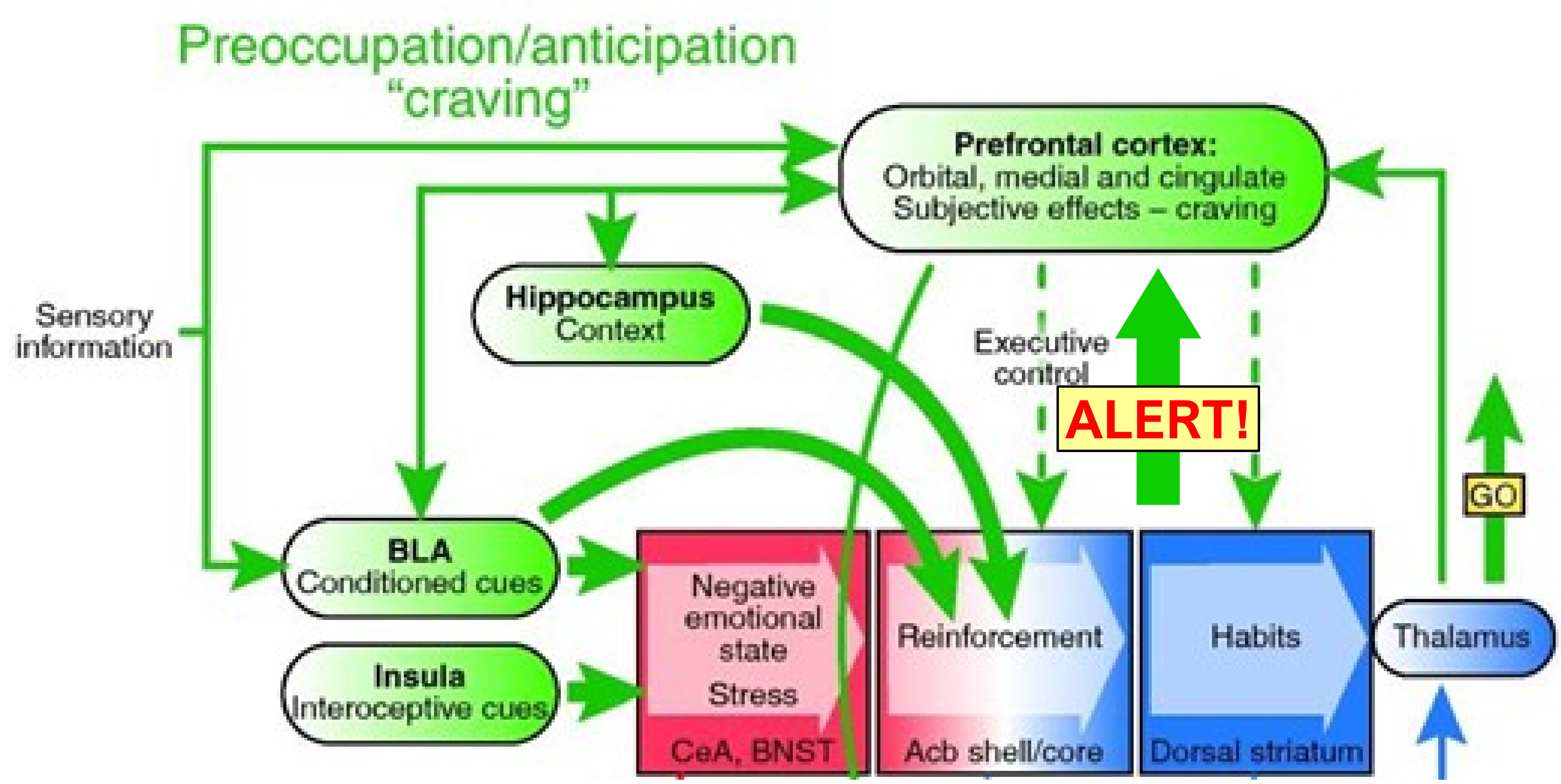
Brewer, et al 2008

- Dorsal striatum integrated into several networks
- Responders (N=11; >80% abstinence) vs non-responders (N=9; <30% abstinence)
- Treatment-responders showed *greater* subcortical engagement than non-responders
- No striatal engagement in non-responders
- Counter to hypotheses of hyperactive subcortical functioning being disruptive to executive functions in CUD



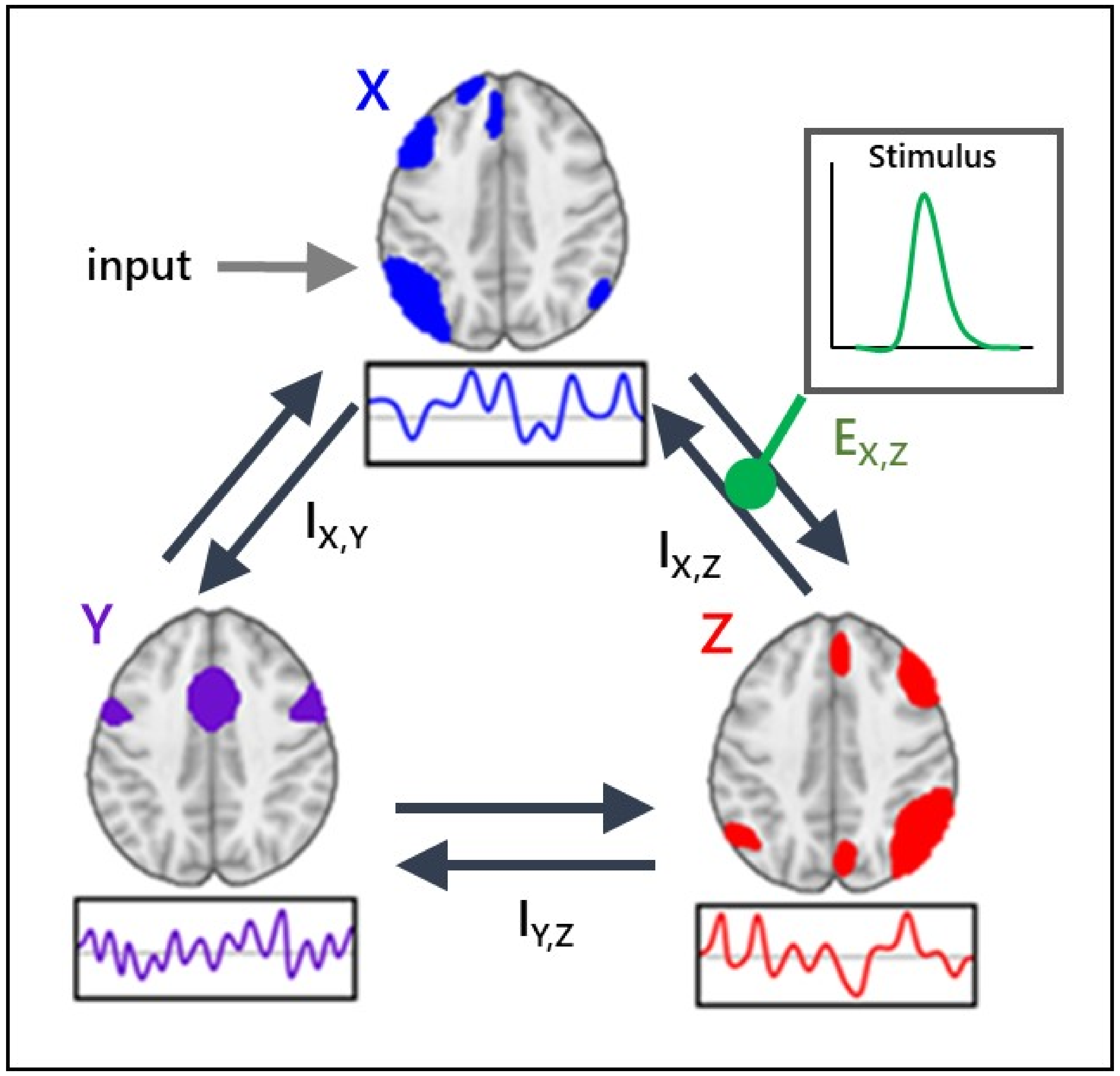
Functional networks in CUD

- **Executive control in CUD**
  - Bottom-up 'alert' mechanism may be disrupted in CUD?
  - Greater alert signals in CUD slowed conflict responding (perhaps avoiding errors)
  - Healthy-levels of alert signaling associated with better treatment outcome



Functional network dynamics in CUD

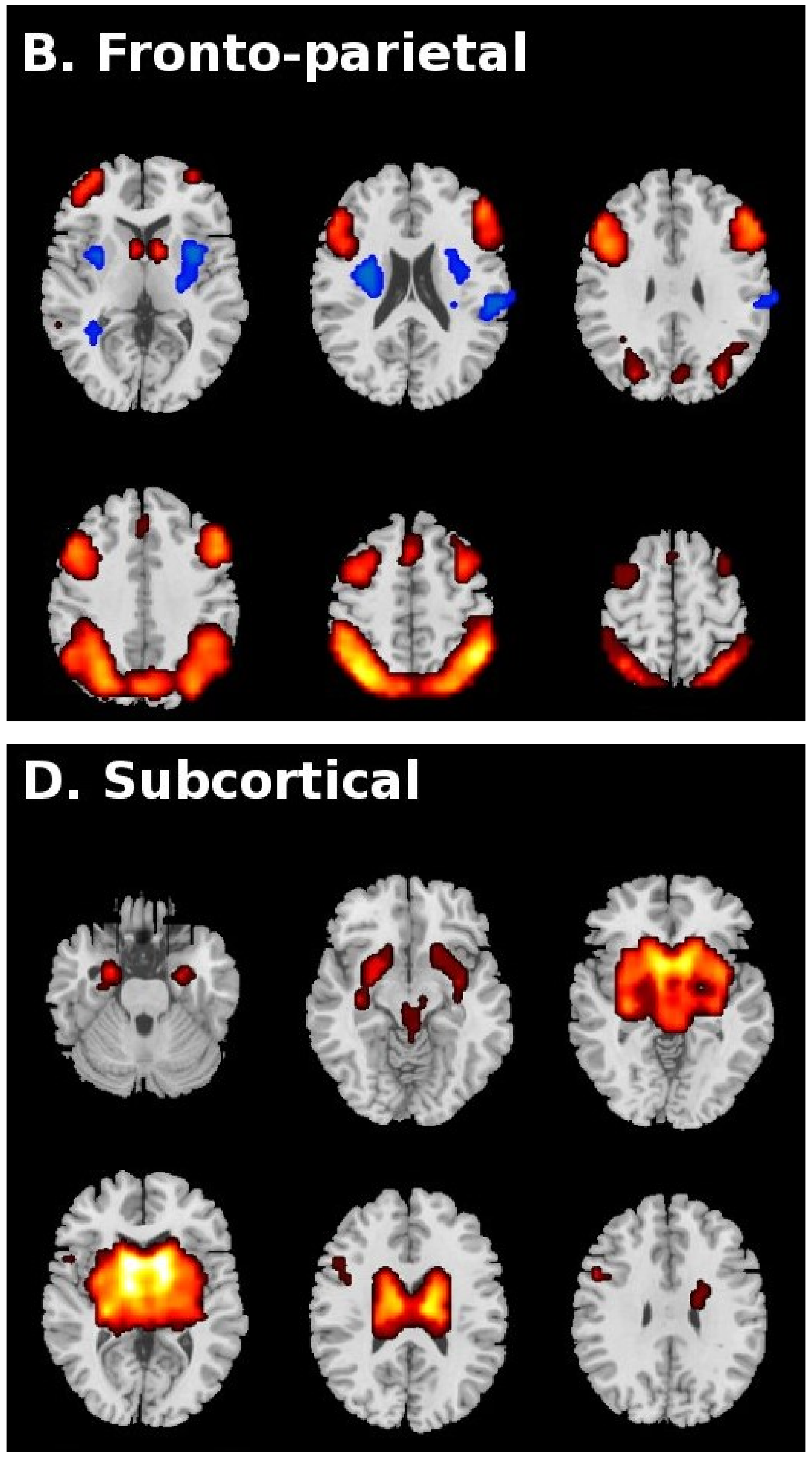
- **Dynamic Causal Modelling (DCM) of network interactions**
  - Input-state-output modeling of neural propagation
  - How do components X, Y, Z effect each other (and does stimulus S influence effectivity)?

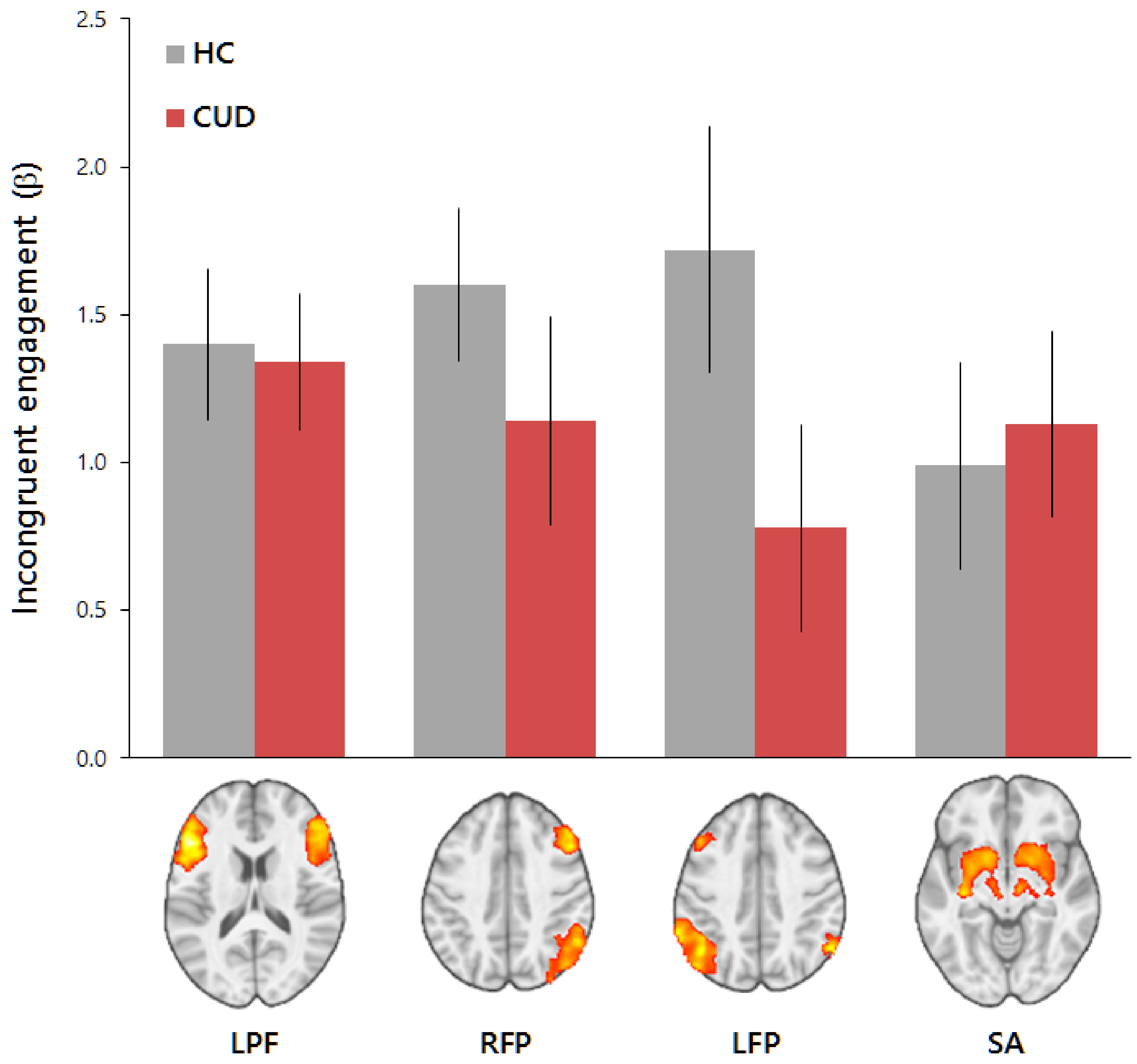


- Intrinsic (baseline) effectivity
- Extrinsic (context-modulated) effectivity
- How do network dynamics change in response to Stroop conflict?

Functional network dynamics in CUD

- Non-treatment seeking CUD (N=16) and HC (N=16)
  - Extracted more ICA sources, separation of frontoparietal and bilateral IFG networks
  - No group differences (Ns=16) in Stroop-related network engagement

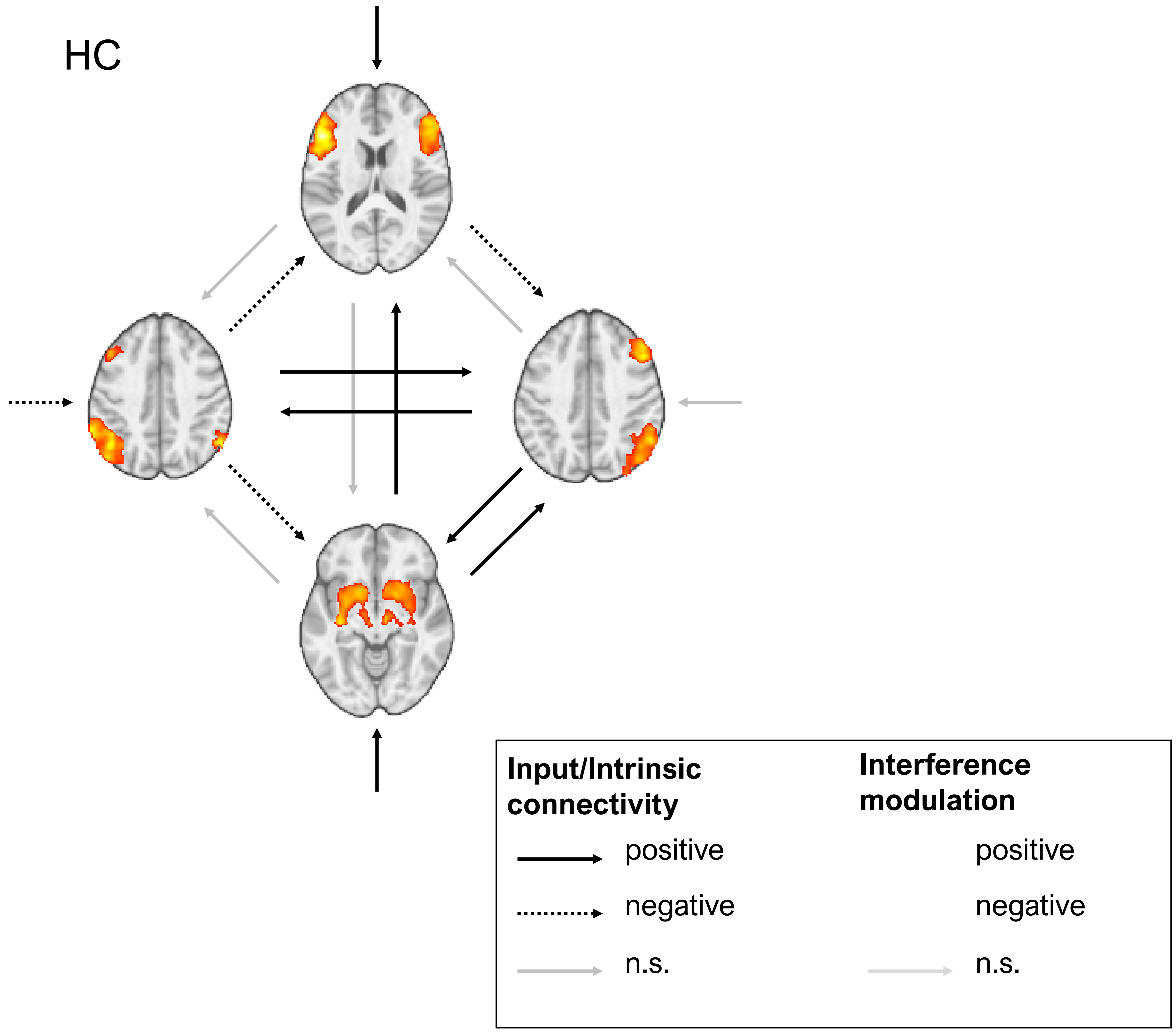




Error bars are SE; all pairwise n.s. (LFP: P=0.10)

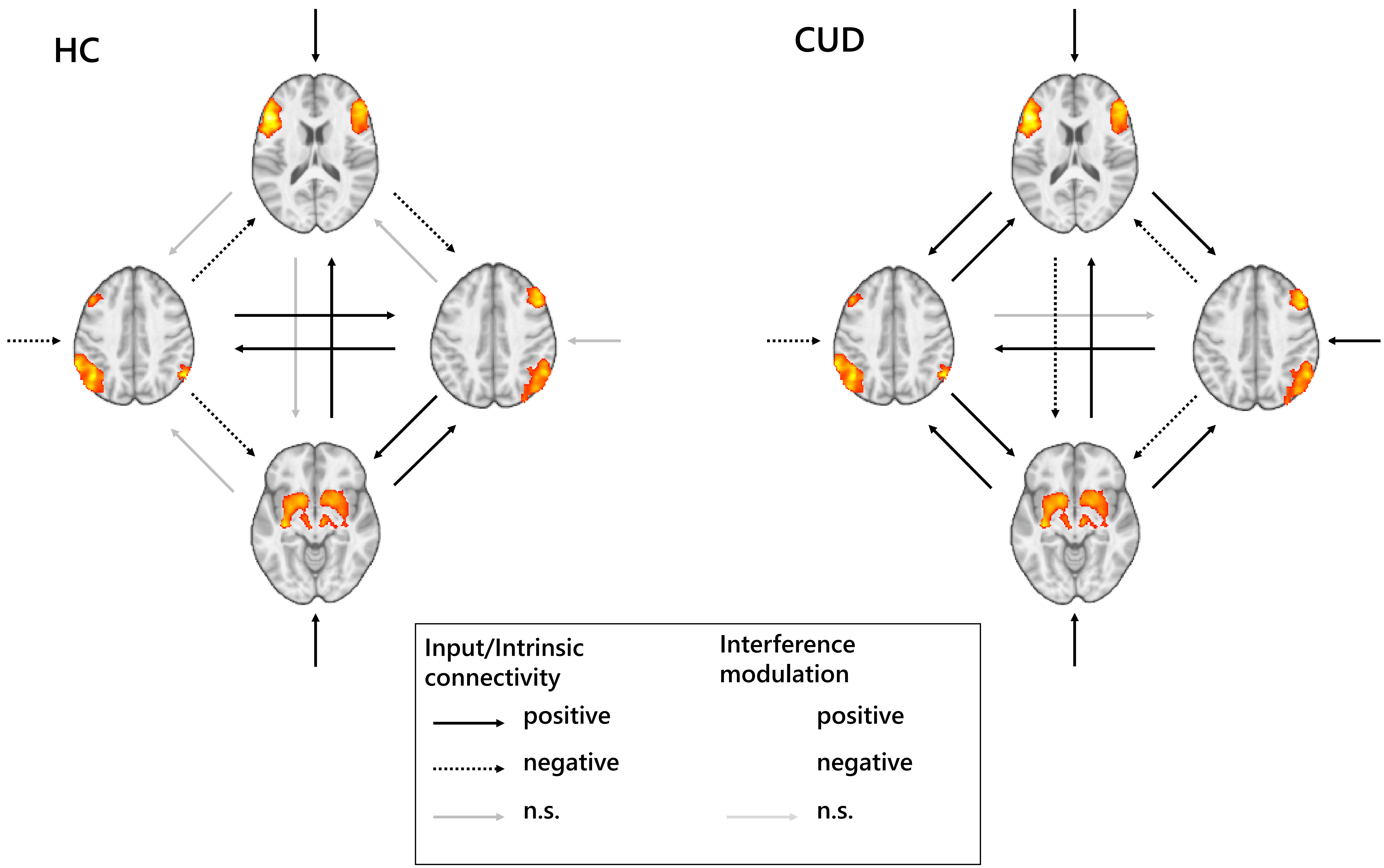
Functional network dynamics in CUD

- **Network effective connectivity of Stroop control**
  - Subcortical activates lateral prefrontal, which activates right frontoparietal
  - Right frontoparietal distributes inhibitory signals



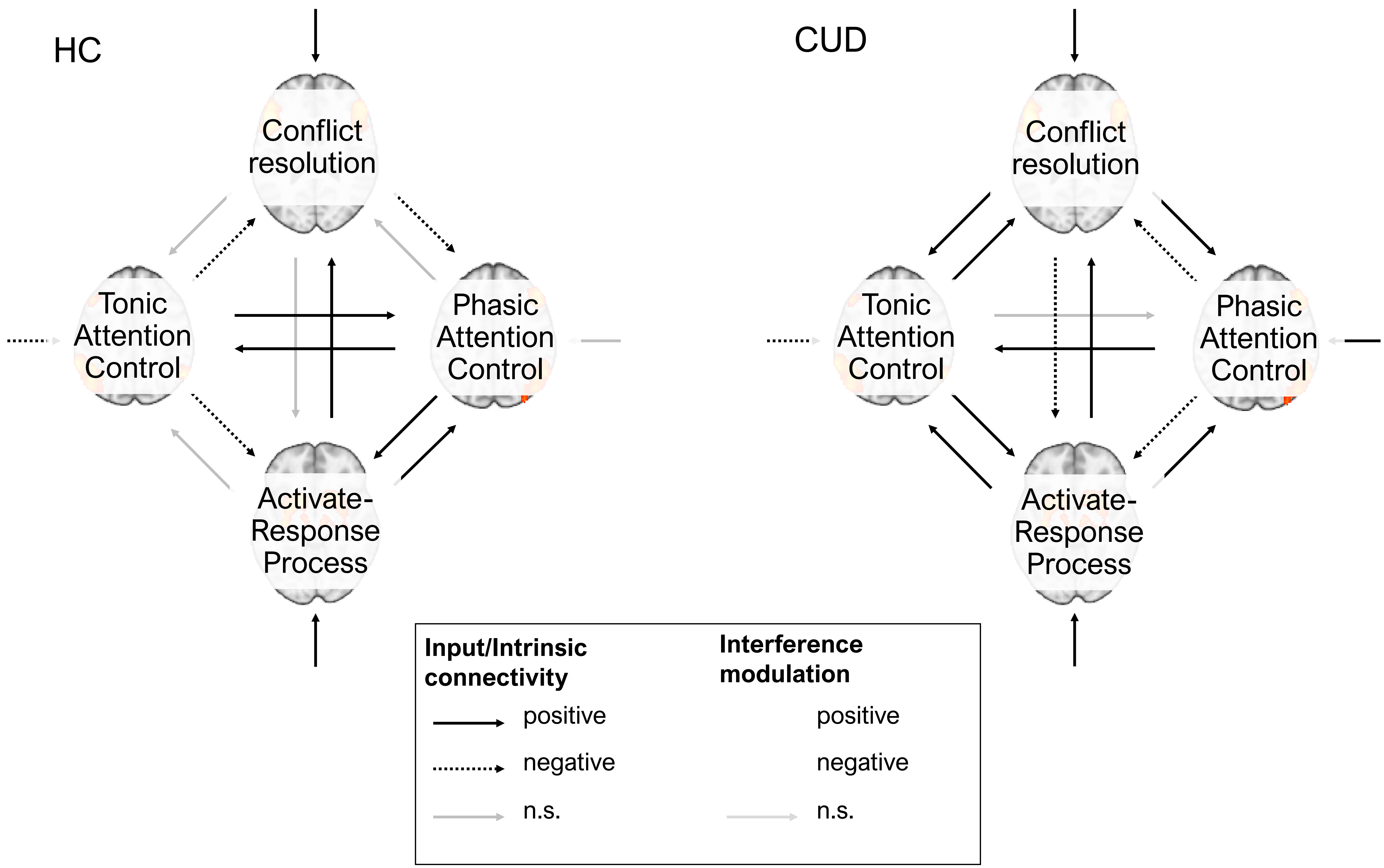
Functional network dynamics in CUD

- **Network effective connectivity of Stroop control**
  - Subcortical activates lateral prefrontal, which activates right frontoparietal
  - Right frontoparietal distributes inhibitory signals
  - Subcortical activates both frontoparietals, lateral prefrontal goes left
  - Re-organized inhibitory signals



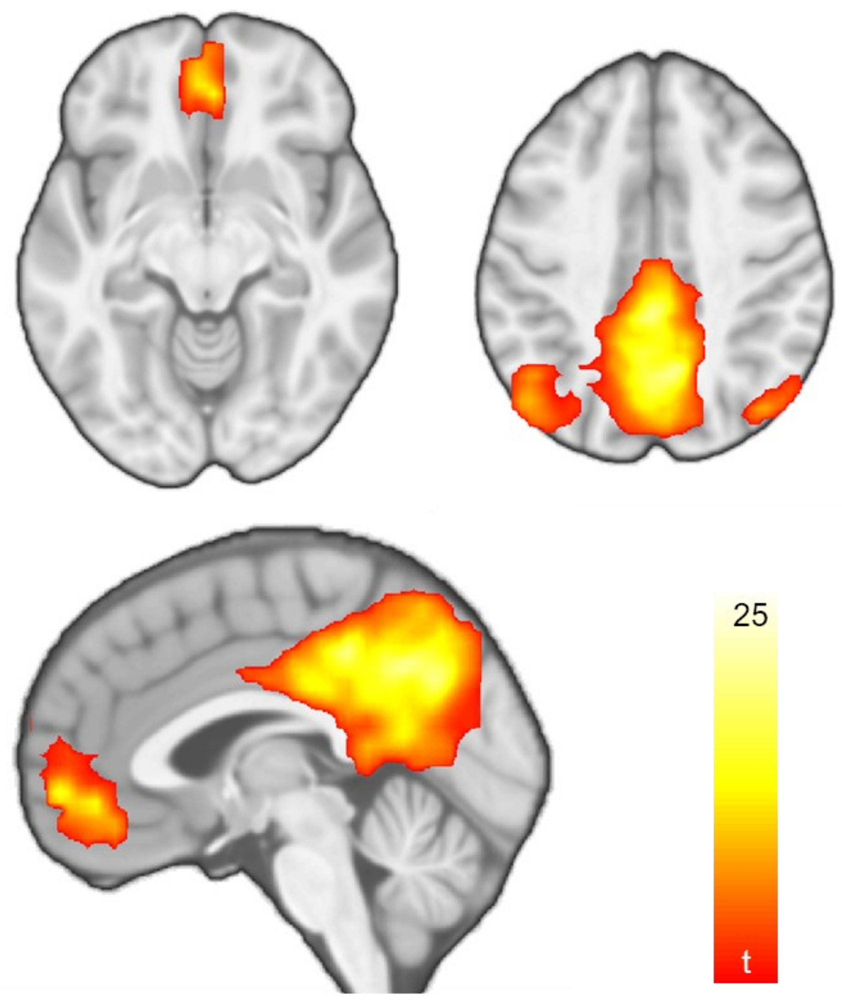
functional component dynamics in CUD

- **Functional source dynamics of Stroop control**
  - No differences in regional BOLD signals, no performance differences
  - No differences in how much networks are engaged during performance
  - But how the component functions coordinate to resolve conflict is markedly different



DMN suppression in CUD

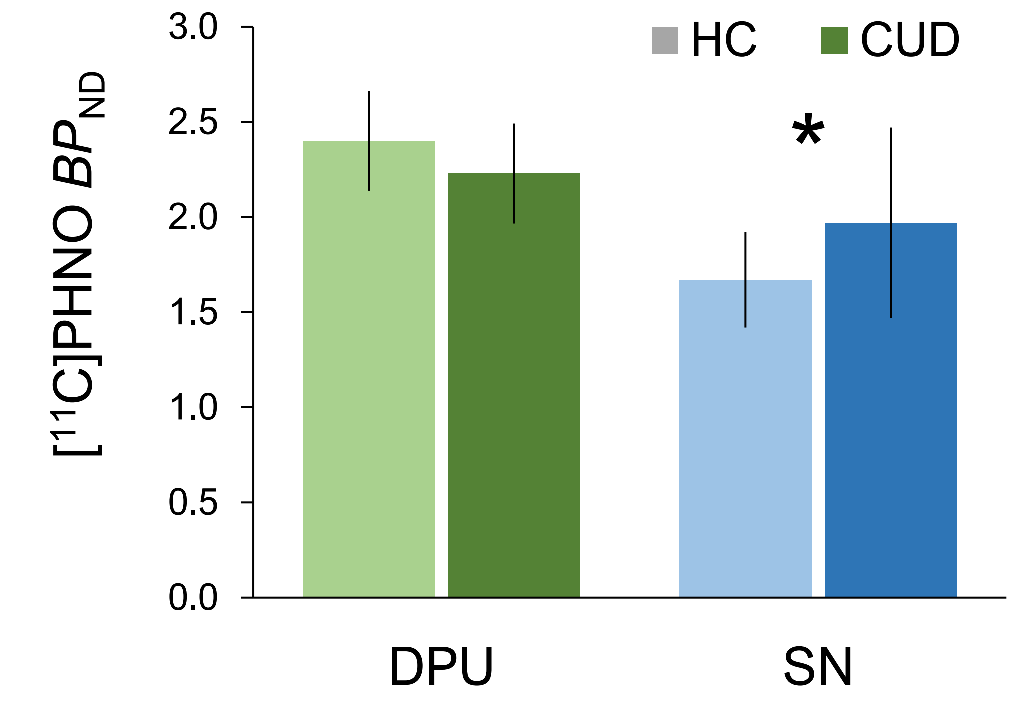
- **Default mode network (DMN) suppression**
  - DMN is a core resting-state functional network
    Buckner et al, 2008
  - During task performance DMN is suppressed (more negative)
  - Degree of suppression may be a marker of global executive functioning
    Anticevic et al, 2012; Binder, 2012



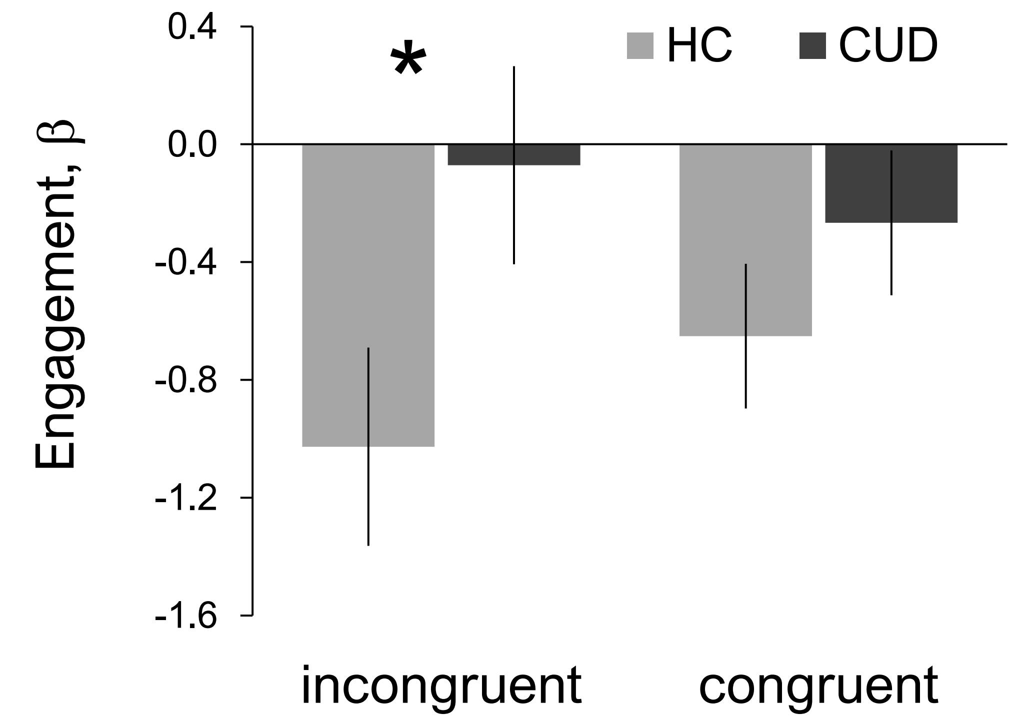
- Stroop executive control networks reliably-tended to be lower CUD than HC.
- Perhaps DMN suppression might capture this difference in global functioning
- Explore relationships with D2- and D3-related binding from $[^{11}C]$-(+)-PHNO scans

DMN, D2/D3, and Stoop outcomes

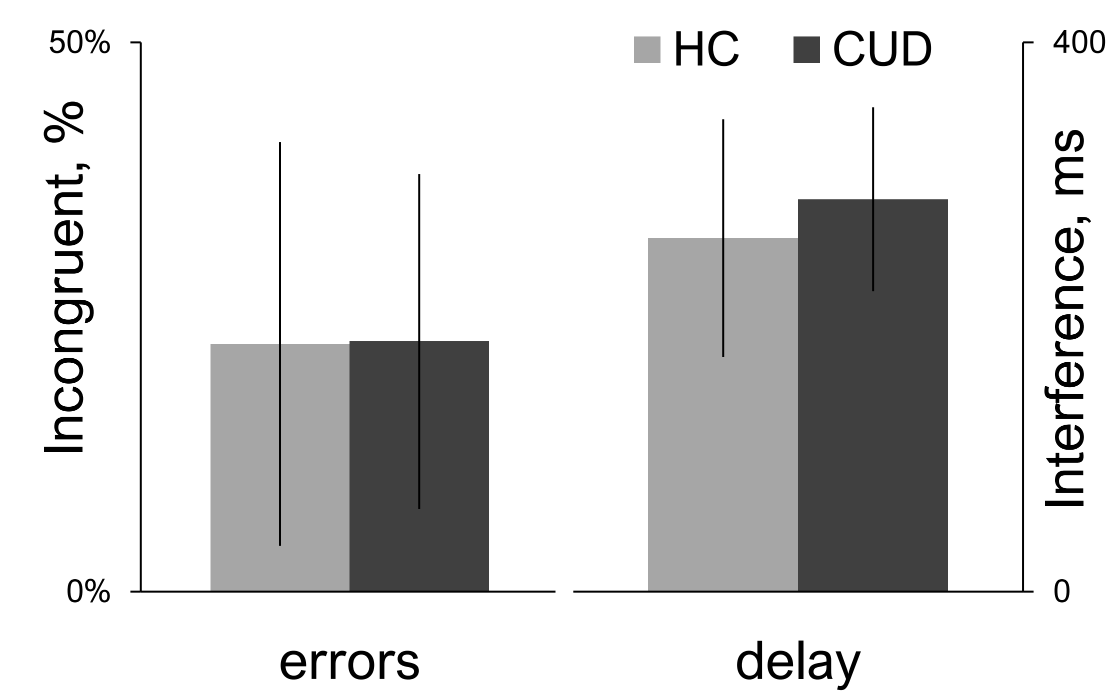
- **D2/D3 availability**
  - CUD had greater D3-related binding in the SN (Ns=16)
    p=0.04
  - D2-related binding in the DPU tended to be lower in CUD
    p=0.07



- **DMN suppression**
  - CUD tended to exhibit generally less DMN suppression
    p=0.09
  - Group difference in response to high-conflict stimuli
    p=0.01

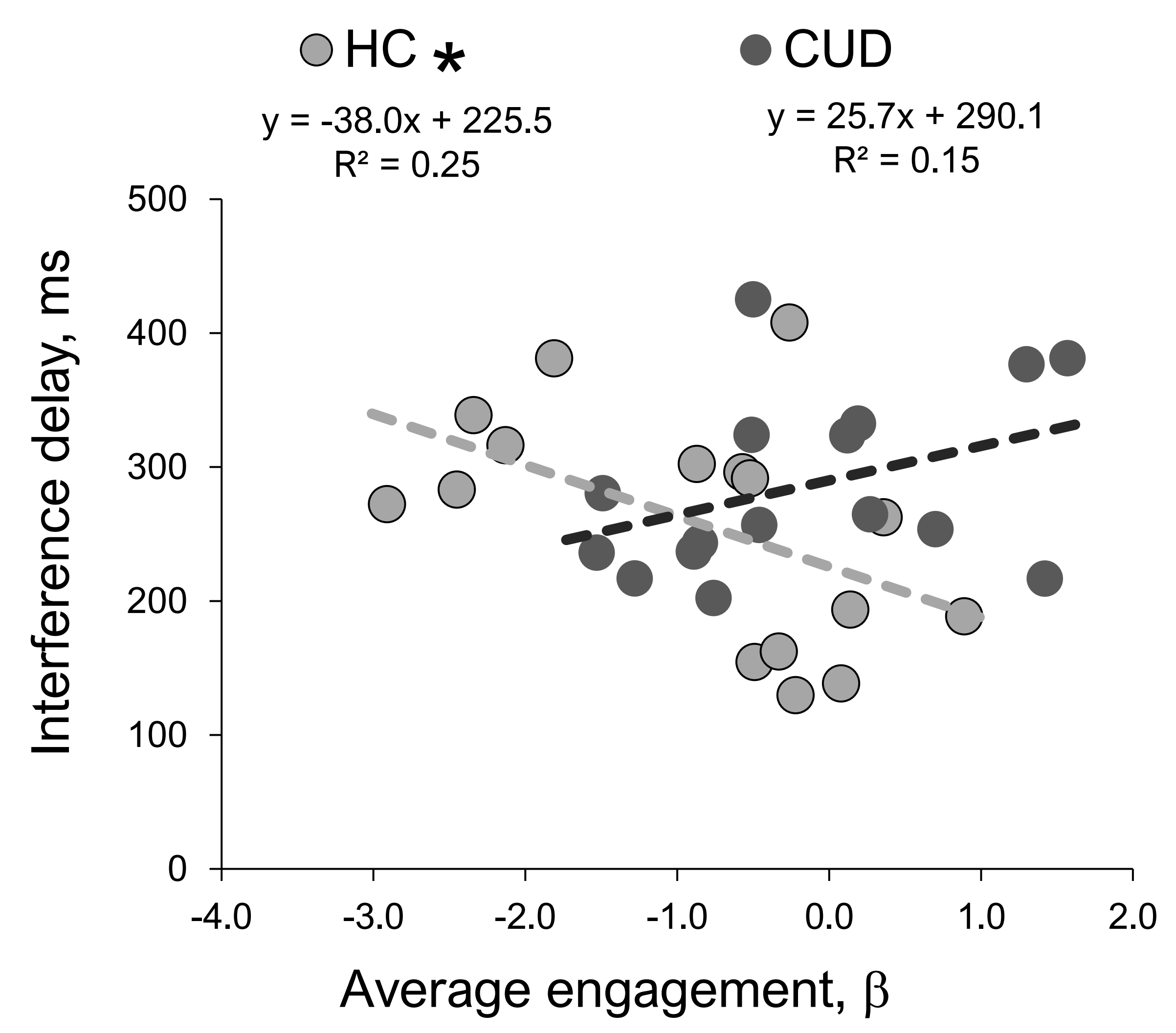


- **Stroop performance**
  - No group differences in incongruent error rates or interference delays



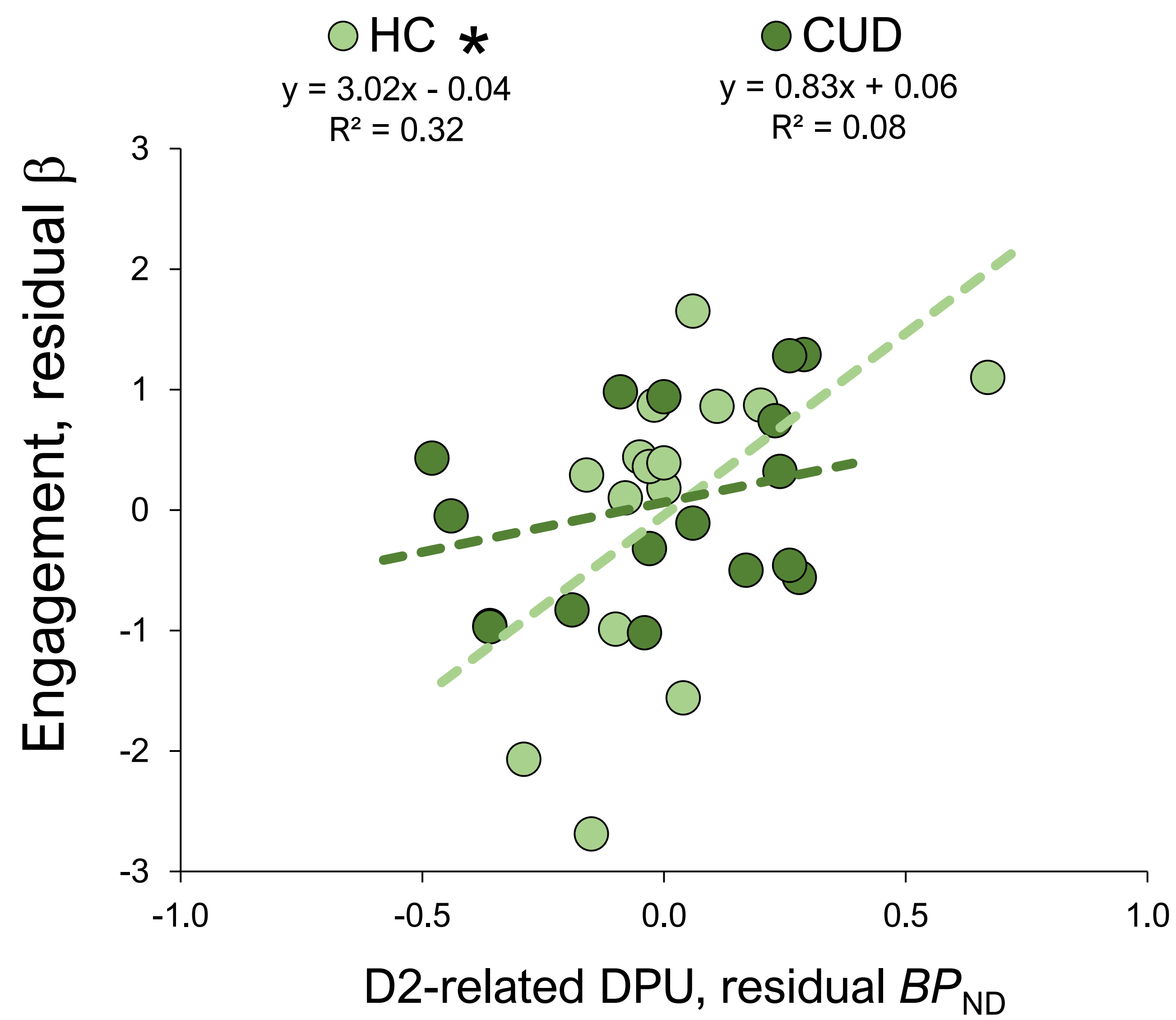
DMN suppression and performance

- HC: Greater suppression associated with longer delays
  $p<0.01$
- CUD: Greater suppression tended to be associated with shorter delays
  $p=0.10$
- Both consistent with the inverse of executive control network findings
- DMN suppression not related to error rates

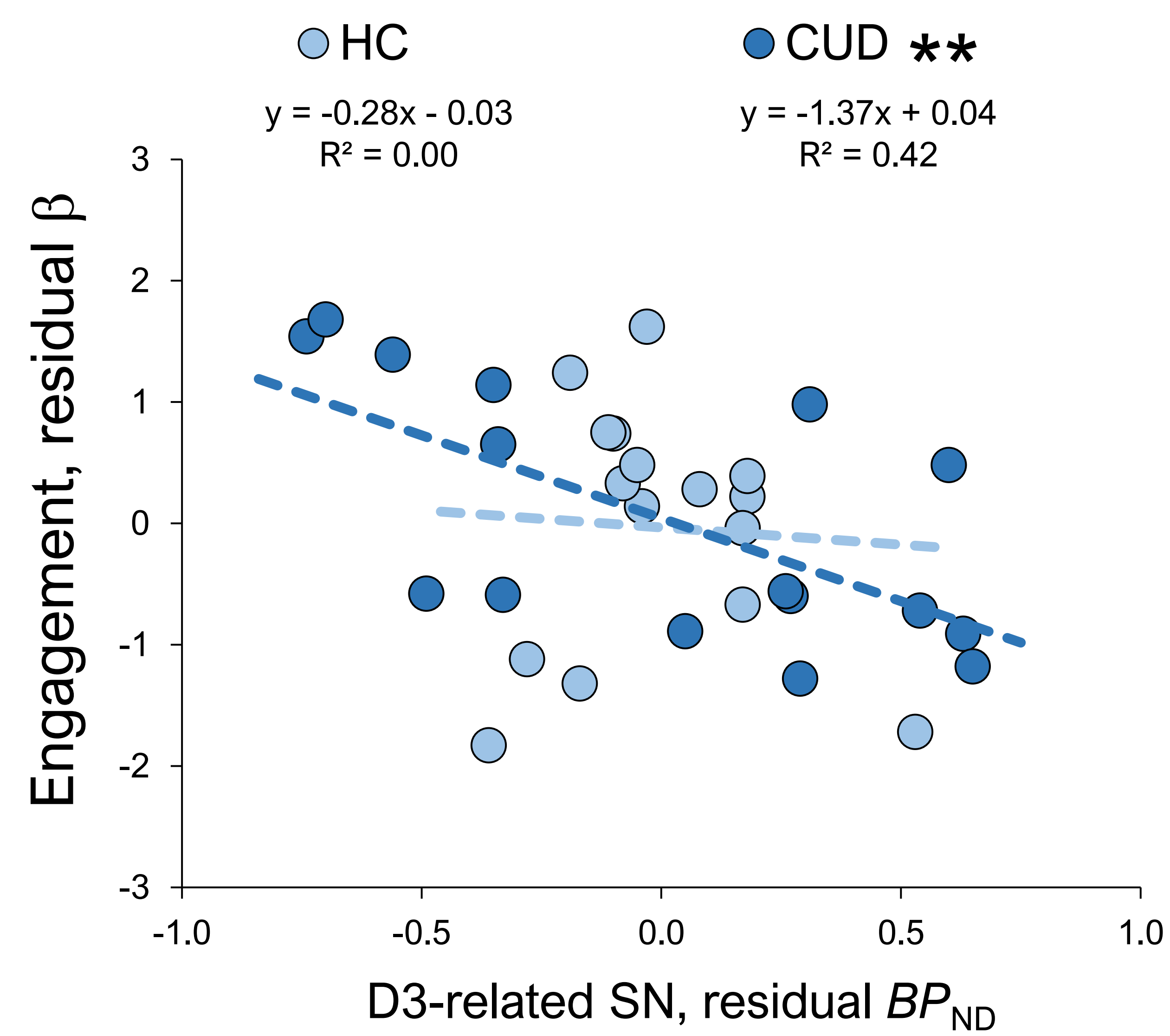


DMN suppression and D2/D3

- **D2-related binding**
  - HC: Greater D2 associated with less suppression
    p=0.05
  - CUD: No association with DMN
    p=0.40

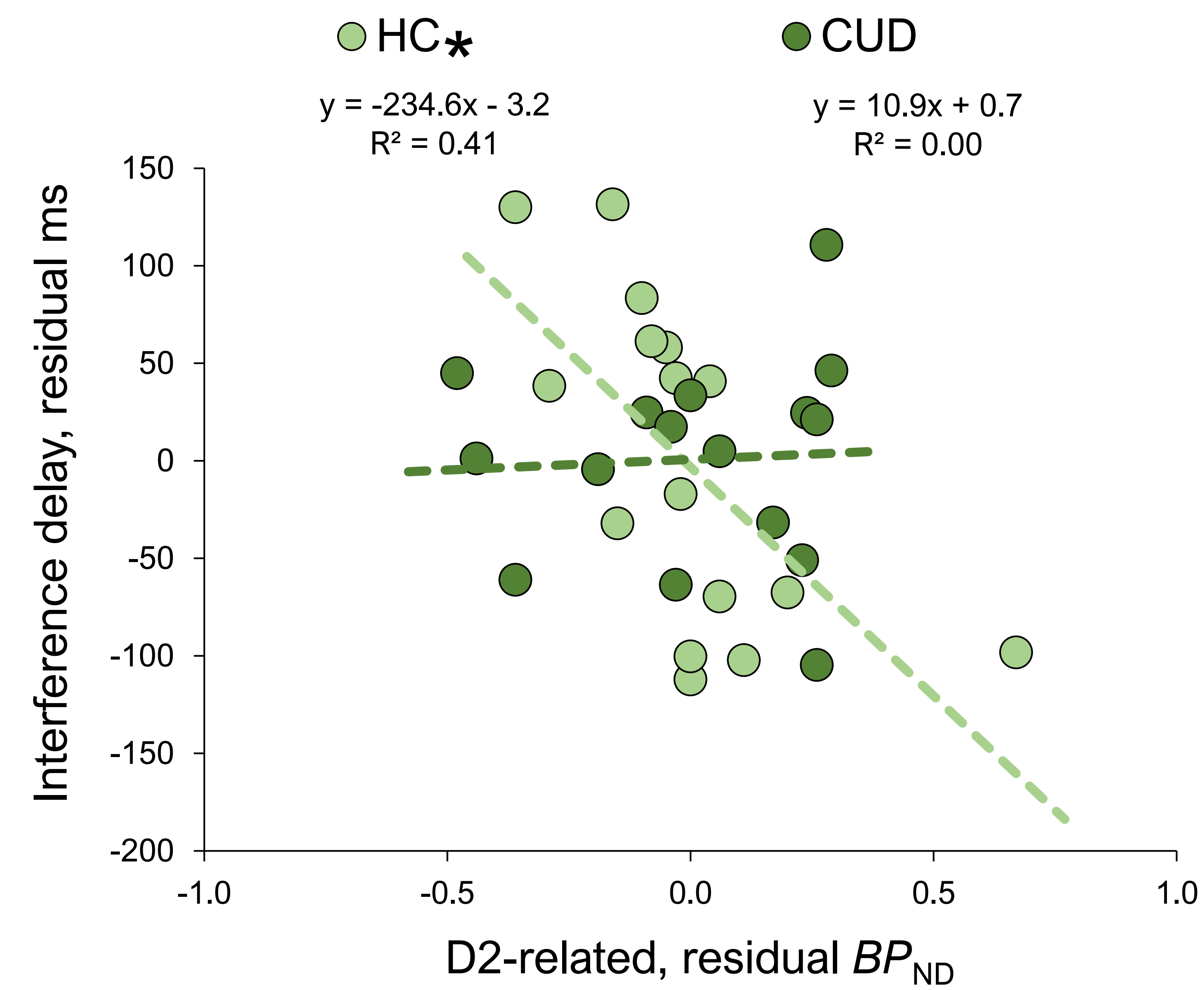


- **D3-related binding**
  - HC: No association with DMN
    p=0.60
  - CUD: Greater D3 associated with stronger suppression
    p<0.01

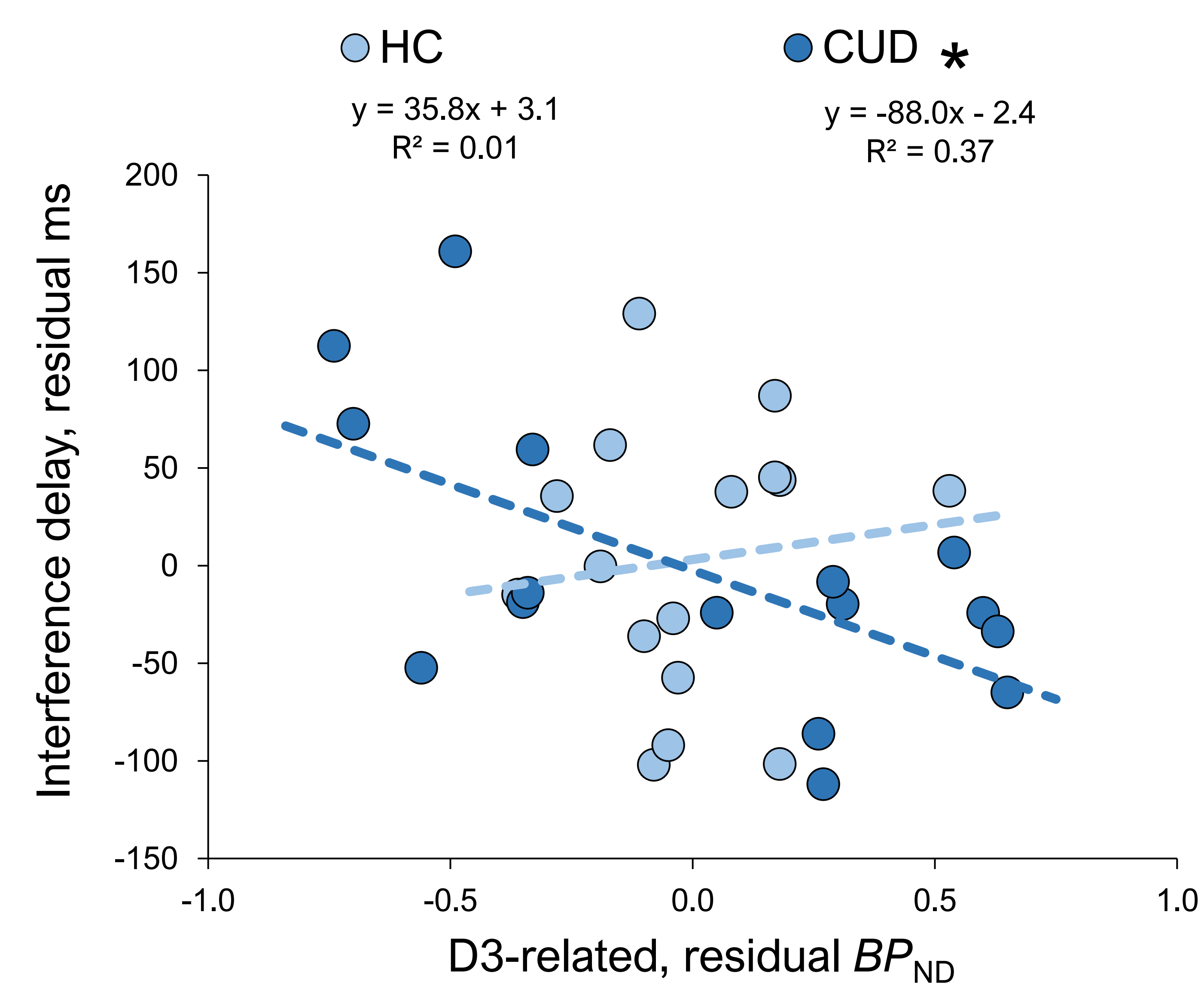


D2/D3 and performance

- **D2-related binding**
  - HC: Greater D2 associated with shorter delays
    p<0.01
  - CUD: No association with interference delay
    p=0.88
  - Error rates not associated with D2

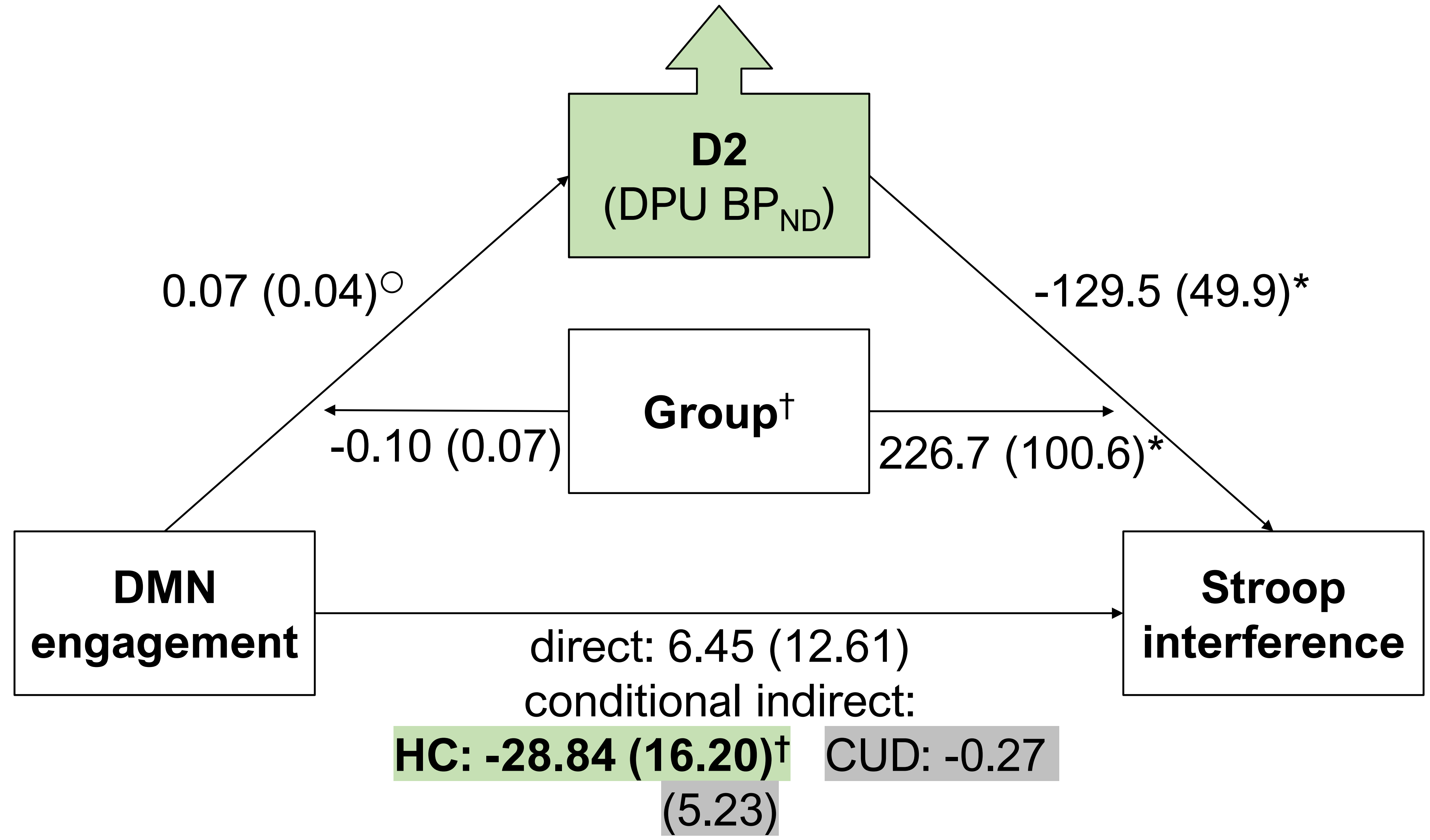


- **D3-related binding**
  - HC: No association with interference delay
    p=0.38
  - CUD: Greater D3 associated with shorter delays
    p=0.01
  - Error rates not associated with D3



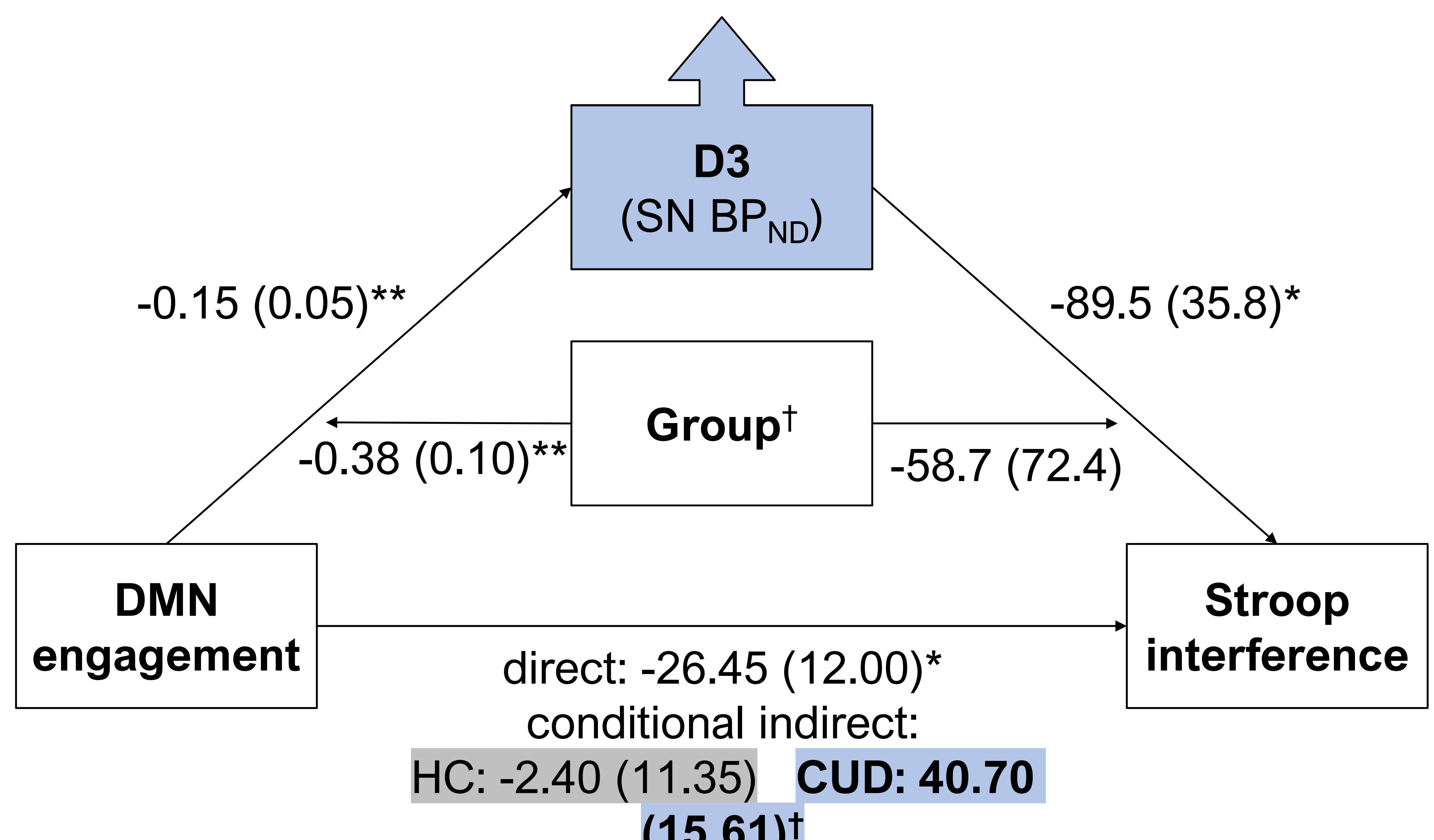
Exploratory moderated-mediation

- **DMN–to–behavior through D2**
  - DMN engagement had a significant indirect effect through D2 mechanisms on interference delays only in HC
  - Differed from no indirect effect in CUD
    index=28.57, SE=16.53; 95%CI=6.75, 71.81
  - D2-mechanisms facilitate faster conflict resolution with *less* DMN suppression in HC



○ p<0.10, * p<0.05; ** p<0.01. † 95%CI indicate a significant effect.

- **DMN–to–behavior through D3**
  - DMN engagement had a significant indirect effect through D3 mechanisms on interference delays only in CUD
  - Differed from no indirect effect in HC
    index=43.10, SE=16.84; 95%CI=11.05, 77.03
  - D3-mechanisms facilitate faster conflict resolution in CUD but with *more* DMN suppression.



* p<0.05; ** p<0.01. † 95%CI indicate a significant effect.

Un-mixing addiction in the brain

- **Addiction is a complex and multifaceted disease**
  - Substantial variability in individual disease profiles, motivations, functional impairments, etc.
  - An improved understanding of the many different sources of variability will inform interventions
- **Re-thinking the ‘re-wired’ addicted brain**
  - How components of information are distributed across circuits may have changed
    (e.g., school buses are taking people to the casinos)
  - How information flows from circuit to circuit may have changed
    (e.g., people are dropping kids off at school on their way home from work)
- **Understanding sources of addiction toward prevention and treatment**
  - Are there ‘at-risk’ source profiles (which sources are dominate in youth who develop a SUD)?
  - How do source dynamics change during early abstinence toward sustained recovery?
  - Understanding sources of addictive function may more directly translate to clinical application

Un-mixing addiction in the brain with ICA

- **Not all variance is created randomly**
  - Underlying sources of variance suggest imperfect or imprecise measurements
  - Total scores can be helpful, subscales provide greater precision of underlying sources
- **The most variance explained is not always best**
  - Analyses fitting the dominate variance distributions (e.g., PCA) may still be mixing true sources
  - Mixed-source profiles can be help explain most of the variance in a dataset, understanding how underlying sources mix leverages all the variance in a dataset
  - Many independent small effect sizes can contain a lot of information that adds up to big effects
- **Data-driven and blind does not mean hypothesis-free**
  - ICA is best applied with a rationale for the expectation of types of variance sources
  - Sources require replication, validation and support for interpretation

acknowledgements

Robert Malison
Richard Carson
Marc Potenza
Vince Calhoun

Gustavo Angarita
David Matuskey
JD Gallezot
Edward Gaiser
Sarah W Yip
Jessica Costeines
Ben Kazer

Yale IICD
Yale CNRU
Yale MRRC
Yale PET Center

This research was funded by the National Institute on Drug Abuse (NIDA) (K01-DA042998, K12-DA00167, P20-DA027844, R03-DA027456, R01-DA020908, P50-DA09241), with additional support from the National Institute of Health (NIH) (P20-GM103472, R01-EB005846) and the National Center for Advancing Translational Science (NCATS) (UL1-TR000142).