NS+: A New Meta-analysis Tool to Extend the Utility of NeuroSynth*

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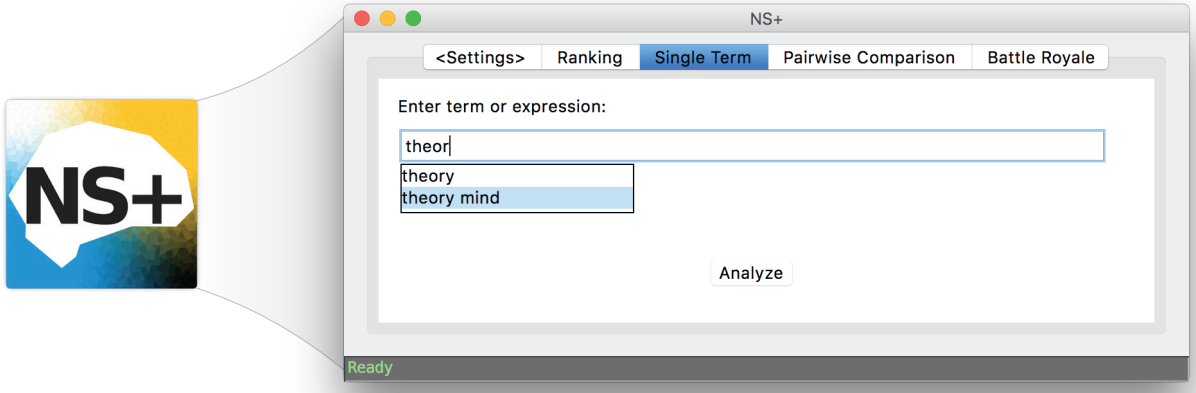
Much of human neuroimaging research seeks to understand the functional mapping of brains with forward inference analyses, which show brain activities produced by specific manipulations, but do not indicate causal relationships in the opposite direction. On the other hand, a reverse inference approach, such as NeuroSynth analyses, reveals the cognitive functions of brain regions, but is limited in its flexibility. To address this issue, we developed a new meta-analysis tool (NS+) based on NeuroSynth, together with a graphical interface, to support highly customizable forward and reverse inference analyses within any given region of interest. Specifically, it allows analysis and comparison of custom terms, ranking of all 3000+ NeuroSynth terms in any ROI, and multi-term comparison that shows the territory where each term dominates in a region. Here, we use NS+ to examine the functions and subdivisions of the temporoparietal junction (TPJ) as a demonstration. Based on previous literature and an exploratory term ranking, we consider a few customized NeuroSynth terms including mentalizing (theory of mind), language comprehension, autobiographical memory, episodic memory, and attentional orienting. The results suggest a strong link between mentalizing and most of the central TPJ, as well as associations of posterior TPJ with autobiographical memory, right anterior TPJ with attentional orienting, and left caudal superior temporal sulcus with language comprehension. We also further recognized and examined the relatively non-selective TPJ areas. In this demonstration, we will show how to conduct these analyses with only a few button clicks in NS+.



NS+ Interface (Partial)

* The contents included here are based on Du, M., Lieberman, M.D. NS+: A New Meta-analysis Tool to Extend the Utility of NeuroSynth. *Unpublished manuscript.*

NS+ is a Neurosynth-based software package, plus a graphical user interface, for fMRI meta-analysis. NeuroSynth allows you to explore relevant brain regions given a term. In NS+, we made it easy to explore relevant terms given a region of interest (ROI).

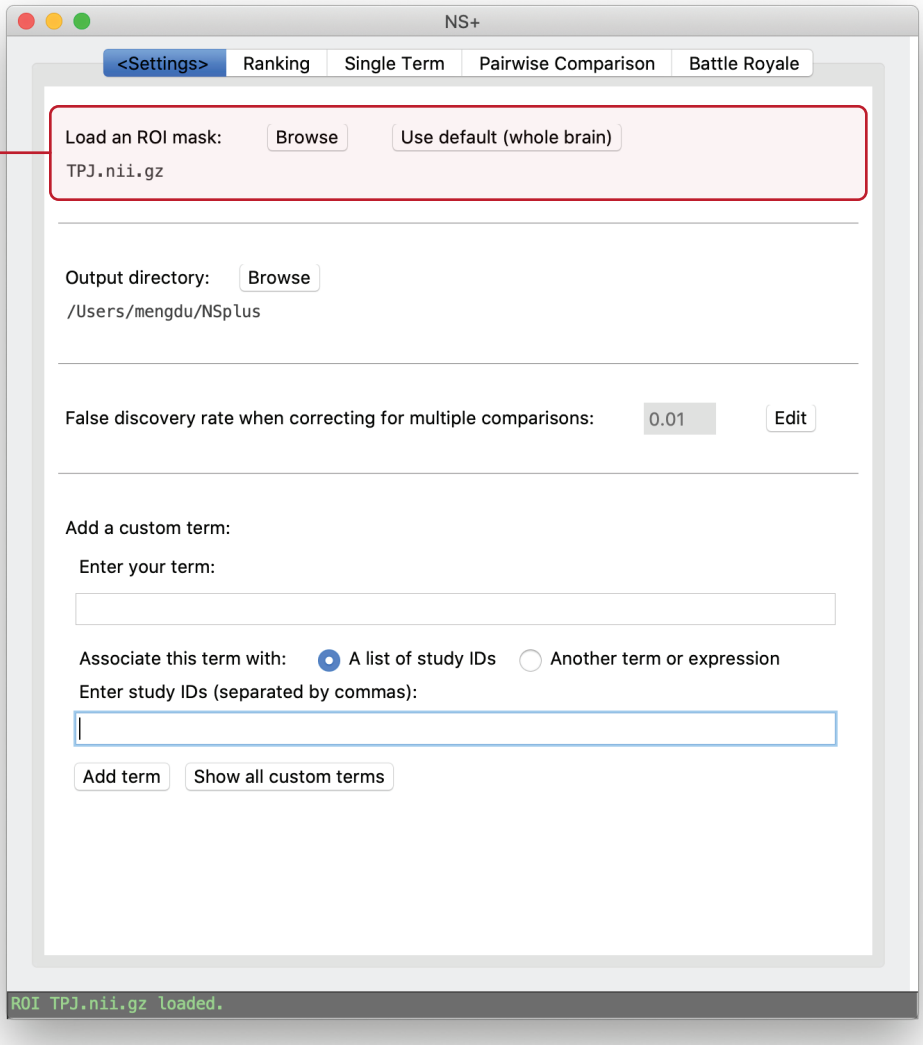
In this NS+ demonstration, we explored the functions of the temporoparietal junction (TPJ) with a reverse-inference approach, and further studied how the TPJ and its surrounding areas are functionally subdivided.

To provide an overview, we first generated two lists of NeuroSynth term rankings in left and right TPJ, respectively, based on the reverse inference probability of each term. Among the top 50 terms in each list, many terms clearly belong to the same categories. Based on the ranking list, therefore, we summarized a few custom NS+ terms, while also taking the previous TPJ literature into consideration. With these newly constructed terms, we performed a "battle royale" analysis to determine the territory where each term dominates in TPJ.

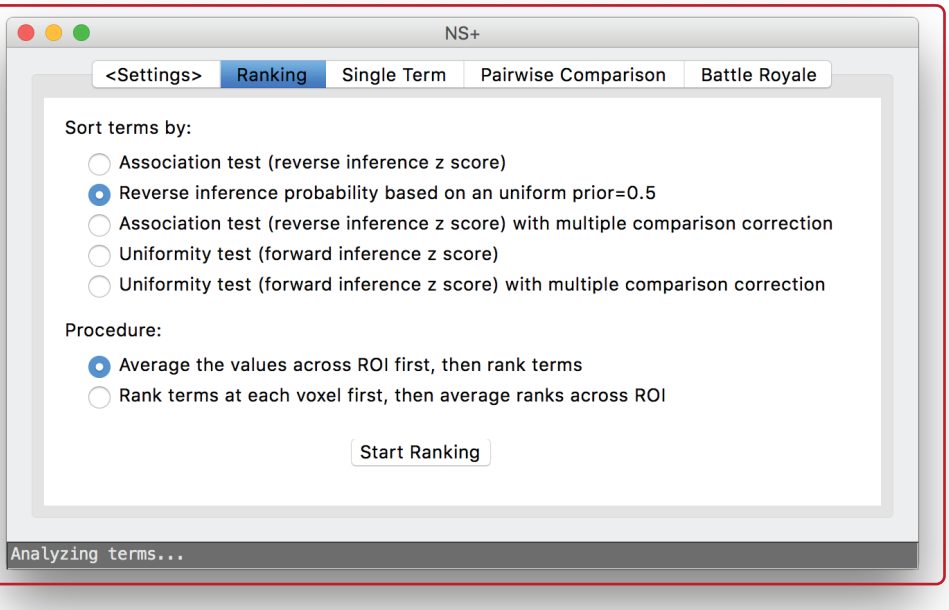
Download: https://github.com/MetaD/NSplus (see "Releases")

1. Explore the Temporoparietal Junction (or any other ROI) with Reverse Inference: Rank All 3000+ NeuroSynth Terms

Step 1
Load ROI mask



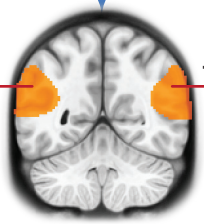
Step 2
Ranking
Note: this step may take a few hours



1. Explore the Temporoparietal Junction (or any other ROI) with Reverse Inference: Rank All 3000+ NeuroSynth Terms

<Settings> | **Ranking** | Single Term | Pairwise Comparison | Battle Royale

Rank by posterior probability *p(term | brain activation)* given a uniform prior *p (term)* = 0.5



Top 50 NeuroSynth Terms* in Left TPJ

Posterior Prob.	# Rank	NS Term
0.70	2	mind tom
0.70	4	theory mind
0.69	5	tom
0.68	8	mentalizing
0.67	10	mental states
0.66	12	mind
0.65	17	autobiographical
0.64	19	retrieved
0.64	20	default network
0.63	24	intentions
0.62	26	sentences
0.62	27	retrieval
0.62	28	lexical
0.62	29	comprehension
0.62	30	semantic
0.62	33	sentence
0.62	34	person
0.62	35	judgments
0.61	36	episodic
0.61	38	verbs
0.61	39	mental state
0.61	40	linguistic
0.61	41	memory retrieval
0.60	44	memories
0.60	45	autobiographical memory
0.60	46	beliefs
0.60	47	read
0.60	50	theory

Category 1
Mentalizing, Social

Category 2
Memory
Autobiographical Memory
Episodic Memory

Category 3
Language Comprehension

Others
Too broad or ambiguous

Top 50 NeuroSynth Terms* in Right TPJ

NS Term	# Rank	Posterior Prob.
theory mind	2	0.72
mind tom	7	0.70
mentalizing	10	0.69
tom	11	0.69
intentions	12	0.68
mind	14	0.67
person	15	0.65
mental states	16	0.65
beliefs	17	0.65
social interactions	20	0.63
belief	21	0.63
theory	23	0.63
default network	24	0.62
social cognitive	25	0.62
mental state	26	0.62
social	27	0.62
thinking	28	0.62
classic	29	0.61
observing	31	0.61
autobiographical	32	0.61
social interaction	34	0.61
autism	35	0.60
states	36	0.60
stimulus driven	37	0.60
mental	39	0.60
attribution	40	0.60
social cognition	41	0.60
univariate	42	0.60
autism spectrum	43	0.59
shifts	44	0.59
real world	45	0.59
connectivity analyses	46	0.59
engaged	47	0.59
empathy	48	0.59
network	49	0.58
asd	50	0.58

* Anatomical terms, such as *TPJ*, *temporoparietal* and *angular gyrus*, were excluded from the lists here.

2. Construct Our Terms

Side note:
In NS+, the OR operator ("**A | B**") takes the union of studies that are tagged by **either term A or term B**;
The AND operator ("**A & B**") takes the intersect of studies that are tagged by **both term A and term B**;
The WILDCARD operator (" **A*** ") takes studies that is tagged by **any terms that starts with A**.

a) Based on the TPJ ranking results, we summarized the 3 categories as 4 custom NS+ terms:

Term 1
Mentalizing: "`tom | mind tom | theory mind | mentalizing`"
(310 studies) or or or

Term 2
Language: "`sentence* | semantic* | lexical | linguistic | language*`"
(2197 studies) or or or or
*sentence** covers *sentence*, *sentences*, *sentence comprehension*
*semantic** covers *semantic*, *semantics*, *semantically*, *semantic memory*
*language** covers *language*, *languages*, *language comprehension*, *language network*

Term 3
Autobiographical: "`autobiographical*`"
(143 studies)
Covers *autobiographical*, *autobiographical memory*

Term 4
Episodic: "`episodic*`"
(488 studies)
Covers *episodic*, *episodic memory*

b) Based on the previous literature + ranking results, we constructed another custom term:

Previous research suggested that rTPJ is a crucial part of the ventral attentional control network, and is specifically more involved in attentional (re)orienting than maintaining (e.g. Shulman et al., 2009).

NeuroSynth does not provide any term directly related to "attentional (re)orienting", but we could still see clues in the list hinting this function of rTPJ:

Posterior Prob.	# Rank	NS Term
0.60	37	stimulus driven
0.59	44	shifts
0.58	51	directed
0.57	65	attention network
0.57	77	goal directed
0.56	83	attentional
0.56	91	orienting
0.56	100	attentional control

Term 5
Attentional Orienting: "`(orient* | shift*) & attention*`"
(357 studies) or and
*orient** covers *orientation*, *oriented*, *orienting*
*shift** covers *shift*, *shifts*, *shifted*, *shifting*
*attention** covers *attention*, *attention deficit*, *attention network*, *attention task*, *attentional*, *attentional control*

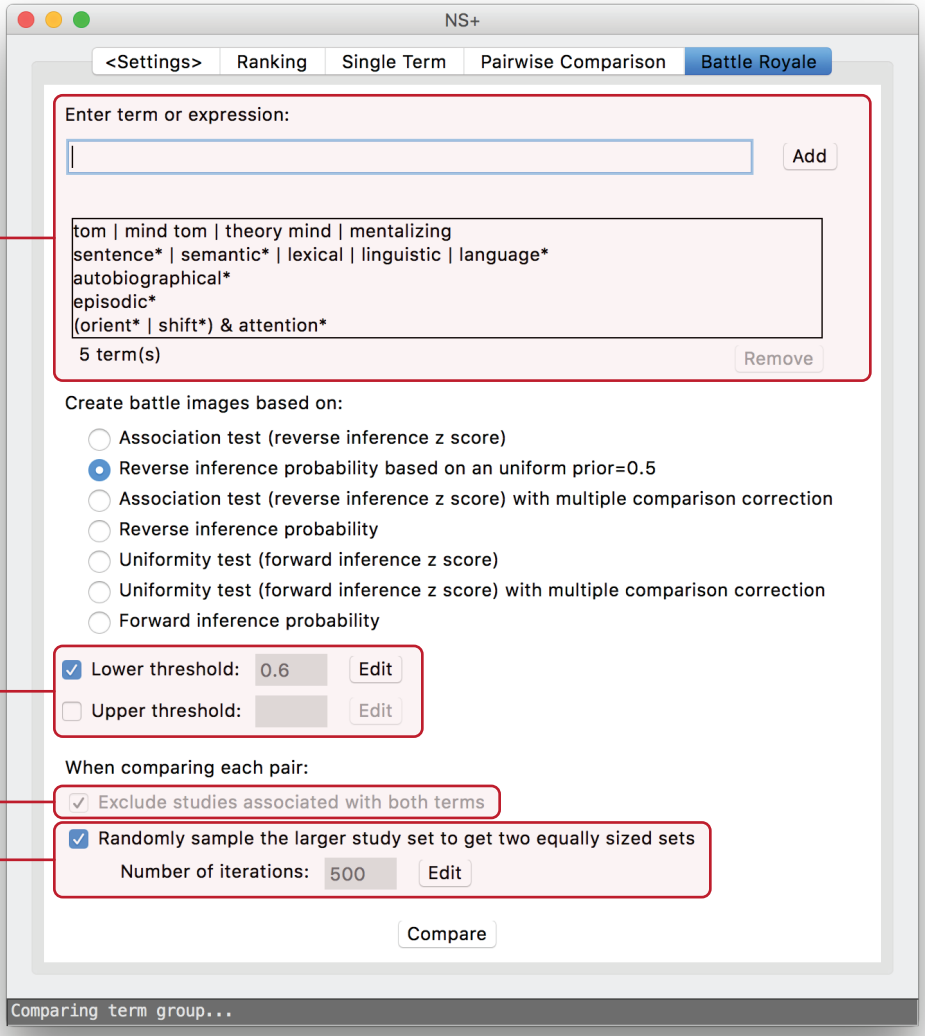
3. Battle Royale!
Compare the Terms and Find Out Where in TPJ (or any other ROI) Each Term Wins

Step 1
Enter Terms

Step 2, (c) in figure
Set Threshold

Step 3, (a) Exclusion

Step 3, (b)
Random Sampling

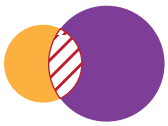


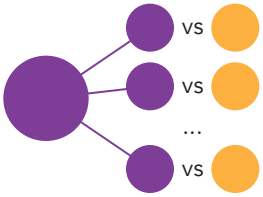
3. Battle Royale!
Compare the Terms and Find Out Where in TPJ (or any other ROI) Each Term Wins

<Settings> | Ranking | Single Term | Pairwise Comparison | **Battle Royale**

For each of the 20 possible pairs of terms (term A, term B)

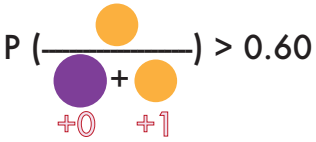
(a) Studies associated with both term A and term B were excluded from comparison.



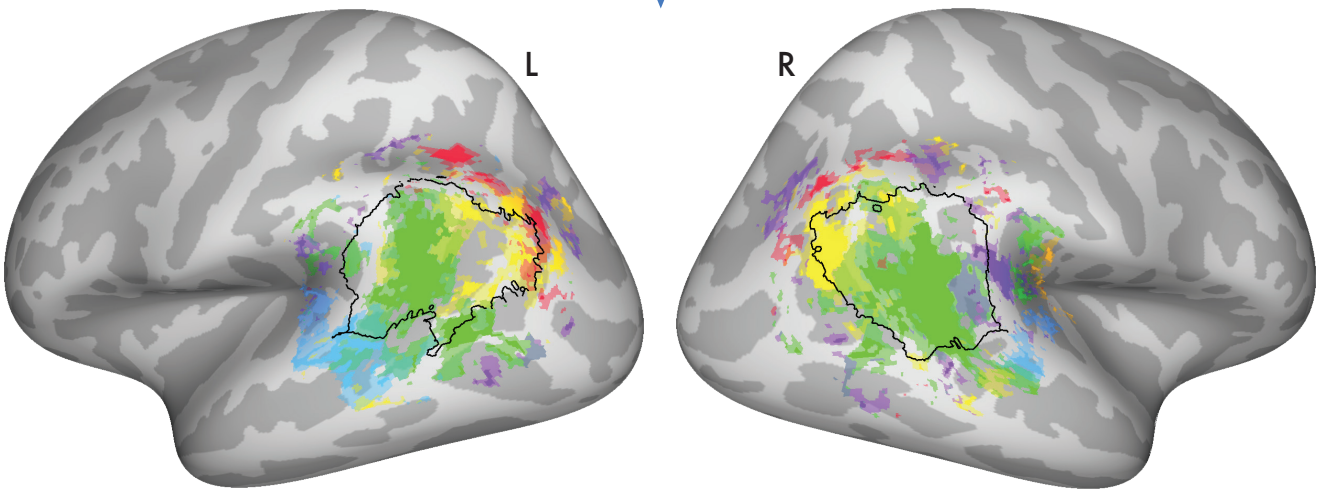


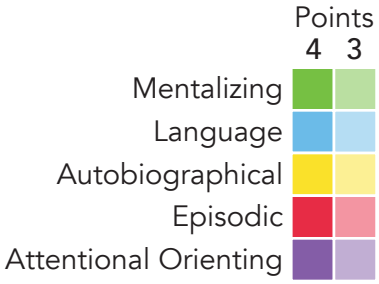
(b) The larger study set was randomly sampled, so the two study sets in comparison had the same size. We repeated this random sampling 500 times, and averaged the meta-analysis comparison results.

(c) If a comparison (term A vs. term B) showed a **posterior probability > 0.60** at a voxel (i.e., when this voxel is active, it's > 50% more likely to come from a term-A study than a term-B one), **term A scored 1 point.**



Each term ended up getting a point in the range [0, 4] at each voxel.





A dilated TPJ mask was used to run the Battle Royale analysis.
The black contour shows the original non-dilated TPJ mask (Dufour et al., 2013).

Note: When combining terms in NS+ (e.g., the two memory terms "autobiographical* | episodic*"), if one of the terms has a much larger study set, the result for the combined term will be primarily driven by that term (e.g. "episodic*"). Thus terms with drastically different study set sizes were analyzed separately, even if they can be conceptually similar.

With NS+, these analyses can be easily done in any ROI, with any term, and by anyone with or without programming experience.

We have published another paper that uses NS+ to help recognize the functional subdivisions of mPFC:

Lieberman, M. D., Straccia, M. A., Meyer, M. L., Du, M., & Tan, K. M. (2019). Social, Self,(Situational), and Affective Processes in Medial Prefrontal Cortex (MPFC): Causal, Multivariate, and Reverse Inference Evidence. *Neuroscience & Biobehavioral Reviews*.

References:

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature methods, 8*(8), 665.

Dufour, N., Redcay, E., Young, L., Mavros, P. L., Moran, J. M., Triantafyllou, C., ... & Saxe, R. (2013). Similar brain activation during false belief tasks in a large sample of adults with and without autism. *PloS one, 8*(9), e75468.

Shulman, G. L., Astafiev, S. V., Franke, D., Pope, D. L., Snyder, A. Z., McAvoy, M. P., & Corbetta, M. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *Journal of Neuroscience, 29*(14), 4392-4407.