Dissociations in Socioemotional Test Performance Predict Neurodegeneration in Intrinsic Connectivity Networks

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INTRODUCTION

Background:

Intrinsic Connectivity Networks: The brain is organized into intrinsic connectivity networks (ICNs) which reflect the brain's natural functional connectivity (Yeo et al 2011; Seeley et al 2009). For this study, we focused on four ICNs:

- Default mode network (DMN): episodic memory retrieval (Seeley et al 2009)
- Fronto-parietal network (FPN): complex adaptive attention and set-shifting (Seeley et al 2007)
- Semantic appraisal network (SAN): also called the "limbic" ICN (Yeo 2011), personalized hedonic evaluations based on learned information and experience (Guo et al 2013)
- Salience network (SN): identification of personally salient stimuli (Seeley et al 2007)

Neurodegenerative Disease and ICNs: ICNs are selectively but differentially vulnerable in specific neurological and psychiatric diseases (Menon 2011), and patterns of neural degeneration in different neurodegenerative disease syndromes target specific ICNs (Seeley et al 2009; Zhou et al 2012). However, further research is needed to understand how atrophy in these ICNs during neurodegenerative disease causes specific changes in socioemotional functioning.

Behavioral Assessments as a Predictive Tool: We have previously identified emotional and cognitive social tasks that quantify impairments in patients with neurodegenerative disease (Tal Shany-Ur et al 2012; Solberger et al 2014). Correlating these social tasks to atrophy in specific ICNs can provide a basis for using bedside assessment to predict ICN involvement in a patient's syndrome. Such an approach could be used to improve precision of differential diagnosis of neurodegenerative disease in clinical settings even when neuroimaging is unavailable.

OBJECTIVE

To evaluate the additive benefit of testing dissociable (emotional and cognitive) social functions to predict structural damage and diagnostic syndrome in patients with neurodegenerative disease.

METHODS

Patients: We enrolled a total of 402 subjects (316 patients and 86 normal controls (NC)) who underwent sociocognitive testing and structural MRI. Patient demographics are shown in Table 1.

Cognitive Social Task:

UCSF Cognitive Theory of Mind Test (cTOM): Subjects viewed eight videos of two characters (X and Y) and their beliefs about an object's location. The scenario involved change of object location, with and without knowledge of one character. Half of the scenarios had a "cheat" condition in which one character observed an activity without the knowledge of the other. Each scenario was followed by one control question ("Where is the object?") and two TOM questions (First order; "Where does X think the object is?"; Second order: "Where does Y think that X thinks the object is?").

Emotional Social Task:

The Awareness of Social Interference Test – Emotion Evaluation Task (TASIT–EET): Subjects watched 14 brief videos of actors portraying one of the seven basic emotions (happy, surprised, neutral, sad, anxious, frightened, revolted) and chose the correct emotion from a visual array of options.

Voxel-Based Morphometry:

Preprocessing and Statistical Analysis: Preprocessing of T1 weighted structural images (segmentation, normalization, and modulation, smoothing) done using VBM8 Toolbox. We built separate VBM regression models predicting the relationship between grey matter atrophy and performance on TASIT-EET and UCSF cTOM tasks. We included age, sex, Mini Mental State Examination (MMSE) scores, scanner type, total intracranial volume, and Peabody Picture Vocabulary Test (PPVT) scores (a task measuring receptive vocabulary comprehension) as nuisance covariates.

Network Volume Analysis: To investigate how the changes in structural regions of interest (ROIs) representing key ICNs related to UCSF cTOM and TASIT-EET scores, we calculated the total network volume by adding individual ROI volumes corresponding to the default mode network (DMN), fronto-parietal network (FPN), semantic appraisal network (SAN), and salience network (SN). Regression modeling was performed to investigate how each network volume independently contributed to task performance (Allen-Cady backwards selection approach, forcing confounds to remain in the model).

RESULTS

BEHAVIORAL TASK PERFORMANCE

Behavioral Performance on TASIT–EET and UCSF cTOM:

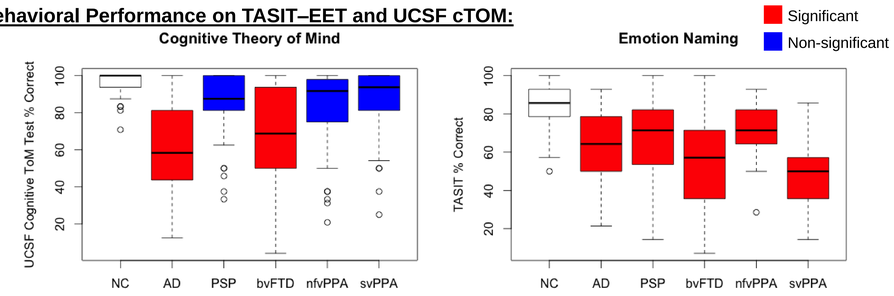

Figure 1. A comparison of performance on sociocognitive behavioral tasks. All patient groups scored significantly lower on TASIT–EET compared to NCs ($p<0.05$). AD and bvFTD groups scored significantly lower on UCSF cTOM than NCs ($p<0.05$). To control for effects of generalized semantic loss on test performance, the regression model included scores from a vocabulary task (PPVT) as a confounding covariate.

WHOLE-BRAIN VBM

Whole Brain Voxel-Based Morphometry:

When cognitive tests were correlated with brain atrophy across all patients,

- **UCSF cTOM**: Impaired performance on cognitive theory of mind task significantly predicted atrophy in the left inferior frontal gyrus, right middle temporal gyrus, right posterior cingulate, right precuneus, bilateral superior frontal gyrus, and right superior temporal gyrus ($p<0.05$, FWE corrected).
- **TASIT-EET**: Impaired performance on emotion naming task significantly predicted atrophy in the brain volumes in the bilateral amygdala, bilateral anterior insula, bilateral caudate, bilateral orbitofrontal gyrus, right posterior insula, right superior frontal gyrus (orbital part), and the right superior medial frontal cortex ($p<0.05$, FWE corrected).

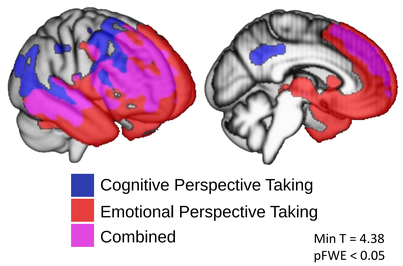

Figure 2. Volume loss corresponding to impairment on socioemotional tests

Demographics and Subject Performance:

Table 1.

	NC *n= 86*	AD *n= 102*	PSP *n= 47*	bvFTD *n= 77*	nfvPPA *n= 36*	svPPA *n= 54*	F(df/χ^2)	Overall p-value
Age	67.98(0.89)	63.16(0.82)*	67.87(1.20)	60.62(0.94)*	67.28(1.38)	63.52(1.12)	9.49(402,5)	p<0.001
Sex (M/F)	38/48	50/52	25/22	51/26	9/27	29/25	18.79(402,5)	p<0.01
Education	17.74(0.32)	16.30(0.29)*	16.49(0.44)	16.26(0.34)*	16.60(0.49)	16.39(0.40)*	3.06(394,5)	p<0.05
MMSE	29.32(0.49)	22.70(0.43)*	26.45(0.62)*	24.29(0.47)*	26.39(0.71)*	23.48(0.59)*	24.42(358,5)	p<0.001
CDR tot	0.00(0.04)	0.80(0.04)*	0.82(0.06)*	1.17(0.04)*	0.43(0.06)*	0.68(0.05)*	79.78(367,5)	p<0.001
Box Score	0.01(0.24)	4.37(0.21)*	5.20(0.30)*	6.57(0.23)*	1.71(0.35)*	4.05(0.28)*	91.97(367,5)	p<0.001
Avg. PPVT	14.74(0.27)	13.94(0.25)	14.70(0.36)	13.74(0.28)*	14.52(0.41)	9.21(0.34)*	40.89(402,5)	p<0.001
TOM	86.85(2.38)	66.61(2.03)*	83.34(2.74)	70.85(2.14)*	77.29(3.18)	92.14(3.20)	14.10(358,5)	p<0.001
TASIT	10.63(0.28)	9.22(0.24)*	9.16(0.33)*	7.72(0.25)*	9.38(0.38)*	8.07(0.38)*	12.15(358,5)	p<0.001

* significantly different from NCs at $p<0.05$

†controlling for age, sex, and total MMSE with Dunnett-Hsu test, **NC** - normal controls; **AD** - Alzheimers Disease; **PSP** - progressive supranuclear palsy; **bvFTD** - behavioral variant frontotemporal dementia; **nfvPPA** - nonfluent primary progressive aphasia; **svPPA** -semantic variant primary progressive aphasia.

NETWORK ANALYSIS

Network Volume Changes Differentially Predict Social Task Scores:

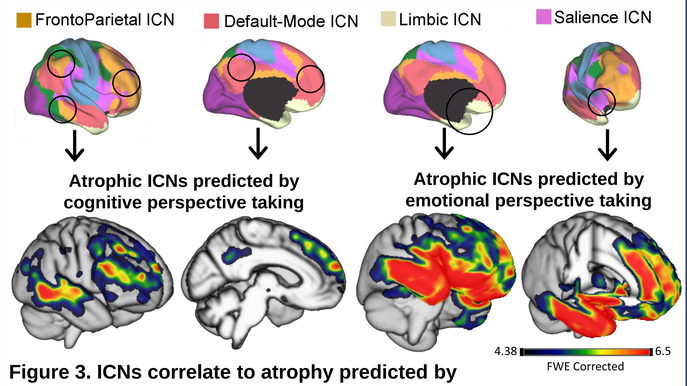

Figure 3. ICNs correlate to atrophy predicted by sociocognitive test performance. ICNs (top) from Yeo et al 2011.

- **UCSF cTOM:** Primarily correlated with dorsal atrophy (DMN, FPN). Regression analyses showed that DMN (precuneus, posterior cingulate, dorsomedial prefrontal ROIs) ($\beta=0.27$, $p=0.0002$), FPN (dorsolateral parietal/frontal) ($\beta=0.18$, $p = 0.005$), and SAN (anterior temporal, subgenual PFC) ($\beta= -0.16$, $p=0.0026$) volumes all independently predicted cognitive TOM score.
- **TASIT-EET:** Primarily correlated with anterior ventral atrophy (SN, SAN). Regression analyses showed only the SN (anterior temporal, subgenual PFC) ($\beta=0.35$, $p<0.001$) volume independently predicted emotion naming score.

CONCLUSIONS

- Atrophy in distinct ICNs contributes to differential performance deficits on emotional versus non-emotional aspects of social function in neurodegenerative disease patients.
  - Poor non-emotional social cognition appearing in isolation predicts damage to dorsal networks (DMN, FPN), suggestive of AD or nfvPPA.
  - Severe isolated deficits in emotion reading predict more ventral networks (SN), suggestive of bvFTD or svPPA.
- UCSF cTOM and TASIT-EET assessments can provide important neuroanatomic and diagnostic information to clinicians even when structural neuroimaging is unavailable.

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