Presentation 7 – Jim Bartlett

Conjunction Memory Paradigm: Preliminary Data

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Meeting Guidelines of the Research Advisory Committee on Gulf War Veteran's Illnesses

- The proposed research
  - will use a imaging approach to capture the spatial aspects of brain function underlying memory in ill-GWV and compare it to that of controls.
  - will attempt to distinguish between the three subcategories of GWS –I, II, & III.
  - will attempt to provide tangible diagnostic tools that can be used to discriminate between various subtypes of GWS.
  - will attempt to deliver results relevant to the treatment of the cognitive deficits that accompany GWS.

Binns et al. *Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations.* September, 2004.

Gulf War Syndrome

- Studies of the symptoms of ill-GWV have resulted in a diagnostic classification scheme broadly referred to as Gulf War Syndrome (GWS), with three syndrome variant:
  - 1) impaired cognition
  - 2) confusion-ataxia
  - 3) central pain

Haley, R.W., G.D. Luk, and F. Petty, *Use of structural equation modeling to test the construct validity of a case definition of Gulf War syndrome: invariance over developmental and validation samples, service branches and publicity*. Psychiatry Res, 2001. 102(2): p. 175-200.
Nisenbaum, R., et al., *Dichotomous factor analysis of symptoms reported by UK and US veterans of the 1991 Gulf War*. Popul Health Metr, 2004. 2(1): p. 8.

Gulf War Syndrome

- The cognitive deficits are associated with prior exposure to a combination of low-dose organophosphate nerve agents (sarin), pesticides, pyridostigmine, and DEET-containing insect repellant.

Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf war: A cross-sectional epidemiologic study. JAMA 1997;277:231–37.

Exposure to Neurotoxins

- Repeated sub-clinical exposure to sarin gas to results in reduced acetylcholineserase activity in the *hippocampus*, cortex, striatum, and olfactory bulb of rats.
- Suggesting a reduction in cholinergic receptors and as such, cholinergic activity in the affected regions.

Abdel-Rahman, A., A.K. Shetty, and M.B. Abou-Donia, *Disruption of the blood-brain barrier and neuronal cell death in cingulate cortex, dentate gyrus, thalamus, and hypothalamus in a rat model of Gulf-War syndrome.* Neurobiol Dis, 2002. 10(3): p. 306-26.

Exposure to Neurotoxins

- Stress, in combination with low doses of pyridostigmine bromide, DEET, and permethrin results in significant neuronal death in the *hippocampus*, thalamus, and cingulate cortex

Abdel-Rahman, A., et al., *Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum.* J Toxicol Environ Health A, 2004. 67 (2): p. 163-92.

Henderson, R.F., et al., *Response of F344 rats to inhalation of subclinical levels of sarin: exploring potential causes of Gulf War illness.* Toxicol Ind Health, 2001. 17(5-10): p. 294-7

Exposure to Neurotoxins

- MR spectroscopy and single photon emission computed tomography (SPECT) have identified *hippocampal* dysfunction in Gulf War veterans (GWV) reporting cognitive deficits
- Unclear whether the damage is
  - bilateral or largely restricted to the right hippocampus.
  - present in the hippocampal commisures connecting the left and right hippocampal formations.

Menon, M. et al. (2004). Hippocampal dysfunction in Gulf War Syndrome. A proton MR spectroscopy study. Brain Research, 1009, p. 189-194.

Gulf War Syndrome & Memory

- ill-GW vets commonly self-reported cognitive deficits in memory as well as in word finding, and concentration.
- Although memory deficits are among the most commonly reported symptoms associated with GWS, these self-report data have been met with considerable concern and occasional derision.
- GWV identified as having GWS commonly demonstrate performance on neuropsychological memory test batteries equivalent to that of controls.

Gulf War Syndrome & Memory

- However, difficulty in detecting objective memory deficits in ill-GWV could result from several causes.
  - 1) the use of neuropsychological testing instruments that fail to precisely target mnemonic functioning of the hippocampus
  - 2) compensatory strategies used by ill-GWV that may ameliorate effects of hippocampal damage in standard paper and pencil neuropsychological tests of memory.

Gulf War Syndrome & Memory

- Both hypotheses necessitate a targeted investigation comparing ill-GWV with appropriate controls with respect to
  - 1) behavioral performance in memory tasks known to involve the hippocampus
  - 2) hippocampal activity (inferred from BOLD response in fMRI) during performance of these tasks
  - 3) activity in other brain regions and larger brain circuits during the performance of these tasks (inferred from BOLD response in fMRI).

A key hippocampal function is memory *binding* (or conjunctive coding)

- Binding processes can be assessed in the *conjunction paradigm*.

The conjunction paradigm: Faces

STUDY


TEST

The conjunction paradigm: Words

STUDY		TEST
JAILBIRD	BLACKBOARD	BLACKBIRD

The conjunction paradigm: Face Names

STUDY		TEST
 Robin	 Mandy	 Robin

A Typical Outcome (Jones, Bartlett & Wade (2006)

- Hit rate to old faces = .69
- False-alarm rate for conjunctions = .46
- False-alarm rate for new faces = .25

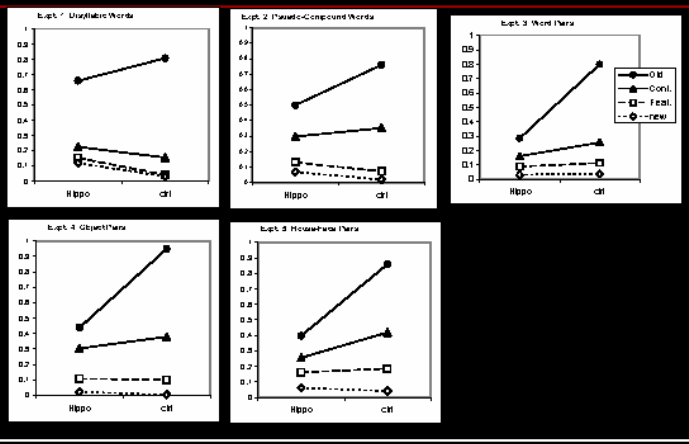
The hippocampus & conjunctions

- Several fMRI studies have found activation in hippocampal regions linked to encoding and retrieval in conjunction paradigms
- Hippocampal damage has been linked to impaired performance with conjunctions

Hippocampal damage reduces Old/Conj. Discrimination

- Kroll et al. (1996)
  - Left-sided damage ⟹ Impairments with words
  - Left- or right-sided damage ⟹ Impairments with cartoon faces
- Stark & Squire (2003)
  - Bilateral damage ⟹ Impairments with five different stimulus types

Stark & Squire (2003)

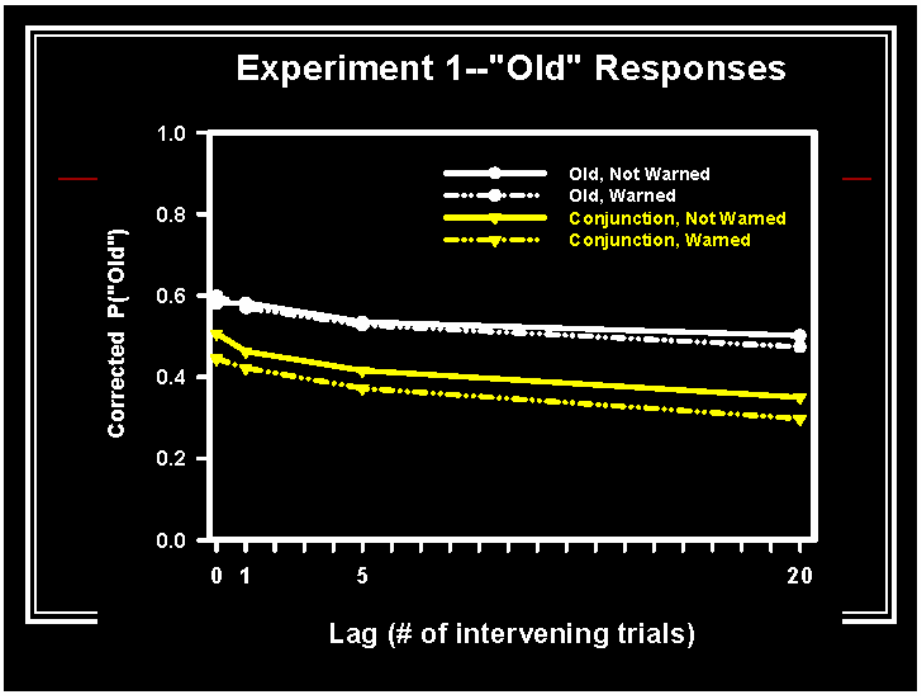


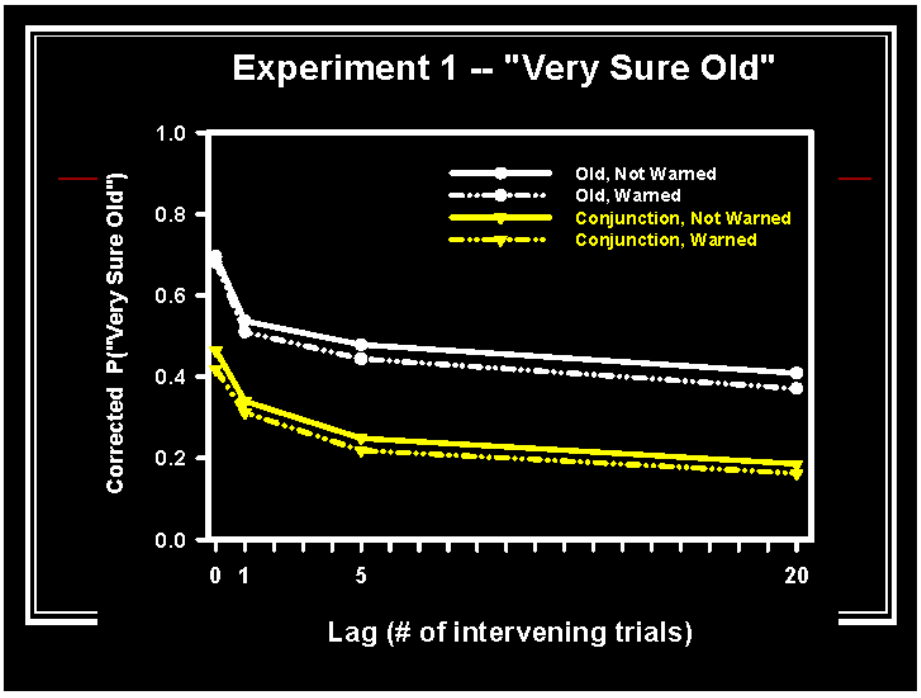
But the pattern varies

- Kroll et al. found increases in conjunction errors
- Stark & Squire found only declines in hits
  - And on this basis questioned the binding hypothesis
- A possible explanation: "Recollection-rejection" by controls in Kroll et al.

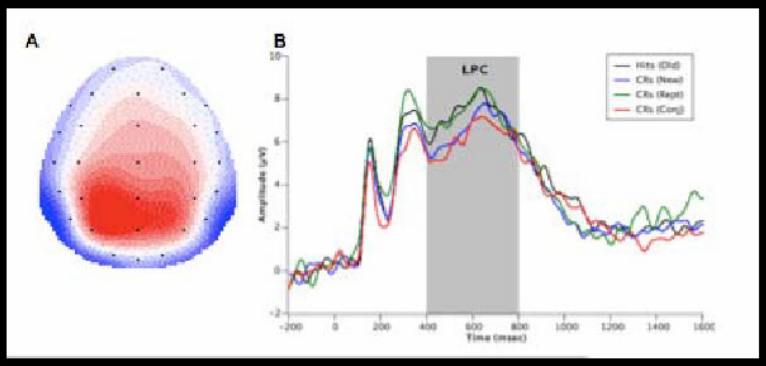
Facial conjunctions show minimal recollection-rejection:

- Jones & Wade (submitted)
- Shastri et al., in preparation)


Experiment 1--"Old" Responses
Corrected P("Old")
1.0
0.8
0.6
0.4
0.2
0.0
0 1 5 20
Lag (# of intervening trials)
Old, Not Warned
Old, Warned
Conjunction, Not Warned
Conjunction, Warned

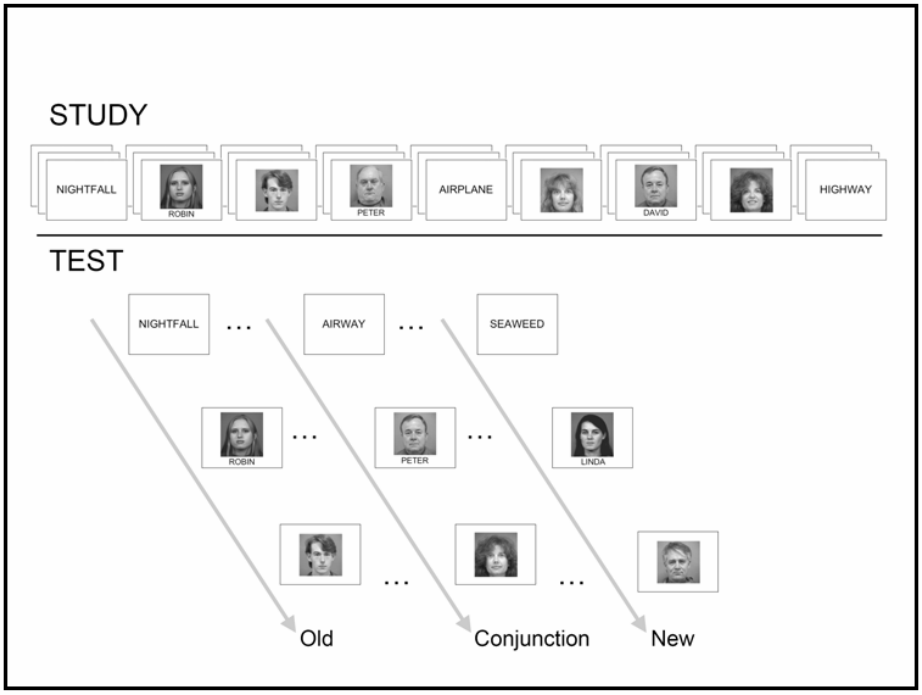

Experiment 1 -- "Very Sure Old"
Corrected P("Very Sure Old")
1.0
0.8
0.6
0.4
0.2
0.0
0 1 5 20
Lag (# of intervening trials)
Old, Not Warned
Old, Warned
Conjunction, Not Warned
Conjunction, Warned

Shastri et al.: Conjunctions = new in the late positive component



Two aims for the project

- To determine the memorial profile of four groups of GWV (including GWV controls)
  - Using face- word-, and face-name conjunctions
- To assess right- and left-hippocampal dysfunction linked to performance impairments using fMRI
- To examine compensating strategies using fMRI



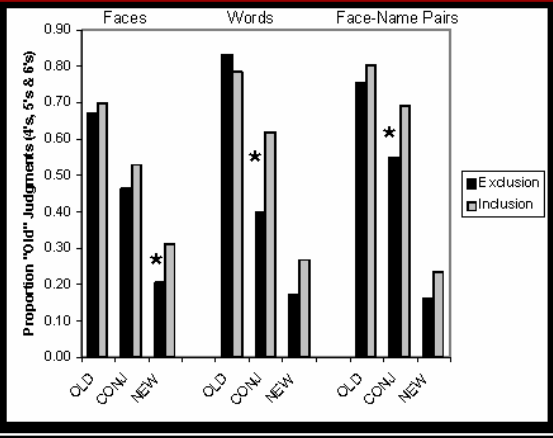
Behavioral Experiment 1 (n = 48)

- Compared conjunction-task performance with face, word and face-name stimuli:
  - To check performance levels
  - To assess recollection-rejection with all three item-types
    - Exclusion vs. inclusion instructions

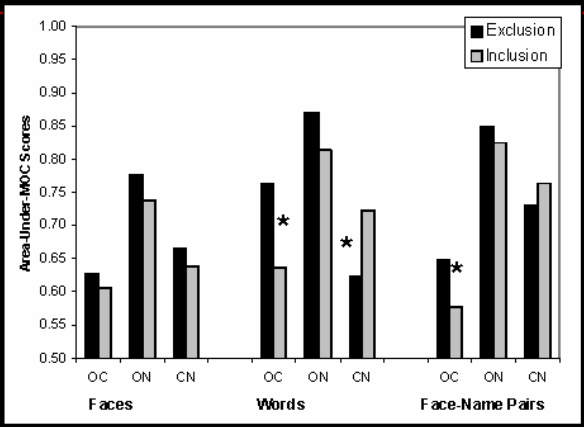
The logic:

- If a person is performing recollection-rejection . . . . . s/he should ***know*** that conjunctions are conjunctions
- If not, s/he will only know that conjunctions have a certain level of familiarity
  - As when a friend looks different but you cannot say what has changed.

Exclusion & Inclusion Recognition Performance with Faces, Words, and Face-Name Pairs



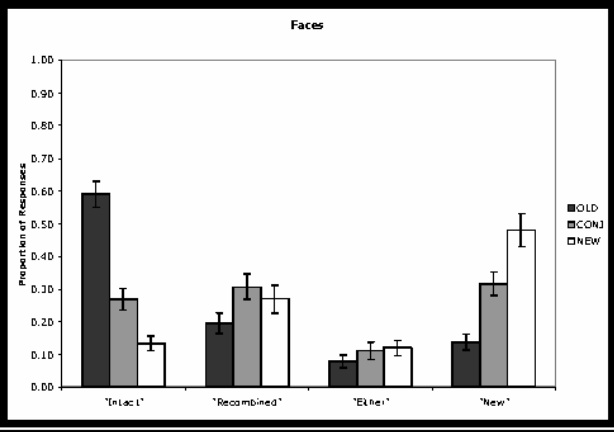
Discrimination Measures:



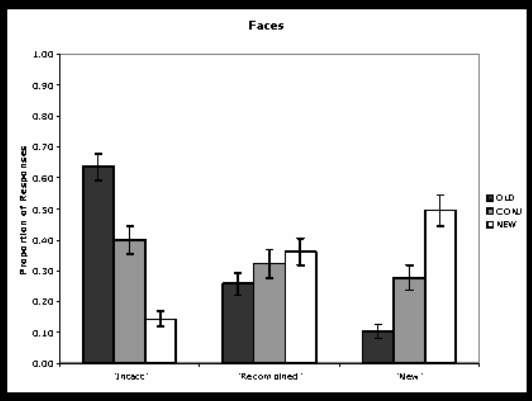
Behavioral Experiment 2 (n=24) and behavioral data from fMRI study 1

- Examined whether recollection-rejection might be enhanced in a paradigm suitable for the scanner
- The key change: Subjects made explicit "Intact" and "Rearranged" Judgments

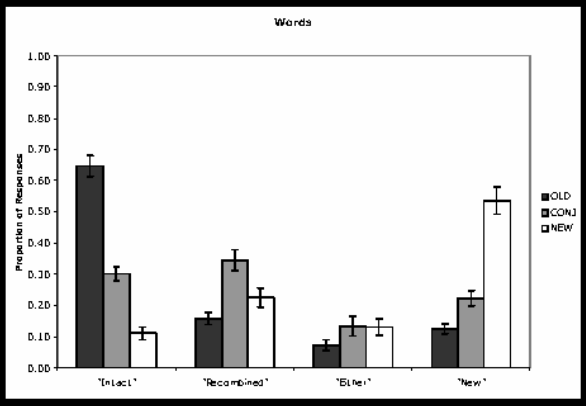
Face Recognition in Behavioral Experiment 1(n=24)



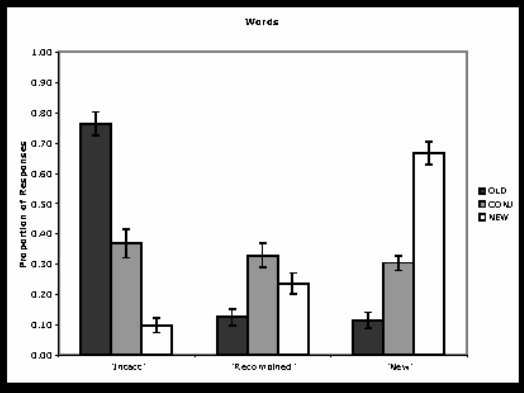
Face Recognition in fMRI Experiment 1(n = 12)



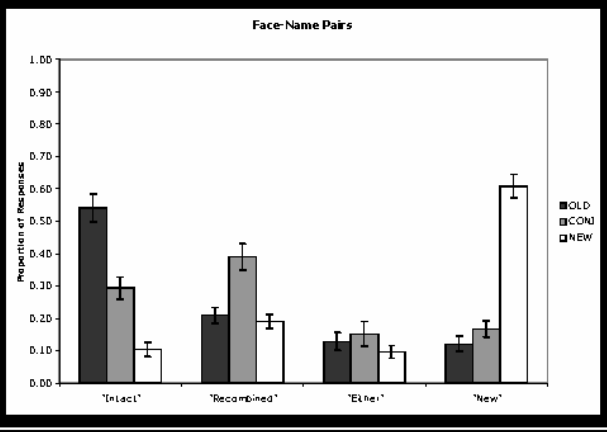
Word Recognition in Behavioral Experiment 1



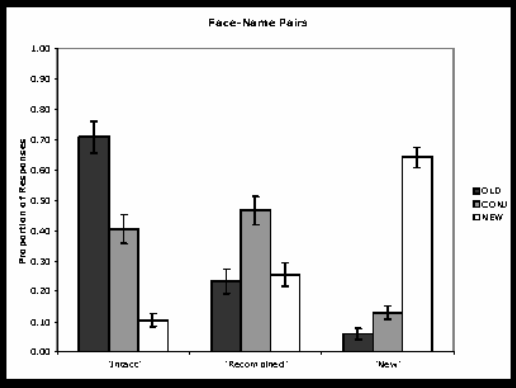
Word Recognition in fMRI Experiment 1



Face-Name Recognition in Behavioral Experiment 1



Face-Name Recognition in fMRI Experiment 1



Predictions for GWVs:

- GWS-III: No difference from GWS-controls
- GWS-I & GWS-II: Impaired accuracy of "old" judgments with faces and face-name pairs.
  - Impairment with words, if left-hippocampal damage is present
- Impaired accuracy of "intact" judgments with face-name pairs

One question for fMRI:

- Will hippocampal activation at study:
  - Predict discrimination conjunctions from old faces with "old" (and perhaps "intact" judgments)
  - Be reduced in GWS-I and GWS-II veterans
  - Explain performance differences between these veterans and controls