How midazolam can help us understand human memory:

3 illustrations & proposal for a new methodology

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What is Midazolam?

- Anxiolytic (less anxious / worried) drug used commonly in surgery
  - Benzodiazepine (Valium is most famous)
  - Causes temporary **anterograde amnesia**
- Metabolized quickly with minimal side effects
  - Effects of drug do not last long; become normal in <60 minutes
- Cognitive functions are unimpaired even though sedated.

Why use midazolam to study memory?

- Patients with memory loss help us understand normal functioning
  - Draw inferences based on brain damage and performance deficits.
- Patients often have other problems (comorbidity)
  - Difficult to find suitable controls (avoid confounds)
- We do not have to rely on patients to study amnesia:
  - College students are plentiful, suitable controls, ability to perform complex experiments

3 illustrations of how midazolam facilitates theory development. Research using drug:

- Provides evidence *against* "modal view" that there exist separate implicit & explicit memory systems
- Provides support *for* hypothesis that recognition is affected by ease of generating a (unique) label
- Enables *test of claim* that most forgetting is a failure of consolidation

Example 1: Contextual cuing under midazolam

- Demonstrates that *some aspects* of an implicit task are affected by amnesia
  - Challenges the view that memory systems divide on conscious awareness

Park, Quinlan, Thornton & Reder *PNAS* (2004)

What do we mean by implicit (vs. explicit) memory?

- **Task defined: no intention to learn or remember; but performance shows an effect of exposure anyway**
- **Awareness defined: performance is affected by previous exposure but subject is unaware of any influence on performance**

Example of tasks

- View a series of target words:

  ANEMONE, CATERPILLAR, DUNGEON, ….

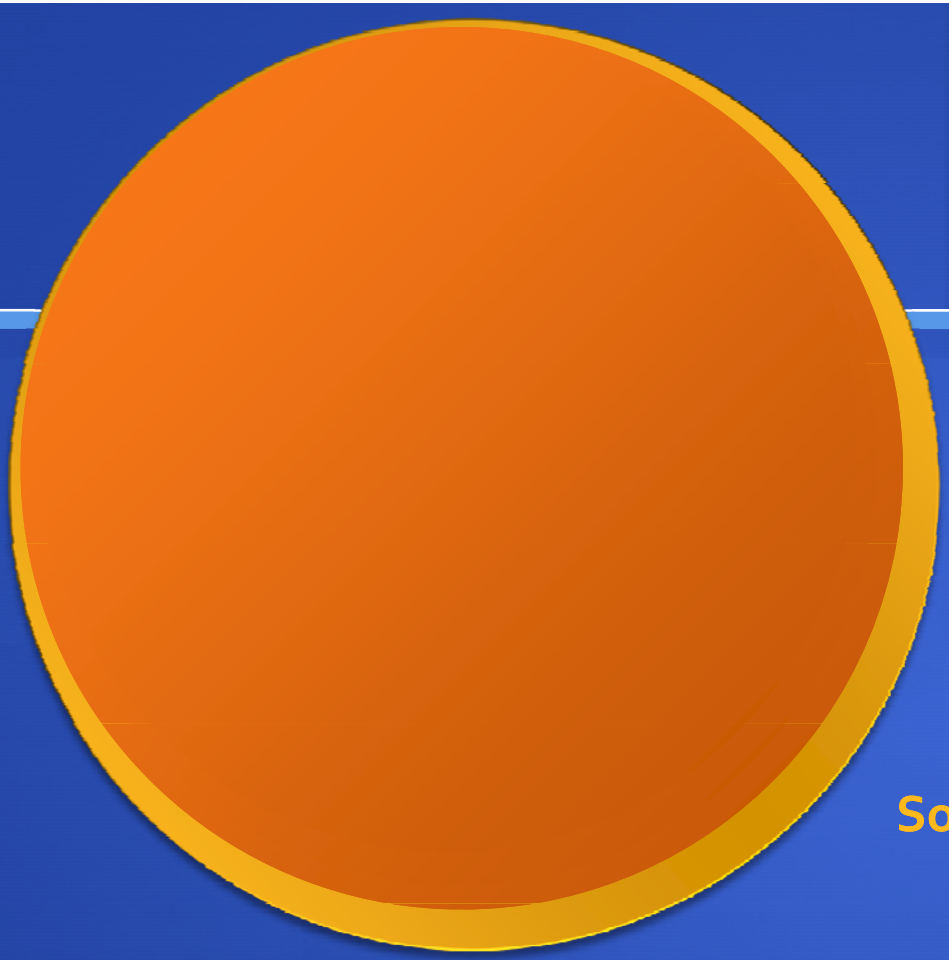
- Explicit memory task: "Did you see the word *dungeon*?"
- Implicit memory task: "Fill in blanks to make a word"

  _NE_O_ _ER_U_E

  _UN_E_N _SS_SS_N

Conventional wisdom: *implicit & explicit memory are separate systems*

- *Amnesiacs seem not to be able to learn or remember anything new explicitly.*
- *For implicit memory tests, amnesiacs perform much like normal individuals.*

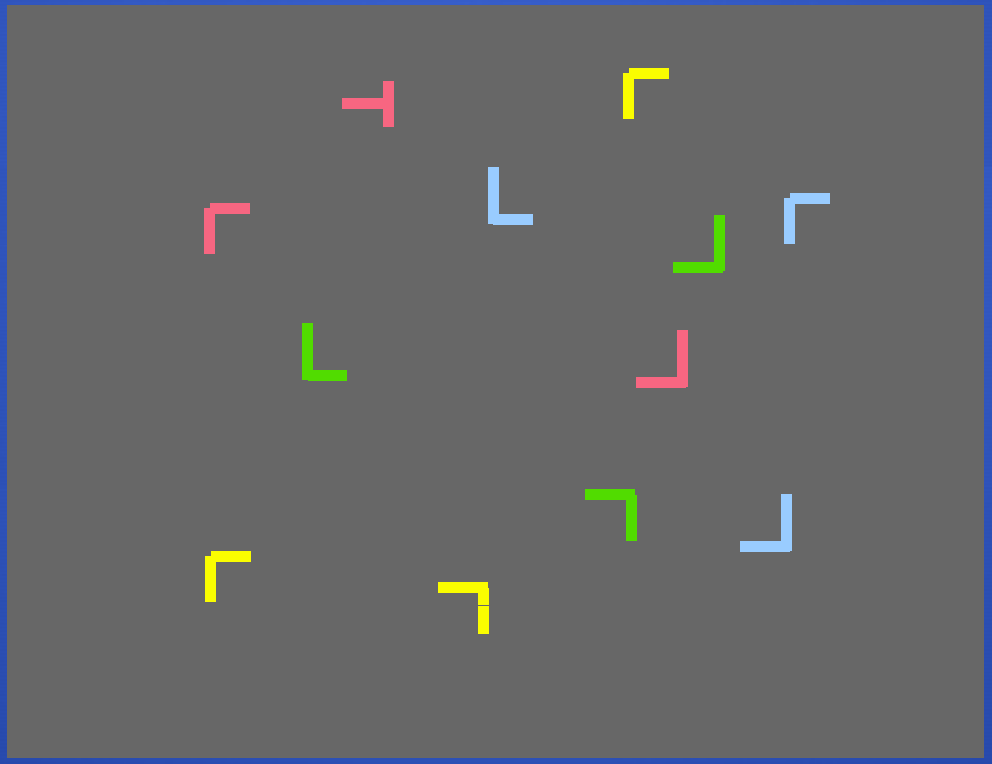


In reality, not so simple

Some tasks indicate that amnesiacs fail to learn information acquired implicitly

TASK: Find the T in display of "Ls"

The role of contextual cues in visual search (Chun & Jiang, 1998)

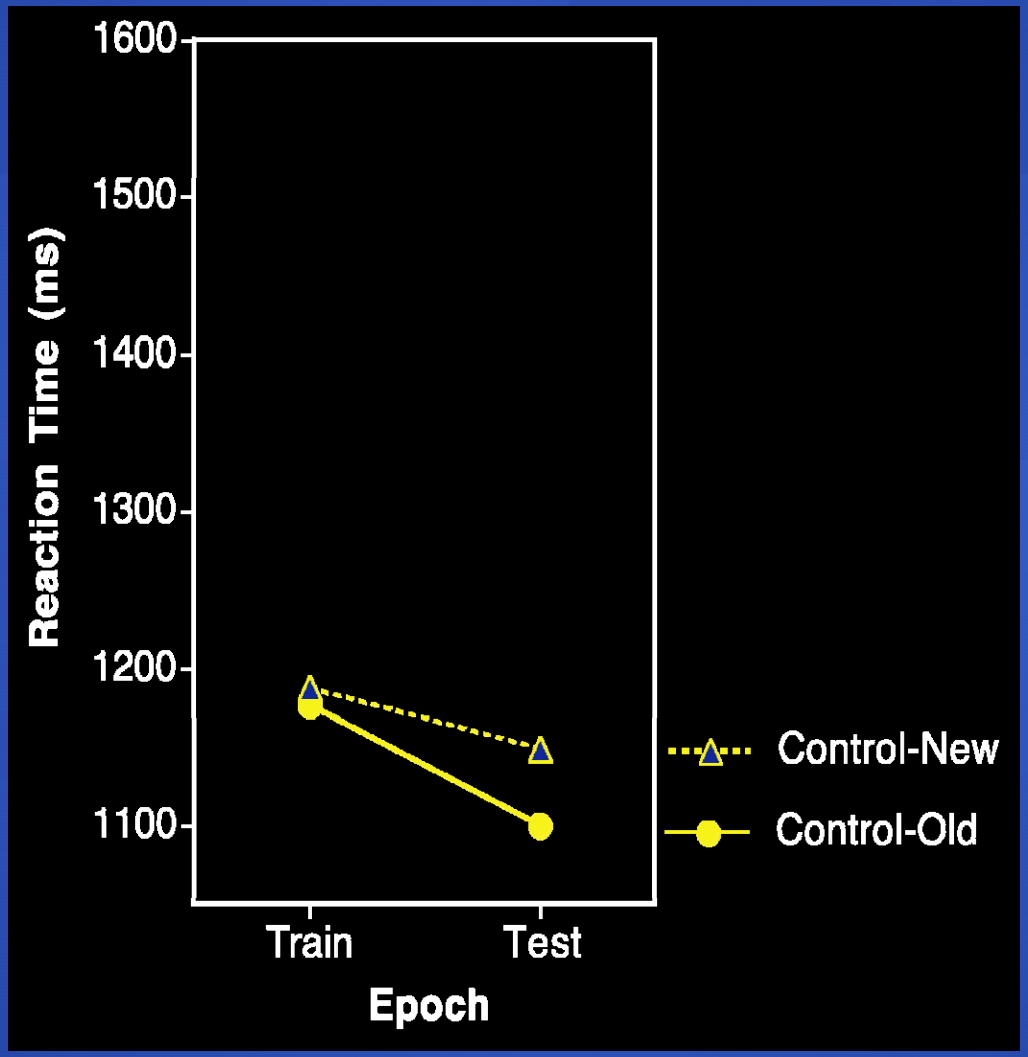


Many trials like this one; 24 blocks with 24 displays per block

Logic of the task

- Repeated display vs. new display
  - The target appeared in the same location within an invariant configuration across blocks
  - A new, previously unseen configuration
- Improvement for old configurations
  - Learning the association between target and repeated visual context
    - Contextual cuing effect

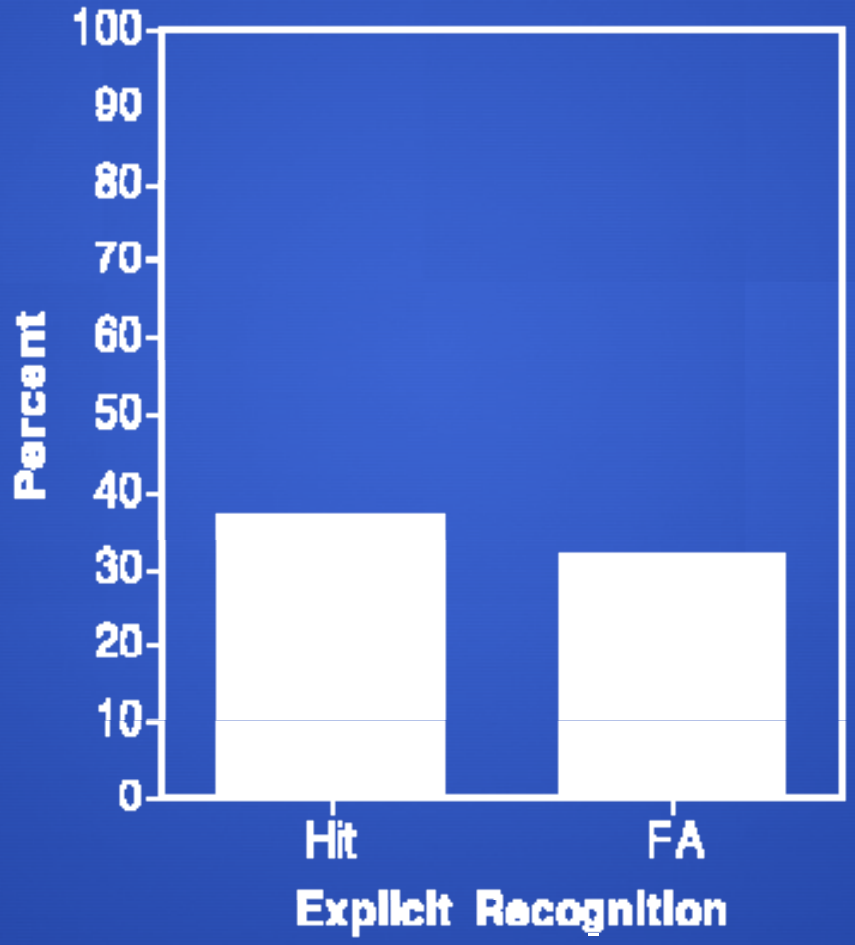
Data from Chun & Jiang



($p < .002$)

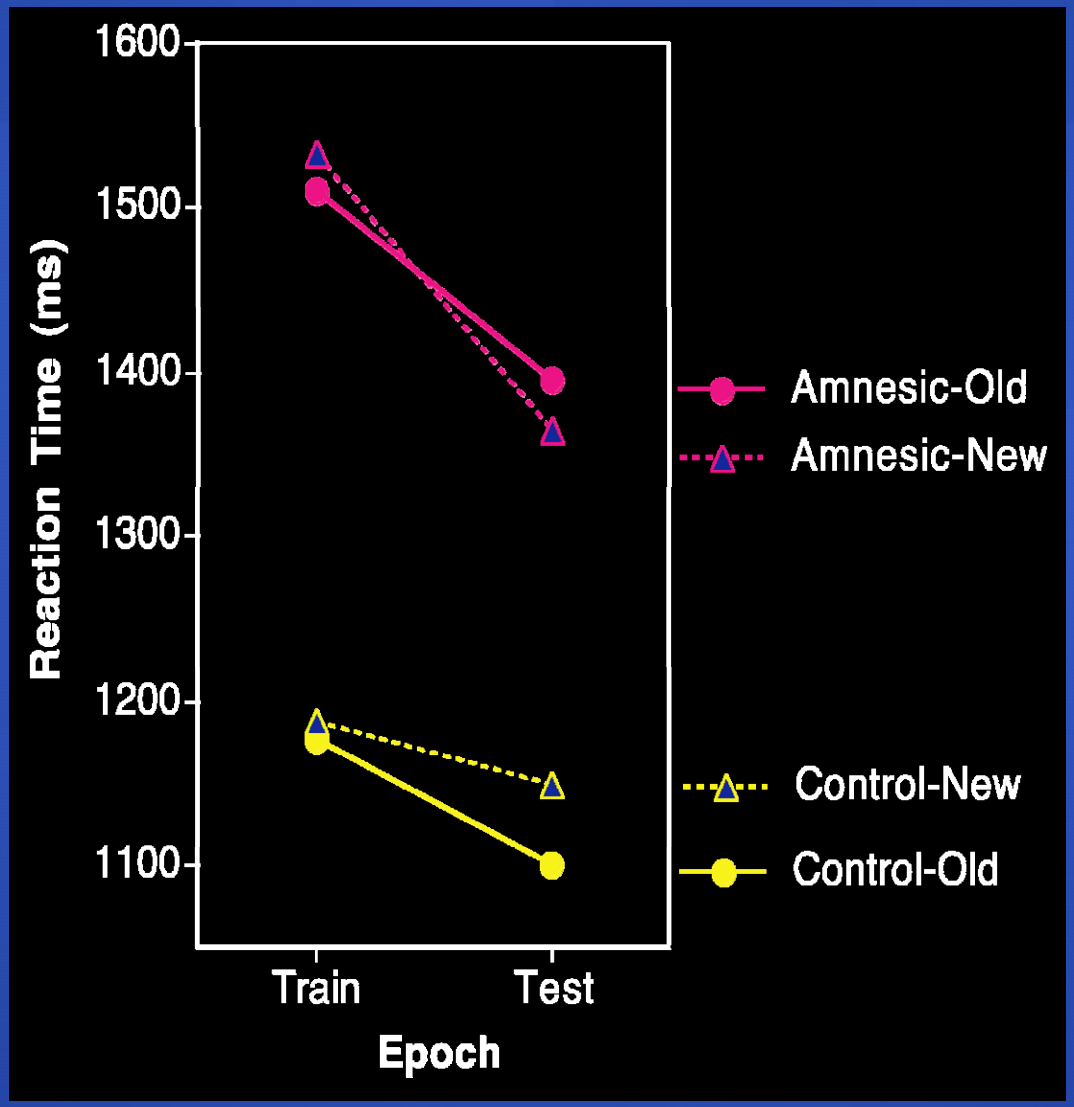
Subjects get faster at task over time; more facilitation for repeated displays

Memory for context was *implicit:* *faster RTs for repeated but no ability to recognize repeated displays*



could not discriminate repeated from new displays

Chun and Phelps (1999)
Compared amnesiacs with controls



($p < .005$)

Chun & Phelps found:

- General improvement with practice for *all* subjects, amnesiacs & controls
- Contextual cuing effect for controls
- No contextual cuing effect for amnesiacs *even though learning was implicit*
- Thus, amnesia interferes with learning of *implicit* contextual information

Controversy re: amnesic data

- Some amnesic patients show a different pattern (Manns & Squire)
- Even within a consistent pattern, may be a different etiology or pattern of damage
- We need to test this with drug-induced amnesia!

Will drug-induced amnesia affect implicit learning in contextual cuing task?

- Within-subject, double-blind, cross-over design: Saline one session, Midazolam the other
- Different, equivalent, visual search tasks for two sessions: T/L & 2/5
- Manipulation check: study list of word pairs immediately after injection for later cued recall;
  - tested pairs at end of experiment
- Otherwise the design follows Chun & Jiang / Chun & Phelps.

Predictions

- Subjects will show general speed up over trials regardless of drug condition
- Saline condition: benefit of repeated pattern when searching for a target
- Midazolam condition: no contextual cuing effect
  - why? Midazolam inhibits formation of new associations/bindings

Procedure

- Study instructions
- Drug injection (saline/midazolam)
- Present list of paired associates (e.g., volume-child) as a drug manipulation check
- Implicit visual search task (T/L or 2/5)
- Post-test (quadrant guessing task)
- Cued recall (e.g., volume-?)
- Awareness questionnaire on Day 2 (did subject know there were repetitions?)

Performance on quadrant guessing task

Subjects at chance predicting quadrant that contained target

Cued recall performance after visual search task: volume-___?___

Midazolam produced very strong anterograde amnesia!

General speed-up with practice

One epoch = 4 blocks of 24 trials

General improvement in accuracy

One epoch = 4 blocks of 24 trials

Drug x Repetition: RT difference between repeated & new for saline only

One epoch = 4 blocks of 24 (12 repeated, 12 new)

Contextual cuing effect (new – repeated)

Advantage of repeated displays increases with repetitions but only for saline

Summary of results for healthy participants:

- No awareness of repeated displays in either drug condition=> *implicit task*
- General improvement in the task, with practice, regardless of drug condition
- Under *saline*, facilitation in locating target with repeated patterns
- Midazolam condition showed no such benefit

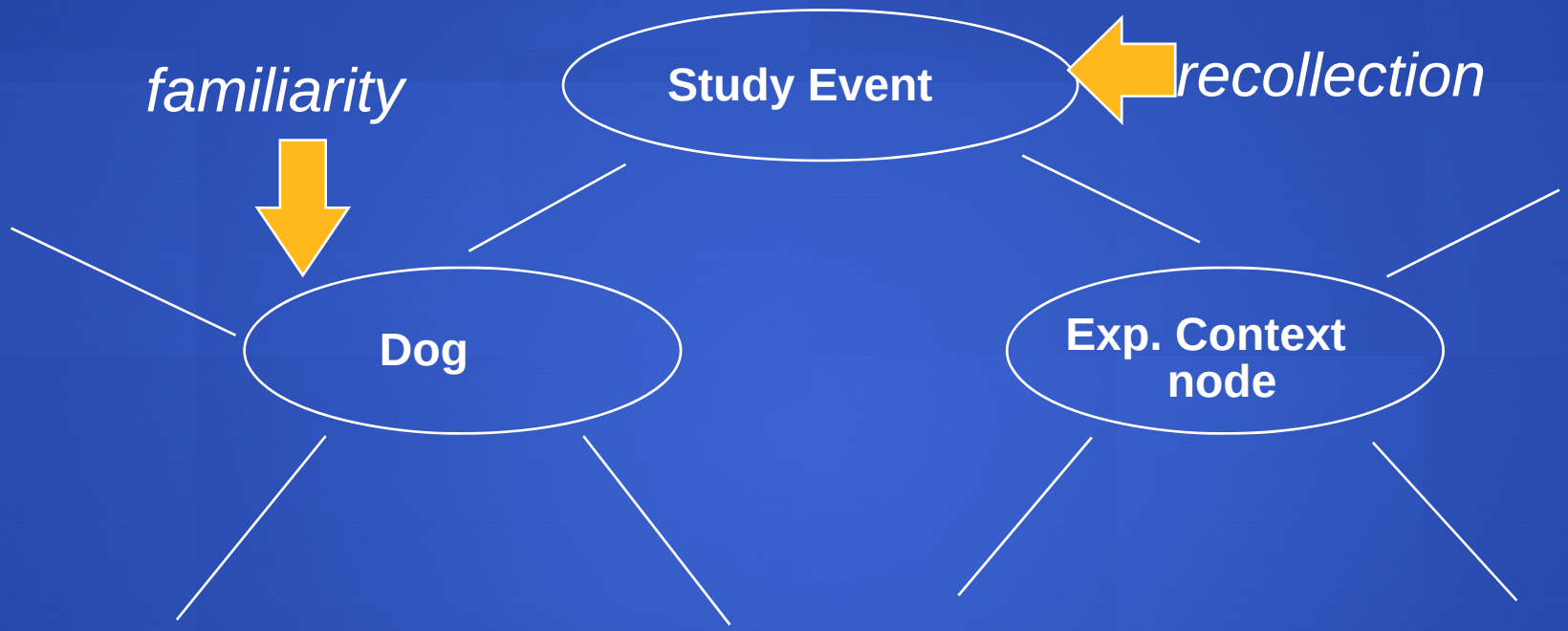
$\Rightarrow$amnesia can produce implicit task deficits

Example 2: Midazolam only affects memory for stimuli that are unitized

- Recognition can be based on familiarity or recollection.
- Recollection requires retrieving contextual information
- Midazolam only affects the binding process;
  - Familiarity judgments are unaffected
- Claim: Stimuli that are not unitized cannot be bound to context & thus cannot be "recollected"

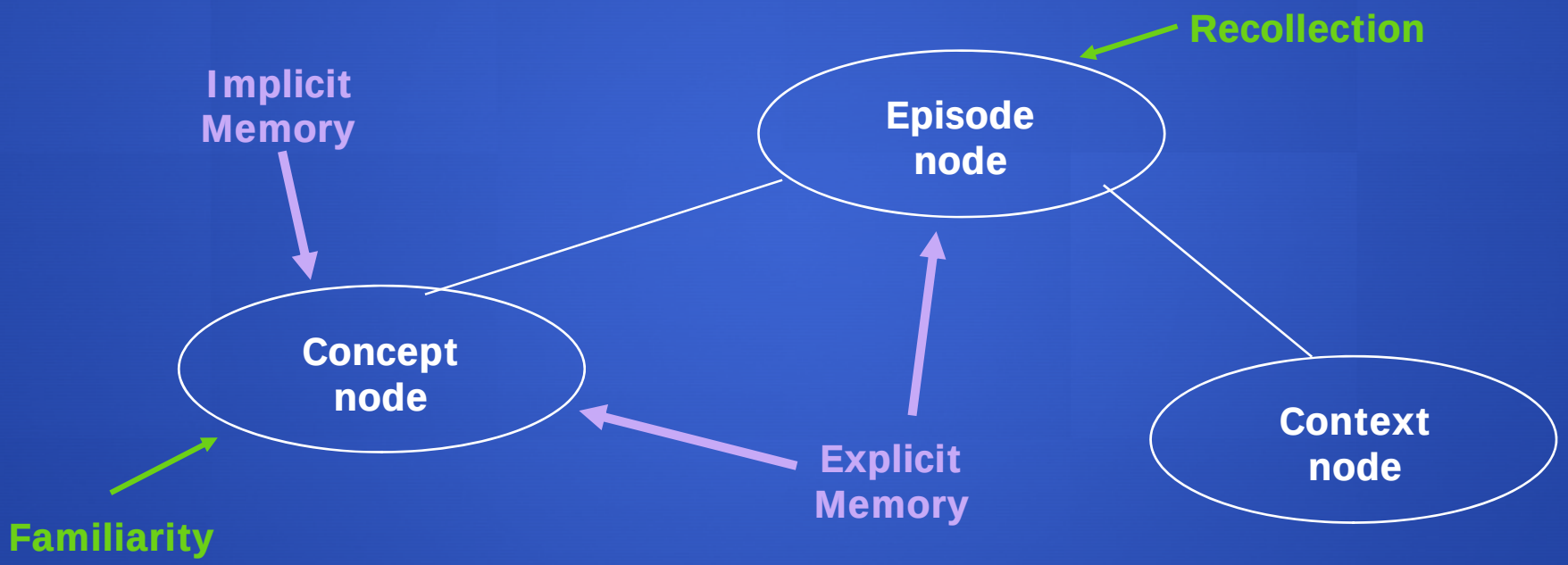
Reder, Oates, Thornton, Quinlan, Kaufer & Sauer

Schematic representation of episodic & semantic memory



When recollection fails (encoding or retrieval failure), recognition is inferred from the familiarity of the concept node

The binding matters for recollection, but not for familiarity or priming



(Midazolam affects binding but does not affect priming or familiarity)

When are episode nodes (binding stimulus to context) *not* formed?

- When a person has organic amnesia
- When a person is given midazolam
- When a person has insufficient working memory capacity to create the binding
- When the information does not have a stable memory representation to bind to context
  - *Resources devoted to creating a chunk*

What do we mean by *unitized* or a *chunk*?

- In 1950's George Miller and Herb Simon demonstrated that people can hold only so many "chunks" in working memory
  - Chess experts have bigger chunks
  - Prior knowledge affects chunk size.

Our conjecture about familiarity & encoding

- The more familiar the item, the easier it is to bind it to a context
  - If something is unfamiliar, the features of the input must be bound together multiple times before it becomes a "chunk"

Support for idea that only "chunks" can be associated (Musen, Szerlip & Szerlip, 1999)

- First, Ss studied colors paired with: words, random shapes or non-words
- Later, color naming task
  - Pre-cued with associate or not
  - Priming (RT facilitation) to name color
  - *But ONLY IF* the stimulus was word
    - No priming when paired with non-word or random shape
    - Musen et al. concluded only words could be linked

Will midazolam differentially affect stimulus classes ?

- MZ should *only* affect stimuli that can *otherwise be recollected*
  - Should *not* affect stimuli that are recognized on the basis of *familiarity*.
- We varied the type of stimuli to be learned
  - Words (high and low frequency)
  - Photographs (unfamiliar faces & outdoor scenes)
  - Abstract pictures

Examples of the Pictorial Stimuli

Design using midazolam

- Within Subject Design
  - Midazolam one session; saline the other
    - Double blind and randomly assigned
- Both sessions involved studying all three stimulus types in a random order
  - Different stimuli each session
- Old/New recognition for all items same day
  - Different random order for each subject and different for test;
  - equal number of foils of each stimulus type

Recognition *d'* as a *fn* of stimulus type and drug condition

Conclusion from Exp. 2

- Unfamiliar stimuli that are not "unitized" or can only be labeled generically are recognized on the basis of familiarity, not recollection.
- Midazolam causes amnesia by inhibiting the binding to stimuli to context

Example 3: Using midazolam to test claim about consolidation's role In memory

- Using midazolam to investigate the role of consolidation on forgetting
- Recent *Annual Review* on Forgetting (Wixted, 2004)
  - Strong claim that consolidation is the major memory mechanism
- Wixted's claim: Mental exertion is primary source of forgetting because it disrupts consolidation

Reder, Oates, Dickison, Anderson, Gyulai, Quinlan, Ferris, Dulik & Jefferson *Psychological Bulletin & Review*, 2007

Claim of Retrograde *Facilitation* with amnesia drug

- Recall of words studied *post*-drug was worse than control
  - BUT recall of a list studied *pre*-drug was better!
- "…the interference that matters most is not necessarily task related--it is the interference that accompanies ordinary mental activity and the memory formation associated with that activity (p. 257)"

"To summarize,

sleep, alcohol, and *benzodiazepines* all result in retrograde enhancement of memory, and, theoretically, they all do so for the same reason:

The reduced rate of memory formation *protects recently formed memories from interference*, interference that would otherwise arise because of the demands placed on a *limited-resource* hippocampal system (p.257)."

Wixted strongly implies that *cue-overload* is over-rated as a source of forgetting.

Was it really Retrograde *Facilitation or less* Retrograde Interference?

- List studied post-drug showed worse recall than saline control
- List studied pre-drug showed better recall than control
- They did not compare general vs. specific interference
- Maybe effect was due to specific interference, not enhanced consolidation.

Goal of this study

- Stronger test that midazolam has its effect on binding (using computational model)
- Compare the relative contribution of general vs. specific interference (mental exertion vs. cue overload) to forgetting
  - Will the performance benefit in the midazolam condition, compared to the saline condition be different for *general interference* compared to *specific interference*?

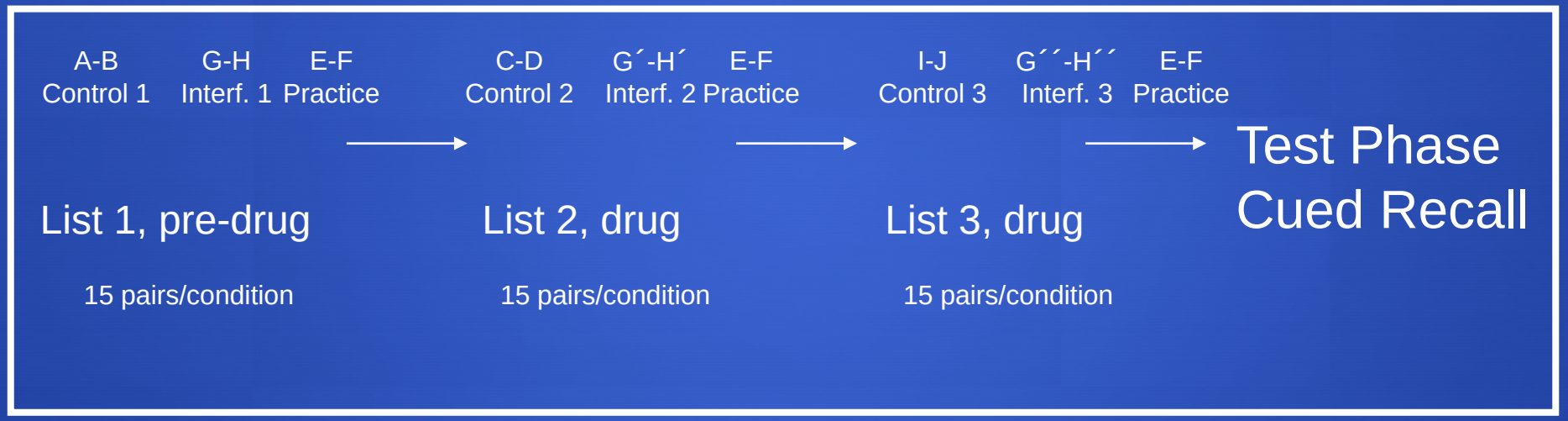
Basic Design

- Learn a list of paired-associates prior to injection (saline or midazolam)
  - Study each pair for 3 seconds, followed by
  - 2 study-test trials/pair with 2.5 sec additional study
- After injection, receive 2 more paired associate lists to learn.
  - Then a snack before final test
- Final cued recall test on all pairs in random order
  - cued by first word and list the pair came from
- Double-blind, within subject, two sessions

Design cont.

- 3 types of pairs in each list
- Practice pairs
  - Studied on all 3 lists
- Interference pairs
  - Cue and response terms swapped with other pairs from one list to next
- Control pairs
  - Only studied on one of the 3 lists

Design Summary

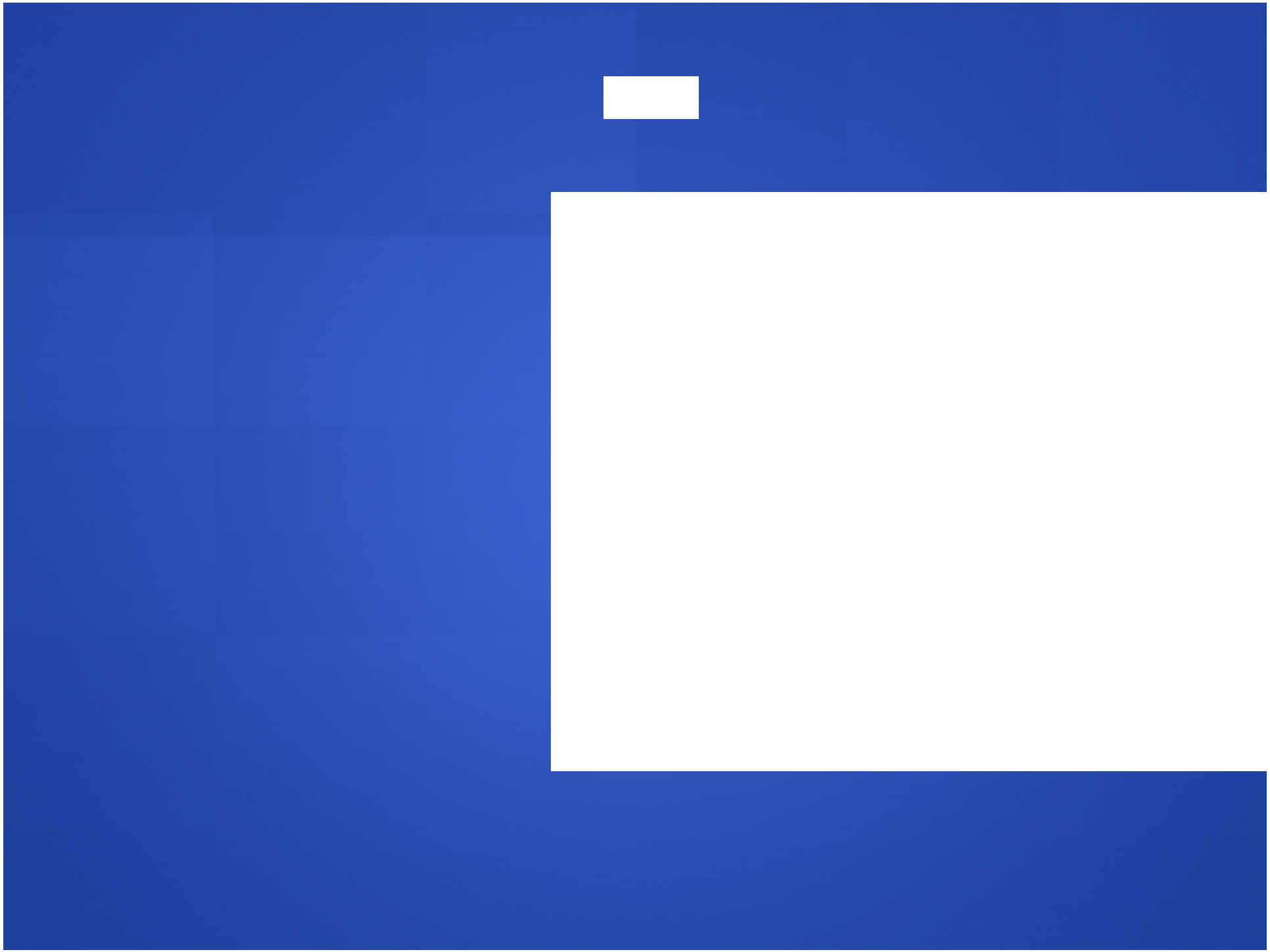


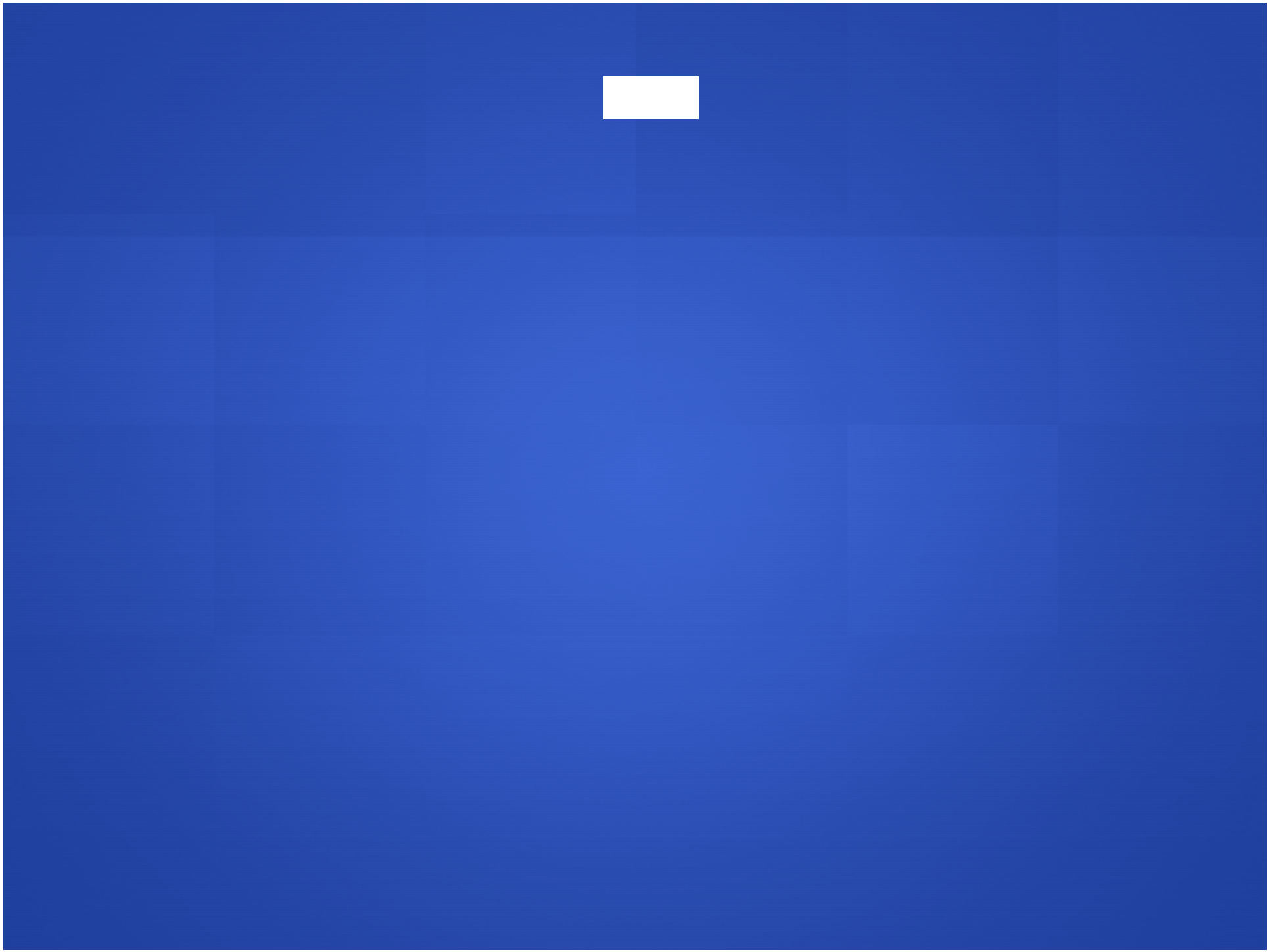
3 Study Lists, cued recall cycles 2X.

Final Test Phase

List 3

court _____



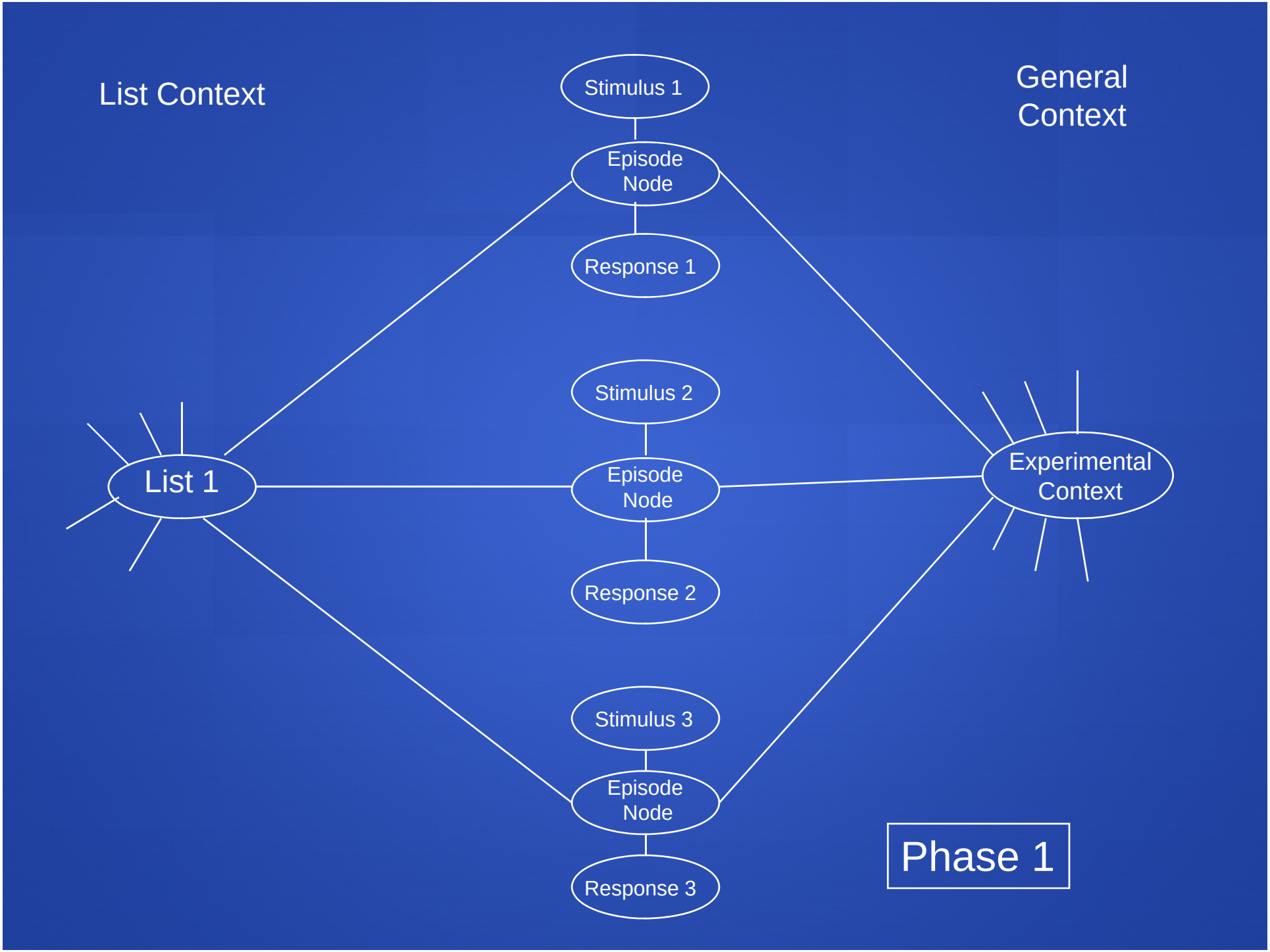


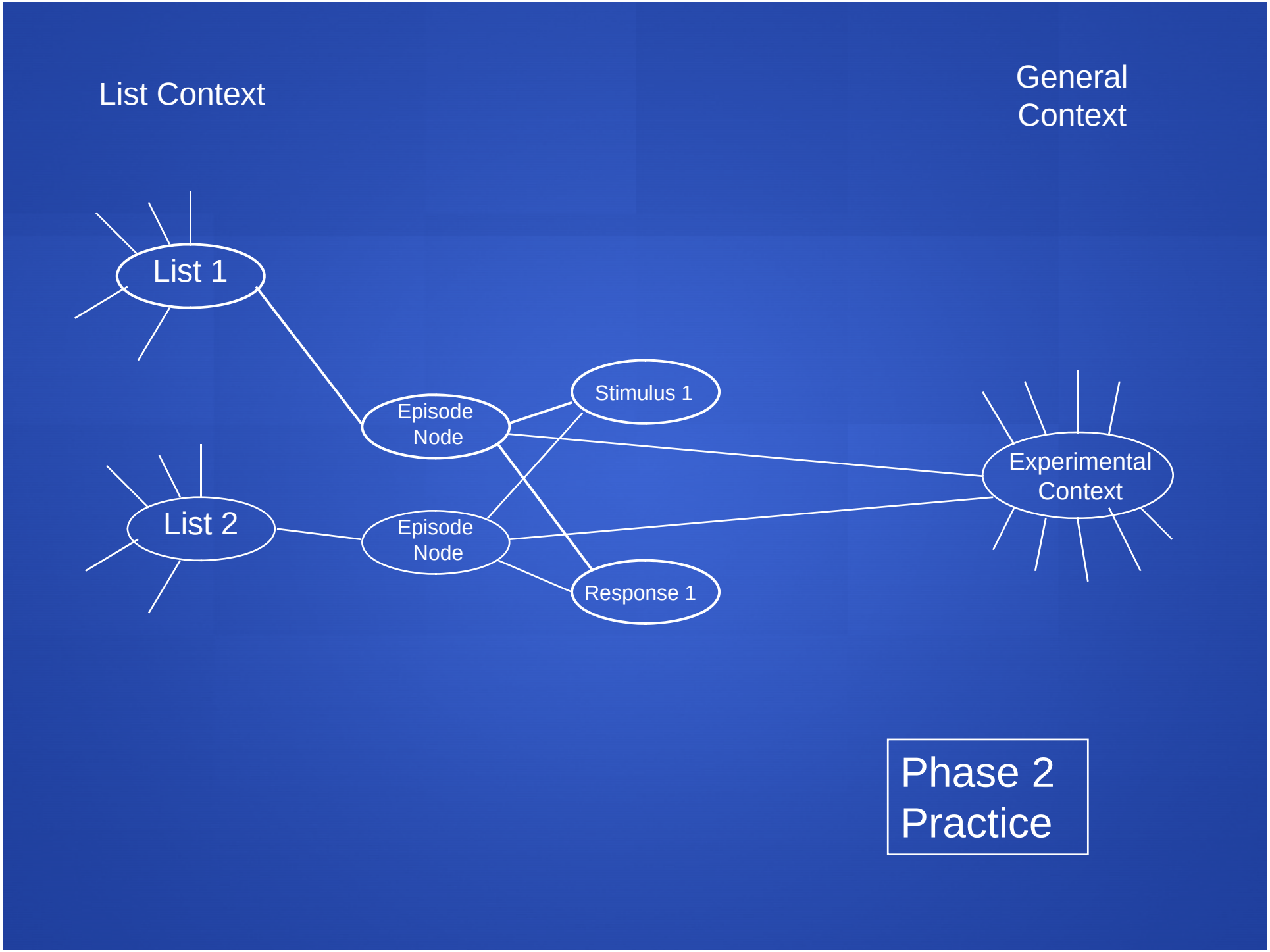
Was Mz benefit due to enhanced consolidation?

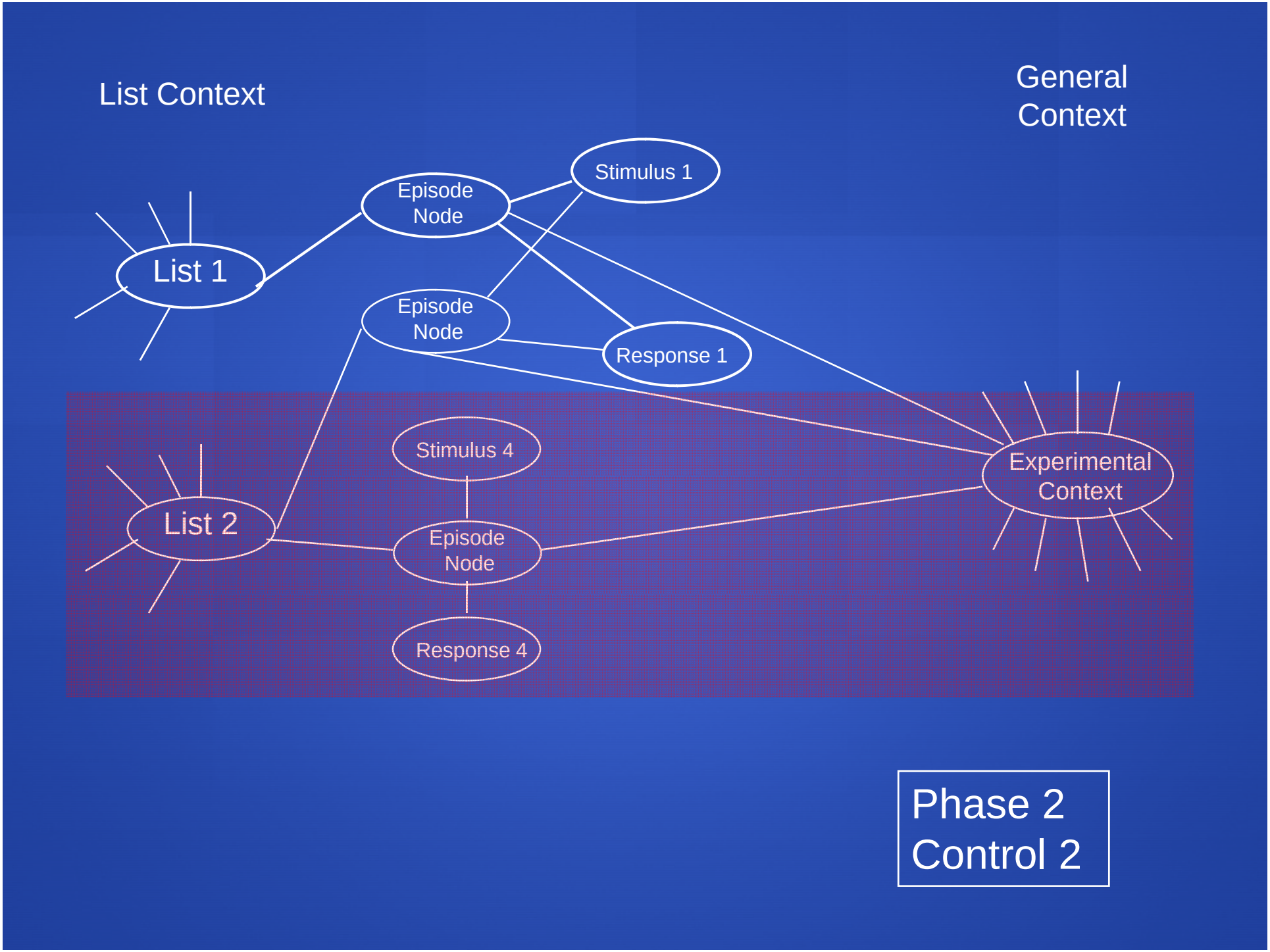
- *General interference (adversely)* affects retention
- *Cue overload* also *(adversely)* affects retention
- Is *Retrograde Facilitation* from less mental exertion?
  - freeing up of the hippocampus to consolidate earlier learning?

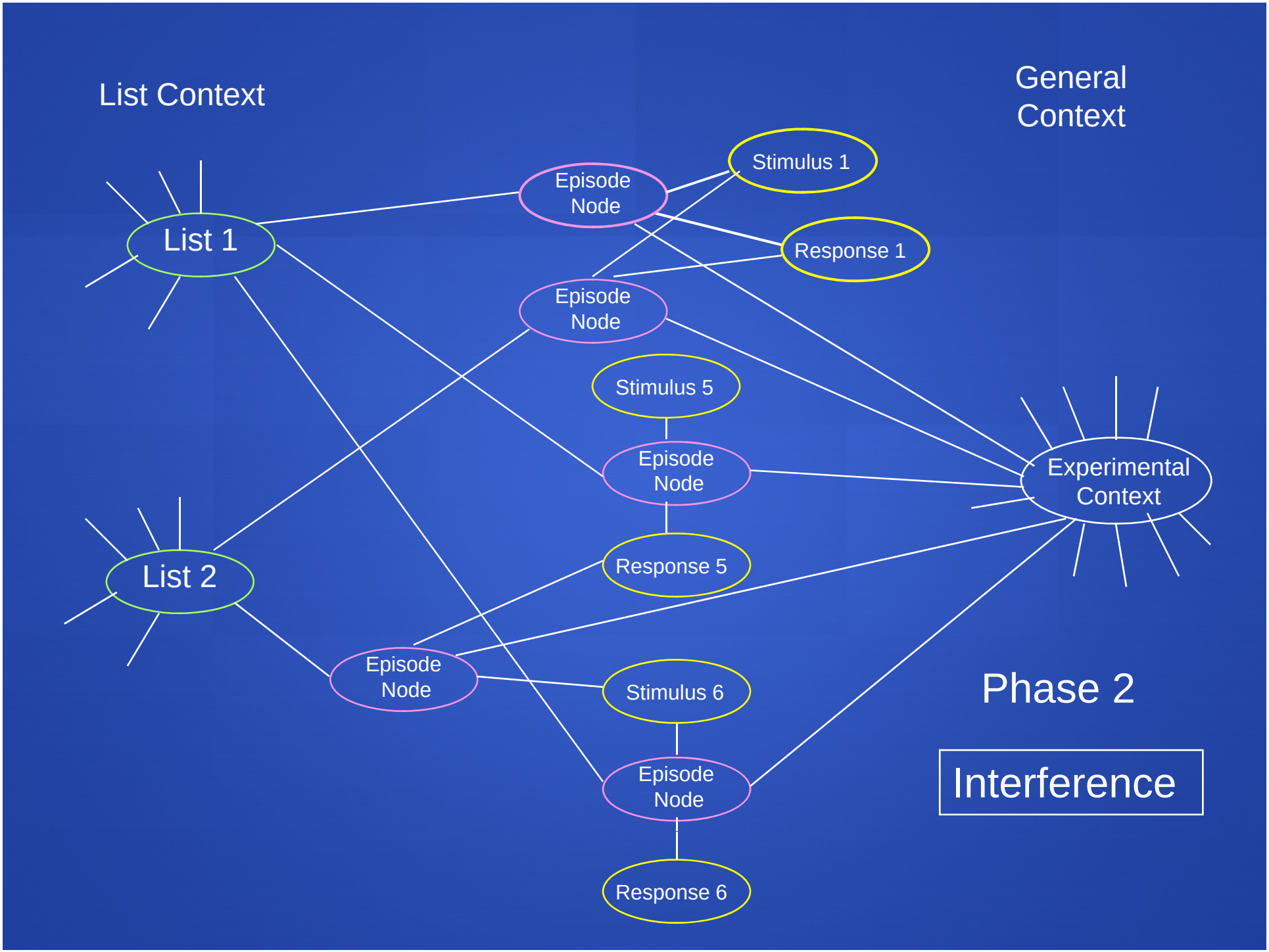
Consolidation-free explanation

- Our account also assumes the role of the hippocampus in forming new memories
- But, unlike Wixted, it assumes that "general interference" is contextual interference, not mental exertion.
  - no need to posit an effect on the consolidation process.


List Context
General Context
Stimulus 1
Episode Node
Response 1
Stimulus 2
Episode Node
Response 2
Stimulus 3
Episode Node
Response 3
List 1
Experimental Context
Phase 1


List Context
General Context
List 1
List 2
Episode Node
Episode Node
Stimulus 1
Response 1
Experimental Context
Phase 2 Practice


List Context
General Context
Stimulus 1
Episode Node
List 1
Episode Node
Response 1
Stimulus 4
List 2
Episode Node
Response 4
Experimental Context
Phase 2
Control 2


List Context
General Context
List 1
Episode Node
Stimulus 1
Response 1
Episode Node
Stimulus 5
Episode Node
Experimental Context
List 2
Response 5
Episode Node
Stimulus 6
Episode Node
Response 6
Phase 2
Interference

Midaz Assumptions

- Midazolam lowers probability of forming a link.
- Effects of midazolam decay as a function of time since injection to the 3rd power (arbitrary, fits well).

$R^2 = .963$ RMSE = 0.048

In Summary

- Wixted is right that general interference is a big source of forgetting and that is an important insight
- It is not the only source of interference--specific interference *aka* cue-overload contributes more.
- The same mechanism can explain both without positing a role for consolidation.

Conclusion

- Midazolam is a useful tool to simulate anterograde amnesia
- Using midazaolam is helpful in answering questions about the nature of human memory processes

New approach: Combine midazolam and fMRI

- fMRI studies reveal many regions that respond when performing a task
  - which are critical vs. spuriously correlated?
- Midazolam can provide converging evidence as to whether the region is essential to function
  - Scan same brain performing same task with and without experiencing anterograde amnesia

Triangulation to determine regional brain function

Possible effects of MZ on behavior and brain region that normally responds to a manipulation

	Function affected	Function not affected
Region affected	(1) Critical	(2) Not critical
Region not affected	(3) May not be critical	(4) Provides little new information

If brain region & function are both affected by drug….

- Hypothesis: HC responsible for recollection.
  - Under saline activation seen in HC correlates with recollection
    - More activation seen in HC when item subsequently remembered.
  - Under midazolam, reduced activity in HC and very little recollection
- Converging Evidence that region is critical to the function of recollection.

If drug affects brain region but not behavior….

- Assuming that we show that the HC is affected by midazolam
- The behavior (e.g., priming) is unaffected by the drug
- Evidence that the HC is not responsible for priming effects

If drug affects behavior but not brain region…

- MZ does not affect Striate
  - LOP manipulations show differential BOLD function in Striate regardless of drug condition.
  - Normally BOLD in Striate correlates with differential recall
- MZ does affect LOP manipulation (no longer an effect of LOP)
- Suggests that the region is only spuriously correlated with the task and is unrelated to the function (recollection/recall)

What if neither the brain region nor the function are affected by the drug?

- Region (e.g., striate) is affected by a manipulation and is correlated with observed priming effects
- Region is NOT affected by MZ
- Behavior (priming) is unaffected by MZ
- Consistent with view that region is critical to function (e.g., priming)
  - BUT drug study does not contribute much to this conclusion.

Conclusion

- Midazolam provides an additional tool to elucidate human memory function
- Combining MZ with fMRI may allow us to get a better handle on brain function.

Thank you for your attention!

- Thanks also to Daniel Dickison, Jennifer Ferris, Joyce Oates, Heekyeong Park, Ed Thornton, Joseph Quinlan
- National (US) Institute of Mental Health

Midazolam
Effects on Memory

Midazolam – an anxiolytic drug that creates temporary anterograde amnesia

- Participants are unable to remember facts and events that occurred while under the influence of the drug
- Commonly used during surgical procedures

Midazolam

Benefits in Memory Research

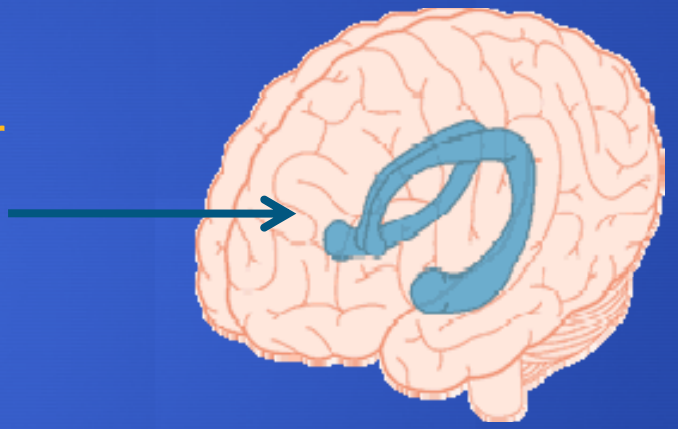
The drug midazolam can be used as a tool to study memory in an impaired state

- Creates a highly specific cognitive deficit, allowing for a controlled study of its effect on memory
- Eliminates the need to use patients with clinical amnesia
- Allows participants to act as their own controls – within-subjects design with midazolam and saline conditions

Midazolam

Sites of Action

Midazolam creates anterograde amnesia by blocking long-term neural potentiation – responsible for the memory mechanisms of brain regions like the hippocampus

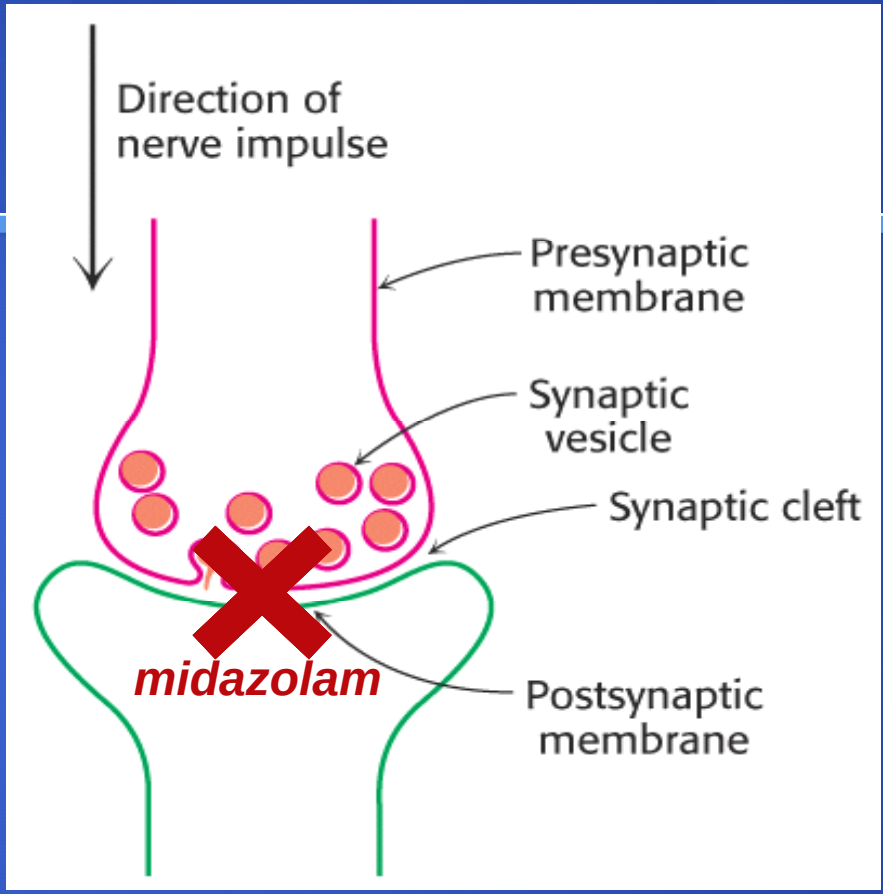


- Facilitates GABA, a negative neurotransmitter
  - Specifically targets $GABA_A$ receptors – prominent hippocampal receptors

Midazolam

Sites of Action

Inhibits firing of neurons and formation of synapatic connections in the hippocampus, which has a primary role in memory binding and consolidation



- Rat hippocampal brain slices injected with midazolam showed decreased neural potentiation and firing rates when stimulated with electrodes (Evans & Viola-McCabe, 1996)

Why use midazolam to study memory?

- Patients with brain damage help us understand normal functioning
- We do not have to rely on patients to study amnesia
  - Easy access to participants, suitable controls, ability to perform complex experiments
- Multiple causes of organic amnesia
  - Korsakoff, cerebral hypoxia, cerebral trauma
  - Performance does not differentiate according to causes
    - Giovanello et al, 2006; Verfaellie et al., 2001, 2002
- Damage to different parts of brain that result in amnesia affect same functional loop or system (Caulo et al., 2005)

Repeated vs. New Displays

- Half of displays per block (12 of 24) repeated for each block of 24 trials
  - Repeated displays had target (T) in the same location within an invariant configuration of Ls across blocks
- Other half of displays (12/24) were never repeated
  - New, previously unseen configuration of Ls for each target T location.

The challenge:

- "I do not mean to imply that other elements of the laundry list of factors that might contribute to forgetting are irrelevant… *even though that has not yet been convincingly established* (p. 265)"

- Strongly implies that "cue-overload" is over-rated as a source of 'forgetting.'

"Conventional Wisdom" concerning amnesia

- Selective impairment of explicit memory
- Skill memory & unconscious learning and memory are unaffected
  - different memory systems are subserved by different brain regions
- Squire & Schacter argue that accessibility to consciousness is the criterion for different memory systems.

Midazolam affects *binding* but not strengthening of existing structures

- Familiarity judgments do not depend on binding
  - Familiarity judgments based on activation level of existing chunks
    - Not retrieving newly formed episode node
- If normal subjects do not use recollection in recognition task, performance is the same under *amnesia*

When recognition must be based on familiarity

- If stimuli are not "unitized" then normal subjects may not bind to context
- Then recognition must be based on familiarity only
- When a label is generic retrieval of the episode is difficult
- Midazolam inhibits binding; it does not affect (hurt) activation of existing traces
- Maybe stimuli that

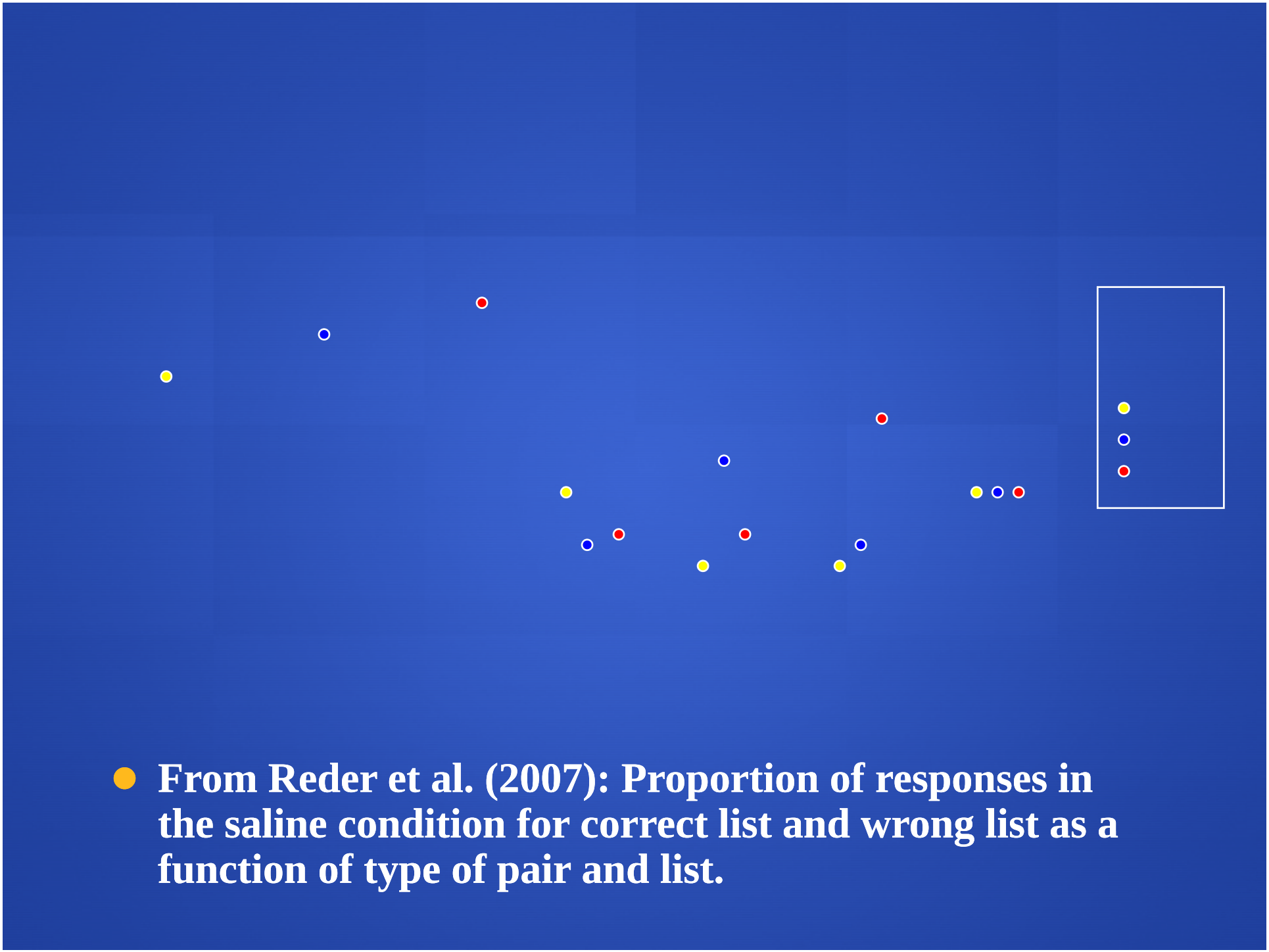
Contextual cuing effect (new – repeated)

Advantage of repeated displays increases with more repetitions but only for saline

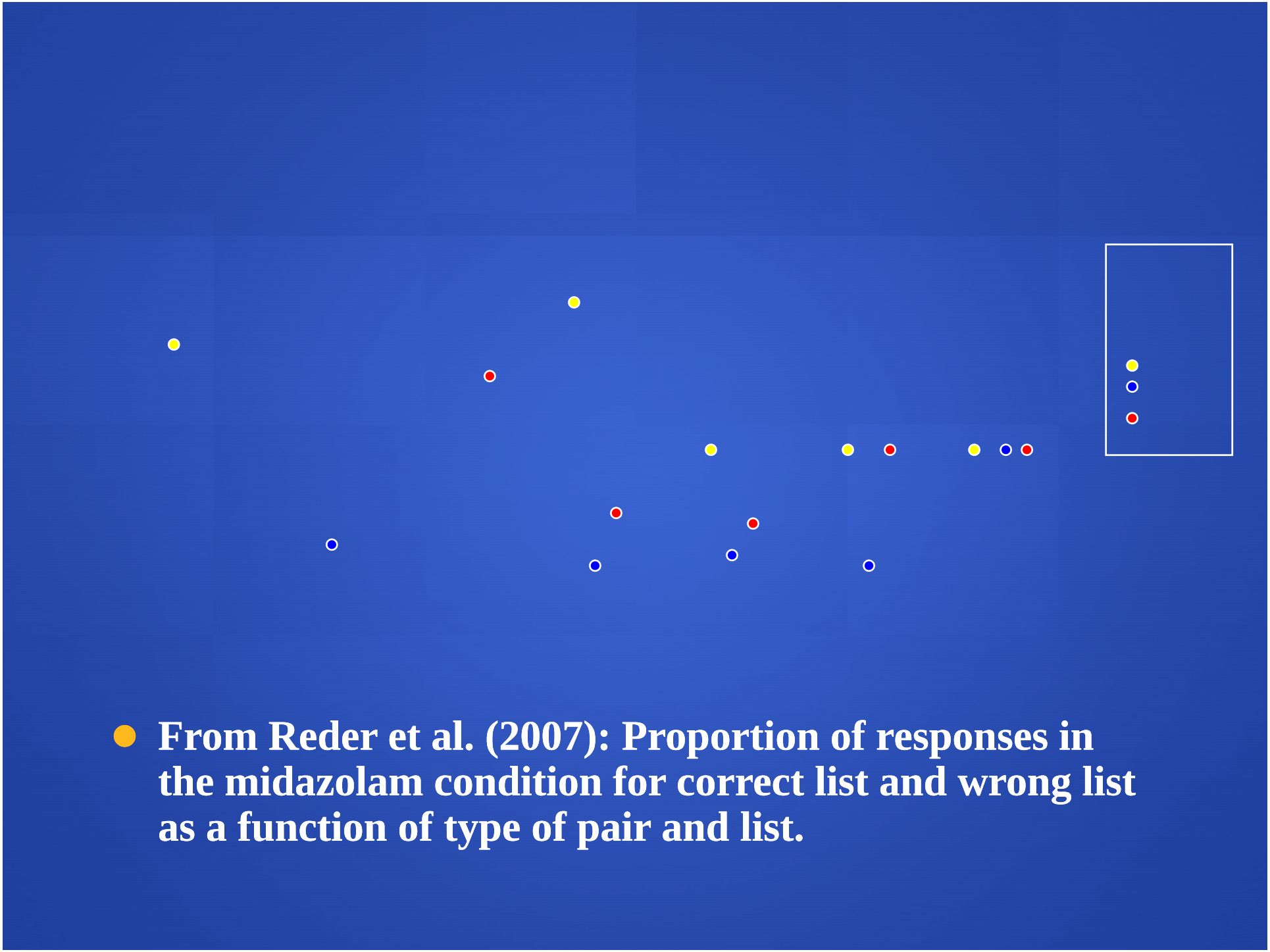
Hits and False alarms as a function of stimulus & drug condition

Converging Evidence

- Hupert & Piercy (1976; 1978) found amnesiacs were good at recognizing pictures
  - So long as list discrimination was not part of the task.
- Koutstaal et al. (2003) found old subjects recognized abstract items as well as young subjects
  - Older adults have no previous familiarity with abstract stimuli so lower false alarm rate than other stimuli
  - Young adults can not bind abstract items either



- From Reder et al. (2007): Proportion of responses in the saline condition for correct list and wrong list as a function of type of pair and list.



- From Reder et al. (2007): Proportion of responses in the midazolam condition for correct list and wrong list as a function of type of pair and list.

Role of Hippocampus

- All these results can be explained by the concept of interference, without postulating a role for enhanced consolidation
- Hippocampus is probably inhibited from forming new bindings with midazolam, but that does not imply that previously formed bindings are better consolidated

RMSE = 390.9 ms