

# Frontal lobe dysfunction may give rise to episodic memory deficits in mild cognitive impairment



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## Background

- Cerebrovascular Disease (CVD) is prevalent in the aged population
- Recent studies suggest that CVD may compromise dorsolateral prefrontal cortex (DLPFC) functions.
- We propose that CVD may indirectly affect episodic memory in MCI by compromising frontal lobe dependent working memory functions

### Experiments

- . To compare performance of individuals with MCI and CVD (MCI-CVD) with MCI and hippocampal atrophy (MCI-HA) on episodic memory and working memory
- 2. To use fMRI to examine the effect of CVD on DLPFC activity during a working memory task in normal elderly individuals

#### Participants

MCI-CVD: severe white matter hyperintensities, low hippocampal atrophy MCI-HA: severe hippocampal atrophy, low white matter hyperintensities Normal elderly controls: range of HA and CVD

#### Subject Characteristics

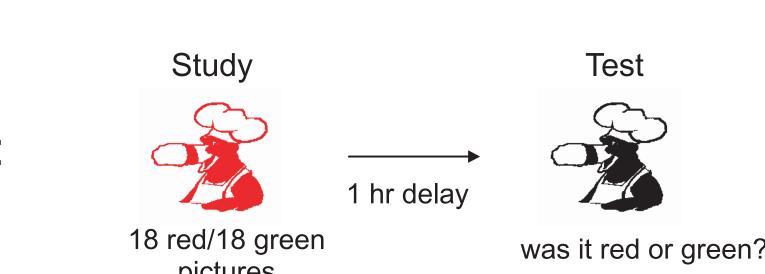
	Controls	MCI-HA	MCI-CVD
n	20	11	11
Age	78.65 (6.34)	74.55 (5.65)*	77.64 (3.56)
Education	15.6 (2.79)	15.8 (3.46)	13.5 (1.51)*
Gender (M/F)	5/15	4/7	5/6
MMSE	29.63 (0.49)	27.46 (1.81)**	27.27 (2.45)**
Left HC Volume	.147 (.03)	.102 (.03)**	.148 (.02)
Right HC Volume	.152 (.02)	.107 (.03)**	.147 (.01)
CVD Severity	13.15 (15.185)	7.66 (2.93)	34.38 (12.2)**

\* borderline group differences (p < .15) - included as covariates in further group analyses \*\* differs from other groups p < .05

#### **Behavioral Tasks**

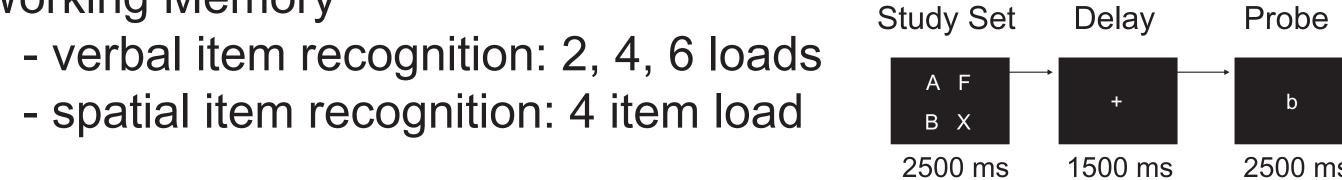
**Episodic Memory** 

- color-object association task:

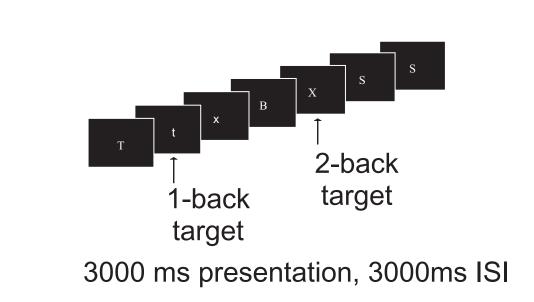


Working Memory

- spatial item recognition: 4 item load



- n-back: 1 & 2-back



### Experiment 1 - Results

Figure 1a MCI-CVD and MCI-HA are equally impaired on the episodic memory task

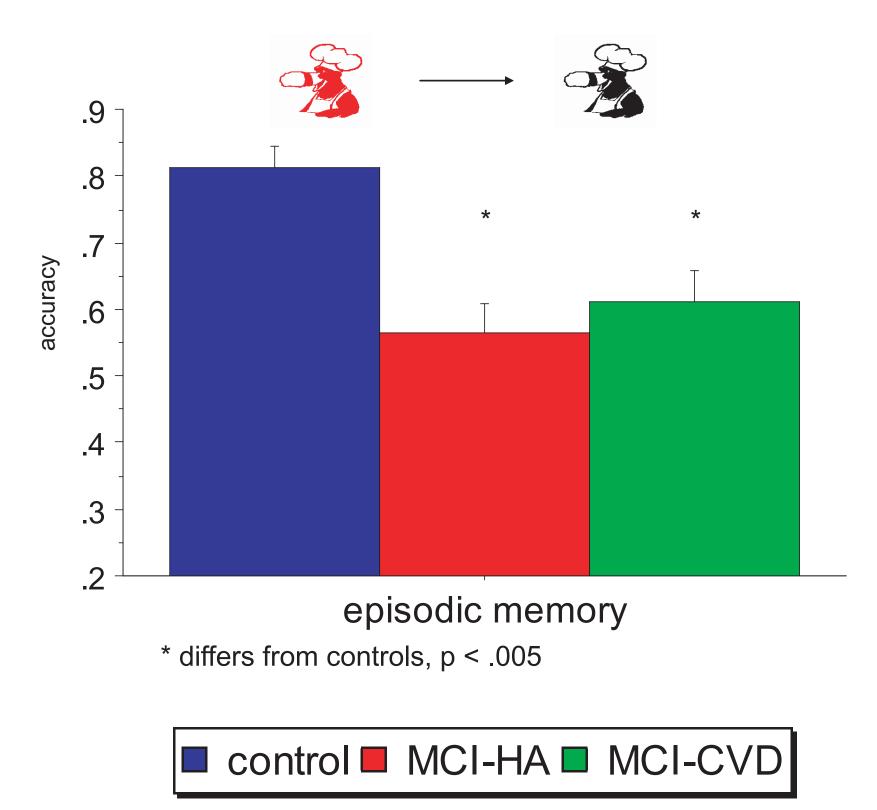


Figure 2a Hippocampal Volume and CVD Severity correlate with episodic memory performance

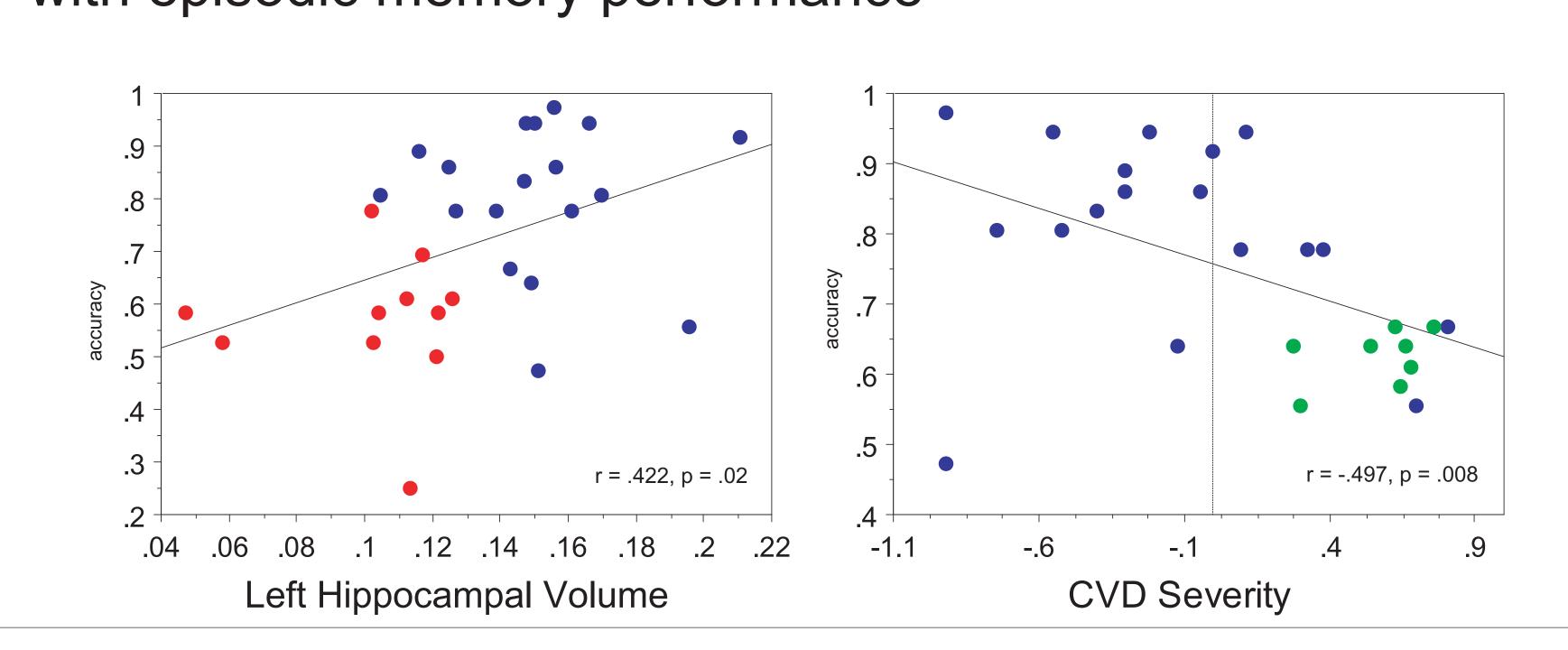


Figure 1b MCI-CVD are additionally impaired on working memory tasks

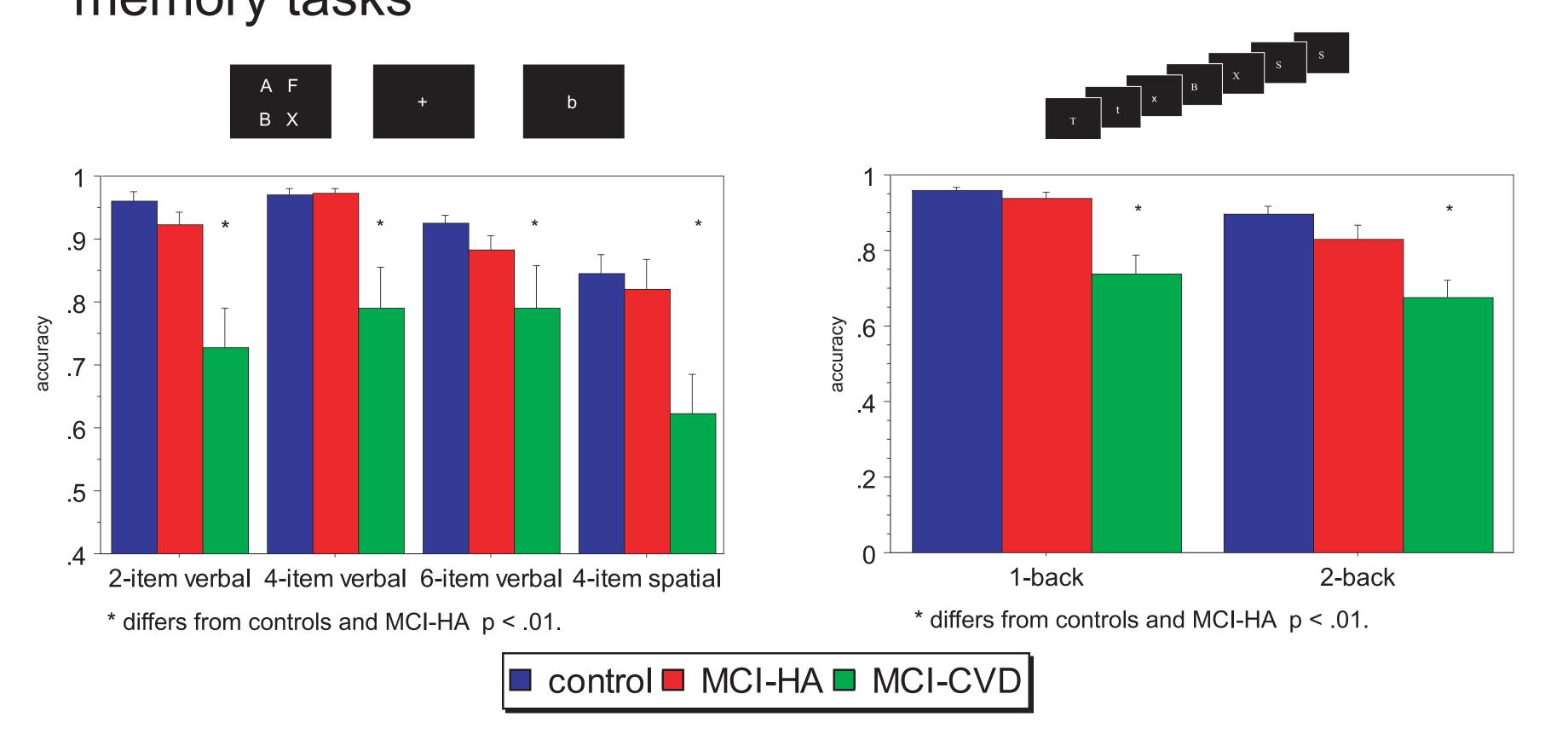
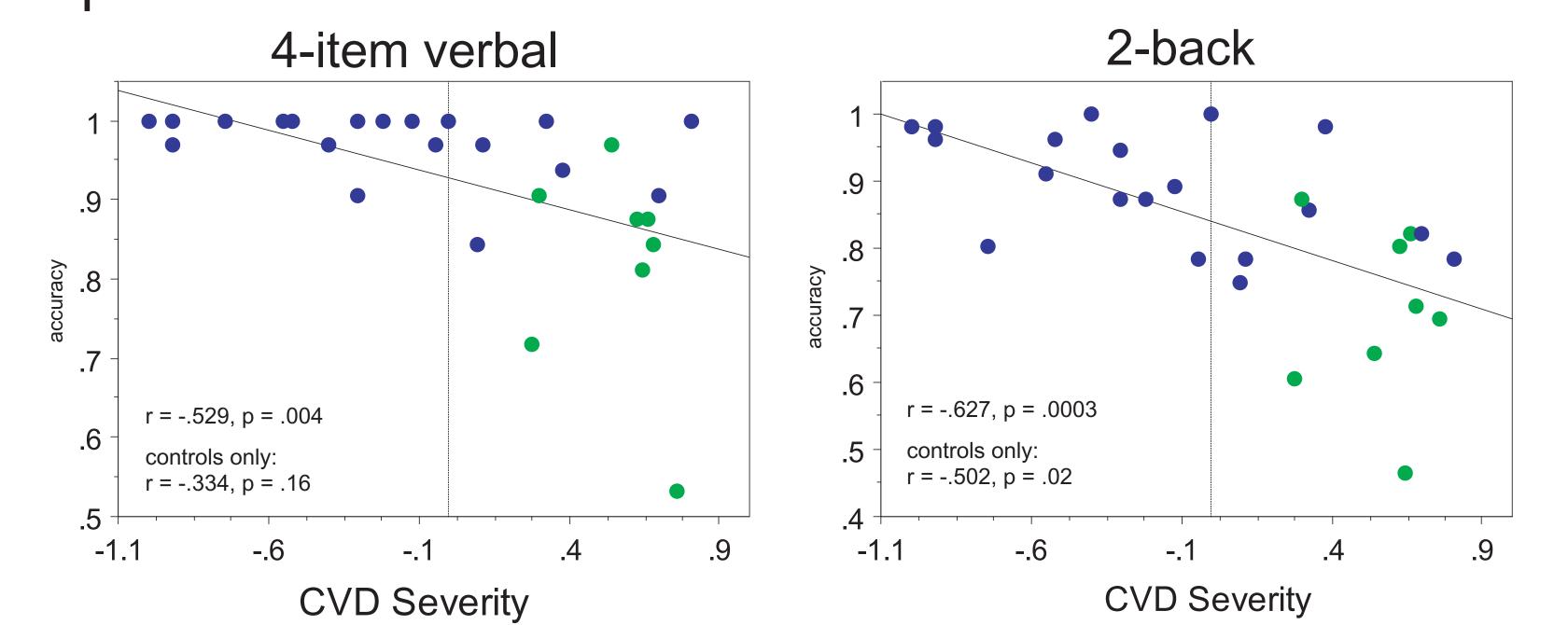


Figure 2b CVD Severity correlates with working memory performance in MCI-CVD and normal controls



Experiment 2 - Results

Figure 3a Working memory performance is correlated with CVD severity in normals

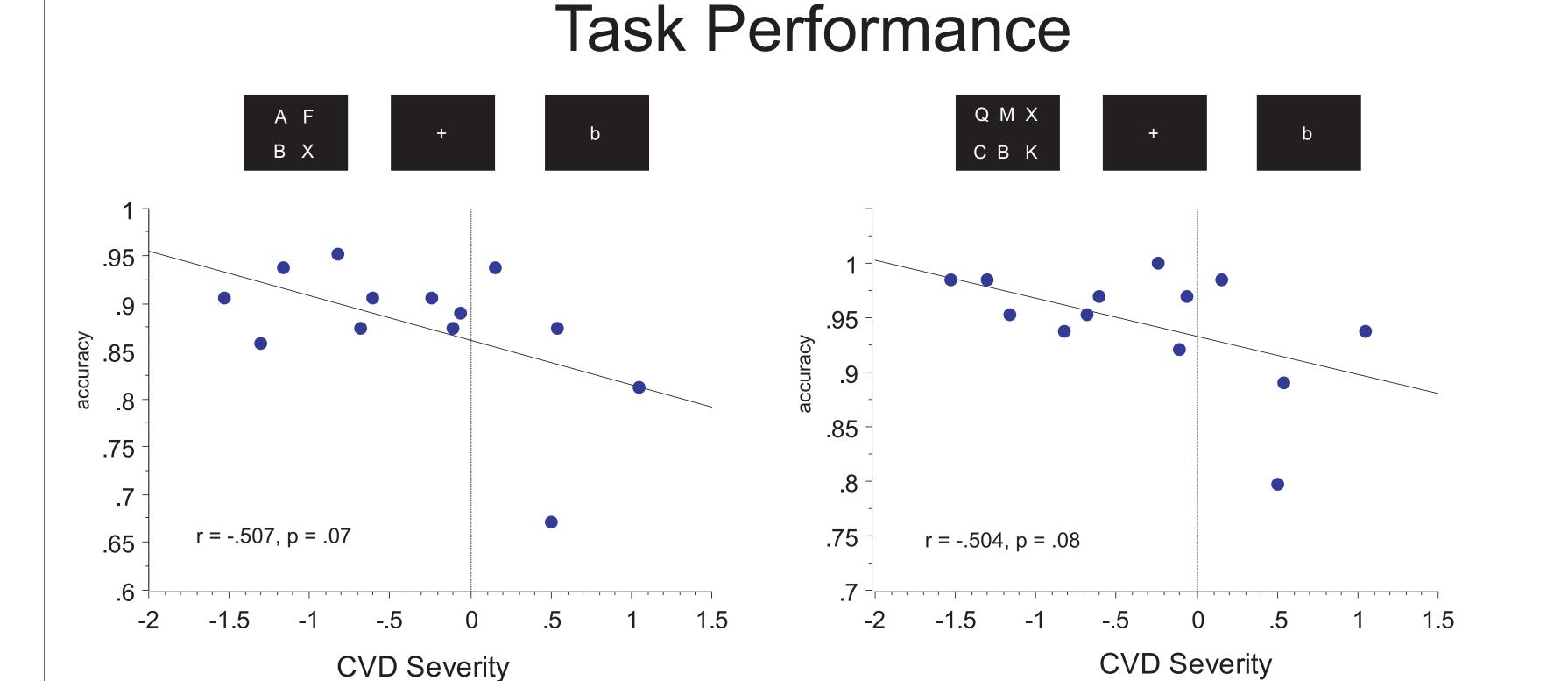


Figure 3c DLPFC regions of interest

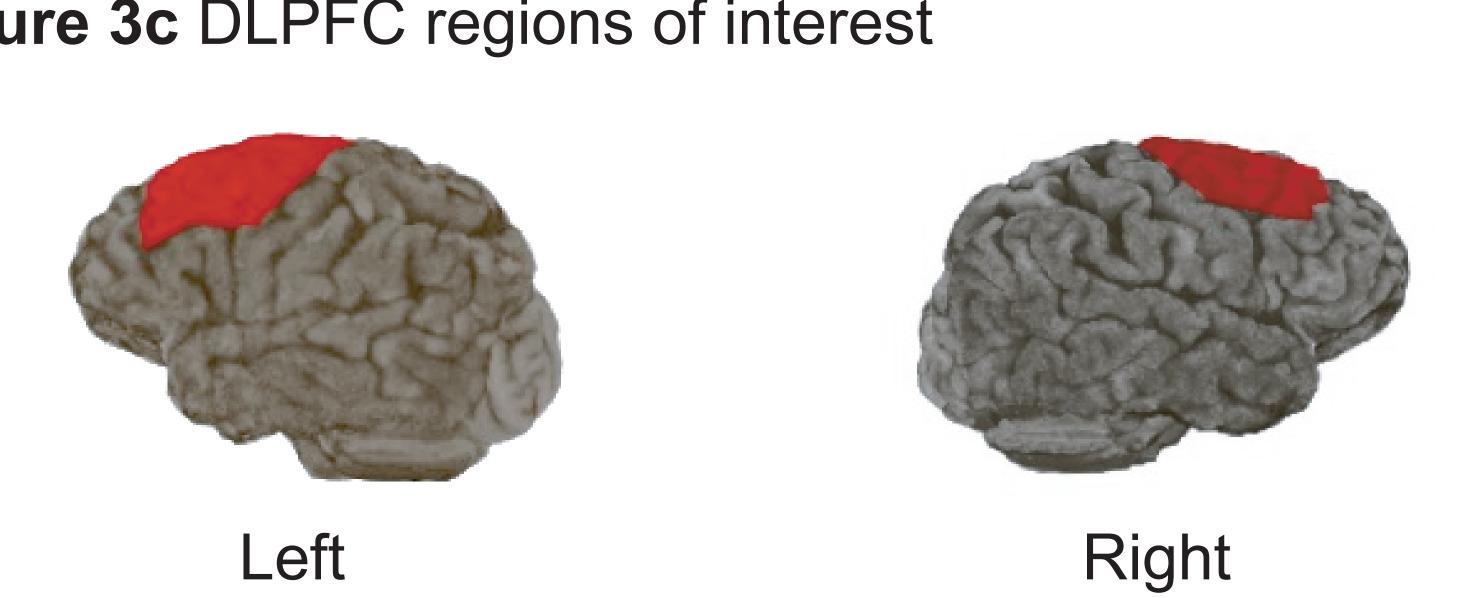
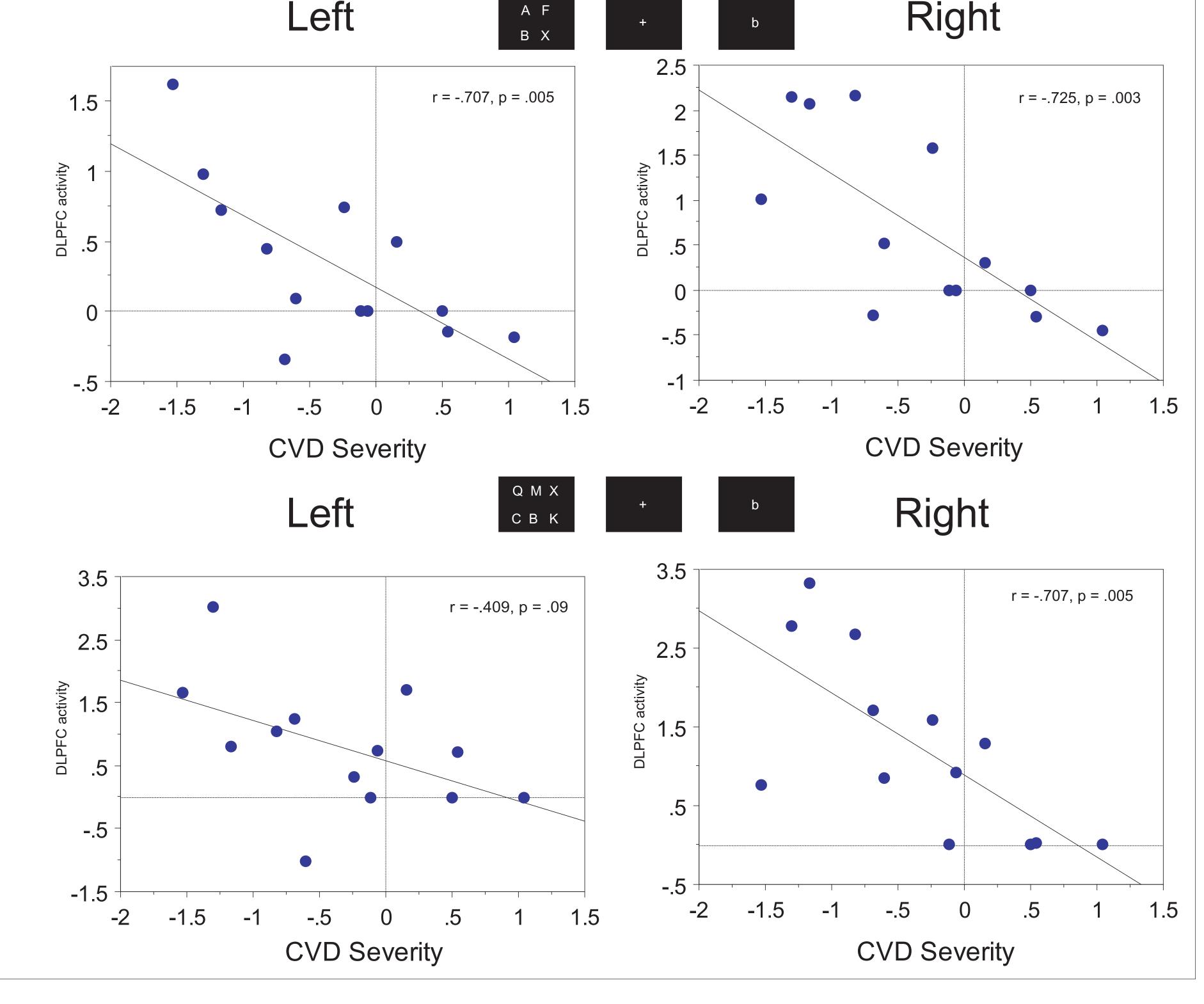


Figure 3b Left and Right DLPFC activity is negatively correlated with CVD severity on working memory tasks



### Summary of Results

#### **Experiment 1**

- MCI-HA and MCI-CVD are equally impaired on the episodic memory task
- MCI-CVD are additionally impaired on working memory tasks
- CVD severity is negatively correlated with 2-back performance in normal elderly individuals

#### **Experiment 2**

- In cognitively normal elderly, DLPFC activity is negatively correlated with severity of CVD on the 4-item and 6-item working memory task
- No correlation between severity of CVD and visual cortex activity

### Conclusions

- 1. CVD can lead to MCI by disrupting frontal dependent working memory processes critical to episodic memory
- 2. CVD can impair working memory performance even in cognitively normal elderly
- 3. The mechanism of CVD impairment on working memory performance may be compromised DLPFC activity
- 4. CVD may be a mechanism for 'frontal lobe' deficits seen in normal aging studies

### Detailed methods

Recruited from UC Davis Alzheimer's Disease Center. All subjects had neuropsychological testing, neurologic exam, and physical. MCI clinically diagnosed based on presence of episodic memory impairment. Participants were excluded for presence of cortical stroke or clinical depression.

MRIs used to further categorize MCI into MCI-CVD and MCI-HA. Hippocampal volumes quantified on T1weighted images and white matter hyperintensity (WMH) load rated on proton density weighted images using a semi-quantitative scale. 25th percentile cutoff for hippocampal volume was used to classify sever HA. 75th percentile cutoff for WMH load used to classify severe CVD. Percentile cutoffs were based on a separate study population (n=122)

#### **Memory Testing - Experiment 1**

Task Presentation

All tasks administered using Presentation (Neurobehavioral Systems) on a laptop computer The order of tasks was held constant: Episodic memory study, 2-item verbal, 4-item verbal, 6-item verbal, 4-item spatial, 1-back, 2-back, Episodic memory test

Data Analysis Group effects - Ancovas with age and education as covariates Correlations - Pearson correlation coefficient with correlation Z test

#### Functional Imaging - Experiment 2

Data Acquisition 13 normal elderly subjects recruited from Experiment 1 1.5T GE scanner EPI: 22 5mm slices, TR=2000, TE=50 FOV 24 coplanar anatomical - FSE: 22 5mm slices, FOV 24

Block Design

4 item verbal recognition - 2 runs, 16 trials per run, 8 seconds per trial 6 item verbal recognition - 2 runs, 16 trials per run, 8 seconds per trial

visual sensory task - flickering checkerboard alternating with fixation - 1 run 16 trials, 8 sec per trial DLPFC region of interest

Left and right DLPFC drawn on the lateral surface of each subjects' rendered image

Data Processing and Analysis

Images realigned and smoothed (3mm FWHM kernel) in SPM 99 Filtered and adjusted for global signals in Voxbo

Task related boxcar convolved for hemodynamic response Parameter estimates for each region determined for each task