Resting State Connectivity Predicts Implicit Sequence Learning Performance

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BACKGROUND

- **Implicit probabilistic sequence learning (SL)** involves extracting regularities from sequences of events
- Task-dependent fMRI studies have identified a neural network supporting SL, including the caudate, MTL, and regions in the frontal lobe (e.g., Simon et al., 2011)
  - Caudate and MTL thought to underlie the *learning* during SL tasks
  - Better learning associated with pattern of recruitment of MTL and caudate
- Neural regions that comprise functional networks during cognitive tasks form similar networks at rest (Fox & Raichle, 2007)
  - Regions having similar functionality tend to be positively correlated in their resting state activity
  - Close correspondence between task-evoked and resting functional networks suggests that associations of inter-subject behavioral variability with functional networks observed during cognitive tasks may also be observed in the resting state
- No studies have examined whether the intrinsic connectivity of a neural region relevant for implicit SL relates to individual differences in SL performance

AIM

- To test whether resting state connectivity of the caudate predicts learning in an implicit sequence learning task

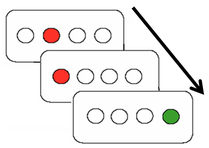
METHOD

PARTICIPANTS

▪22 college-aged adults (14 female), ages 18-22 years ($M \pm SD$ = 20.43 ±.98)

BEHAVIORAL TESTING

▪Took place 17-367 days following (N=20) and 179 vs. 542 days before (N=2) scan
▪750 trials of Triplets Learning Task (TLT; Howard, Howard, Dennis, & Kelly, 2008)
▪Stimuli appear at 1 of 4 locations that fill in red, then green in discrete, three-event sequences or 'triplets'
▪Observe red cue events and respond only to the third, green target
▪48 triplets presented: arbitrarily chosen 16 triplets occur with High Probability (HP) and 32 occur with Low Probability (LP)
▪SL assessed by comparing RT to LP vs. HP triplets



fMRI DATA ACQUISITION

▪Subjects scanned for 5:04 minutes during resting state in 3T Siemens Trio magnet
▪152 whole brain images, gradient EPI acquisition (TR = 2000ms, TE = 30ms, 90ºflip angle, FOV = 192 x192mm, voxel size = 3 mm isotropic)
▪Data preprocessing in SPM8 (Realignment, Normalization to EPI template, Smoothing {8mm FWHM}, and Band-pass filtered)

RESTING STATE FUNCTIONAL CONNECTIVITY CALCULATIONS

▪Bilateral dorsal caudate (DC) seed created in Marsbar as two spheres of radius 6mm, centered around coordinates taken from Di Martino et al. (2008)

Voxelwise resting state connectivity:

▪For each subject, partial correlations computed between timecourse of DC seed and those of every other voxel in brain, controlling for motion (from realignment parameter timecourses) and physiological noise (approximated by timecourses of WM and CSF); resulting *r*-values converted to *Z*-scores before statistical analyses of correlation strengths
▪Produced brain map of intrinsic connectivity strength with the DC for each subject

Mean overall DC connectivity:

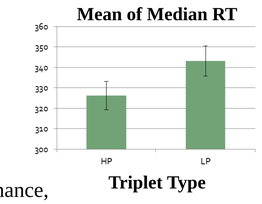
▪Subjects' connectivity maps entered onto voxelwise one-sample t-test in SPM 8
▪Results corrected for multiple comparisons at $p < .05$ using Monte Carlo simulation

Correlations with SL performance:

▪Single-subjects' whole brain connectivity maps entered as the DV in a regression (SPM8) testing for correlations with SL performance in a voxelwise fashion
▪Results Monte Carlo corrected at $p < .05$

SEQUENCE LEARNING PERFORMANCE

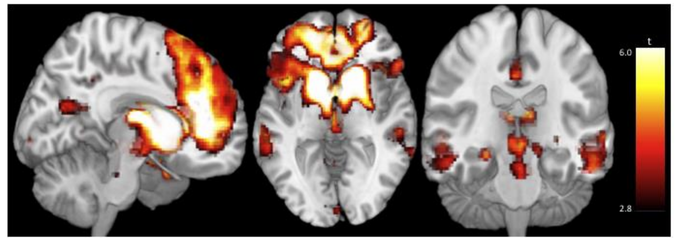
- Subjects responded significantly faster on average to HP than to LP triplets, $t(21) = 7.8$, $p < 0.001$



- To compare inter-individual differences in SL performance, calculated implicit associative learning (IAL) scores (Howard et al., 2008)
  - Median RTs calculated for all correct responses to each unique triplet for each subject
  - These median RTs were then correlated with the number of times that triplet had occurred in the task, partialling out effects of unequal target frequency
  - *r*-values multiplied by -1 so that higher IAL scores reflect greater SL
- IAL scores ($M \pm SD$ = .19 ±.08) were significantly greater than zero, $t(21) = 10.81$, $p < 0.0001$
- No correlation between IAL scores and overall mean of median RT or accuracy

MEAN DC CONNECTIVITY NETWORKS

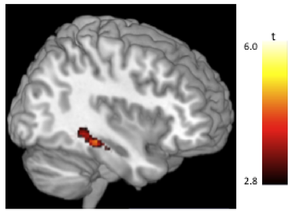
- Mean connectivity pattern of the DC observed across all subjects was similar to that observed by Di Martino et al. (2008) using the same bilateral seed



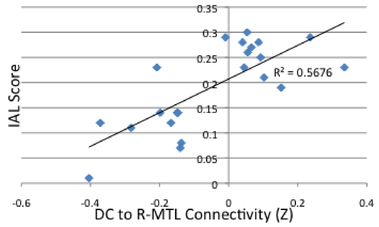
*Medial prefrontal cortex (ACC)	*Bilateral middle frontal gyrus	Bilateral putamen
*Supplementary motor area	Middle cingulate gyrus	Bilateral anterior insula
*Inferior frontal gyrus	*Bilateral angular gyrus	Left hippocampus
Precuneus	*Bilateral middle temporal gyrus	brainstem

* Indicates regions also found to be strongly connected on average to DC by Di Martino et al., 2008

CONNECTIVITY CORRELATIONS WITH SEQUENCE LEARNING



Right MTL

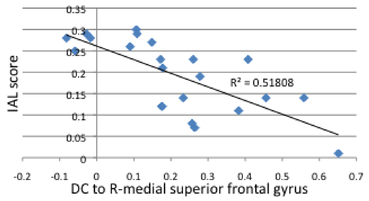


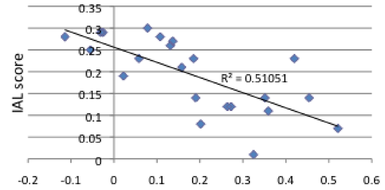
POSITIVE CORRELATION WITH LEARNING (above)

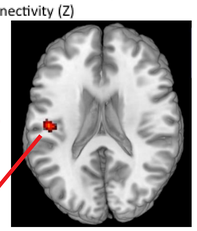
- Connectivity between the DC and a cluster in the right MTL (k = 169 voxels, peak MNI coordinates x = 38, y = 30, z = 13) predicted higher IAL scores
  - This was the only positive correlation between whole-brain intrinsic connectivity of the DC and IAL scores to survive correction

NEGATIVE CORRELATIONS WITH LEARNING (right)

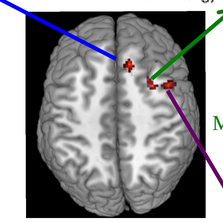
- Connectivity between DC and clusters in left postcentral gyrus (BA1), right precentral gyrus (BA8), right medial superior frontal gyrus (BA8), and right middle frontal gyrus (BA6) predicted lower IAL scores



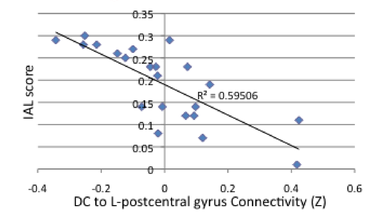


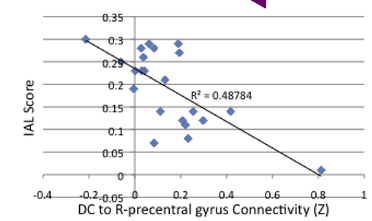


Postcentral Gyrus



Medial Superior Frontal Gyrus
Middle Frontal Gyrus
Precentral Gyrus





SUMMARY & DISCUSSION

- Subjects who had greater connectivity between the DC and the right MTL tended to attain higher IAL scores, suggesting that optimal patterns of caudate-MTL interaction during SL tasks is facilitated by the persistent (positive) connectivity of these regions at rest
  - On average, DC seed did not exhibit strong connectivity to the right MTL, but values varied considerably across subjects
  - IAL scores did not correlate with overall mean of median RT or accuracy, suggesting that the scores were not biased by individual differences in speed or accuracy
- Subjects who had lower connectivity between the DC and motor planning regions tended to attain higher IAL scores, suggesting that SL is maximized when such regions communicate independently at rest from those supporting learning
- Results consistent with recent findings implicating the importance of both the caudate *and* MTL in implicit sequence learning (e.g., Bennett et al., 2011 Poldrack & Packard, 2003, Rieckmann, et al., 2010; Simon, et al., 2011)
- Findings suggest that the magnitude of SL depends upon the integrity of the association between DC and MTL at rest; intrinsically stronger functional associations between these regions may enable more efficient activation/suppression during the course of acquisition of sequential information

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Society for Neuroscience. 42nd Annual Meeting. November, 2012. New Orleans, LA.
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This research is supported by: NIA/NIH grant, R01AG036863, NIMH grant R03MH086709, and NIMH grant MH088066