

Identification of Symptom-Specific Brain Circuit Abnormalities in Obsessive-Compulsive Disorder

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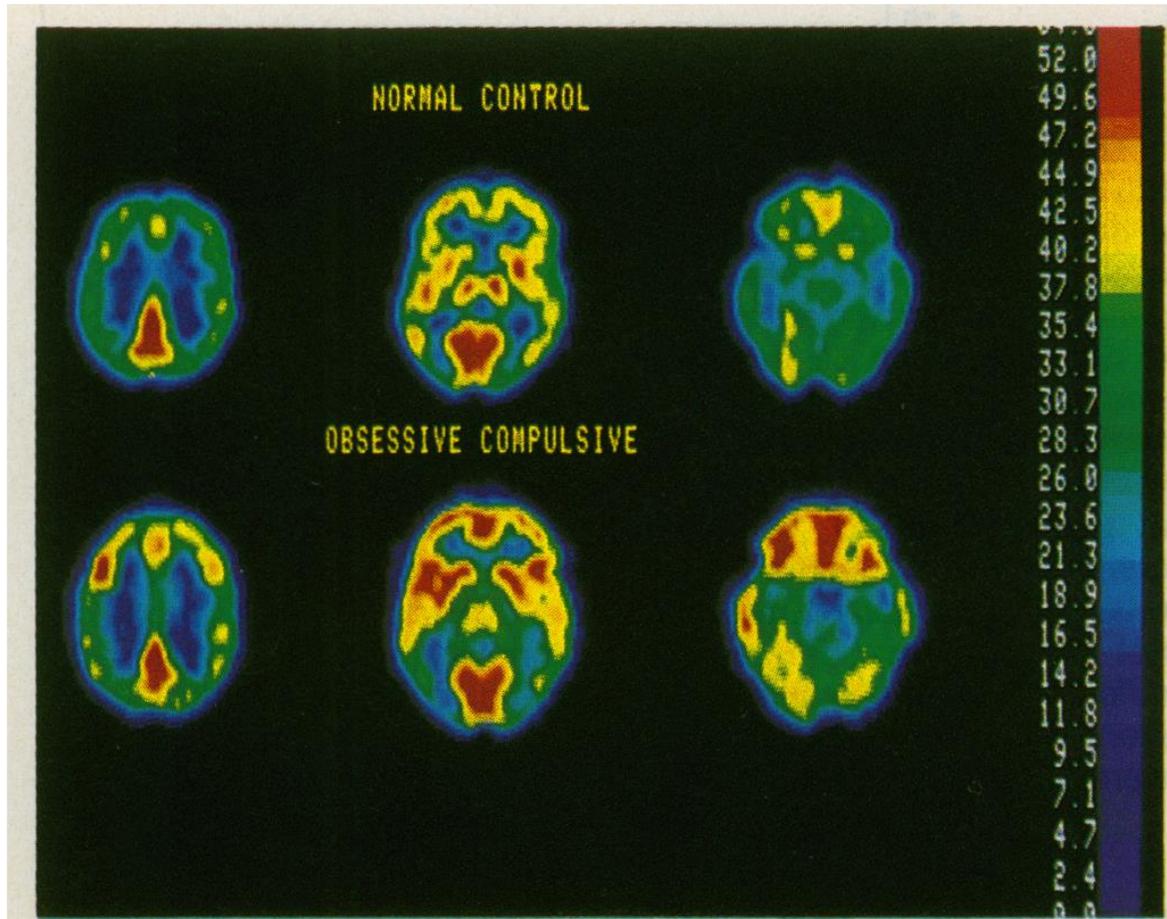
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Local Cerebral Glucose Metabolic Rates in Obsessive-Compulsive Disorder

A Comparison With Rates in Unipolar Depression and in Normal Controls

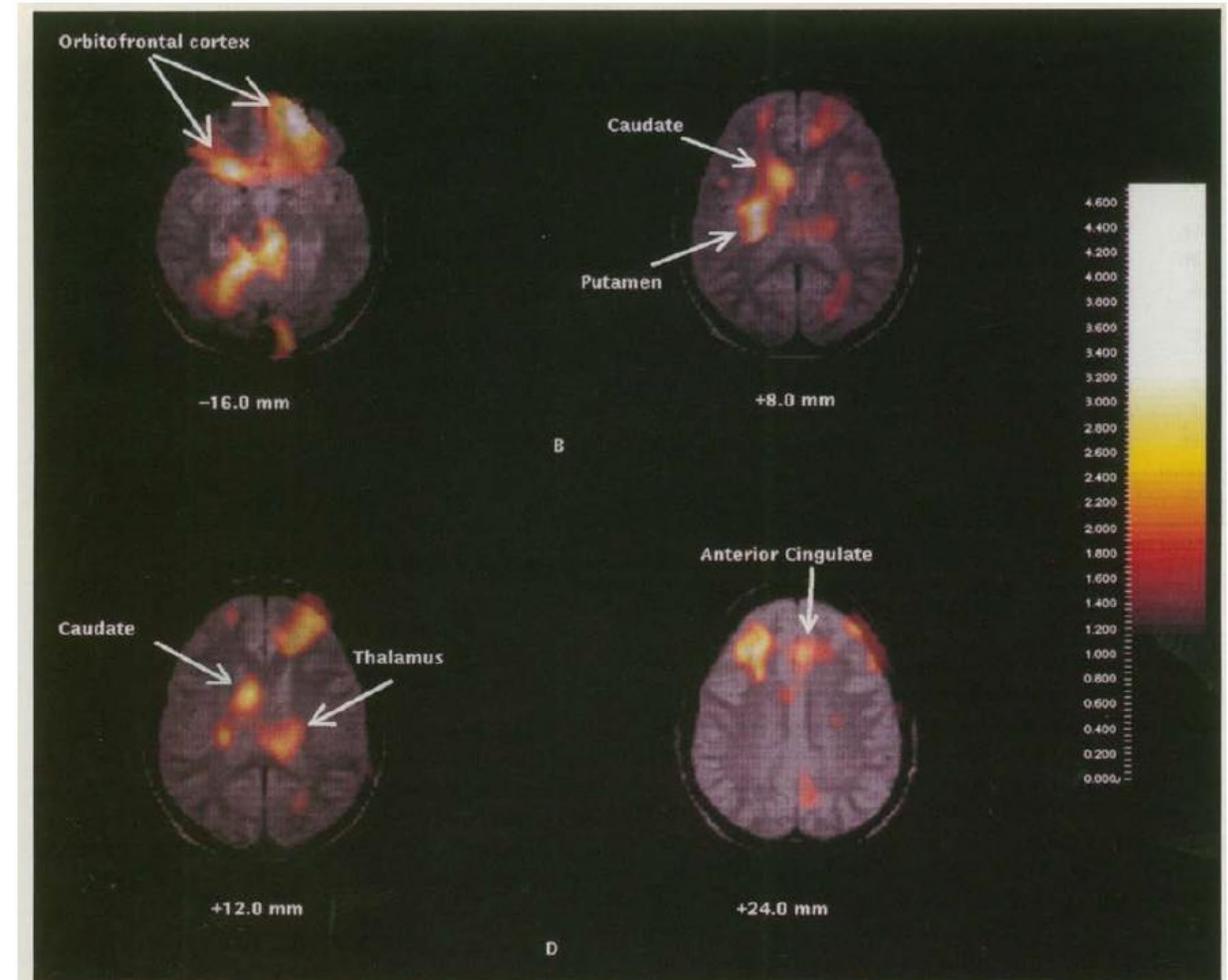
Lewis R. Baxter, Jr, MD; Michael E. Phelps, PhD; John C. Mazziotta, MD, PhD;
Barry H. Guze, MD; Jeffrey M. Schwartz, MD; Carl E. Selin, MS



Baxter et al., *Arch Gen Psych* 1987

Regional Cerebral Blood Flow Measured During Symptom Provocation in Obsessive-Compulsive Disorder Using Oxygen 15-Labeled Carbon Dioxide and Positron Emission Tomography

Scott L. Rauch, MD; Michael A. Jenike, MD; Nathaniel M. Alpert, PhD; Lee Baer, PhD; Hans C. R. Breiter, MD;
Cary R. Savage, PhD; Alan J. Fischman, MD, PhD

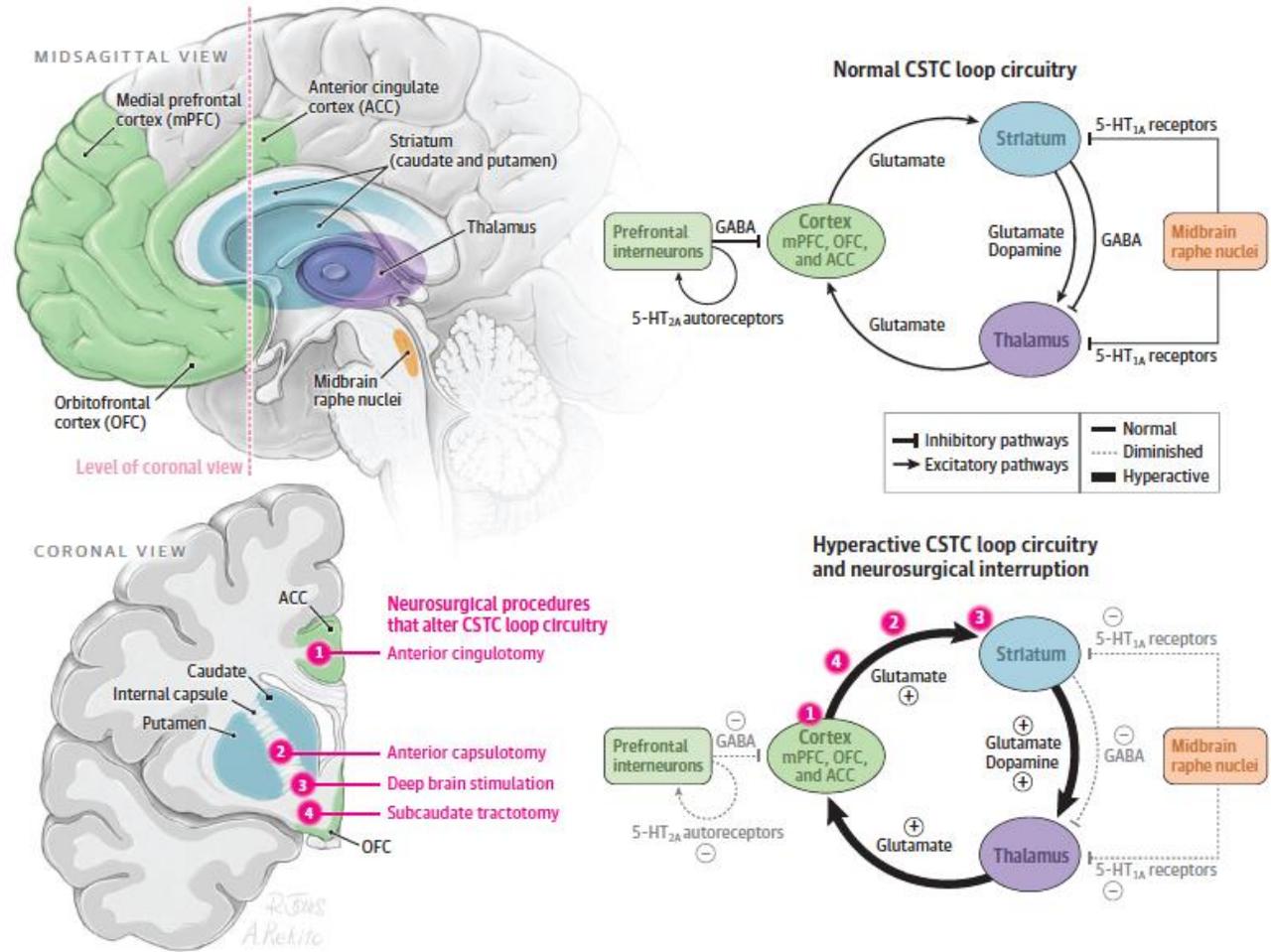


Rauch et al., *Arch Gen Psych* 1994

JAMA Psychiatry | Review

Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder A Review

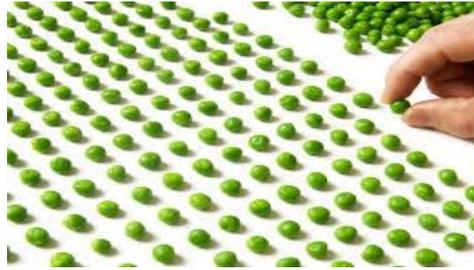
Darin D. Dougherty, MD; Brian P. Brennan, MD, MMSc; S. Evelyn Stewart, MD; Sabine Wilhelm, PhD;
Alik S. Widge, MD, PhD; Scott L. Rauch, MD



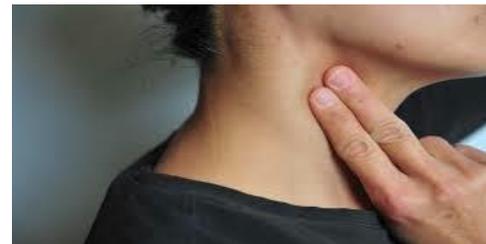
Despite years of neuroimaging research in OCD we have yet to identify definitive neuroimaging biomarkers to guide clinical care:

- Diagnosis
- Treatment selection
- Precision medicine





OCD



Neuroimaging of Symptom Dimensions in OCD

- Surprisingly, only a small number of functional neuroimaging studies (only 8 out of ~120 studies) have examined dimension-specific neural correlates in OCD
- Those that have, are limited by:
 - Small samples (most included 20 or less subjects)
 - Primarily examined washers vs. checkers
 - Used a categorical approach dividing subjects into mutually exclusive symptom groups rather than a dimensional approach examining neural correlates of all subgroups in the same subjects. **This makes more sense as OCD patients who experience only one symptom subtype are extremely rare.**
 - Used group level analyses employing population-based brain templates (more on this later!)

Neuroimaging Research at the Obsessive-Compulsive Disorder Institute at McLean Hospital (OCDI)



Advantages:

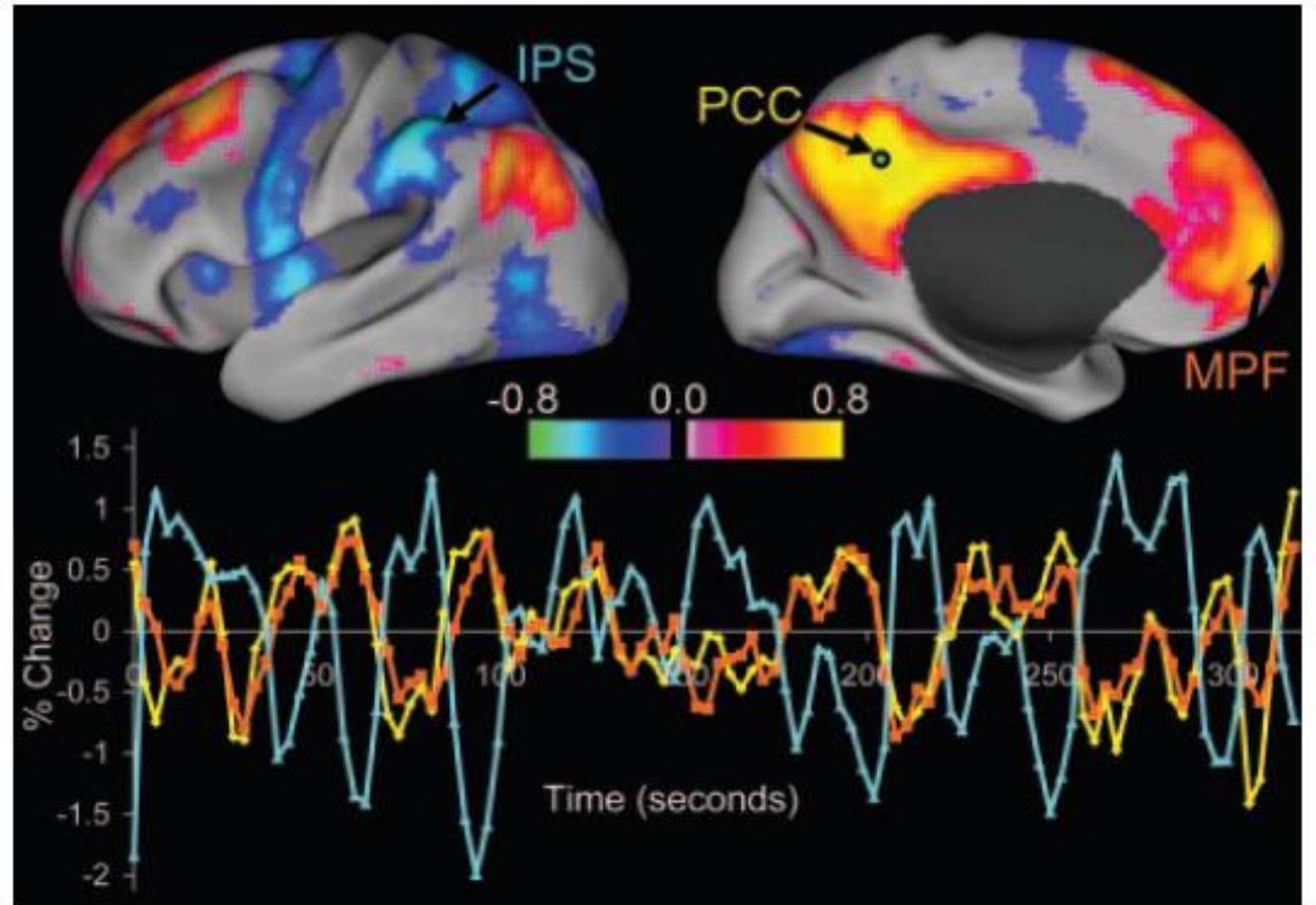
- Patients with severe OCD
- **Diverse OCD population – patients experience wide variety of symptoms covering all the widely accepted symptom dimensions**
- Extended length of stay allows for longitudinal follow-up and MRI scanning at multiple time points
- Patient population generally interested in participating in research and advancing the field

Disadvantages:

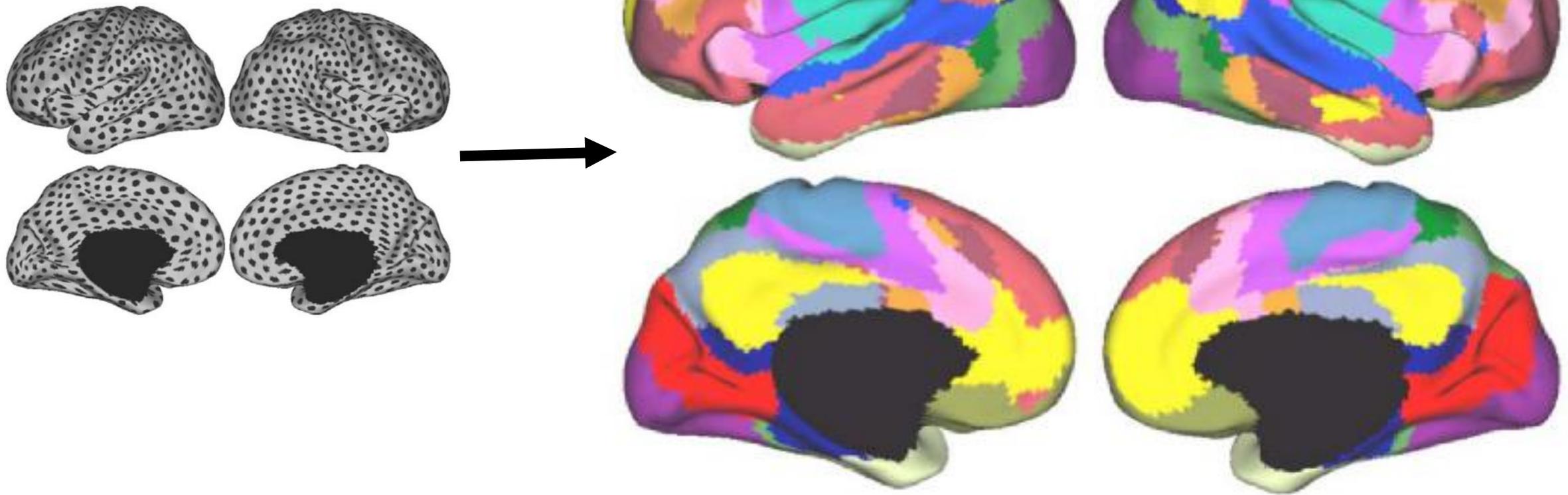
- Heterogeneous OCD population – comorbid disorders are common and varied making it difficult to control for non-OCD effects
- Multimodal treatment makes treatment-specific analyses difficult
- Unexpected discharges due to insurance, patient willingness, etc.
- Symptom severity (particularly at admission) makes recruitment challenging

Resting-State Functional Connectivity MRI (rs-fcMRI)

- Takes advantage of spontaneous low-frequency MRI signal present during rest (in the absence of a task or stimulus).
- rs-fcMRI examines the correlation in activity between brain regions – identifying collections (“networks”) of functionally connected brain regions.
- Scans can be performed in relatively short period of time (~30 min)
- Can be done at rest (while awake) – No need for subjects to do cognitive tasks inside the scanner



Cortical parcellation based on resting-state functional connectivity MRI





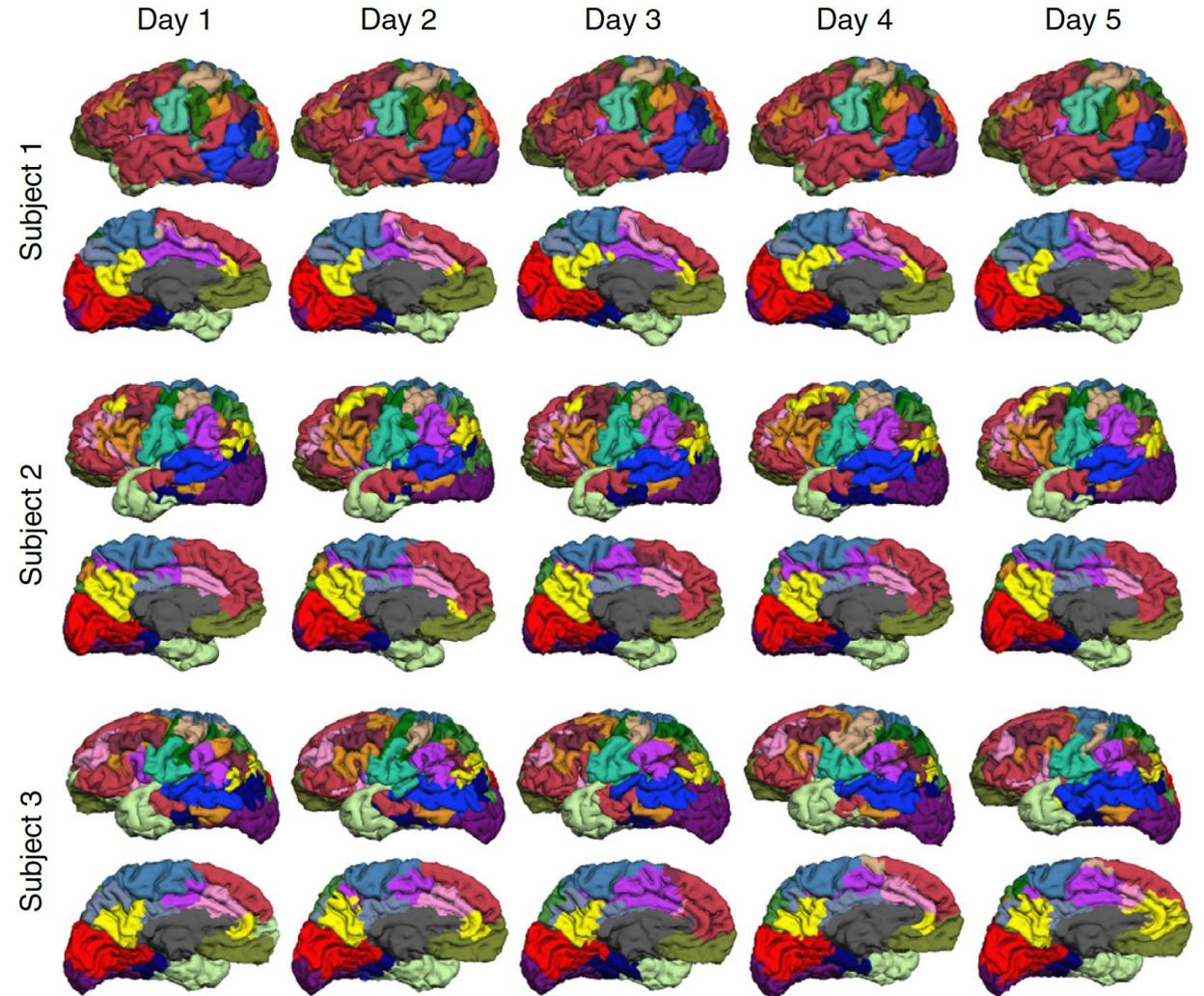
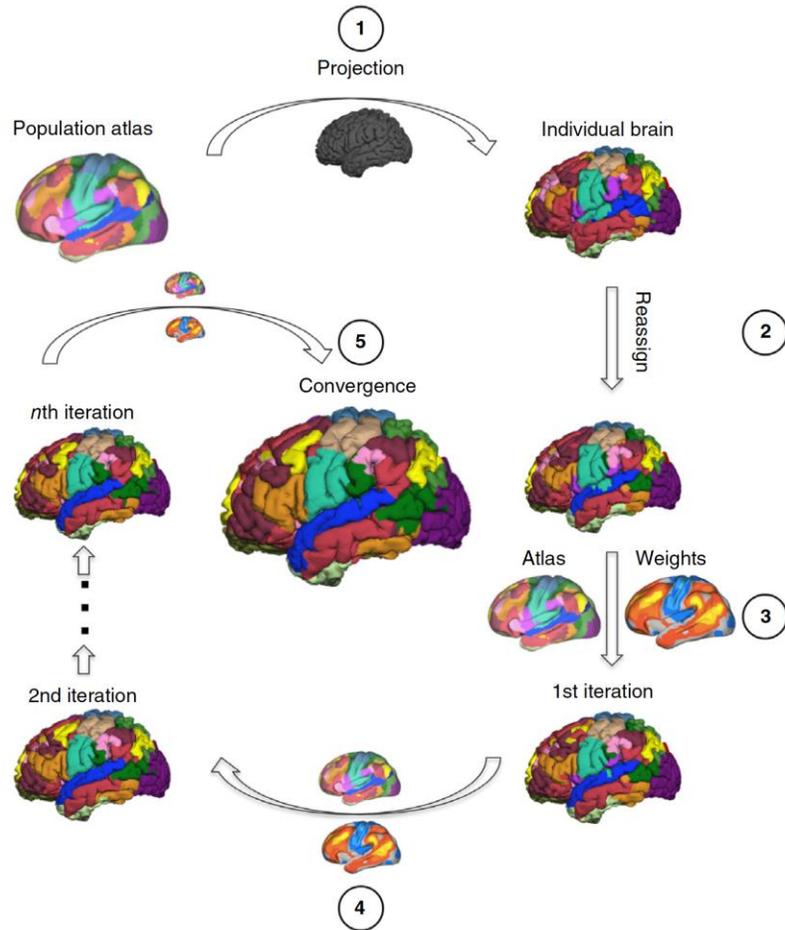
A Major limitation of previous neuroimaging studies is the lack of an individual-level approach to analysis

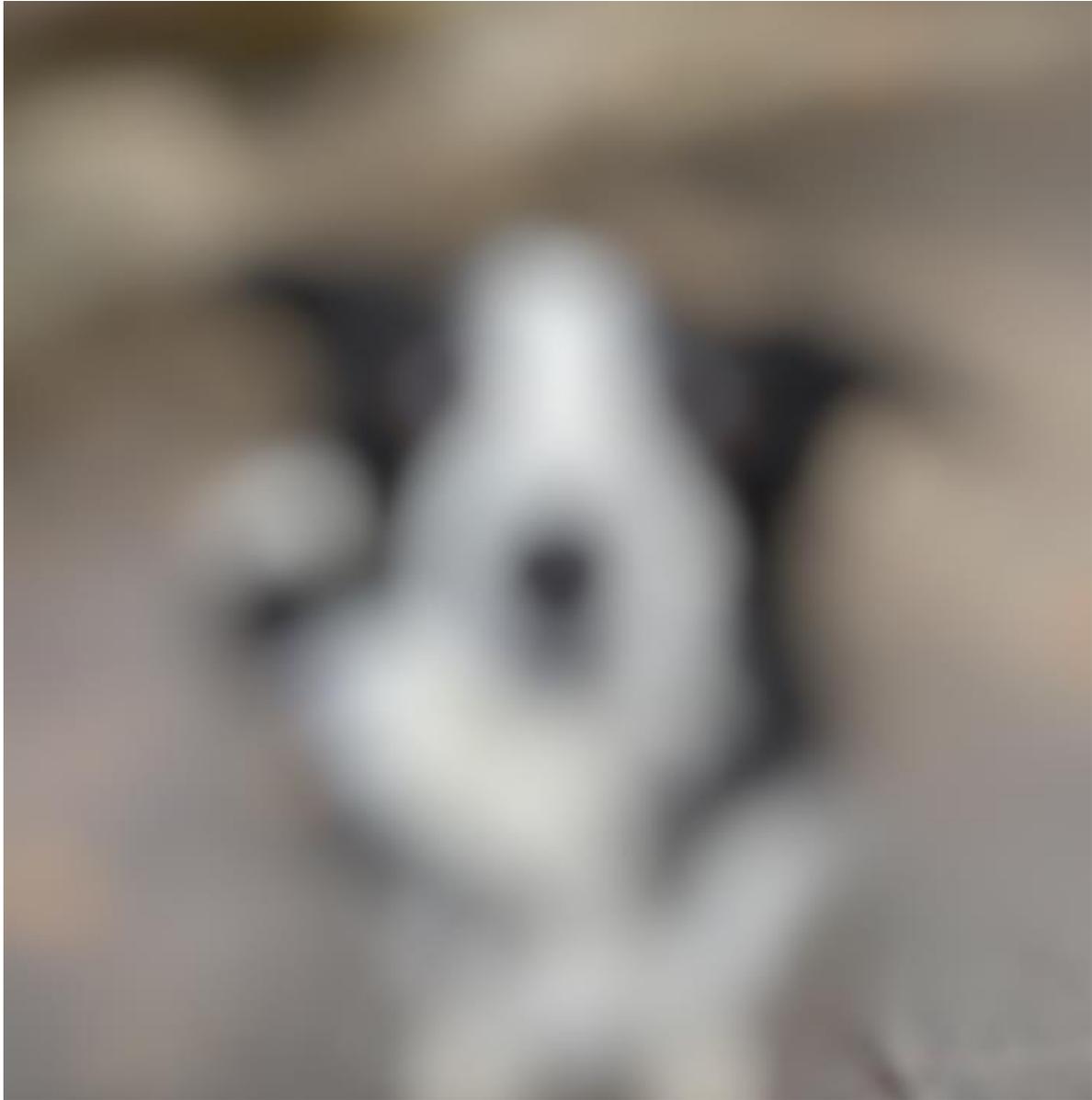
- The conventional approach to fMRI analysis uses anatomy or population-based atlases (“average brain”) to define regions of interest in the brain.
- This is problematic as there is significant variability in the structural and functional organization of the brain within the population.
- The lack of an individual-level approach may have obscured biologically important differences in previous between-group studies



Parcellating cortical functional networks in individuals

Danhong Wang^{1,2}, Randy L Buckner¹⁻³, Michael D Fox^{1,4,5}, Daphne J Holt^{1,2}, Avram J Holmes^{2,6}, Sophia Stoecklein^{1,7}, Georg Langs^{8,9}, Ruiqi Pan¹, Tianyi Qian^{1,10,11}, Kuncheng Li¹², Justin T Baker^{2,13}, Steven M Stufflebeam^{1,14}, Kai Wang¹⁵, Xiaomin Wang¹⁶, Bo Hong¹⁰ & Hesheng Liu^{1,2}





Dimensional Obsessive Compulsive Scale (DOCS)

Category 1: Concerns about Germs and Contamination

Examples...

- Thoughts or feelings that you are contaminated because you came into contact with (or were nearby) a certain object or person.
- The feeling of being contaminated because you were in a certain place (such as a bathroom).
- Thoughts about germs, sickness, or the possibility of spreading contamination.
- Washing your hands, using hand sanitizer gels, showering, changing your clothes, or cleaning objects because of concerns about contamination.
- Following a certain routine (e.g., in the bathroom, getting dressed) because of contamination
- Avoiding certain people, objects, or places because of contamination.

The next questions ask about your experiences with thoughts and behaviors related to contamination over the last month. Keep in mind that your experiences might be different than the examples listed above. Please circle the number next to your answer:

1. About how much time have you spent each day thinking about contamination and engaging in washing or cleaning behaviors because of contamination?
0 None at all
1 Less than 1 hour each day
2 Between 1 and 3 hours each day
3 Between 3 and 8 hours each day
4 8 hours or more each day
2. To what extent have you avoided situations in order to prevent concerns with contamination or having to spend time washing, cleaning, or showering?
0 None at all
1 A little avoidance
2 A moderate amount of avoidance
3 A great deal of avoidance
4 Extreme avoidance of nearly all things
3. If you had thoughts about contamination but could not wash, clean, or shower (or otherwise remove the contamination), how distressed or anxious did you become?
0 Not at all distressed/anxious
1 Mildly distressed/anxious
2 Moderately distressed/anxious
3 Severely distressed/anxious
4 Extremely distressed/anxious
4. To what extent has your daily routine (work, school, self-care, social life) been disrupted by contamination concerns and excessive washing, showering, cleaning, or avoidance behaviors?
0 No disruption at all.
1 A little disruption, but I mostly function well.
2 Many things are disrupted, but I can still manage.
3 My life is disrupted in many ways and I have trouble managing.
4 My life is completely disrupted and I cannot function at all.
5. How difficult is it for you to disregard thoughts about contamination and refrain from behaviors such as washing, showering, cleaning, and other decontamination routines when you try to do so?
0 Not at all difficult
1 A little difficult
2 Moderately difficult
3 Very difficult
4 Extremely difficult

continued →

Category 2: Concerns about being Responsible for Harm, Injury, or Bad Luck

Examples...

- A doubt that you might have made a mistake that could cause something awful or harmful to happen.
- The thought that a terrible accident, disaster, injury, or other bad luck might have occurred and you weren't careful enough to prevent it.
- The thought that you could prevent harm or bad luck by doing things in a certain way, counting to certain numbers, or by avoiding certain "bad" numbers or words.
- Thought of losing something important that you are unlikely to lose (e.g., wallet, identify theft, papers).
- Checking things such as locks, switches, your wallet, etc. more often than is necessary.
- Repeatedly asking or checking for reassurance that something bad did not (or will not) happen.
- Mentally reviewing past events to make sure you didn't do anything wrong.
- The need to follow a special routine because it will prevent harm or disasters from occurring.
- The need to count to certain numbers, or avoid certain bad numbers, due to the fear of harm.

Category 3: Unacceptable Thoughts

Examples...

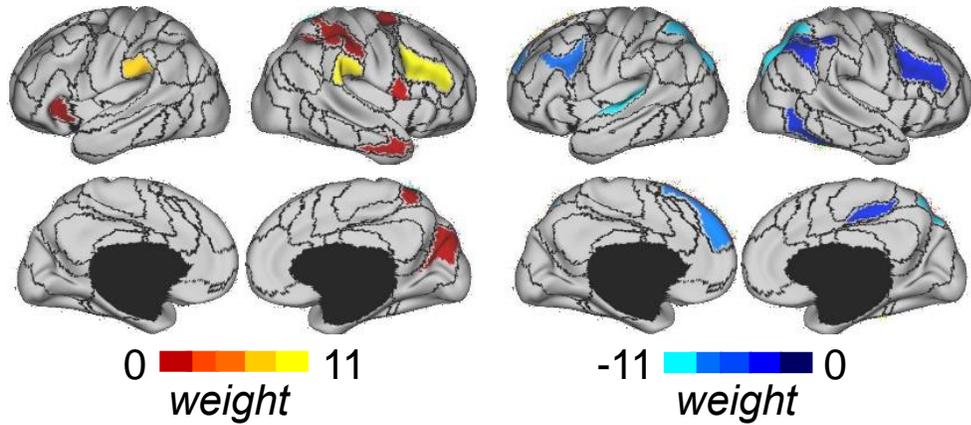
- Unpleasant thoughts about sex, immorality, or violence that come to mind against your will.
- Thoughts about doing awful, improper, or embarrassing things that you don't really want to do.
- Repeating an action or following a special routine because of a bad thought.
- Mentally performing an action or saying prayers to get rid of an unwanted or unpleasant thought.
- Avoidance of certain people, places, situations or other triggers of unwanted or unpleasant thoughts

Category 4: Concerns about Symmetry, Completeness, and the Need for Things to be "Just Right"

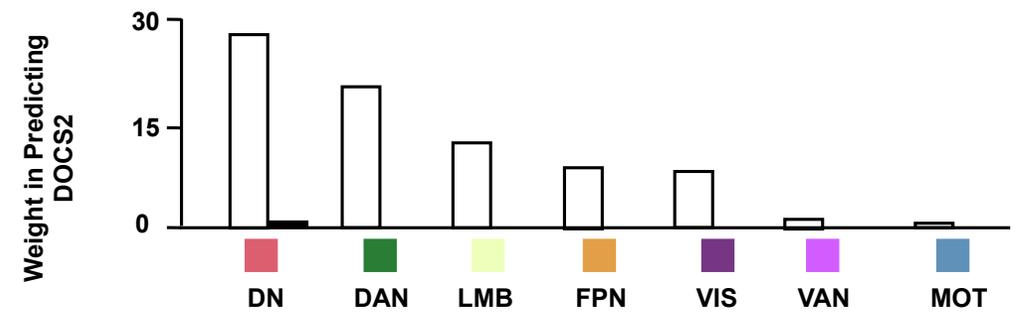
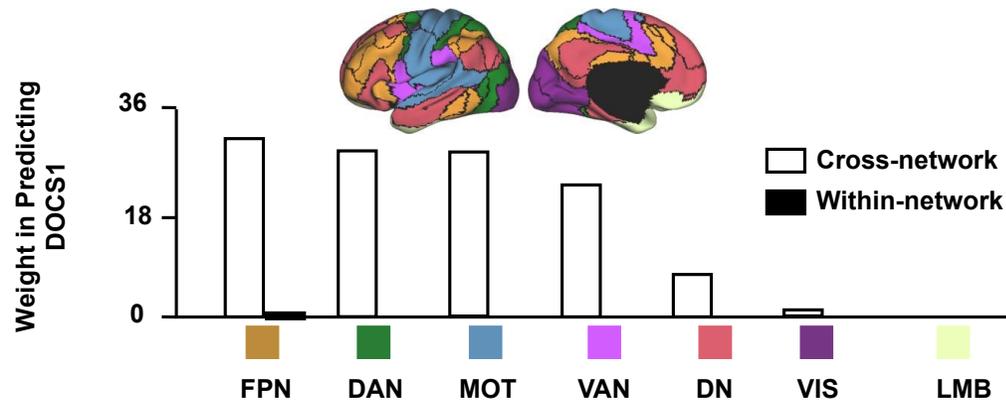
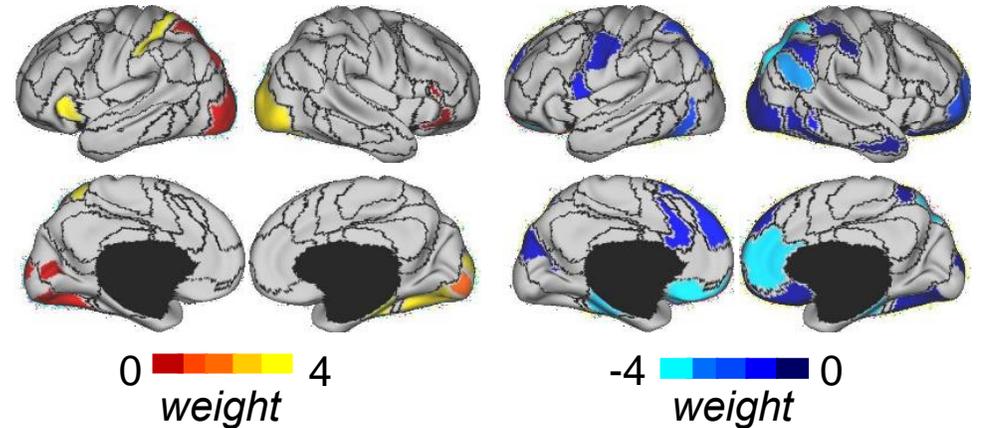
Examples...

- The need for symmetry, evenness, balance, or exactness.
- Feelings that something isn't "just right."
- Repeating a routine action until it feels "just right" or "balanced."
- Counting senseless things (e.g., ceiling tiles, words in a sentence).
- Unnecessarily arranging things in "order."
- Having to say something over and over in the same way until it feels "just right."

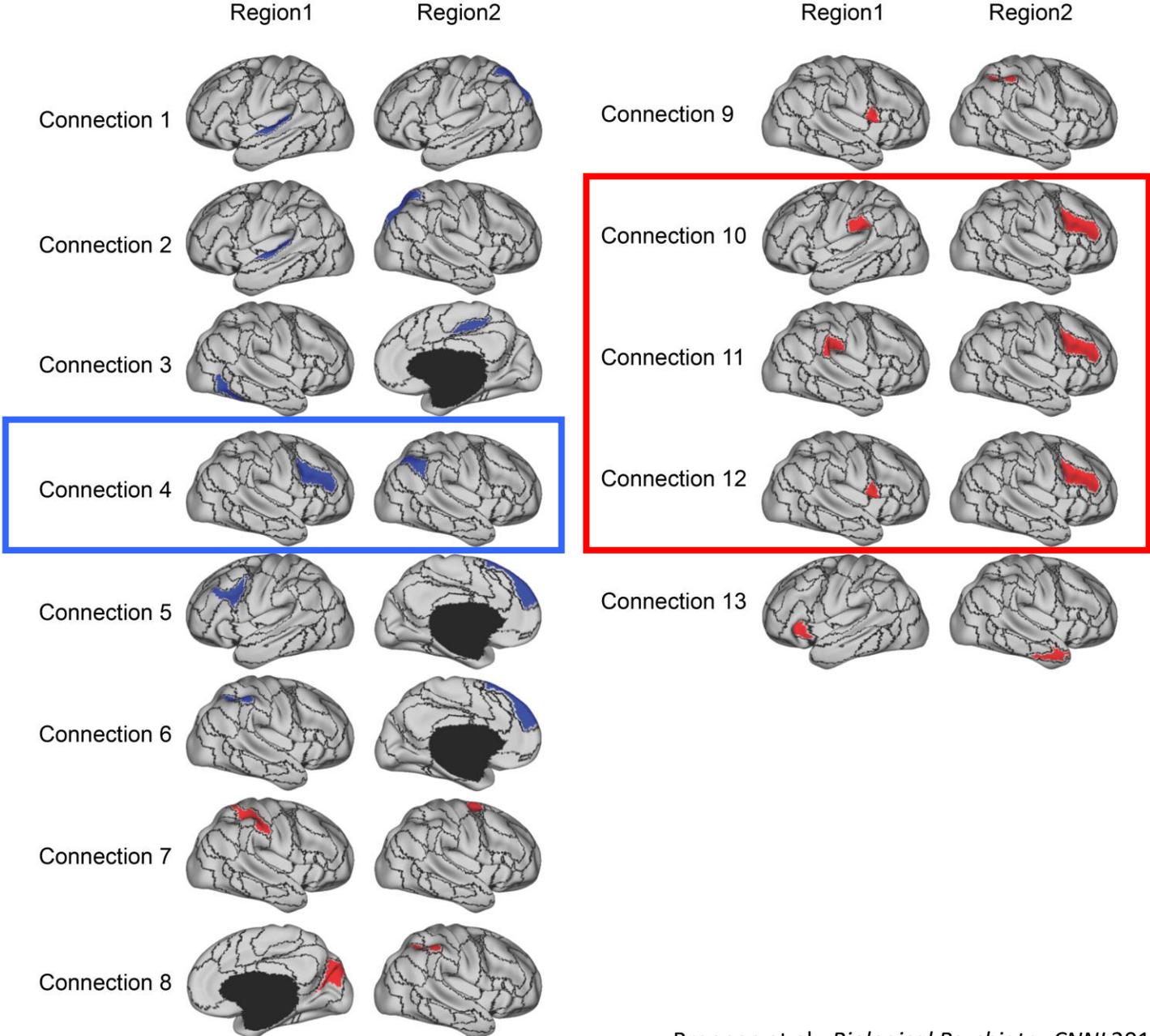
Brain connections predicting contamination/washing (DOCS1)

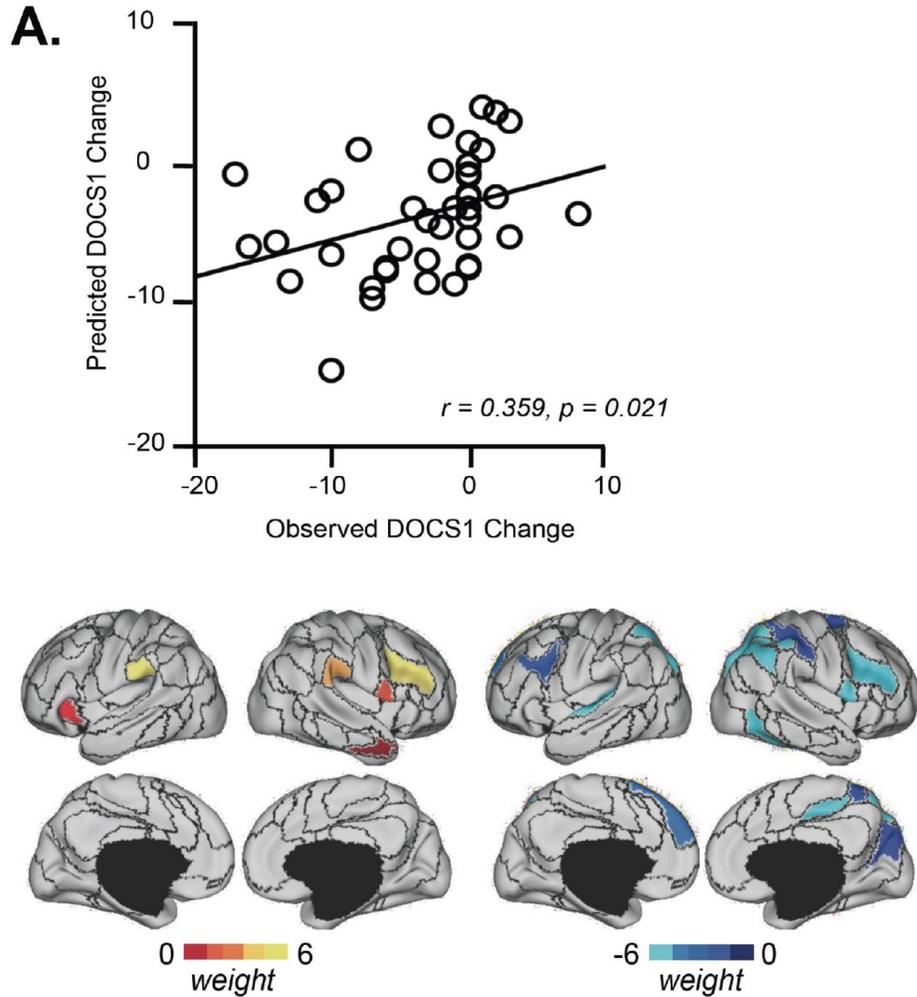


Brain connections predicting responsibility for harm/checking (DOCS2)

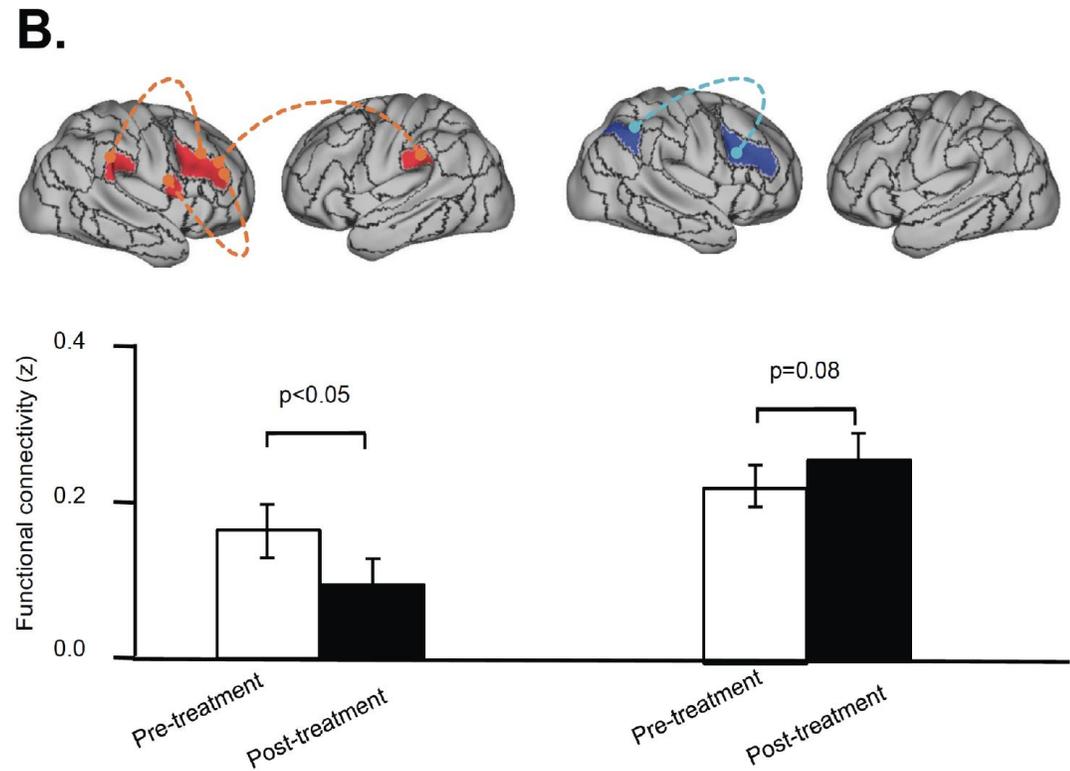


Brain connections most heavily weighted in prediction of contamination/washing symptoms



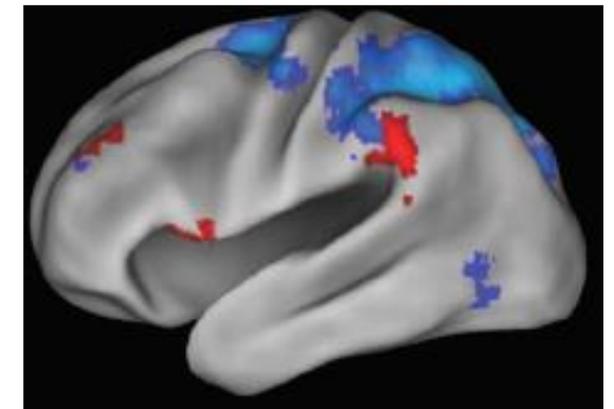
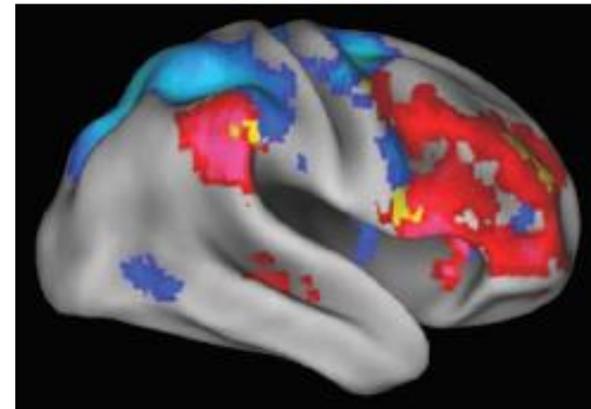
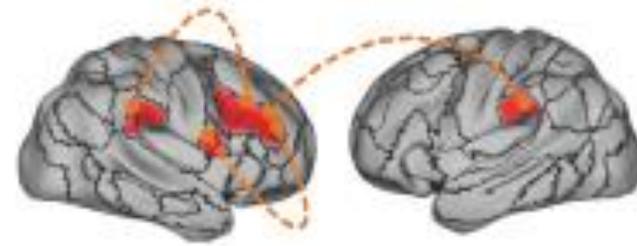


Post-treatment change in connectivity between the 13 identified connections is associated with change in contamination/washing symptoms



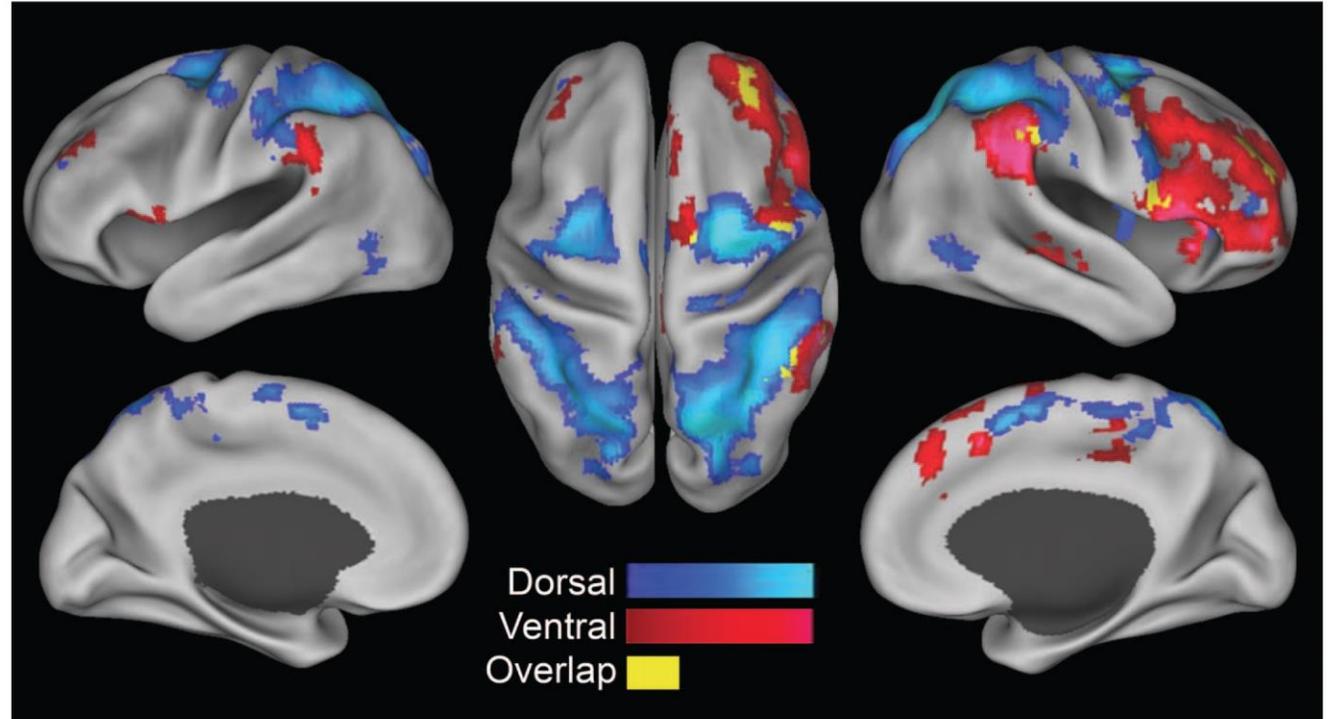
Change in connectivity between **right medial frontal gyrus** connections is significantly associated with reduction in contamination/washing symptoms

Connections strongly implicated in contamination/washing severity and improvement overlap with regions within the Ventral Attention Network



Ventral Attention Network (VAN)

Two brain networks govern attention to external stimuli:



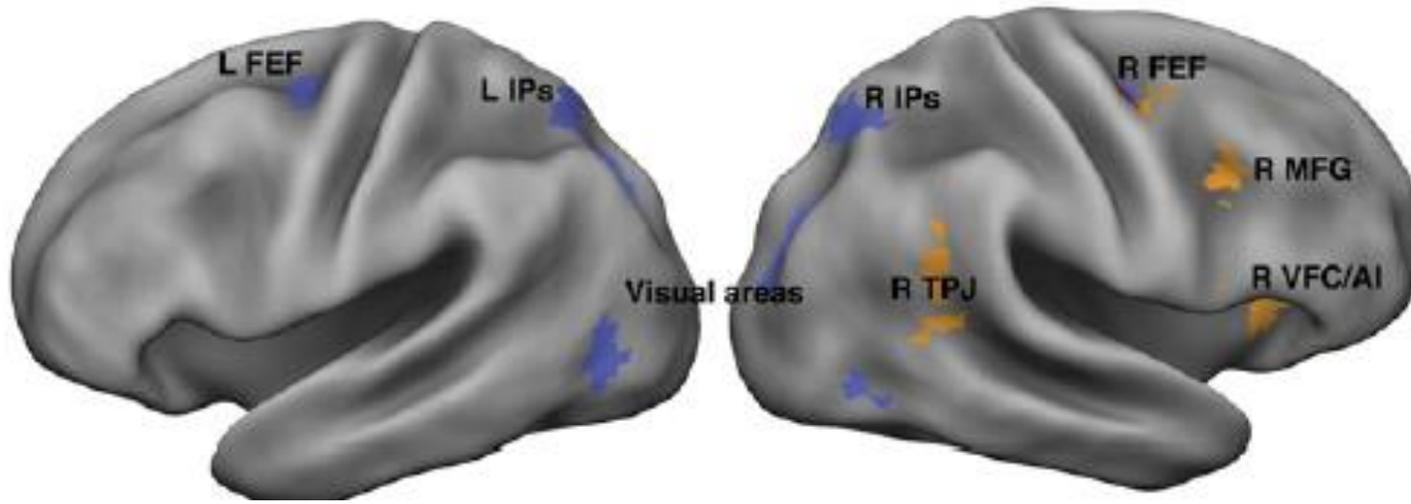
Dorsal Attention Network (DAN)
important for voluntary maintenance of attention in the service of achieving goals (“goal-driven attention”)

Ventral Attention Network (VAN)
important for the detection of unexpected behaviorally relevant stimuli (“stimulus-driven attention”)

VAN is critical in “stimulus-driven reorienting”



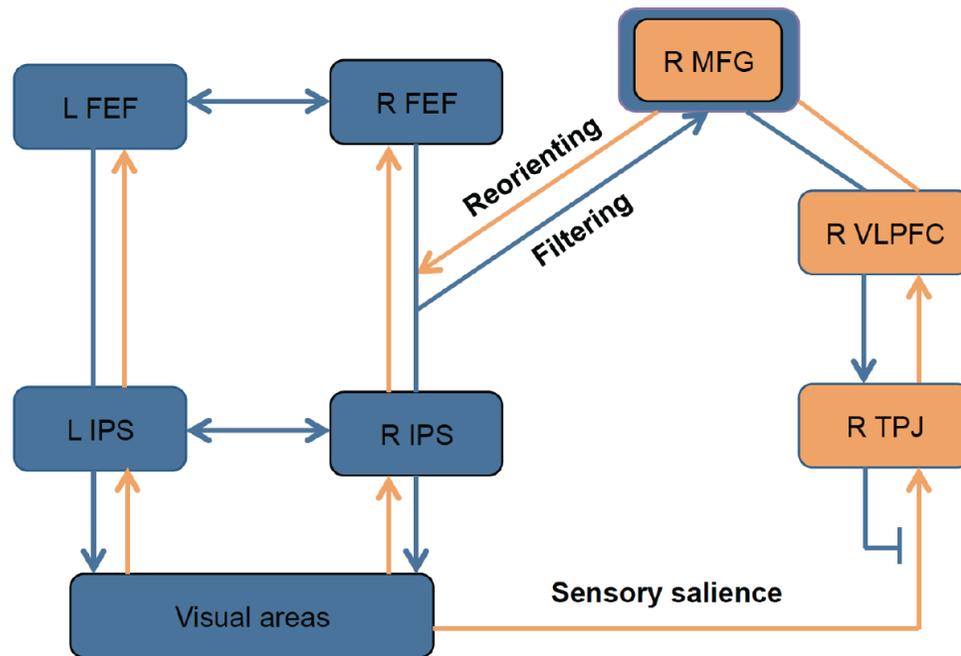
- VAN acts like a circuit-breaker to interrupt DAN-supported goal-directed attention when an unexpected and salient stimulus is detected, requiring a shift in attention.
- To optimize task performance, the VAN is typically not activated by unexpected, irrelevant stimuli. This may involve suppression of the VAN by a sustained top-down signal originating in DAN that filters out irrelevant distractors and prevents reorienting to unimportant stimuli.



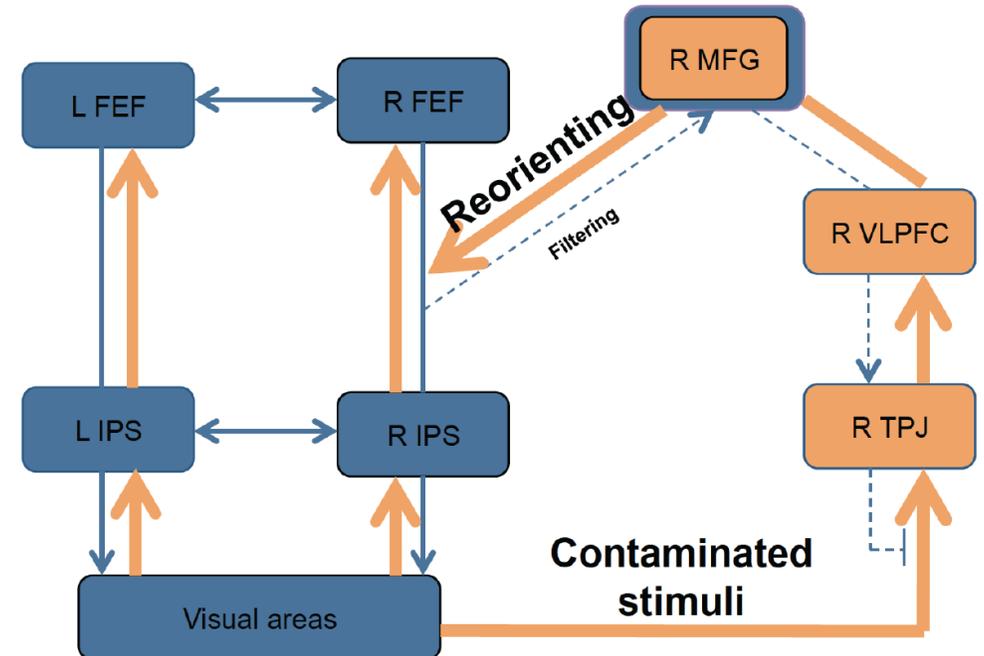
■ Dorsal Attention Network (DAN)

■ Ventral Attention Network (VAN)

Normal

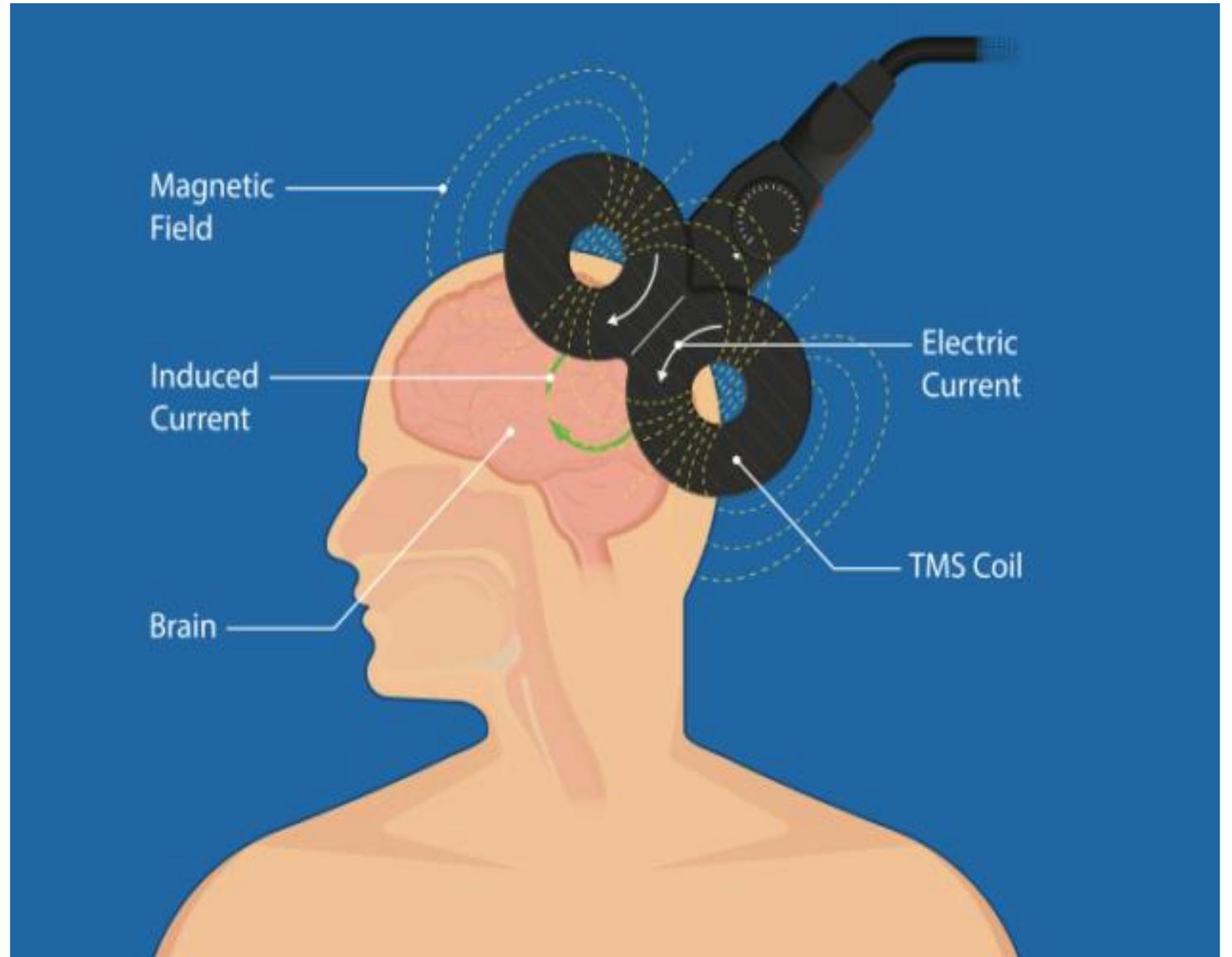


Contamination OCD



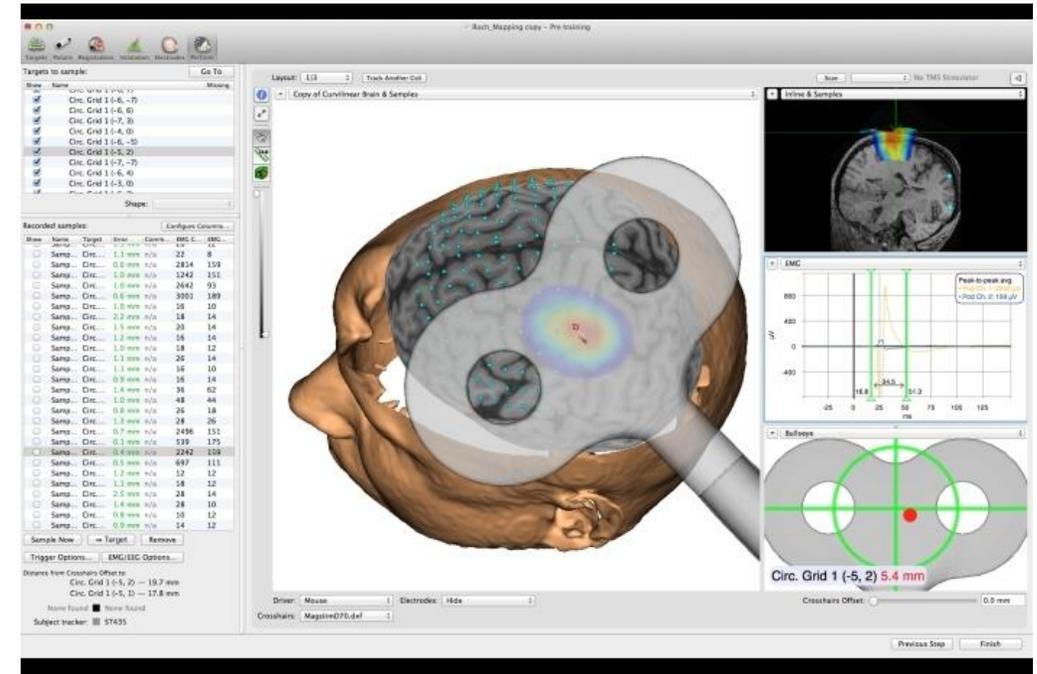
Transcranial Magnetic Stimulation (TMS)

- Insulated coil placed over the scalp generates brief magnetic pulses that penetrate brain tissue resulting in changes in brain activity.
- TMS pulses administered in rapid succession (called repetitive TMS or rTMS) can result in more lasting changes in brain activity and function.
- FDA-approved TMS treatment protocols for depression and OCD. Current OCD protocols are symptom non-specific.
- **One significant limitation is accuracy of targeting** – current approaches use anatomical landmarks, which are inexact and do not account for variation in brain structure and organization.

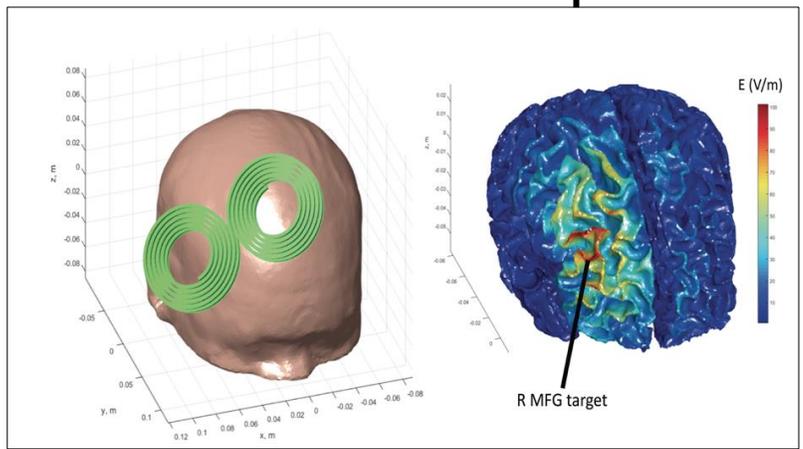
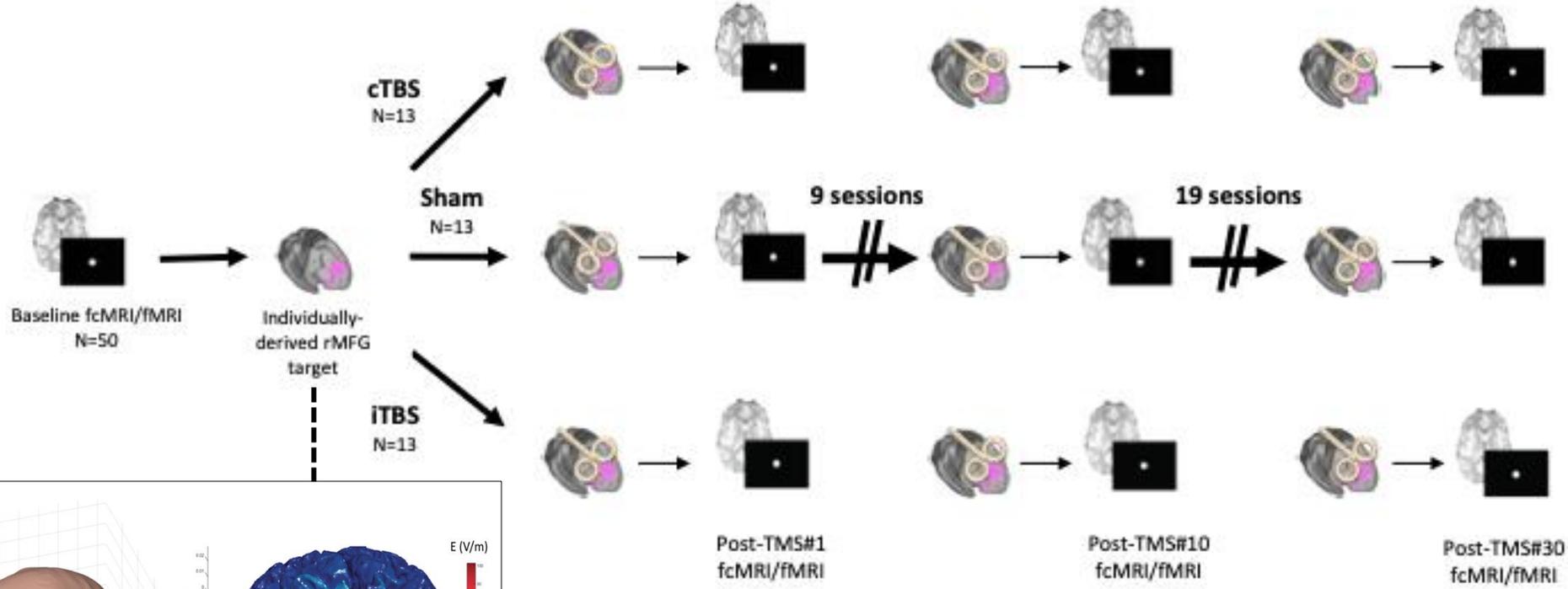


Individually-targeted TMS using rs-fcMRI with neuronavigation

- Use each individual's rs-fcMRI scan to identify the brain coordinates for TMS targeting.
- In our case, we will target the TMS stimulation to the area of **right medial frontal gyrus** that is most strongly connected to VAN in each individual

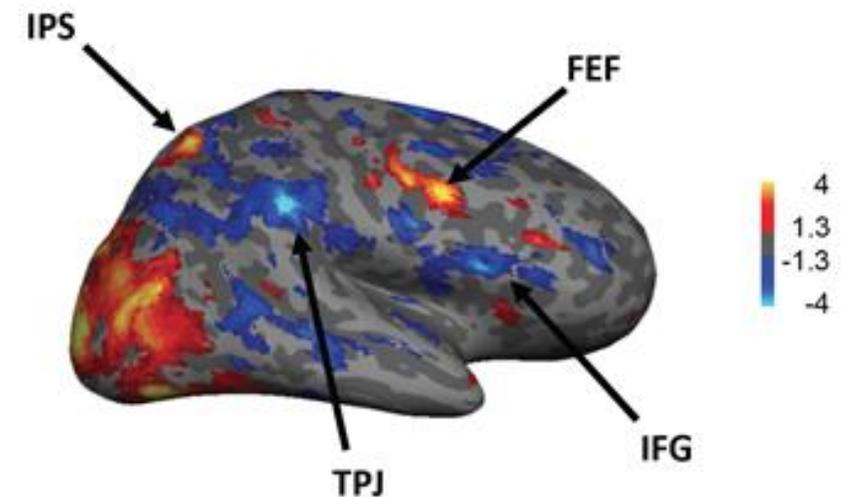


Study Design



Rapid Serial Visual Presentation (RSVP) task

- Sets of 3 images (2 Distractors + 1 Target or 3 Distractors)
- Participants press button when they see the Target
- Neutral and contamination images allowing for three different combinations:
 - Contamination targets and neutral distractors
 - Neutral targets and contamination distractors
 - Neutral targets and neutral distractors



Search-related activations (warm colors) and deactivations (cool colors) in a representative subject using our RSVP task.

Aims of R61 Study

- Primary Aim: Demonstrate decreased functional connectivity between **right medial frontal gyrus** and brain regions within **VAN** following active TMS (cTBS and/or iTBS) but not sham
- Secondary Aims:
 - Demonstrate fewer “false alarms” to RSVP distractors, relative to pre-treatment
 - Demonstrate decreased right medial frontal gyrus and VAN activation during visual search in the RSVP, relative to pre-treatment.
- Exploratory Aim: Demonstrate reduction in total score on Category 4 (Contamination) of the Dimensional YBOCS after active TMS (cTBS and/or iTBS) but not sham
- Successfully achieving our Primary Aim will lead to R33 study – a larger double-blind, sham-controlled trial of cTBS or iTBS (whichever is most effective) primarily investigating clinical efficacy

Collaborators

- **McLean Hospital**

 - OCDI

 - Michael Jenike
 - Scott Rauch
 - Jason Krompinger
 - Jason Elias
 - Nathaniel Van Kirk

 - Biological Psychiatry Laboratory

 - James Hudson
 - Skip Pope
 - Rosie Sokoll

 - Laboratory for Functional Neuroimaging and Bioinformatics

 - Justin Baker

 - Motivated Learning and Memory Laboratory

 - Dan Dillon

 - Schizophrenia and Bipolar Disorder Research Program

 - Mark Halko

- **U of Illinois Urbana-Champaign**

 - Chris Perriello

- **Temple University**

 - Jiana Schnabel

- **MGH**

 - Daisy Wang
 - Meiling Li
 - Mark Eldaief

- **MUSC**

 - Hesheng Liu



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