A COMBINED DTI AND fMRI ANALYSIS OF THE NEURAL CORRELATES OF IMPLICIT PROBABILISTIC SEQUENCE LEARNING

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INTRODUCTION

IMPLICIT PROBABILISTIC SEQUENCE LEARNING describes non-conscious sensitivity to the frequency of sequential regularities

- For example, responding preferentially to a series of events that occur more frequently than others, without having explicit knowledge of this regularity

GRAY MATTER SUBSTRATES

- Early, fast learning: Hippocampus, parahippocampal gyrus (e.g., Schendan et al., 2003)
- Late, slow learning: Striatum (caudate, putamen) (e.g., Doyon et al., 1997)

WHITE MATTER is also important because it connects distributed gray matter regions involved in cognition (Mesulam, 1990)

- Integrity of white matter from underlying brain regions correlates with cognitive performance (e.g., Kennedy & Raz, 2009)

WHITE MATTER INTEGRITY may be an index of neural efficiency (Rypma et al., 2006)

- May directly relate to neural activity in gray matter regions it connects

AIMS OF THE PRESENT STUDY

- Is white matter integrity from tracts connecting gray matter substrates of implicit motor probabilistic sequence learning related to non-motor learning?
- Does white matter integrity from these tracts mediate the relationship between functional activity and learning?

METHOD

PARTICIPANTS

- 10 younger adults (18.8 ± 0.6 years; 5 female)

MRI PROTOCOL

- 3T Siemens Trio

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

- Three T2* sensitive gradient EPI runs per participant
- Parameters:
  - 152 images/run, 42 axial slices, voxel size=4.0 x 4.0 x 3.7 mm, TR/TE=2500/30 ms, 90˚ flip angle, FOV=256 mm^2
- Pre-processing:
  - Realignment, spatial normalization to MPRAGE, spatial smoothing (8 mm) in SPM5

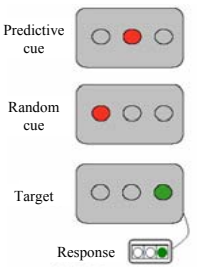
DIFFUSION TENSOR IMAGING (DTI)

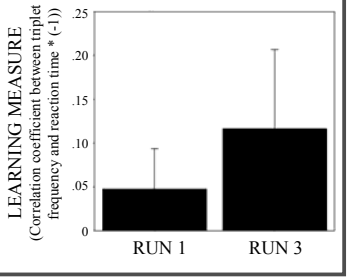
- Two EPI sequences per participant
- Parameters:
  - Diffusion weighted gradients b=0 and b=1000 s/mm^2 applied in 35 orthogonal directions
  - 55 axial interleaved slices, 2.5 mm^3 spatial resolution, TR/TE=7700/100 ms, FOV=240 mm^2
- Pre-processing:
  - Correct eddy current distortion (Eddycorrect), fit diffusion tensors to each voxel (DTIfit), and diffusion parameter estimation (BedpostX) using FSL's Diffusion Toolbox (Behrens, 2003; Smith et al., 2004)

PROBABILISTIC SEQUENCE LEARNING

TRIPLETS TASK:

- Respond only to the Target in 1 of 3 locations with right hand
- 2nd order sequence structure
  - Predictive cue location probabilistically predicts Target location
  - Random cue occurs at any location
- Triplet (runs of 3 events) probability
  - High-frequency triplets occurred more often than low-frequency triplets (probability ratio 8:2)

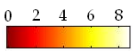




CORRELATIONS: BOLD ACTIVATION x TRIPLET LEARNING

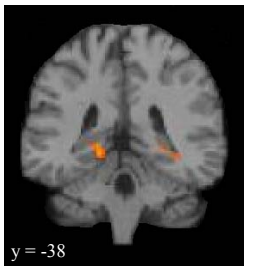
- Negative (Run 1) and positive (Run 3) voxel-wise correlations between BOLD activation from the High Frequency minus Low Frequency GLM contrast and the Triplet Learning Measures

($p < .01$ uncorrected, k=5)



RUN 1

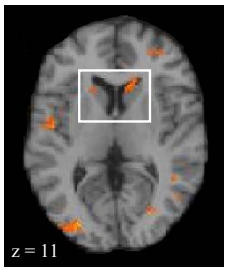
L and R Hippocampus



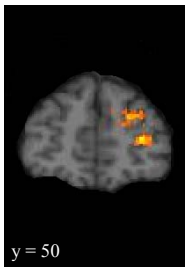
ADDITIONAL REGIONS:
L parahippocampus, R ventral striatum, L putamen, and bilateral cerebellum

RUN 3

L and R Caudate



R Dorsolateral Prefrontal



ADDITIONAL REGIONS:
Bilateral premotor (BA 6), R parietal (BA 7), bilateral temporal (BA 21/22), bilateral occipital (BA 16/17), and bilateral cerebellum

WHITE MATTER INTEGRITY: TRACTOGRAPHY

FRACTIONAL ANISOTROPY (FA)

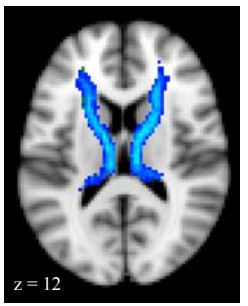
- Measure of white matter integrity that indicates directional coherence of water diffusion
  - Higher values indicating better integrity

PROBABILISTIC FIBER TRACKING

- Using FSL's ProbtrackX (Behrens et al., 2003)
- Subcortical seed, frontal waypoint, and midline exclusion masks (in green) traced in standard space and registered to each individual's diffusion space
- Threshold tracts at 20% of each individual's maximum connectivity value
- Multiply thresholded tracts by each individual's FA map
- Average the FA values along each tract

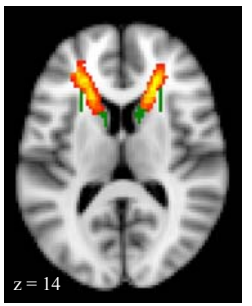
IMAGES show tracts common to 90% of participants

HIPPOCAMPUS-FRONTAL TRACT



- DLPFC → fornix/thalamus → hippocampus (Aggleton & Brown, 1999; Goldman-Rakic et al., 1984)

CAUDATE-FRONTAL TRACT



- "Executive loop": DLPFC/ posterior parietal → caudate → GPi/SNr → thalamus (Seger, 2006)

CORRELATIONS: WHITE MATTER INTEGRITY x TRIPLET LEARNING

LEARNING	FA
Run 1	L caudate-frontal ($r = -.73$, $p < .02$)
	R caudate-frontal ($r = -.85$, $p < .01$)
	L hippocampus-frontal ($r = -.67$, $p < .04$)
Run 3	R hippocampus-frontal ($r = -.66$, $p < .04$)

Better implicit probabilistic sequence learning was associated with lower white matter integrity

- Factors other than myelin (e.g., crossing fibers, axonal diameter) may decrease FA, but not affect tract integrity (Tuch et al., 2005)
- Integrity of other tracts not examined here may positively correlate with this measure of learning

MEDIATION

EARLY LEARNING (RUN 1)

- Negatively correlated with BOLD activity in the striatum and hippocampus (among other regions)
- Negatively correlated with FA in the caudate-frontal and hippocampus-frontal tracts

LATER LEARNING (RUN 3)

- Positively correlated with BOLD activity in the caudate and dorsolateral prefrontal cortex
- Negatively correlated with FA in the hippocampus-frontal tract

MEDIATION

- Both BOLD activity and FA were significantly related to Triplet learning
- But BOLD activity in the regions assessed here was not related to FA in either tract for any run
- Thus, the requirements for mediation were not met in this relatively small young adult sample (Baron & Kenny, 1986)

SUMMARY AND DISCUSSION

Integrity of white matter tracts in the medial temporal and fronto-striatal learning systems was significantly associated with implicit non-motor probabilistic sequence learning

- Consistent with functional imaging results using the Triplet task (re-presented here and in Simon, CNS, 2008)
- However, white matter integrity in these tracts was not a significant mediator of learning-related BOLD activity
- Instead, white matter integrity and BOLD activity make separate contributions to learning

FUTURE RESEARCH should continue to examine:

- The role of white matter integrity as a mediator of BOLD activity-cognitive performance relationships
- Complex structure-function interactions between the medial temporal and fronto-striatal learning systems

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