

INTRODUCTION

Varying degrees of frontal lobe dysfunction are present in patients with ALS^{1,2}. About 49% of patients with sporadic ALS¹, and 62% of patients with familial ALS² (in review), present with cognitive changes that may only be apparent via neuropsychological testing. Dysfunction ranges from mild to frank frontotemporal dementia (FTD). Apathy, executive dysfunction and disinhibition are behavioral changes reported by family members in approximately 29% of ALS patients (unpublished data).

Neuropathological and imaging studies have shown fronto-temporal atrophy and poor activation of thalamo-frontal association pathways in patients with ALS, even if they do not have cognitive impairment^{4,5,6}

Frontal involvement might cause the changes in social cognition described in ALS patients, or this may be due to alterations in other brain regions involved in social cognition. To investigate this further, we administered a test of social behavior called the "trust game" to pairs of ALS patients and controls (people without ALS). They interacted while undergoing simultaneous functional magnetic resonance imaging (fMRI).

Prior studies with the trust game have shown activation of the middle cingulate gyrus in controls playing as investors and activation of the anterior cingulate gyrus in controls playing as trustees³. We tested whether the same areas are activated in patients with ALS and whether controls behave similarly when playing with a physically challenged person.

SUBJECTS

- 16 ALS patients and 16 controls were recruited (goal= 50 ALS patients and 50 controls) from the Baylor College of Medicine ALSA-sponsored ALS Clinic
- Patients had probable or definite ALS by El Escorial criteria.
- Controls were not friends or family members of the paired ALS patient

	ALS	Controls
Male gender (%)	75	75
Age (years)	46.62	44.75
No cognitive impairment (%)	68.75	100

Table 1. Demographics

METHODS

- ALS patients underwent neuropsychological testing
- Participants selected needed to be cognitively intact or mildly impaired
- ALS patients and controls received instructions about performing the trust game; all ALS patients played as trustees
- The trust game was played while undergoing functional imaging (fMRI)
- Regional Blood oxygenation level-dependent (BOLD) response patterns were analyzed to identify activation of different brain areas



The trust game

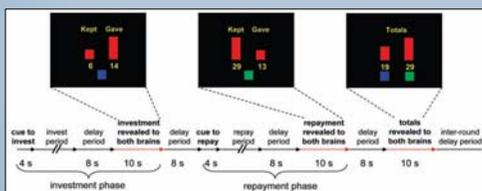


Fig. 1 Trust game³

RESULTS

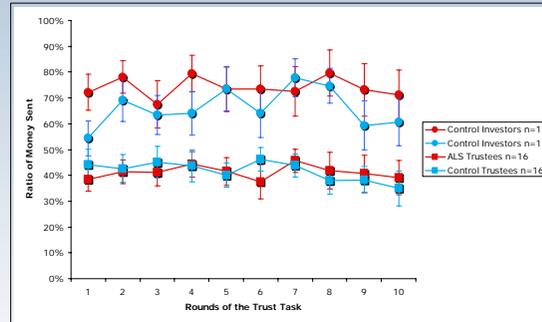


Fig. 3 Behavior: Round-to-round differences. ALS trustees do not show a typical reciprocity response to control investments over the previous 2 rounds (-0.31 vs -0.03, bold= significant). Control investment also differed significantly: their behavior is more positively correlated with the ALS trustee responses than observed between controls (0.65 vs 0.45).

		Inv Change	Tru Change		
semi-matched controls: (n = 16)	Tru Ratio	0.05	-0.09	Inv Ratio	
	Tru Change	0.27	-0.03	Inv Change	
	Tru Recip	0.45	0.25	Inv Recip	
		Inv Change	Tru Change	Inv Ratio	Inv Change
ALS: (n = 16)	Tru Ratio	0.27	-0.17	Inv Ratio	
	Tru Change	0.44	-0.31	Inv Change	
	Tru Recip	0.65	0.05	Inv Recip	

Fig. 2. Behavior: Average Investments and Repayments. The control experiment (in blue) and the ALS experiment (in red) show that ALS pts and controls return, on average, a similar percentage of earnings. However, their pattern of return, round-to-round, differs (Fig 3).

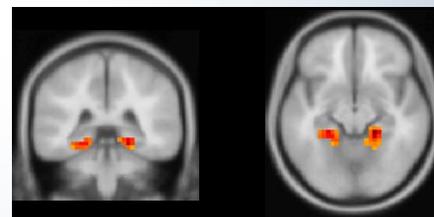


Fig. 4 Brain activation. There was a direct, significant correlation between BOLD signal in the parahippocampal gyrus (PPA, parahippocampal place area) and performance on a measure of attention and concentration (VSAT) when the investment was revealed to the Trustee.

Additional Results

- The ALS trustees from Fig. 2 were separated into cognitively intact (n=12) and cognitively impaired (n=4) groups. Investment returns were the same for the 2 groups.
- 16 pairs was not enough to determine whether there is a difference in the caudate or cingulate gyrus activation in controls vs ALS patients. We estimate that about 14 more pairs will need to be tested before a difference might be demonstrated.

CONCLUSIONS

- While the ALS trustees had a similar average return to the Control trustees (Fig. 2), they respond to their partners behaviors differently than Controls (Fig. 3).
 - ALS patients actively penalize investors when trust would be expected
- The better the score on a neuropsychological measure of attention, the VSAT, the higher the activity in the parahippocampal gyrus (PPA, parahippocampal place area) in ALS patients. Controls also show a robust activation in the PPA at this time point in the game.
 - In the future, VSATs will be done on Controls to test if the same correlation exists.
 - Frontal function as measured by VSAT, did not appear to influence behavior since pts with normal or low VSATs showed the same abnormal behavior
- It is possible that patients with normal frontal function activate PPA when making computations about what the investor just gave them, and that patients with abnormal frontal function do not activate the PPA under these conditions
 - PPA may be involved in tracking visuo-spatial processing of the stimulus information, which may be used for computations
 - Future studies will investigate why this area is interested in processing this contingency
- Future work will investigate the role of the cingulate gyrus & caudate in ALS decisions
- Correlations will be performed with additional measures of cognitive and behavioral performance

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