Research by Olga Dobrushina, Ph.D. *et al*

Clinical Summit, Berg 2017, LA 2018, Berg 2019, LA 2020

Siegfried Othmer

First publication was in 2015: A conference presentation

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Exploring the brain contour of implicit infra-low frequency EEG neurofeedback: a resting state fMRI study

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Modulation of intrinsic brain connectivity by implicit (i.e., covert) infra-low frequency neurofeedback

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Dr. Olga Dobrushina spoke in Berg in 2017:

Modulation of the brain connectivity by infra-low frequency neurofeedback

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Modulation of intrinsic brain connectivity by implicit (i.e., covert) infra-low frequency neurofeedback

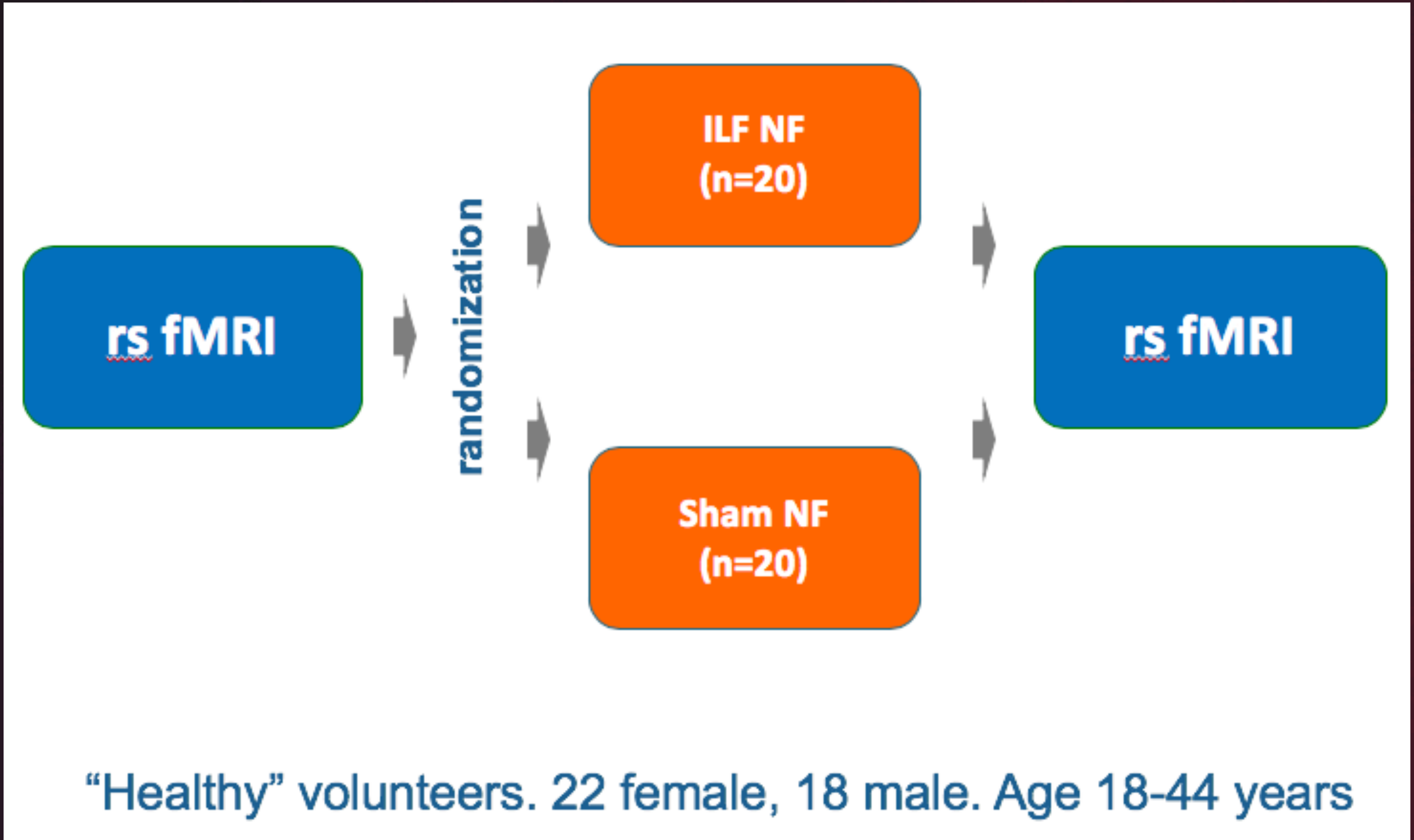
- Objective:
  1. Identify the networks engaged in the execution of implicit (covert) neurofeedback. Since within-session rsfMRI was ruled out, evaluate proximate pre-post-session assessments.
  2. Identify the networks altered in consequence of the neurofeedback process

- Study design: 52 volunteers were randomized to a single session of ILF or sham neurofeedback. Resting state fMRI data were acquired immediately before and after the session, in order to observe training process-induced changes

A bold hypothesis!

- The first objective was to identify the network connectivity alterations related to the neurofeedback process itself, which would be expected to differ between the ILF and sham training arms.
  - The bold assumption is that these would still be detectable right after the training session
- The second objective was to identify the network changes that resulted from the training process itself. These would be expected to differ also between the ILF and sham training arms.
  - The bold assumption here is that single-session effects would already be observable, and that they would be sufficiently systematic to be observable
    - in a random sample of non-clinical individuals
    - in the absence of any optimization of the training

The study design:



Key points:

- Important differences are presented by involvement of the striatum but not the salience network:
- It is proposed that the salience network is responsible for conscious perception of reward, while unconscious reward is mediated by the striatum.
- The involvement of right, but not left, prefrontal cortex may be related to the leading role of the right brain in implicit learning.

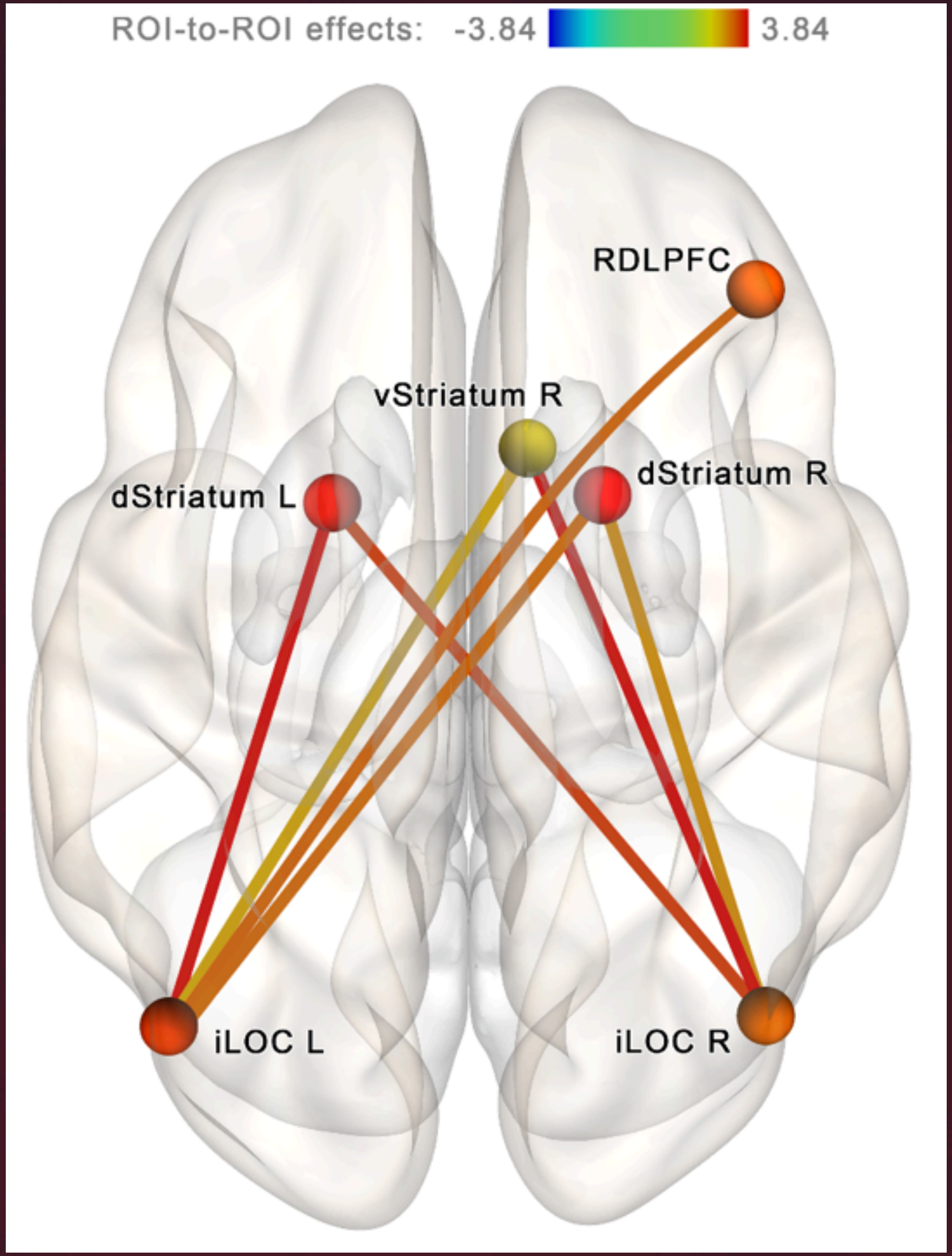
Conclusions:

- We describe the brain circuit of implicit infra-low frequency EEG neurofeedback consisting of the lateral occipital cortex, right dorsolateral prefrontal area and striatum.

Pre-post single-session ILF fMRI connectivity changes

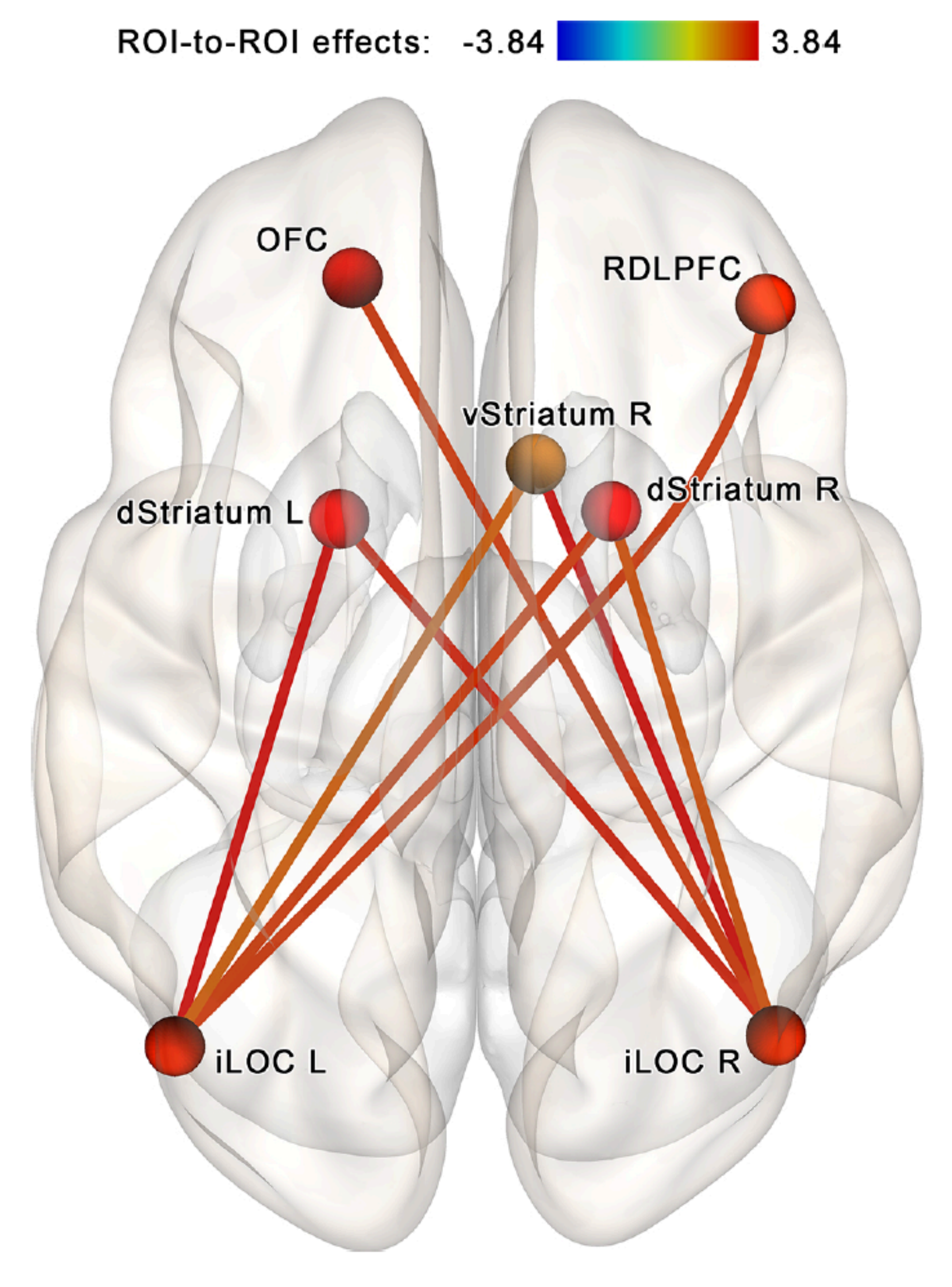
- Increased connectivity within the proposed neurofeedback contour after the ILF NF session
- iLOC: inferior lateral occipital cortex
- RDLPFC: right dorsolateral prefrontal cortex
- vStriatum: ventral striatum
- dStriatum: dorsal striatum

2018 Preprint

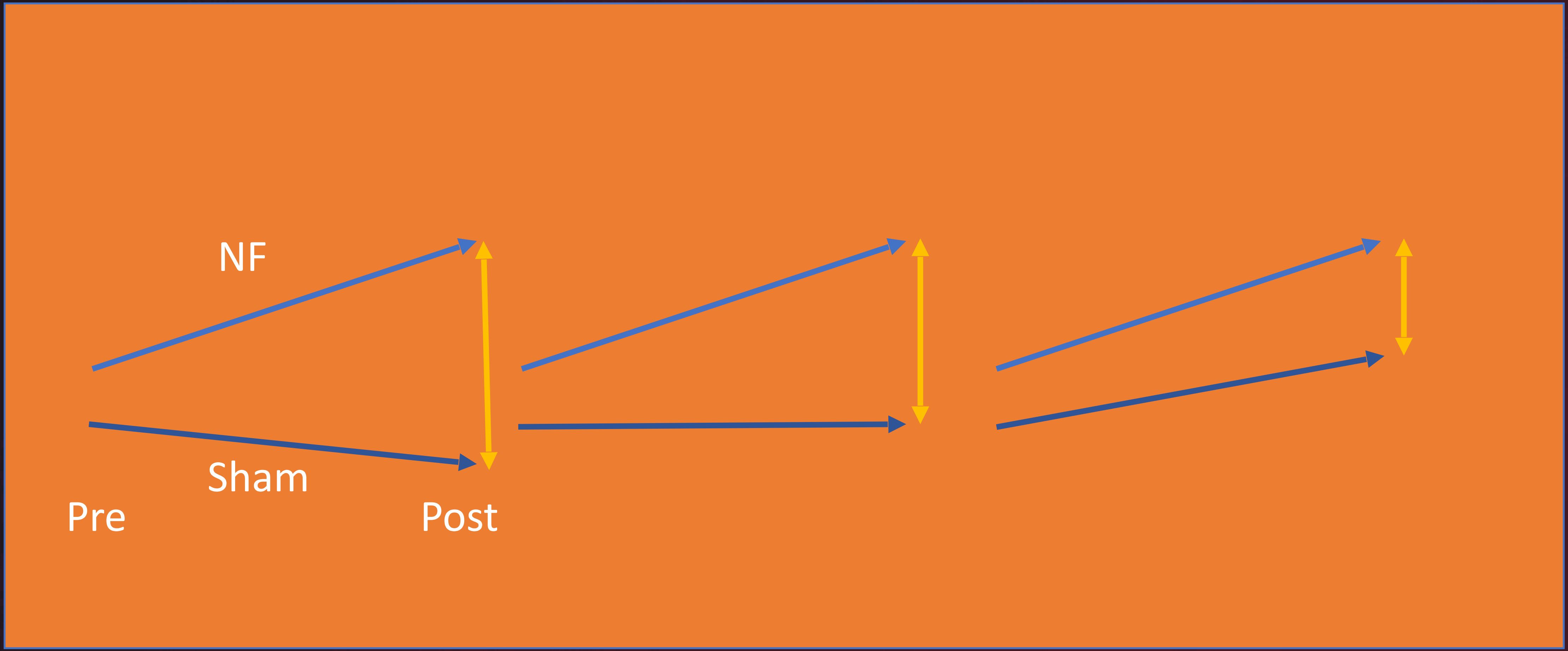


2020 publication

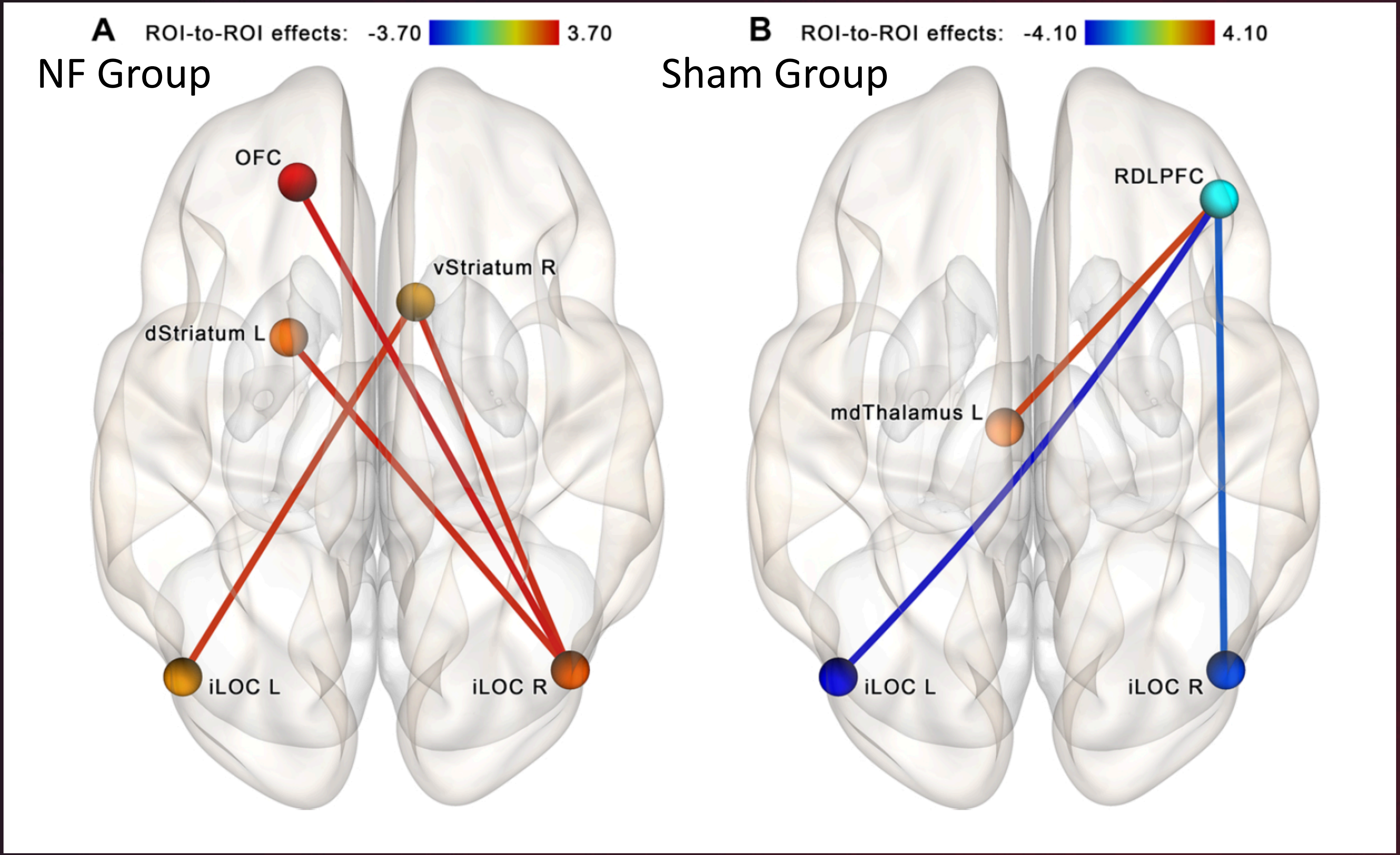
- Increased connectivity within the proposed neurofeedback contour after the infra-low frequency NF session.
- A subnetwork containing the inferior lateral occipital cortex (iLOC), right dorsolateral prefrontal cortex (RDLPFC), left orbitofrontal cortex (OFC), ventral striatum (vStriatum), and dorsal striatum (dStriatum) shows increased connectivity post- vs. pre-, NF vs. sham ($p < 0.05$, FWE-corrected).
- We propose that these connections reflect the coupling of brain areas targeting the accomplishment of the neurofeedback task.



Pre-versus-post, NF versus sham:



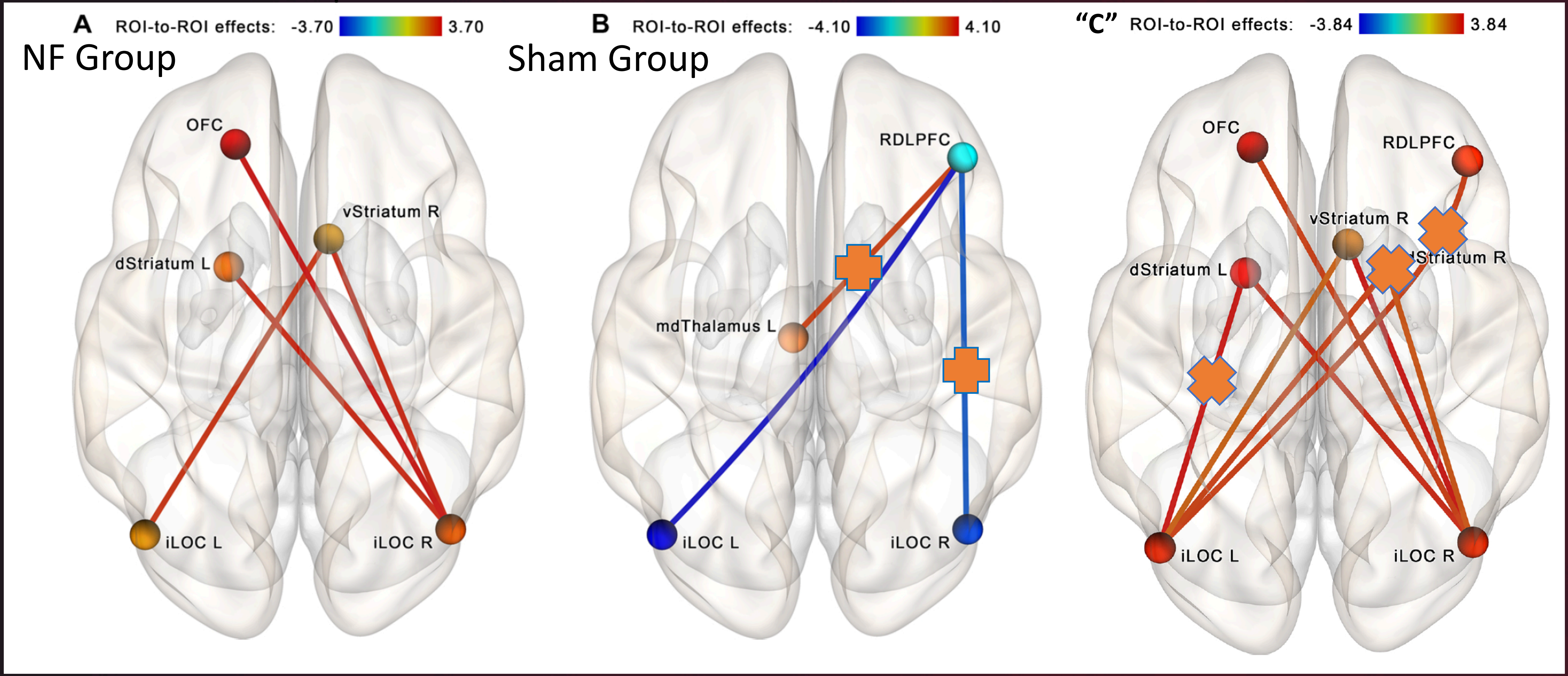
Significant linkages for the two cohorts



Significant linkages for the two cohorts

Additive to what is seen in "C"   Linkages that are insignificant in NF Group

NF Group



Control group:

- In the control group, another set of three connections was altered after a sham-NF session.
- This subnetwork included decreasing connectivity between the RDLPFC and the iLOC bilaterally and increasing connectivity between the RDLPFC and the left thalamus.

Even in covert NF, the brain is trying to figure out what the game is. So even sham training is an active process.

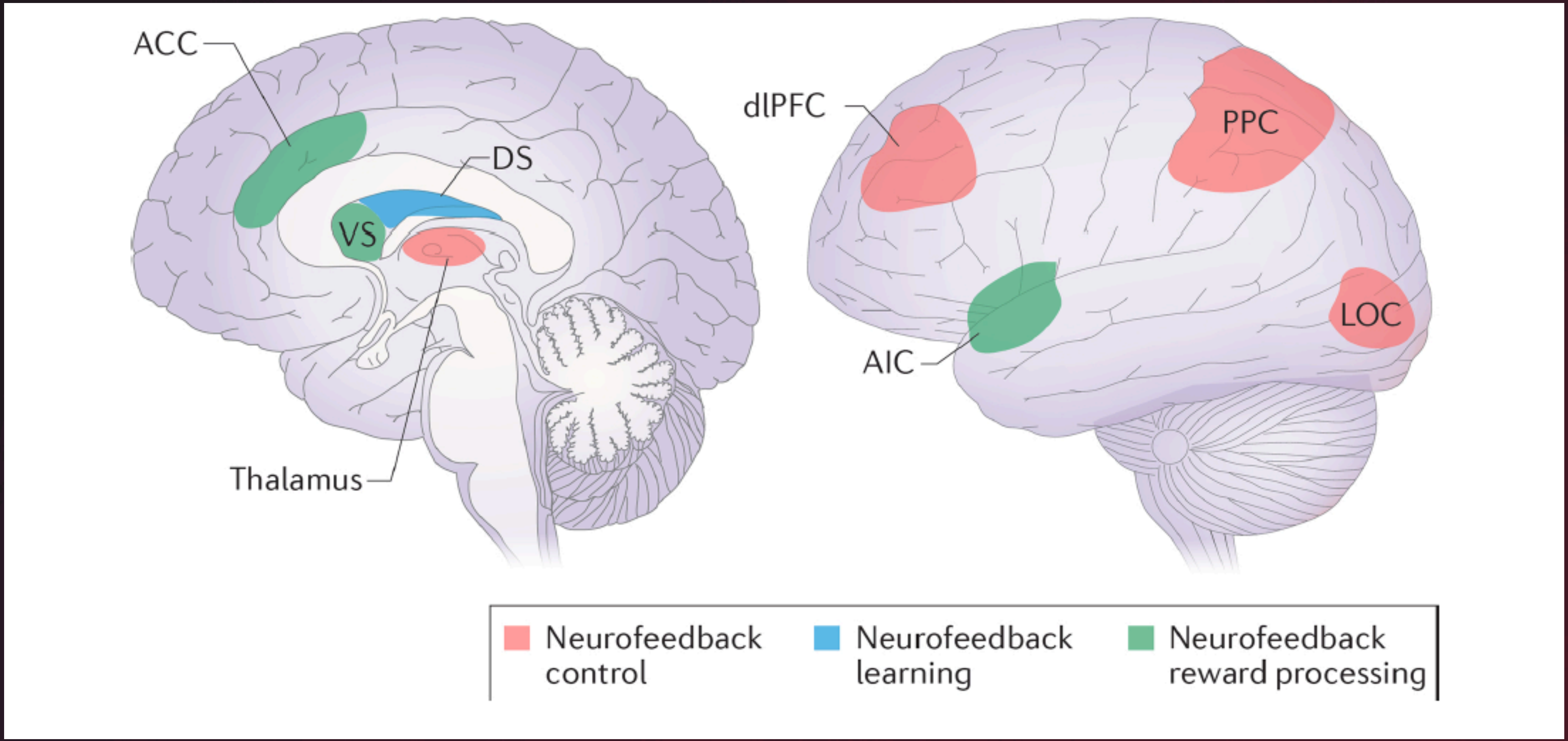


FIGURE 2 | Neurofeedback control, learning and reward processing networks. The regions from the frontoparietal control network (dorsolateral prefrontal cortex—dlPFC; posterior parietal cortex—PPC), in cooperation with the task-relevant modality sensory cortex (lateral occipital cortex—LOC), are supposed to be responsible for neurofeedback control.
Task-related learning involves the dorsal striatum (DS). The reward may be processed either consciously by the salience network (the anterior cingulate cortex—ACC, the anterior insular cortex—AIC), or unconsciously by the ventral striatum (VS).
Reprinted by permission from Springer,from Sitaram et al. (2017).

Second hypothesis: Changes induced by the training process

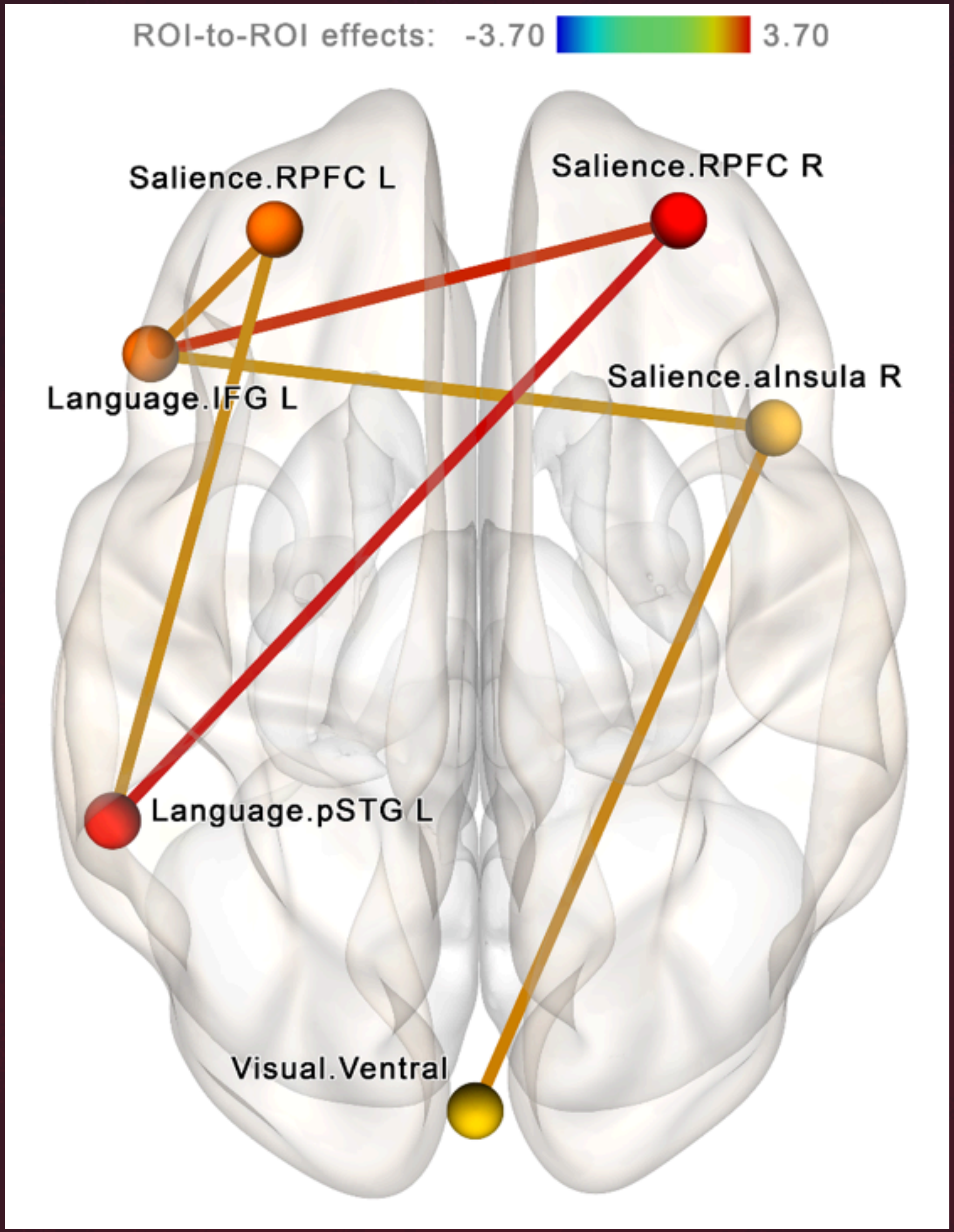
Hypothesis-based:

- Assume that attentional networks are impacted by the training
- Assume that relevant sensory networks are impacted

1. Analysis pre-post and between groups
2. Analysis within-NF group

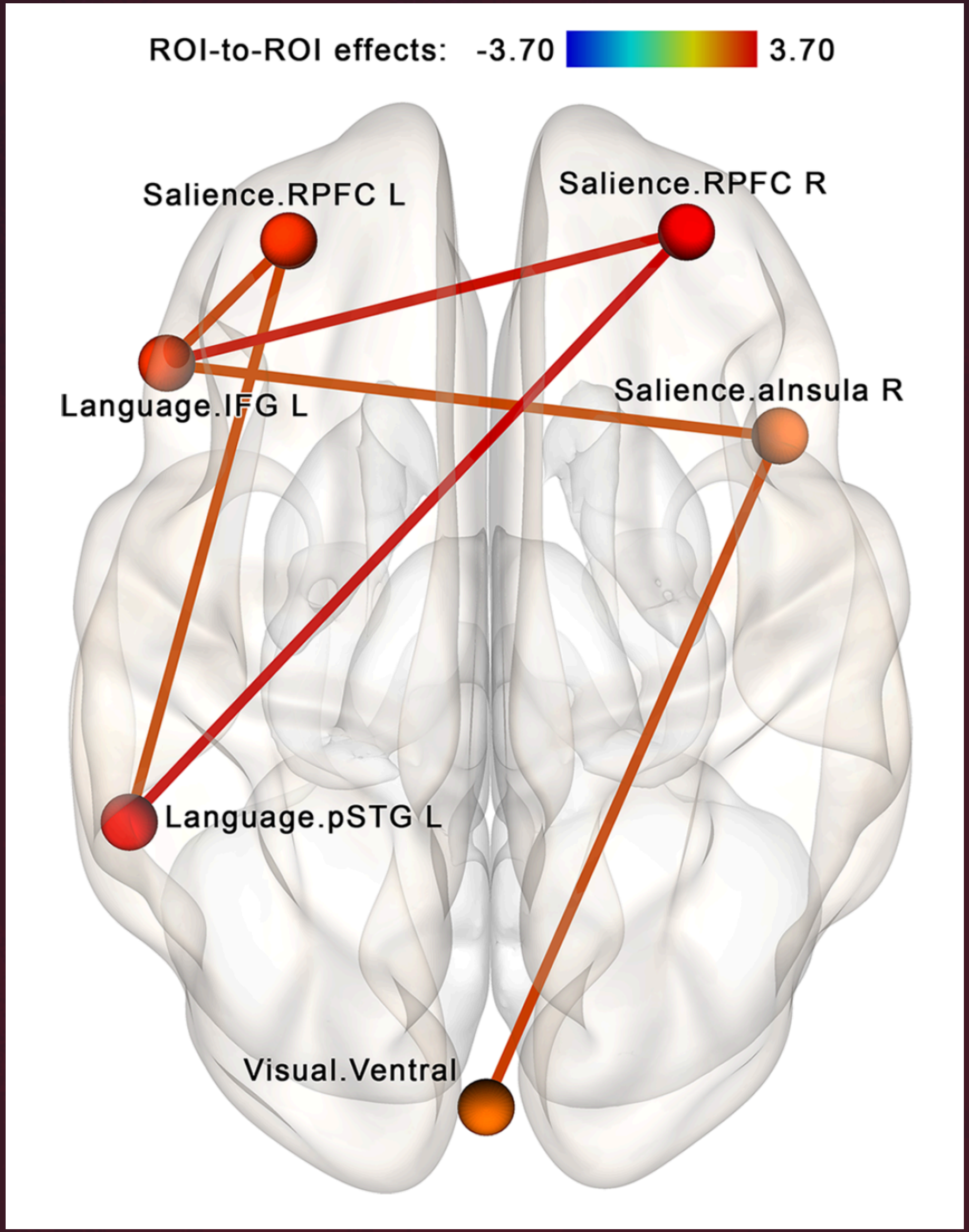
Pre-post single-session ILF fMRI connectivity changes, NF versus Sham –pre-print

- Increased connectivity between the language network and salience and visual networks after the ILF NF session
  - IFG: inferior frontal gurus
  - pSTG: posterior portion of the superior temporal gyrus
  - RPFC: rostral prefrontal cortex
  - aInsula: anterior insula).



Re-analysis just shifted some weights

- Increased connectivity between the salience, language and visual networks after the infra-low frequency NF session.
- A subnetwork containing the right and left rostral prefrontal cortex (RPFC), left inferior frontalgyrus (IFG L; i.e., Broca's area), left posterior portion of the superior temporalgyrus (pSTG L; i.e., Wernicke's area), right anterior insula (aInsula R) and ventral visual pathway shows increased connectivity
- We propose that these connections reflect the desired effects of the neurofeedback: an integrative tendency toward multimodal processing.



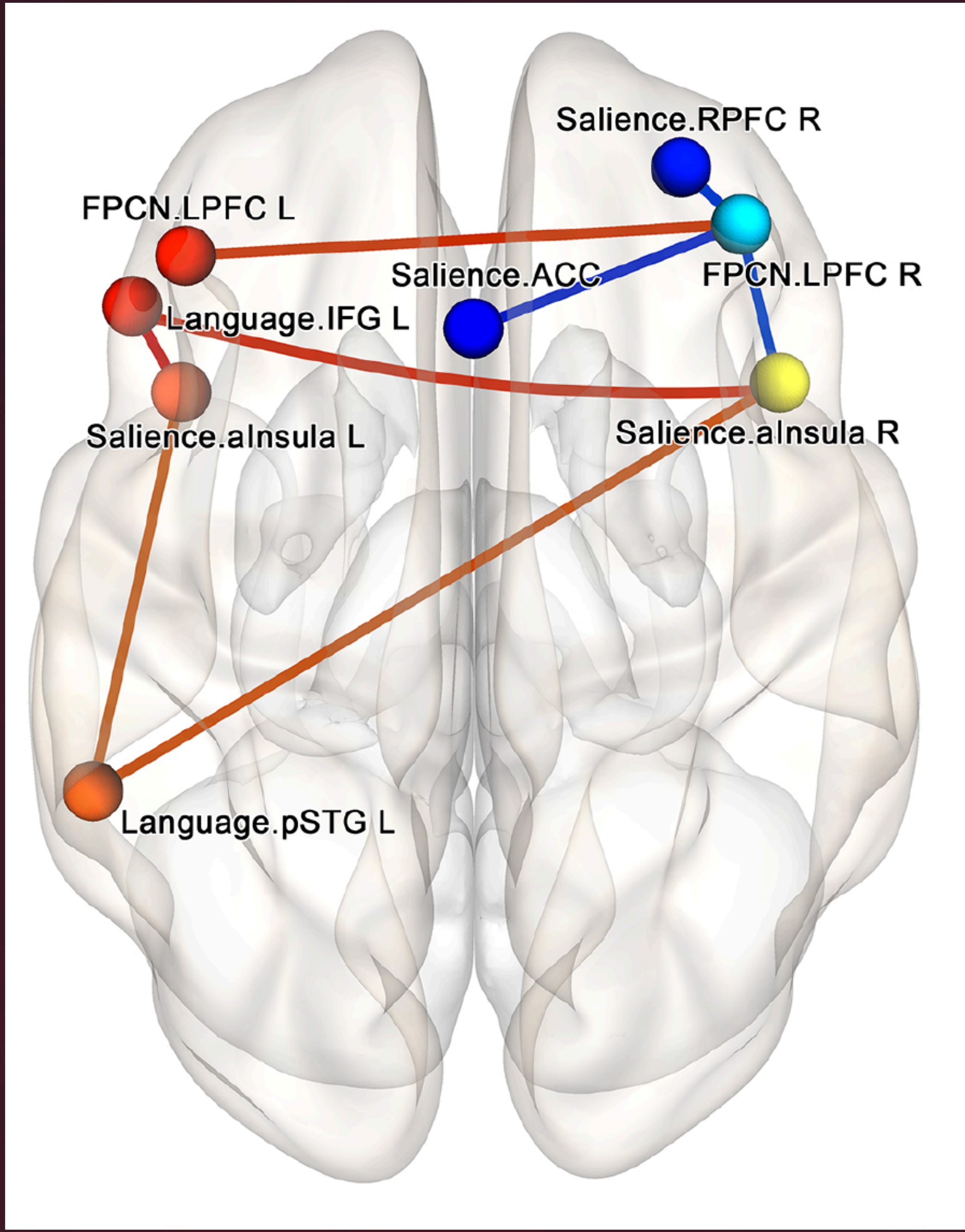
NF group:

Analysis within the components of the attention-related networks:

- Increased connectivity within the salience and language networks.
- This effect is similar to the core findings of the NF vs. sham analysis.

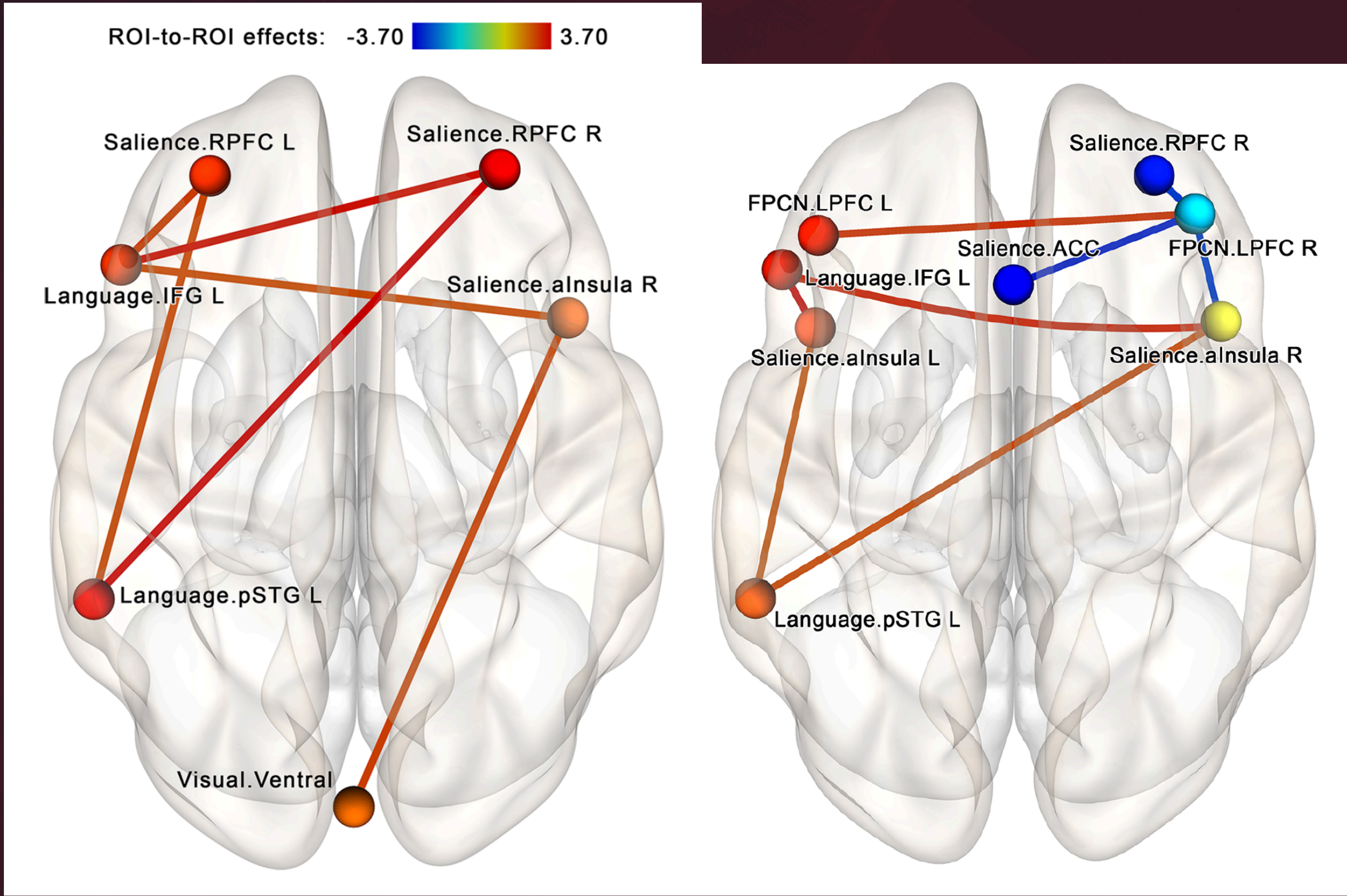
Abbreviation key:

- ACC, anterior cingulate cortex;
- aInsula, anterior insula;
- FPCN, frontoparietal control network;
- IFG, inferior frontal gyrus;
- LPFC, lateral prefrontal cortex;
- pSTG, superior temporal gyrus, posterior portion;
- RPFC, the rostral prefrontal cortex.



Discerning the training effect in sham condition

- By subtraction, we see that the sham group increased activity with respect to the NF group within the salience network.



Salience network

- Increased activity within the salience network over the session in the sham contingent versus the NF group can be explained by the fact that the ‘search for meaning’ in the signal, which is common to both arms, does not reach closure within the sham group, whereas the NF group settles down to training once the connection is made.

Conclusions

- We found no significant within-network connectivity changes in post-EEG vs. pre-EEG sessions in the salience, language or visual networks.
- However, between-network connectivity significantly increased in the NF vs. sham-NF group, at post- vs. pre-session for both tested network pairs
  - $p = .01$ two-sided for salience and language networks
  - $p = .006$ for salience and visual networks

Commentary

- This research was a daunting undertaking, given the complexity of fMRI studies under time constraints.
- A bold hypothesis was under test. A lot was staked on the proposition that single-sessions changes would be observable, first of all, and secondly remain available for inspection after the session.
- We are not dealing with small effects here. The changes are macroscopic, and they appear to be systematic—i.e., consistent across the cohort.
- The work was done with 'healthy' subjects, so presumably we are not dealing with the remediation of deficits here.

Observations

- Note that the linkages affected significantly by virtue of the training process, none were associated with the Default Mode Network!
- And yet our model has assumed that our primary appeal is to the Default Mode organization primarily, and Salience Network secondarily

Matters should perhaps be looked at differently:

- We have chosen to direct the training to resting state organization, and to the foundational core of our regulatory regime
  - That is the Default Mode in its low-frequency organization
- The consequences, of course, are brain-wide, and in no way directed or constrained to what we are explicitly targeting

Implications for our work

- Observe that there were strong impacts on the inferior Lateral Occipital Cortex bilaterally
- Might those sites be useful to us in bilateral training?