Bluegrass Short-term Memory V1.8

By: Soheil Borhani

User Manual

THE UNIVERSITY OF TENNESSEE KNOXVILLE

University of Kentucky

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What is BluegrassSTM?

BluegrassSTM is a free (as in "free speech" and also as in "free beer") platform that can collect behavioral (key presses) and neural (EEG) responses to evaluate and enhance working memory.

The current setup collect data in four different modes, including:

1. Resting-state eyes opened (90 seconds)
2. Resting-state eyes closed (90 seconds)
3. Train

Resting state (Eyes opened, and eyes closed)

Resting-state EEG recording and analysis has been widely applied by clinicians due to its relatively low cost and convenience. EEG reflects the electrical activity of the underlying neurons, and it contains information regarding neuronal population oscillations, the information flow pathway, and neural activity networks. Some features derived from EEG signal processing methods have been proposed to describe the electrical features of the brain during user's consciousness.

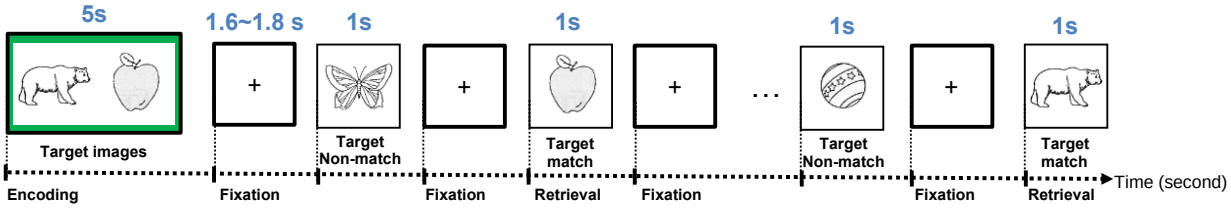


Figure.1. Sample "train" phase.

Bluegrass short-term memory task

We adopted a delayed-match-to-sample (DMS) task to assess simultaneous visual matching ability and short-term visual recognition memory. This short-term memory task, which is a variant of the Sternberg memory-scanning task has been well-studied and shows the potential to modulate various cognitive processes including encoding, decision making, visuomotor selection, rehearsal, and retrieval. In our version of the task, the participants are to memorize two sample target images in five seconds. Then, they are exposed to a sequence of 20 serially presented images of any of the target images or non-target images. The users need to indicate whether each image matches with any of the sample target images or not (Figure1). Stimuli included two-dimensional black and white images of familiar objects borrowed from Snodgrass and Vanderwart, 1980 paradigm. Each picture is presented with a black background.

Setup

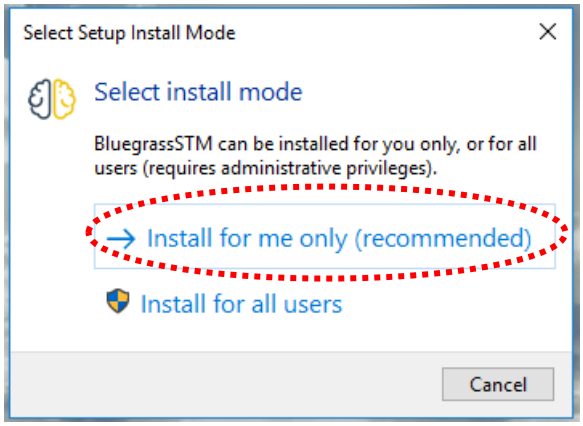
The setup is a working memory analysis experimental paradigm, designed based off of a customized delayed-matched-to sample experiment for familiar objects. The current version of the software has no dependency and the software package is self-contained. It is designed based on Python 3 and includes uses a few Python libraries including pylsl, numpy, psychopy, subprocess, scipy, scikit-learn, winpexpect, etc.

Recording File Format

The recording program (LabRecorder) and Python/C++ library (RecorderLib) record into the XDF file format (Extensible Data Format, hosted at https://github.com/sccn/xdf). XDF was designed concurrently with the lab streaming layer and supports the full feature set of LSL (including multi-stream container files, per-stream arbitrarily large XML headers, all sample formats as well as time-synchronization information).

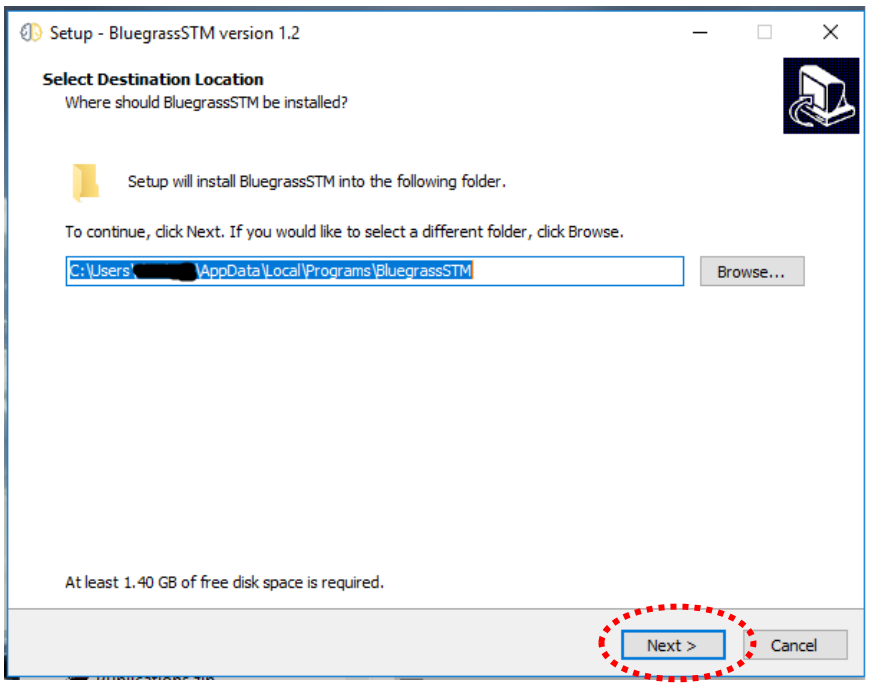
Installation of BluegrassSTM software

1. Double-click on “BluegrassSTM_Setup_Installer.exe”. It is preferred to install following the “the recommended settings.

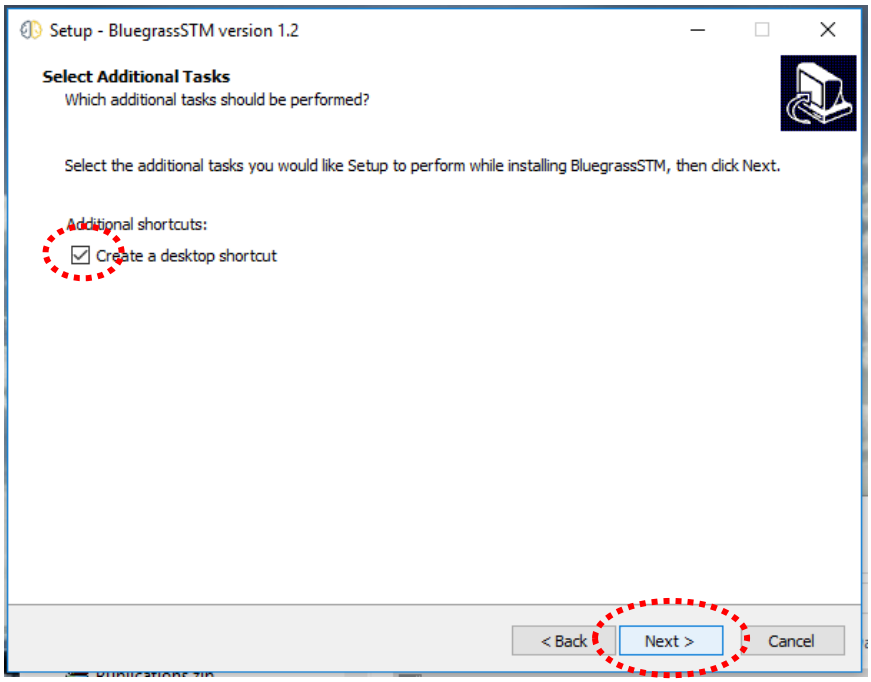


2. The program will be installed in:

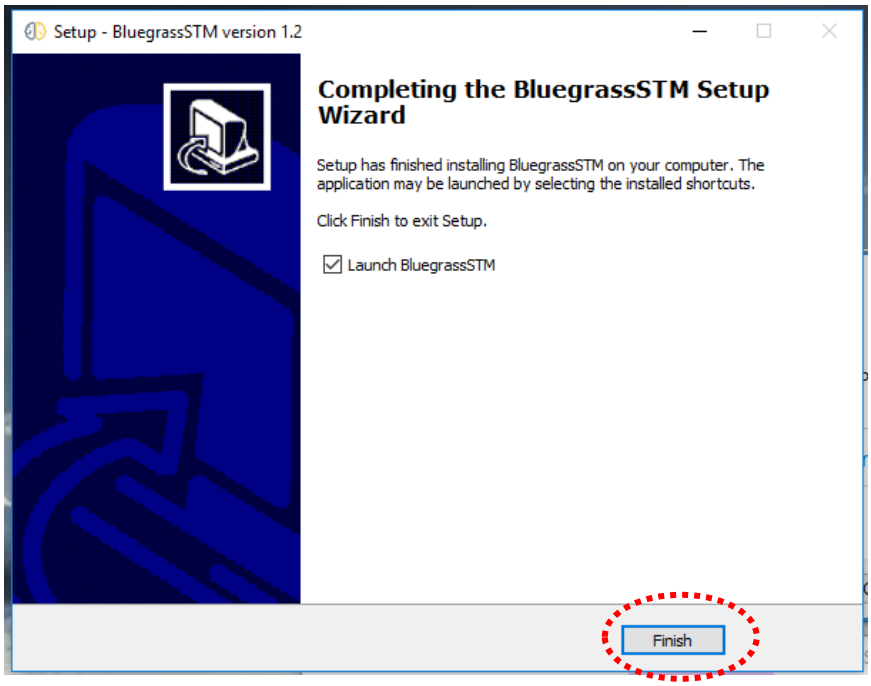
[“WINDOWS_USER_LOGIN_FOLDER”]\AppData\Local\Programs\BluegrassSTM



3. Create the program's shortcut on desktop for your convenience.



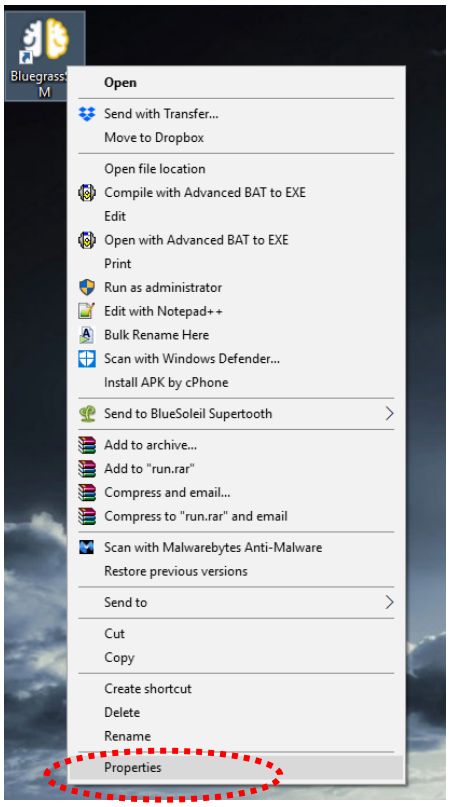
4. Finish installation.



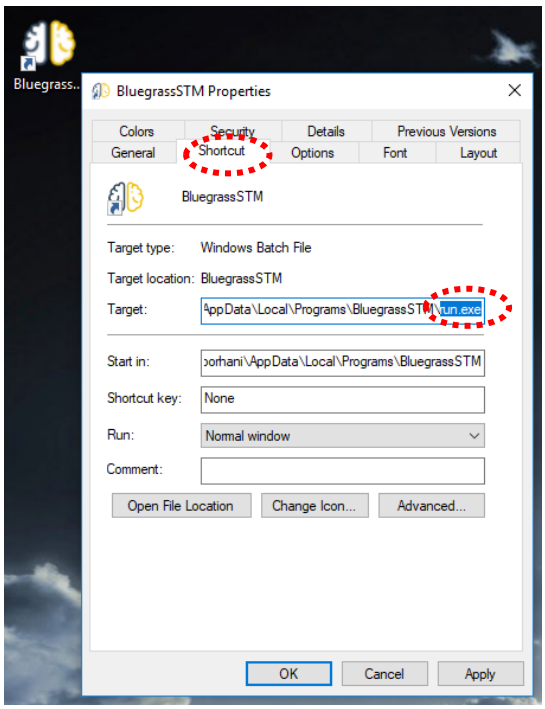
5. Once the installation completes, you will get an error message like:
"This program was made with an Unlicensed compiler. Please buy the PRO version to distribute your EXE."

   To fix this:

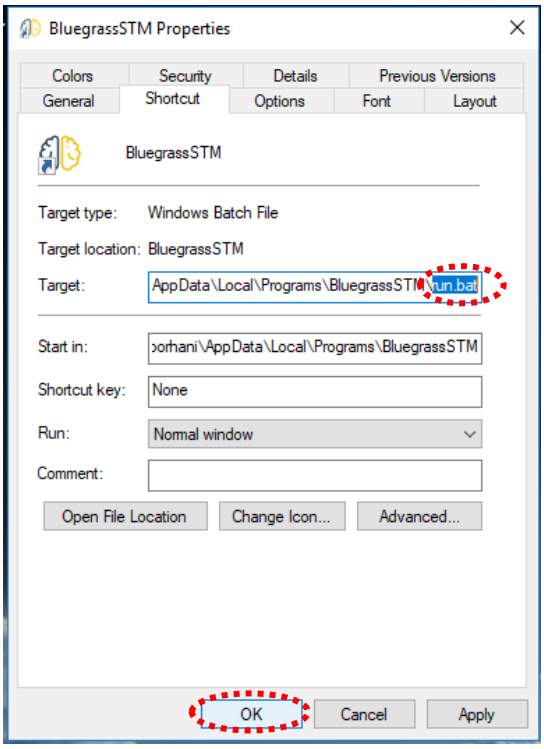
a) Right click the shortcut and click on *Properties.*



b) Click the Shortcut tab

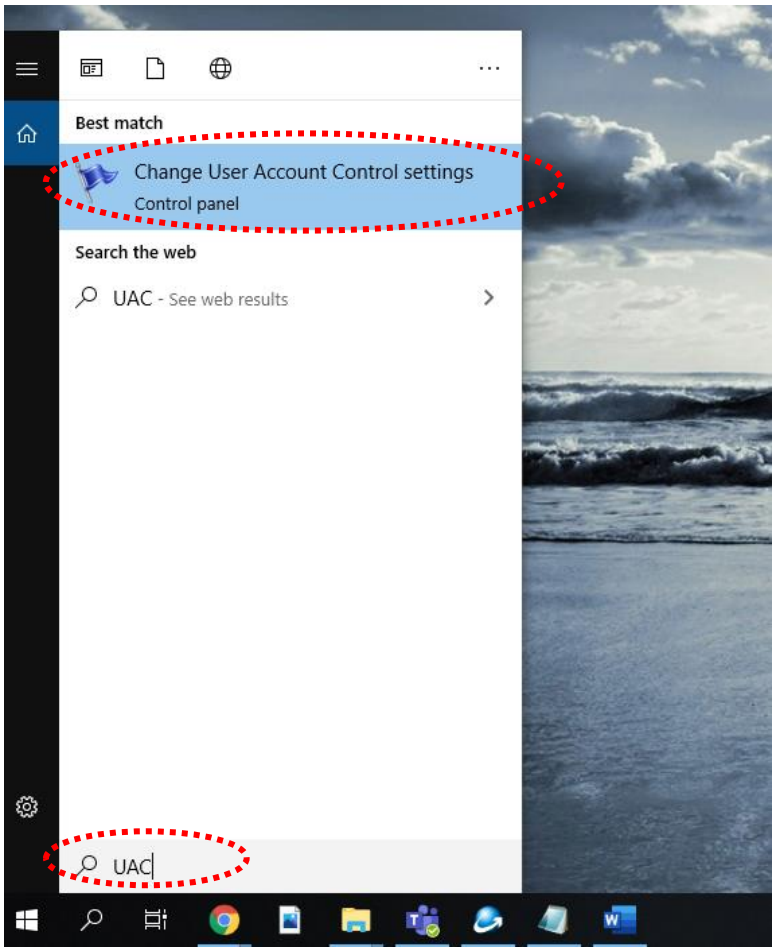


c) Rename run.exe to run.bat and then click OK button.

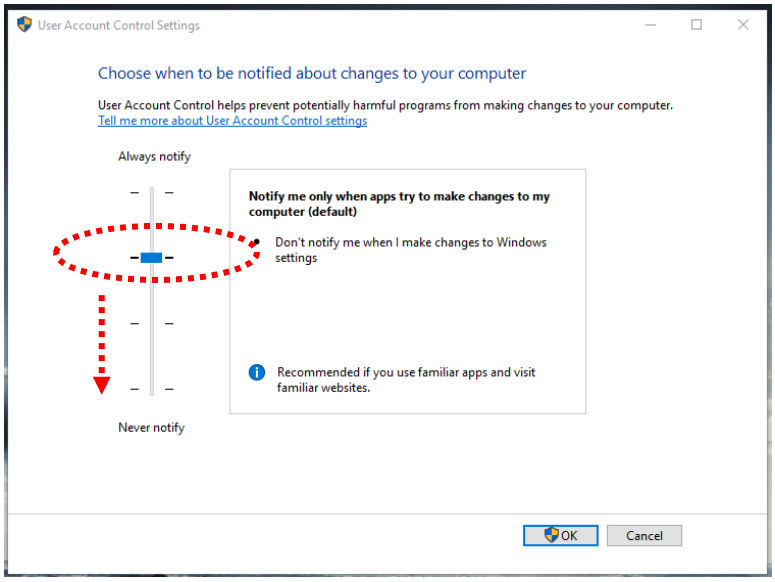


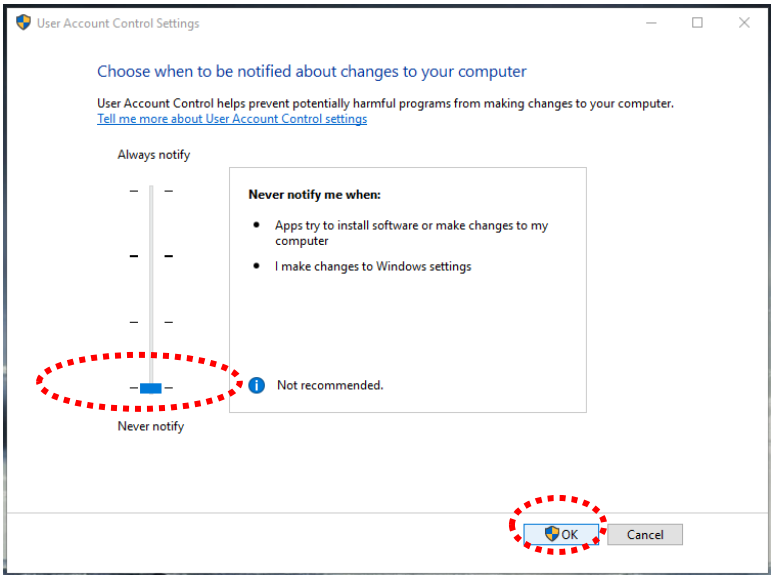
6. Turn of User Account Control (UAC). UAC is a Microsoft security tool that helps prevent intrusion of malicious software. It is not full-fledged anti-malware or an antivirus, but it does notify of changes that are about to be made to the computer. In order to conveniently collect data using LabRecorder, it is recommended to turn-off UAC. These are the steps:

   a) Click the Start menu. In the search field type UAC. Then, Click "Change User Account Control settings."



b) In the window that comes up, move the slider down to "Never Notify."





c) Click OK and then restart the computer.

Installation of Emotiv EPOC(+) LSL Streamer

EmotivLSLStreamer is a standalone software package that streams raw EEG signals into the labstreaminglayer (LSL). We have designed and developed a Java platform to access raw EEG data of Emotiv EPOC(+) in LSL. The software is no longer embedded in the BluegrassSTM package.

You can download it from:

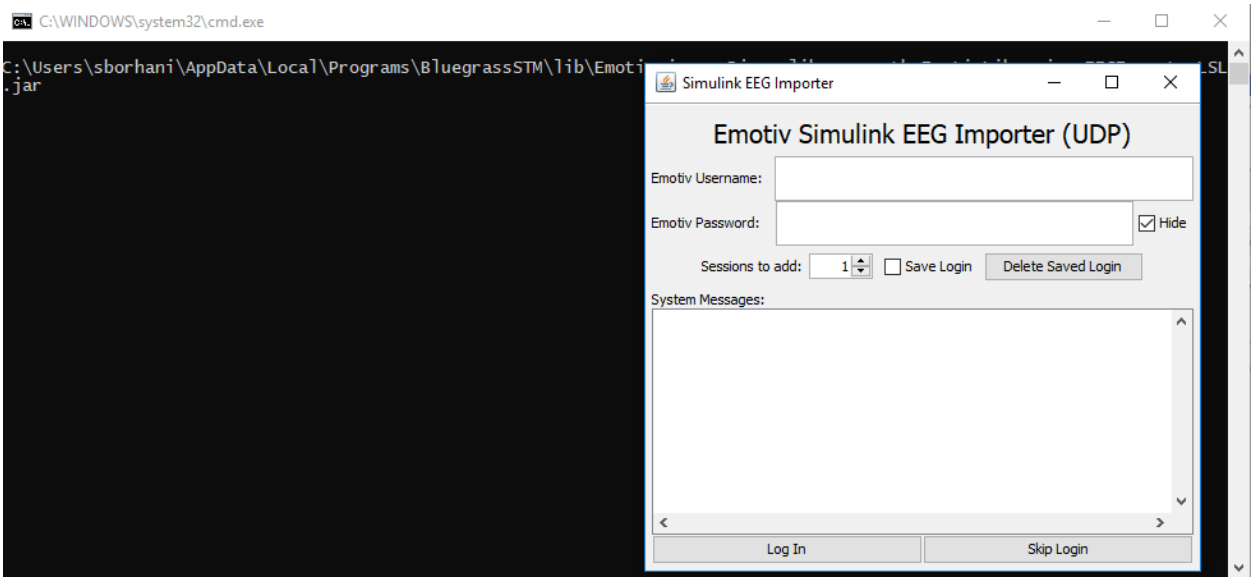
https://github.com/soheilbr82/Emotiv-Headset-LSL/releases/tag/v1.0

The following instruction shows how to conveniently use the application to stream Emotiv EPOC(+) into LSL.

1. Once you download the *EmotivLSLStreamer* installer, installation is pretty much straightforward. It is suggested to make a shortcut of this file on your desktop.

2. You can run the application by double-clicking on the *EmotivLSLStreamer* shortcut on the Desktop.

3. Once you double-click on "**EmotivLSLStreamer.exe**" or its shortcut, you will see the application's GUI.



4. Make sure Emotiv EPOC headset has been turned on and connected to it Bluetooth dongle.

5. In order to use Emotiv EPOC+ and having access to the real-time raw EEG signals with this headset, the company have required users to subscribe into Emotiv company and choose among different business plans to pay a fee. Once you do that, you are given a username and password which is necessary to use this application as well. Emotiv EPOC LSL Streamer uses Emotiv SDK to access real-time EEG and requires your

Emotiv username and password to handshake with Emotiv website and validate your account.

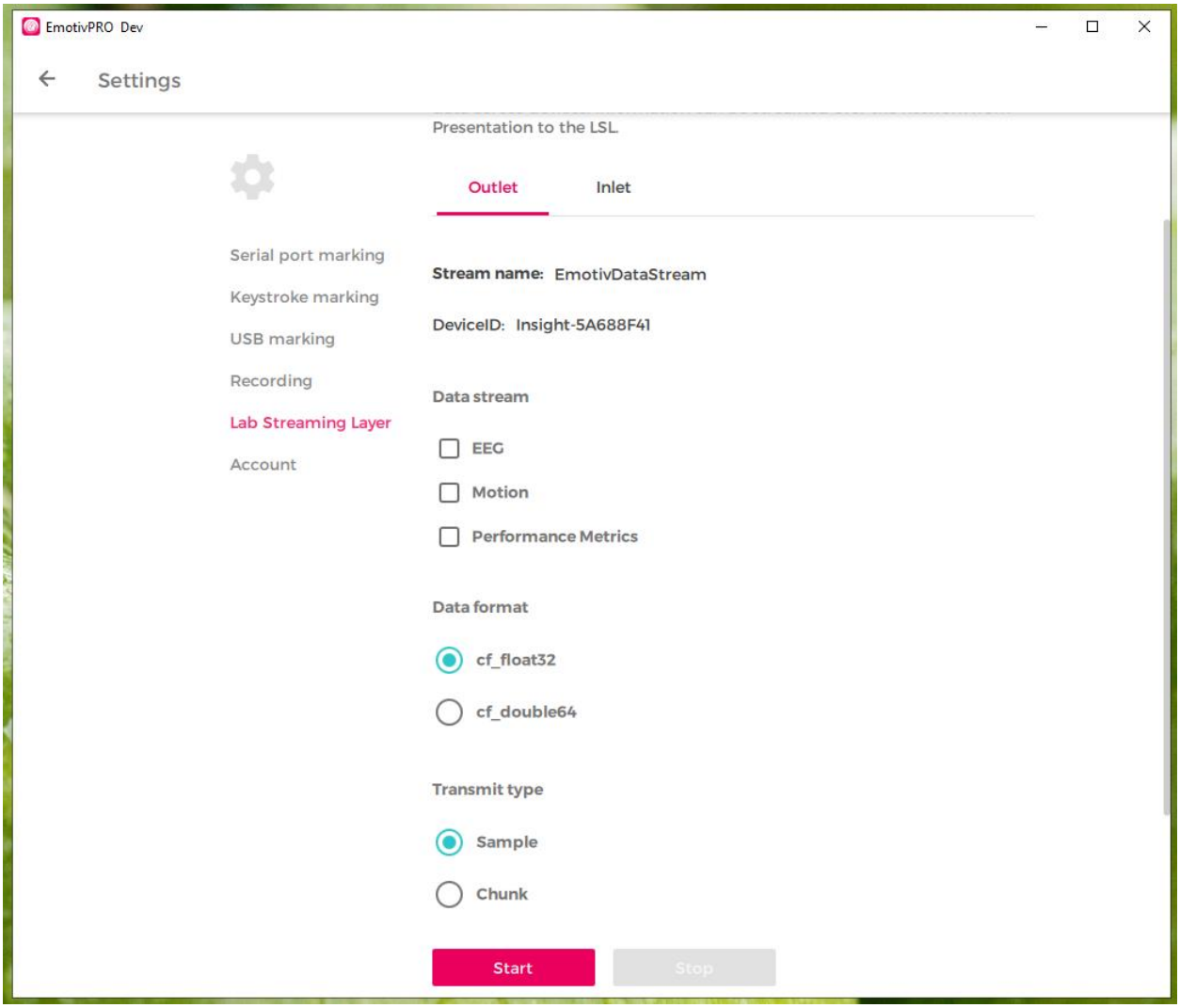
Enter you username and password, add a random positive integer like “100” in “**Sessions to add**” text box in GUI, and click only once on “**Log In**” button. You should be able to see a message in the “**System Messages**” text box showing that you are good to go. Then, click again on “**Log In**” button, then press “**Start**” button to stream data. You can check EEG signal quality using the GUI as well.

You can also contribute to the package using the link below:

https://github.com/soheilbr82/Emotiv-Headset-LSL/releases

Using Emotiv Lab Streaming Layer Interface for Emotiv PRO

Recently, Emotiv PRO has implemented lab streaming layer (LSL) into Emotiv PRO product. After connecting your EMOTIV Brainwear headset, go to LSL settings menu in EmotivPRO. There are separate tabs for LSL Outlet and Inlet functionality. You configure for data streams (EEG, Motions, Performance Metrics) as LSL Outlet.



- **Stream name:** Show the name of LSL stream. The actual stream name on the other side (Inlet) will be EmotivDataStream-EEG, EmotivDataStream-Motion or EmotivDataStream-Performance-Metrics, depending on the type of data stream.

- **Data stream:** There are 3 types of data streams: EEG, Motion, Performance Metrics. Each one will create an individual LSL stream.

- **Data format:** Currently, 2 types are supported: cf_float32 or cf_double64.

- **Transmit type:** We support both Sample and Chunk. A chunk contains certain number of samples, depending on the Chunk size.

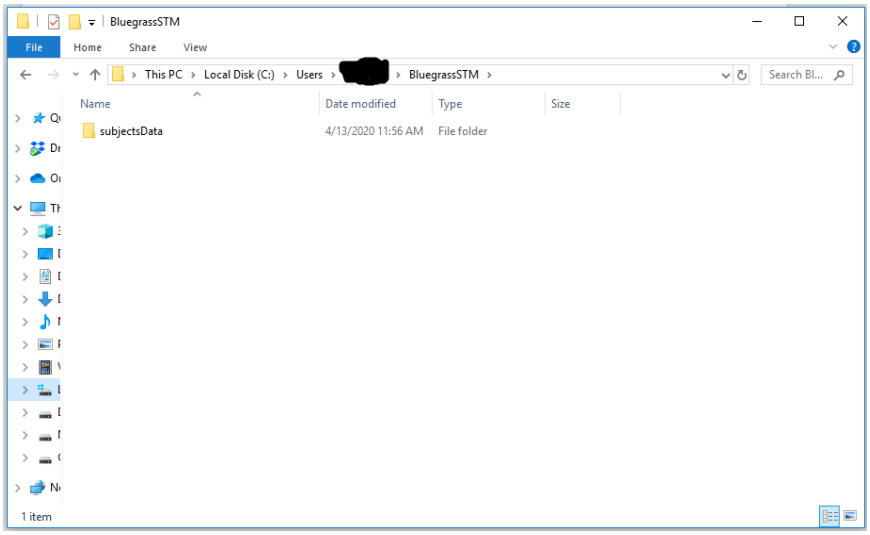
You can get more info from:

https://github.com/Emotiv/labstreaminglayer

Access to recorded data

1. The recorded data will be stored for offline analysis in:

[“WINDOWS_USER_LOGIN_FOLDER”]\BluegrassSTM\subjectsData



Data Markers

'b' : The onset of each block of stimuli

'a' or 'l' : The onset of each trial 'a' for targets and 'l' for non-targets

'f': The onset of fixation

'1': Correct responses

'2': Incorrect responses

'n': The onset of Inter-trial

'e': The end of the experiment

Resting state EEG Markers:

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'f': The onset of fixation

'o': The onset of eyes open

'c': The onset of eyes close

'n': The onset of Inter-trial

'e': The end of the experiment

Release Notes

Version 1.0:

- Basic BluegrassSTM setup

Version 1.1:

- Some bugs are fixed.

Version 1.2:

- Some bugs are fixed.

Version 1.3:

- Allow having response time during training phase even after stimulus presentation for people with low reaction time.
- Modify experimental design files for better readability.

Version 1.4:

- Embed Java portable engine with the setup as the Java engine for EmotivLSLStreamer.
- Embed a piece of code as a batch file to turn-off User Account Control (UAC). It is for the convenience of running LabRecorder as a background process.
- Embed a batch file script to add local python engine to the system path.
- Correct the visual feedback on the keypresses for “train” experiment.

Version 1.5:

- Separate Emotiv LSL Streamer as a standalone software package.
- Add a new feature to the software that gives flexibility of only collecting behavioral data in case the user does not need to collect neural data.
- Add two different versions for train phase, containing different sequence of target and non-target images

Version 1.6:

- Once the program initiated, it will pop up right after each session. Users can choose from another experiment mode or press cancel to stop using the software. So, users are not required to enter demographic information multiple times.
- Two shorter versions of the experiment with 12 instead of 20 consecutive stimuli per trial have been added.

Version 1.7:

- Optimize code to easily enable/disable audiovisual cue

Version 1.8:

- A new feature has been added to send event markers to a serial com port. It gives the user a flexibility of choosing among the available com port via GUI.

More about Bluegrass short-term memory paradigm

The following section is an overview of previous studies with different versions of Bluegrass memory paradigm. This amazing collection has been prepared by Jessey Manison, Jenny Neal and Dr. Yang Jiang all from University of Kentucky, Lexington.

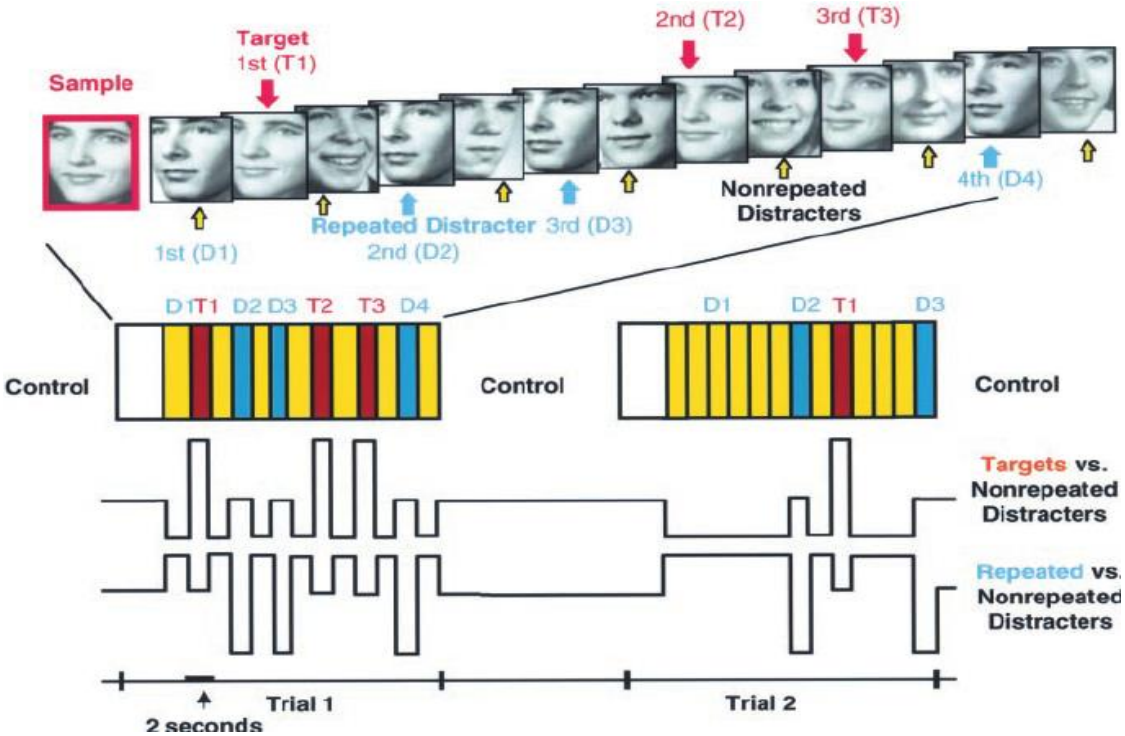
Young, Cognitive Normal, Event-related fMRI (2000)

Complementary Neural Mechanisms for Tracking Items in Human Working Memory

Jiang, Y, Haxby, JV, Martin, A, Ungerleider, LG, & Parasuraman, R (2000). Complementary neural mechanisms for tracking familiar items in human working memory. Science, 287, 643-646. PMID: 10649996.doi: 10.1126/science.287.5453.643.

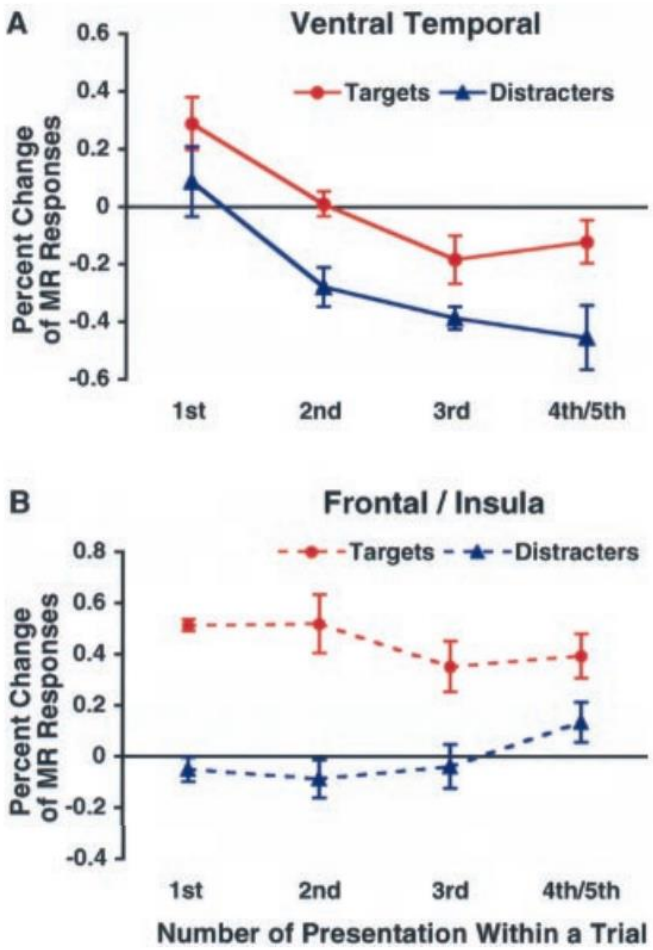
Link: https://doi.org/10.1126/science.287.5453.643

Abstract: Recognition of a specific visual target among equally familiar distracters requires neural mechanisms for tracking items in working memory. Event-related functional magnetic resonance imaging revealed evidence for two such mechanisms: (i) Enhanced neural responses, primarily in the frontal cortex, were associated with the target and were maintained across repetitions of the target. (ii) Reduced responses, primarily in the extrastriate visual cortex, were associated with stimulus repetition, regardless of whether the stimulus was a target or a distracter. These complementary neural mechanisms track the status of familiar items in working memory, allowing for the efficient recognition of a currently relevant object and rejection of irrelevant distracters.



Method: The working memory task and the fMRI time series. For each memory trial, participants were first presented with a sample face to remember; then they viewed faces presented rapidly in succession. Their task was to press a button with their right hand when they saw a face that matched the sample face (target). Targets (red), as well as some distracter faces (blue), were presented in an unpredictable sequence from one to five times on a given trial and were intermixed with distracter faces (yellow). Working memory trials were separated by 18 s, during which participants passively viewed a series of nine nonmeaningful control stimuli. The MR signals were analyzed with multiple regression (represented by square-wave functions) to reveal regional activation patterns associated with repetition of target faces and repeated distracter faces

Key Figure/Results:



Mean percentage of increase, relative to nonrepeated distracters, of within-trial MR responses to repeated targets and distracters in ventral temporal (A) and frontal/insular (B) cortices. (A) In the ventral temporal region, repetition reduction was observed for responses to both targets and distracters within a trial. (B) In contrast, the target enhancement observed in the frontal/insular areas was maintained for repeated presentation. Error bars indicate standard errors after removing the main effect of participant differences in mean response.

- These results suggest that reduced neural responses in posterior cortical areas reflect a neural mechanism that signals the repetition of a stimulus (9), even if the stimulus is a target. Because the enhanced response to targets in these posterior extrastriate areas is

eliminated by the fourth or fifth presentation because of repetition reduction, response enhancement in these areas cannot be a reliable neural signal for identifying targets.

- In contrast to the reduction in response found in ventral temporal areas, the response to targets remained constant with repetition in frontal/ insular areas ($P < 0.05$) (Fig. 3B). Activity associated with repeated distracters in these areas also remained at a constant but low level throughout the trial. Thus, the enhanced neural responses in frontal/insular areas may signal the active maintenance of the target object in working memory.

- The young human results are consistent with electrophysiological results in young behaving monkey reported by Miller & Desimone, *Science*, 1994.

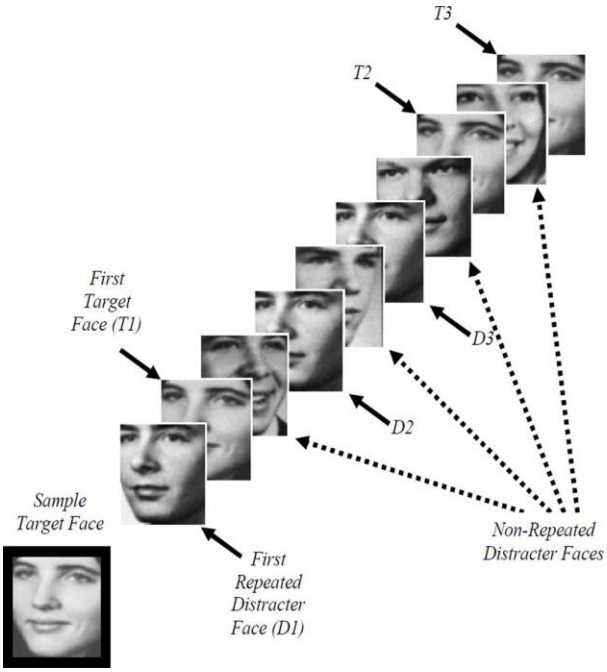
Young, Old, Cognitive Normal, Behavioral (2006)

Aging and Repetition Priming for Targets and Distracters in a Working Memory Task

Caggiano, D, Jiang, Y, & Parasuraman, R (2006). Aging and repetition priming for targets and distracters in a working memory task, Aging, Neuropsychology, and Cognition, 13, 552-573. PMID: 16887789. PMCID: PMC3678549. doi:10.1080/138255890969555.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678549/

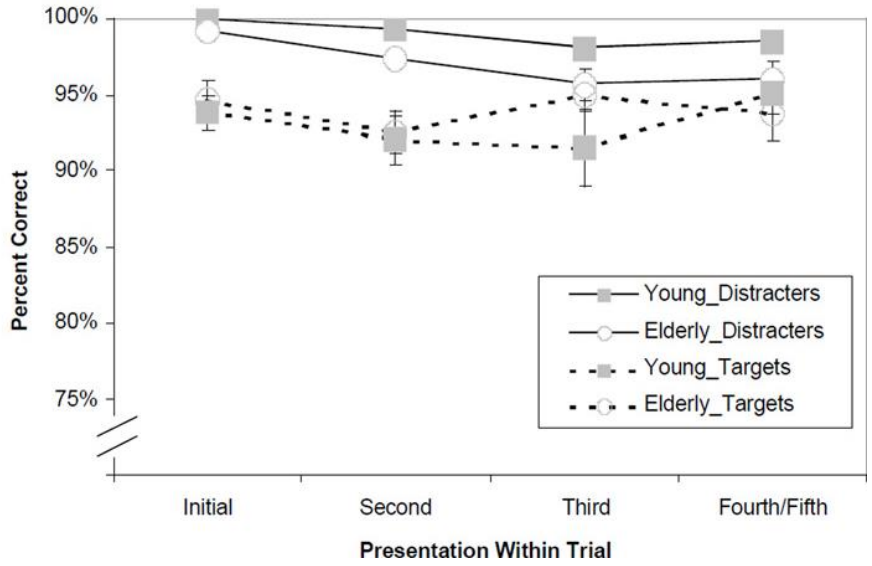
Abstract: A combined working memory/repetition priming task was administered to 13 young (mean age 23) and 13 elderly (mean age 69) adults. Each participant memorized a sample target face at the beginning of a trial and then determined whether each of 13 serially presented test faces matched the sample target. In each trial, both the target and one particular distracter face were repeated during the test phase. Within-trial repetition priming effects indicated the contribution of implicit memory to task performance. Response times decreased as items were tested repeatedly within a trial, but this decrement was greater for distracters than for targets. Young and older participants were equally accurate at identifying targets, but elderly was slightly less accurate for distracters. Elderly participants showed repetition priming effects for both targets and distracters, while the young showed such effects only for distracters. The results suggest that active maintenance in working memory, but not inhibition or rejection of distracters, may suppress implicit memory systems.



Method: Participants viewed a sample target face (outlined in black here) on each trial for 3.76 seconds, followed by a stream of 13 test faces that appeared for 1.88 seconds each. Target faces appeared in this stream of test faces between one and five times (three target repetitions are shown here). A single distracter face also appeared multiple times in each stream of test faces (three repetitions of the first distracter are shown here). All other distracters appeared only once per trial. Participants classified each test face as either a target or distracter by pushing one of two buttons on a button box.

Key Results/Figures

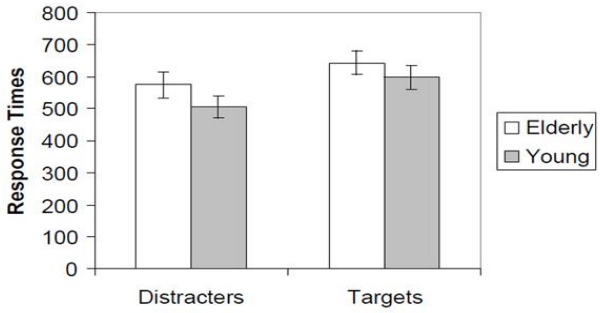
b. Accuracy By Item Type and Repetition



Accuracy of manual responses for repeated targets and distracters only, as a function of repetitions within a trial.

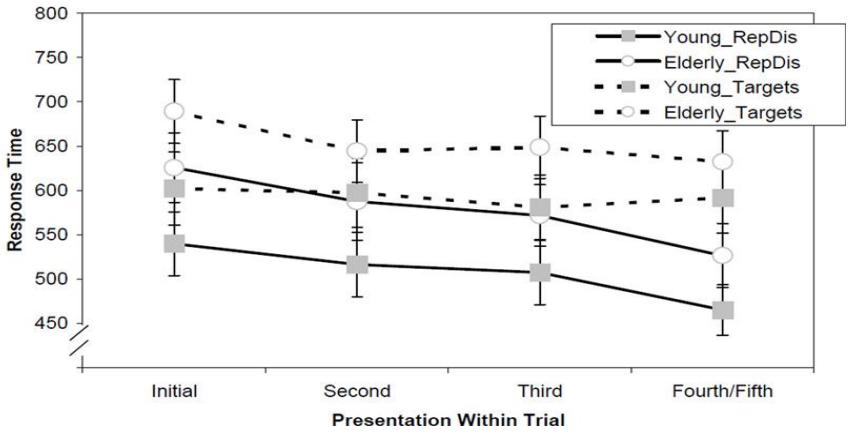
- Accuracy for a particular item declined after its initial presentation within a trial of test faces
- This effect was significantly modulated by whether the test item was a target or a distracter
- Simple effects tests indicated that performance declined linearly as distracter items were repeated, as indicated by a significant linear contrast; however, performance for targets did not decline linearly as the targets were repeated

a. Overall Response Times for Repeated Items



Manual response times for correct responses to repeated targets and distracters only, collapsing across all repetitions within a trial (figure 3a) and as a function of repetitions within a trial (figure 3b).

b. Response Time by Item Type and Repetition



- This study was designed to investigate whether there is an age-related difference in repetition priming and if any such change depends on whether the repeated item is a target or a distracter.

- The age × repetition interaction was significant, indicating that older adults showed a greater reduction in RT with item repetition than the young. Although the age × repetition × item type (target/distracter) interaction was not significant, it is apparent that the major difference between young and old participants was that whereas the old showed repetition-related reduction in RT for both distracters and targets, the young showed a reduction only for distracters.

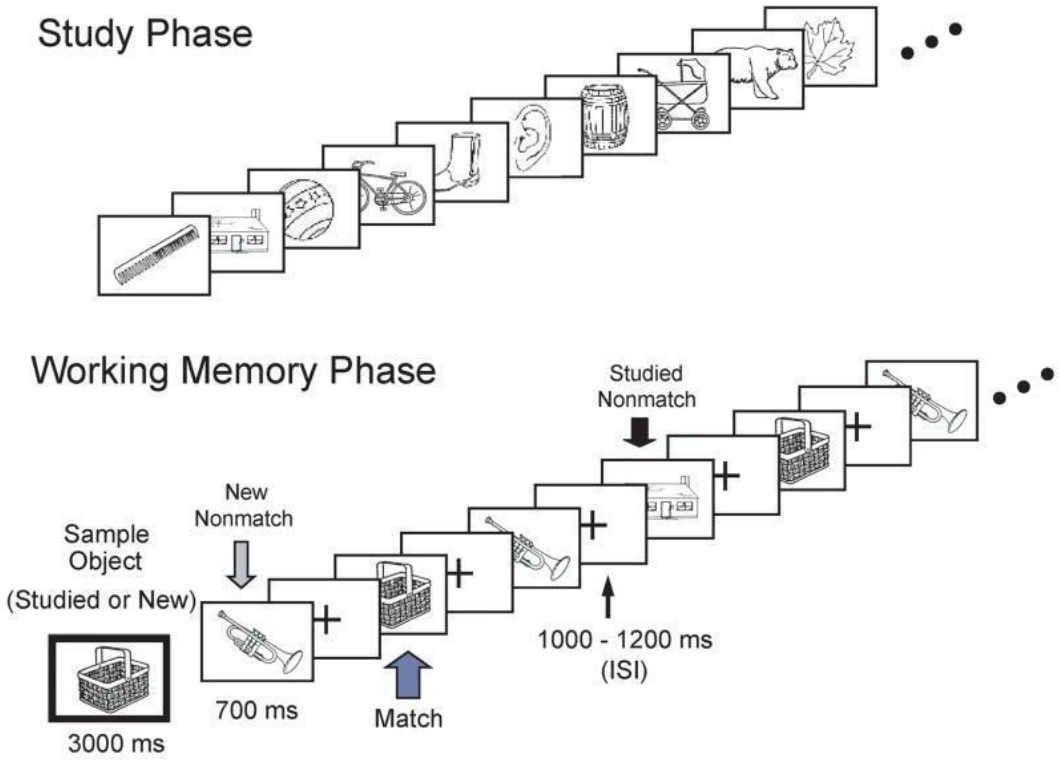
Young, Cognitive Normal, EEG, ERP (2007)

Distinct Neural Mechanisms of Repetition Effects Visual Objects

Guo, CY, Lawson, A, & Jiang, Y (2007). Distinct Neural Mechanisms of Repetition Effects of Visual Objects., Neuroscience, 149, 747-759. PMID: 17949920. PMCID: PMC2203616. doi: 10.1016/j.neuroscience.2007.07.060.

Link: 17949920

Abstract: Repetition of visually common objects was examined in relation to prior intentional learning and memory status using a delayed match-to-sample task. Both response time and two temporally separate ERP components indexed repetition. The early repetition effect (~200 –550 ms) evoked more ERP responses for repeated visual objects, and was diminished by prior intentional learning (old / new) or being maintained in working memory (targets / distracters). In contrast, the late repetition effect (after ~550 ms) evoked reduced ERP activation for repeated items, and was not affected by prior learning nor working memory status. Our source localization results indicate that the late and posterior repetition effect in visual cortex is consistent with repetition suppression results reported in monkey physiology and human fMRI studies. Meanwhile, the early and anterior repetition effect, in temporal pole and frontal cortices, is modulated by explicit memory mechanisms.



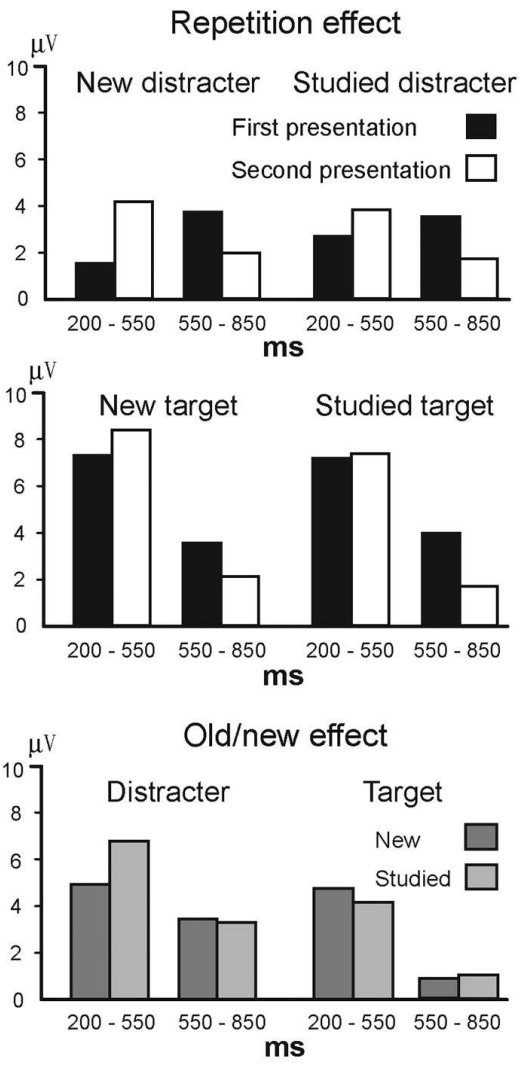
Method: The memory task included a sample target object followed by 9 successive test picture that did (targets) or did not (distracters) match the sample object. Both targets and distracters included prior studied (old) and new objects, and each object was presented up to 4 times in a trial. The short-term memory task consisted of 120 trials separated into 12 blocks of 10 trials each. Each trial began with the presentation of the sample picture (for 3000 msec) that was distinguished by a green border. A single tone presented at the onset of the sample picture

further distinguished it from other pictures. The sample picture was followed by 9 successive test pictures with a stimulus duration of 700 msec per picture. All test pictures were divided by an ISI of 1100± 100 msec that contained a fixation cross. Each trial lasted approximately 21 seconds.

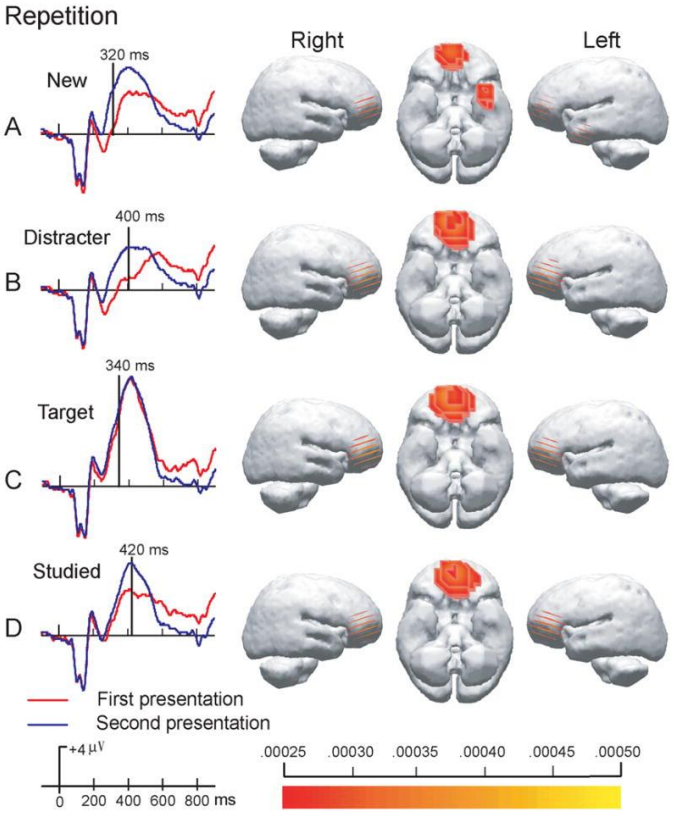
The 120 trials were divided into two groups with 60 trials utilizing a studied sample and 60 trials having a new sample. The order of studied and new sample trials was balanced in a pseudo-random sequence that was consistent across subjects. Within trials, test pictures were classified into one of three groups: (a) matches (studied and new grouping depended on the sample trial type), (b) studied nonmatches, and (c) new nonmatches. On average, two nonmatching objects were presented for every matching object in a trial. Each of the studied pictures (n = 60) initially served as a studied match in one trial and served as a studied nonmatch in another trial. Of the 180 new objects, 60 objects served as new matches, and 120 objects served as new nonmatches. Thus, new objects, whether serving as a match or nonmatch, were not used in any subsequent trials.

The test portion of each trial contained a pseudo-random presentation of matching and nonmatching objects. Matching objects were presented two, three, or four times, and nonmatching objects were each presented two, three, or four times making up a total of nine test objects per trial. This pseudo-random presentation resulted in 180 events for each condition equaling 1080 events total.

Key Figure/Results:



Summary of repetition effects for new distracters, studied distracters, new targets and studied targets. The largest averaged voltages in middle electrodes are seen at Cz for all repetition effects, Pz for the old/new effect of distracters, and Fz for the old/new effect of targets.



Intracranial source analysis for ERP comparisons

Low-resolution current density reconstructions based on the LORETA model are shown via a color scale for current density reconstructions (CDRs) as computed at the designated time point superimposed on left and right hemispheres. The left column shows the time point with the largest difference, i.e. the largest MGFP functions (Mean Global Field Power), between ERPs of the first and the second presentations.

- Our ERP results demonstrate the presence of two dissociable repetition effects.
- The early ERP repetition effect (200 –500 ms) was centered over central sites with more positive-going and larger potentials to repeated items than their initial presentations.

- The late posterior ERP repetition effect, however, was centered over parietal sites and began after 550 ms with less positive and smaller activation to repeated items than their initial presentations.

- The early ERP repetition effect was modulated by both intentional prior learning and working memory processes. For new distracters, the early effect was larger and occurred almost 150 msec earlier than for studied distracters. For targets, the early repetition effect occurred only with new targets.

- This early effect was smaller overall for studied objects than for new objects, and was also visibly smaller for targets than distracters

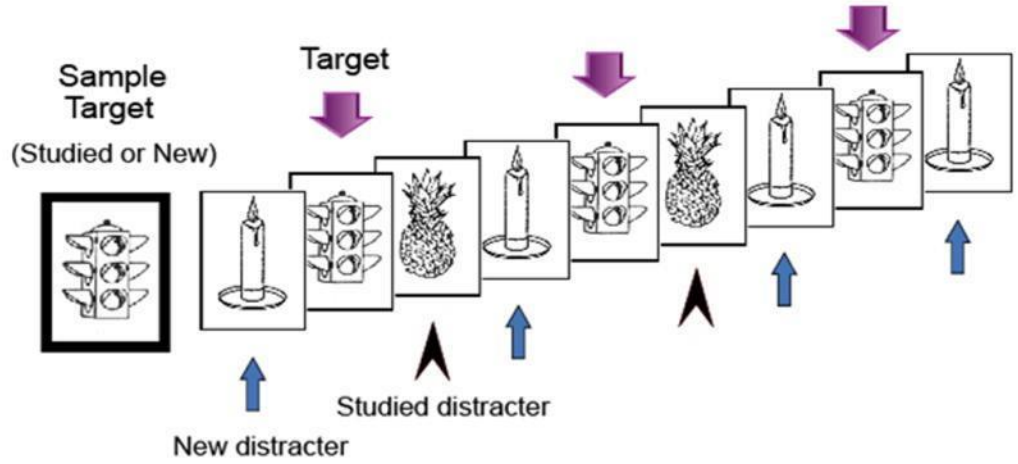
Young, Older, Cognitive Normal, EEG, ERP (2007)

Age effects on brain activity during repetition priming of targets and distracters

Lawson, AL, Guo, C, & Jiang, Y (2007). Age effects on brain activity during repetition priming of targets and distracters, Neuropsychologia, 45, 1223-1231. PMID:17140610. PMCID: PMC1850388. doi: 10.1016/j.neuropsychologia.2006.10.014.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1850388/

Abstract: The effects of age on repetition priming and how such differences were related to intentional learning and working memory status were examined. Fourteen older (age 65–75) and 14 younger (age 18–28) healthy adults performed a modified delayed match-to-sample task consisting of a target object held in mind followed by nine test objects. Sixty four-channel EEGs were recorded as participants indicated whether each test object was the same or different from the target object. Half of all target and distractor objects were intentionally studied prior to the task, and both target and distractor objects were repeatedly presented up to four times in each trial. Although both age groups showed repetition priming effects, speed increases due to repetition were more enhanced for elderly. ERP repetition effects for both younger and older adults were indexed via early (200–550) and late (550–850 ms) components. The early repetition effect was affected by whether a distractor was previously studied or not for younger but not for older adults. In contrast, the late repetition effect was not affected by prior intentional learning, and a marginal age effect suggested that repetitions of distractors likely affected older and younger adults differently. These findings suggest that at least two distinguishable repetition mechanisms differentially affect adult aging.

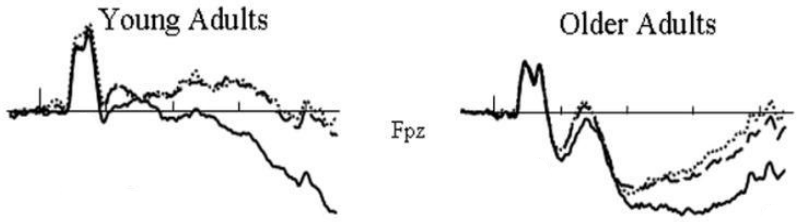


Method: Each trial of the modified delayed match-to-sample task included a sample target object followed by 9 successive test pictures that matched (targets) or did not match (distractors) the sample target. Both targets and distractors included prior studied (old) and new objects, and each object type was presented between 2 and 4 times in a trial.

The short-term memory task consisted of 120 trials separated into 12 blocks of 10 trials each. Each trial began with the presentation of the sample target object (for 3000 msec) distinguished by having a green border. A single tone presented at the onset of the sample target further distinguished it from subsequent test objects. The sample target was followed by 9 successive test objects with an ISI of 700 msec per object. All objects were divided by a fixation cross with an ISI of 1100± 100 msec. Each trial lasted approximately 21 seconds. The 120 trials included

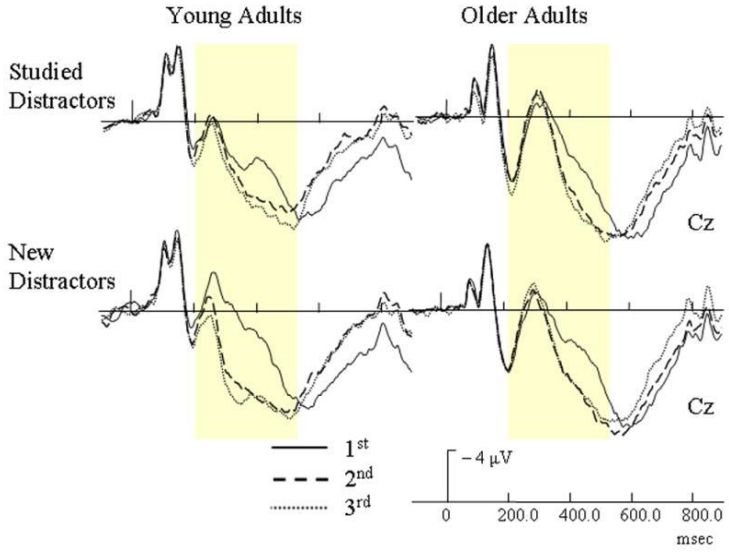
60 trials having a studied target and 60 trials having a new target. The order of studied and new target trials was balanced in a pseudo-random sequence that was consistent across subjects. Within trials, test objects were classified into one of three groups: (a) targets, (b) studied distractors, and (c) new distractors. Each of the studied objects served as a studied target in one trial and as a studied distractor in a later trial. New objects, whether serving as a target or distractor, were not used in any subsequent trials. The test portion of each trial contained a pseudo-random presentation of targets, studied distractors, and new distractors, with each being repeated one to three times, making up a total of nine test objects per trial.

Key Figure/Results:



Age-related differences in our early ERP repetition component. Event-related potentials (ERPs) of target (match) responses for each age group at initial (solid lines), 2nd (dashed line), and 3rd/4th (dotted line) presentations of distractors, and collapsed across study type**.**

- For younger adults, repeated targets had more positive activation than their initial presentations at central sites FCz, Cz, and CPz. At these same electrode sites, however, older adults had incremental decreases in positive activation with additional presentations of targets



Event-related potentials (ERPs) of repetition effects with studied and non-studied distractors for each age group. The yellow bars highlight the early repetition effect (200 – 550 msec).

- Importantly, the early repetition effect for distractors was affected by prior explicit learning for younger, but not older adults.

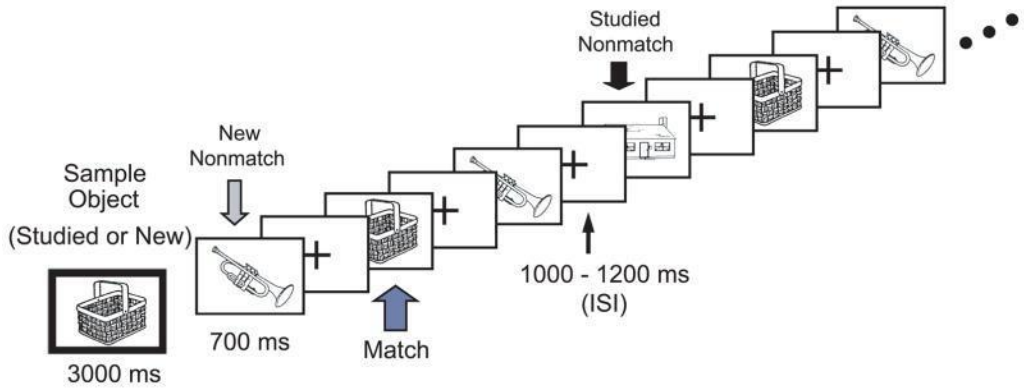
Young, Cognitive Normal, EEG, ERP (2008)

Brain potentials distinguish new and studied objects during working memory

Guo, CY, Lawson, A, Zhang, Q, & Jiang, Y (2008). Brain potentials distinguish new and studied objects during working memory, Human Brain Mapping, 29, (4), 441-452 (Cover Illustration). PMID: 17497630. PMCID: PMC3665269. doi: 10.1002/hbm.20409.

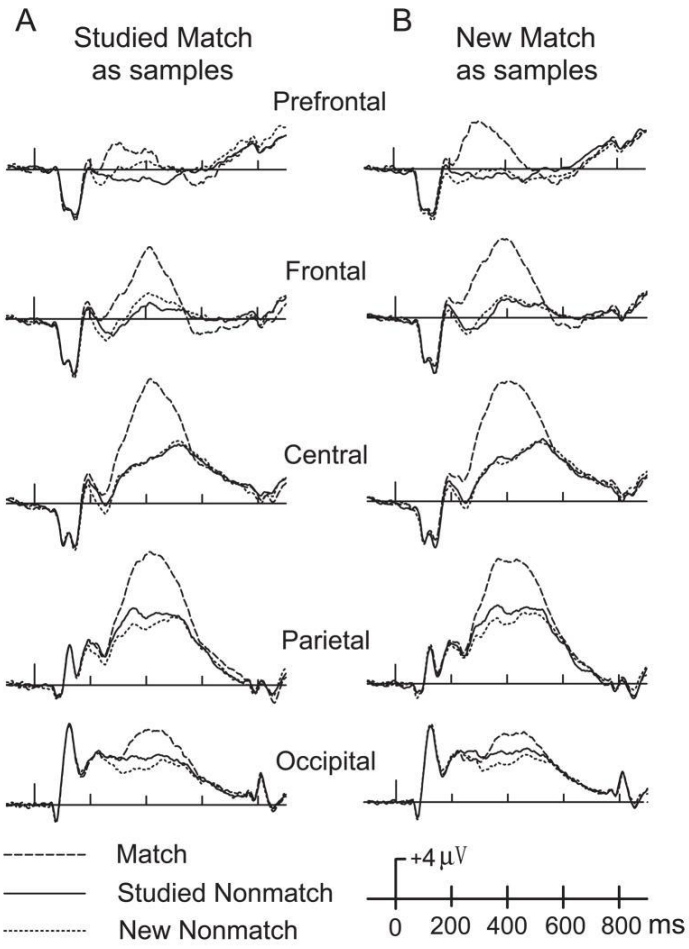
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665269/

Abstract: We investigated brain responses to matching versus nonmatching objects in working memory with a modified delayed match-to-sample task using event-related potentials (ERPs). In addition, ERP correlates of new items (new matches/new nonmatches) and previously studied items (studied matches/studied nonmatches) were examined in the working memory task. Half of the common visual objects were initially studied until 95% accuracy was attained and half were new. Each memory trial began with the presentation of a sample object followed by nine test objects. Participants indicated whether each test item was the same as the object held in mind (i.e., match) or a nonmatch. Compared to studied matches, new matches evoked activity that was 50 msec earlier and largest at frontal sites. In contrast, P3 activity associated with studied nonmatches was larger than for new nonmatches at mostly posterior sites, which parallels previously reported old-new ERP effects. The ERP source analysis further confirms that the cortical mechanisms underlying matching objects and rejecting irrelevant objects during the task are both temporally and spatially distinct. Moreover, our current findings suggest that prior learning affects brain responses to matching visual items during a working memory task.



Method: In this working memory task, a sample object was initially presented, followed by 9 successive test pictures (matching and nonmatching). Each WM trial lasted approximately 21 seconds.

Key Figure/Results



ERPs from the two nonmatch object types (i.e., new nonmatches, studied nonmatches) within a trial along with studied matches (A) or new matches (B) between trials.

❖ Visual inspection of ERP responses among condition types showed that beginning about 200 msec after stimulus onset, ERPs for match responses were more positive than those for nonmatching objects.

❖ Also, ERPs, recorded at parietal and occipital sites, were visually more positive when a studied nonmatch was presented compared to a new nonmatch.

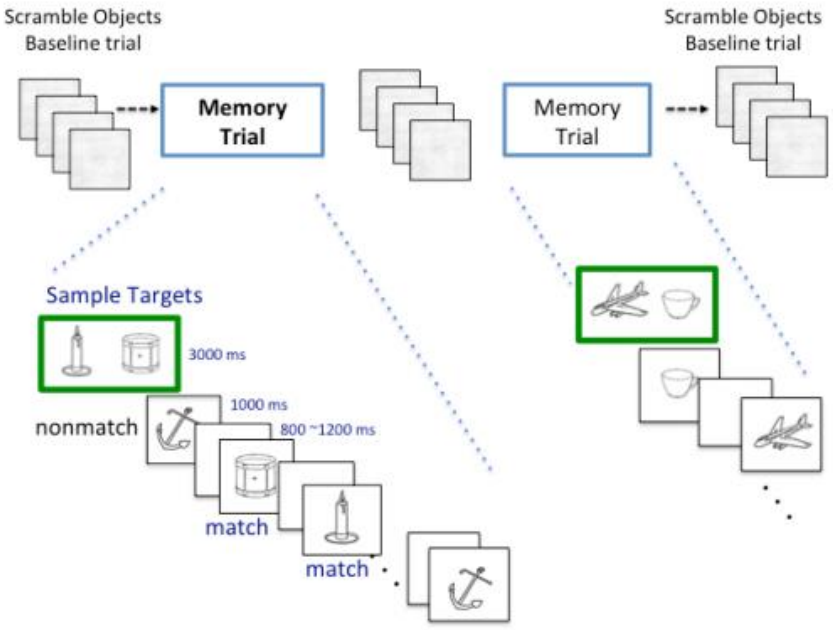
Older, Cognitive Normal, Preclinical AD CSF Biomarker and fMRI (2016)

Alzheimer's biomarkers are correlated with brain connectivity in older adults differently during rest and task

Jiang, Y, Huang, H, Abner, E, Broster, LS, Jicha, G, Schmitt, F, Kryscio, R, Andersen, A, Powell, D, van Eldik, L, Gold, B, Nelson, P, Smith, C, & Ding, M (2016). Alzheimer's biomarkers are correlated with brain connectivity in older adults differentially during resting and task, Frontiers in Aging Neuroscience, 8:15. PMID: 26903858. PMCID: PMC4744860. doi: 10.3389/fnagi.2016.00015 [PubMed]

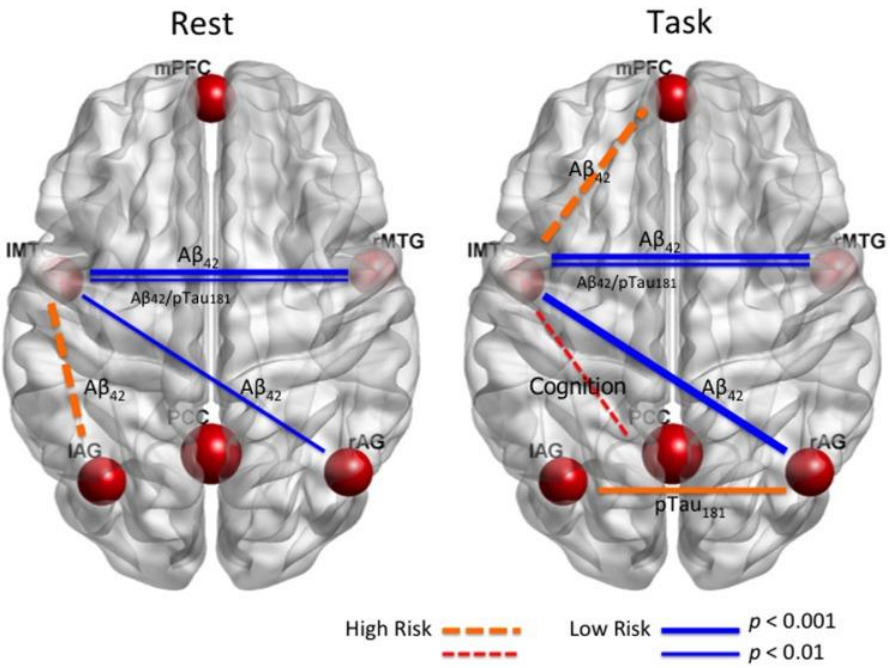
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744860/

Abstract: β-amyloid (Aβ) plaques and tau-related neurodegeneration are pathologic hallmarks of Alzheimer's disease (AD). The utility of AD biomarkers, including those measured in cerebrospinal fluid (CSF), in predicting future AD risk and cognitive decline is still being refined. Here, we explored potential relationships between functional connectivity (FC) patterns within the default-mode network (DMN), age, CSF biomarkers ($A\beta_{42}$ and $pTau_{181}$), and cognitive status in older adults. Multiple measures of FC were explored, including a novel time series-based measure [total interdependence (TI)]. In our sample of 27 cognitively normal older adults, no significant associations were found between levels of $A\beta_{42}$ or $pTau_{181}$ and cognitive scores or regional brain volumes. However, we observed several novel relationships between these biomarkers and measures of FC in DMN during both resting-state and a short-term memory task. First, increased connectivity between bilateral anterior middle temporal gyri was associated with higher levels of CSF $A\beta_{42}$ and $A\beta_{42}/pTau_{181}$ ratio (reflecting lower AD risk) during both rest and task. Second, increased bilateral parietal connectivity during the short-term memory task, but not during rest, was associated with higher levels of CSF $pTau_{181}$ (reflecting higher AD risk). Third, increased connectivity between left middle temporal and left parietal cortices during the active task was associated with decreased global cognitive status but not CSF biomarkers. Lastly, we found that our new TI method was more sensitive to the *CSF* $A\beta_{42}$-connectivity relationship whereas the traditional cross-correlation method was more sensitive to levels of CSF $pTau_{181}$ and cognitive status. With further refinement, resting-state connectivity and task-driven connectivity measures hold promise as non-invasive neuroimaging markers of Aβ and pTau burden in cognitively normal older adults.



Method: The participants performed a modified version of a visual working memory task (delayed-match-to-sample task with repeated retrieval of memory targets and distractors) that has been validated in healthy young subjects (Jiang et al., 2000). The task used two-dimensional pictures of common objects taken from Snodgrass and Vanderwart (1980). In the typical delayed match-to-sample paradigm, the subjects were first shown an item to hold in working memory at the beginning of a trial, and then determine whether a later encountered test item is a match or non-match. In the current 10-min older-adult friendly version, two sample pictures were encoded for each given trial. This reduces scanning time for older adults and increases the number of matches with balanced number of non-matches. Task-induced default network activity was calculated as a whole, with multiple cognitive components, in contrast to resting-state connectivity. Details of the event-related task are presented in Supplementary Material. Participants were trained on the memory task before the scanning session.

Key Figure/Results:



Summary results of relations between functional brain connectivity within DMN during resting state and task, CSF biomarkers (Aβ42 and pTau181), and global cognition (*T*-scores) in cognitively normal older adults.

Blue lines indicate low AD risk, and orange/red lines indicate high AD risk. The stronger the line, the more significant the connectivity with CSF biomarker or cognition. Solid line shows that the correlation was significant in more than one analysis. Left MTG appears to be a hub for connectivity sensitive to AD risk.

- lMTG–rMTG is significantly associated with level of Aβ42 or Aβ42/pTau181 ratio. In other words, cognitively intact older individuals with increased bilateral MTG connectivity were associated with lower risk of β-amyloid deposits.
  - Positive correlation with Aβ42 was found between DMN FC of left MTG and right AG in parietal lobe That is, stronger connectivity indicates increased level of CSF Aβ42, implying less deposition of β-amyloid and, therefore, lower AD risk.
  - Brain connectivity indicating higher risk of β-amyloid deposits was also found. In other words, stronger connections were associated with lower level of CSF Aβ42, i.e., higher β-amyloid burden.
  - Increased pTau181 (higher risk for AD) is positively correlated with bilateral AG. Stronger bilateral AG connectivity was associated with higher levels of CSF pTau181 (pg/ml).

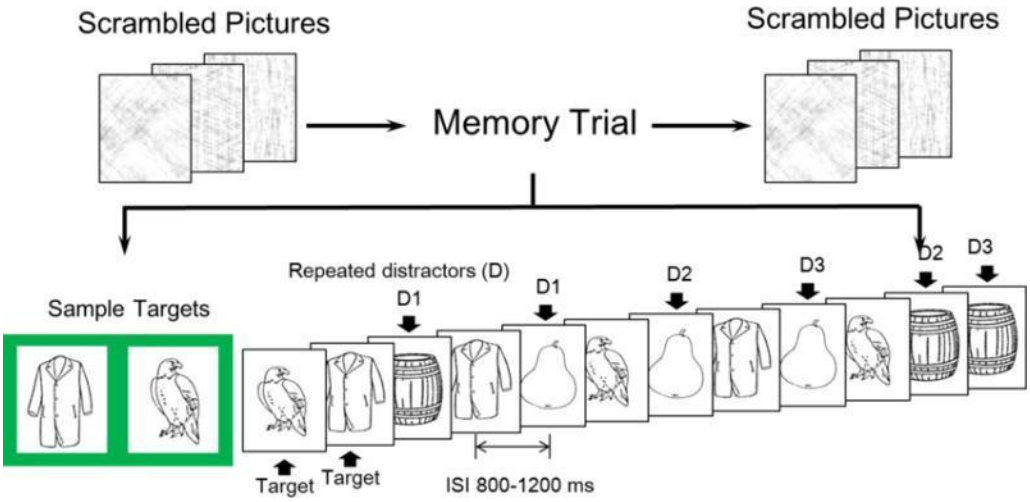
Older, Preclinical AD, Mild Cognitive impairment (MCI), fMRI (2016)

Altered brain activities associated with neural repetition effects in mild cognitive impairment patients

Yu, J., Li, R., Jiang, Y., Broster, L. S., and Li, J. (2016). Altered brain activities associated with neural repetition effects in mild cognitive impairment patients. *J Alzheimer's Disease, 53*(2), 693-704. doi: 10.3233/JAD-160086.

Link: https://doi.org/10.3233/JAD-160086

Abstract: Older adults with mild cognitive impairment (MCI) manifest impaired explicit memory. However, studies on implicit memory such as repetition effects in persons with MCI have been limited. In the present study, 17 MCI patients and 16 healthy normal controls (NC) completed a modified delayed-match-to-sample task while undergoing functional magnetic resonance imaging. We aim to examine the neural basis of repetition; specifically, to elucidate whether and how repetition-related brain responses are altered in participants with MCI. When repeatedly rejecting distracters, both NC and MCI showed similar behavioral repetition effects; however, in both whole-brain and region-of-interest analyses of functional data, persons with MCI showed reduced repetition-driven suppression in the middle occipital and middle frontal gyrus. Further, individual difference analysis found that activation in the left middle occipital gyrus was positively correlated with rejecting reaction time and negatively correlated with accuracy rate, suggesting a predictor of repetition behavioral performance. These findings provide new evidence to support the view that neural mechanisms of repetition effect are altered in MCI who manifests compensatory repetition-related brain activities along with their neuropathology.

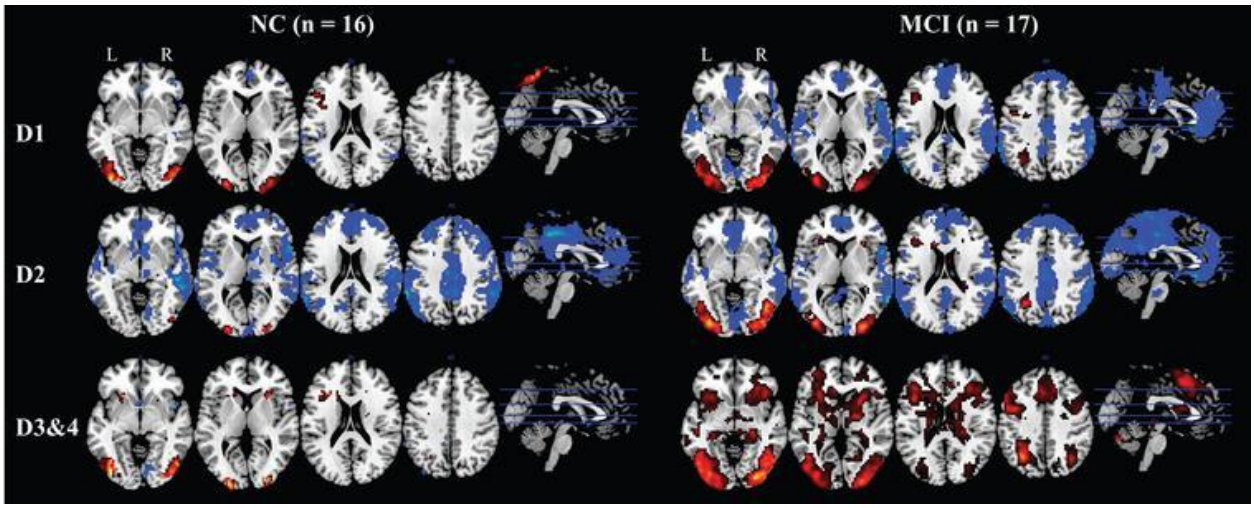


Method: For each memory trial in this delayed match-to-sample task, two sample objects in green borders were initially presented, followed by 12 (or 13) successive test pictures (target or distracter object). D1 stands for the initial presentation of a distracter stimulus (i.e., non-match to either of the sample targets), and so forth for D2, D3, and/or D4.

The hybrid delayed-match-to-sample task (DMST) consisted of 32 trials separated into 4 blocks of 8 trials, which is modified from the previous delayed match-to-sample paradigms. Each trial of the task consisted of two sample objects with green borders presented side by side to be remembered (for 3500 ms). The sample targets were followed by test objects presented for 1000 ms each with variant jitters of 800/900/1000/1100/1200 ms. Each trial lasted

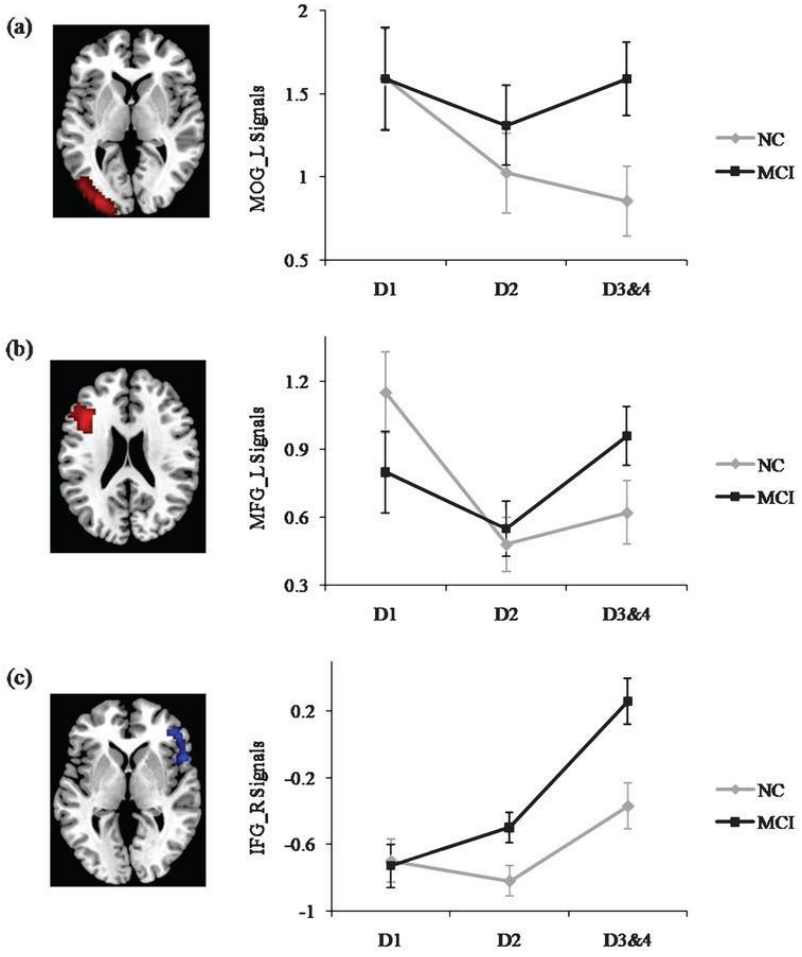
approximately 30 s. Test objects were classified into two groups: matching targets and non-matching distracters. Each trial contained a pseudo-random and counter-balanced presentation of target and distracter objects. Target objects were presented one, two, three, or four times, and distracter objects were each presented one, two, three, or four times making up a total of 12 (or 13) test objects per trial. Thus, of 192 distracter stimuli in total, 64 stimuli served as firstly presented distracters (D1), 64 stimuli served as secondly presented distracters (D2), 44 stimuli served as the thirdly presented distracters (D3), and 22 stimuli served as fourthly presented distracters (D4). Participants were asked to determine whether each of the subsequent test objects matched the sample objects. They were required to respond by pressing a button with their right/left thumb finger for each test object in the trial that matched the sample objects or by pressing another button with their other thumb finger for each test object that did not match the sample objects. The association between hand and matching was counterbalanced among participants. For the visual processing control, the scrambled versions (containing the same spatial frequencies in *Fournier* domain) of the actual objects images were used as a baseline. Each of the scrambled nonsense picture block contains five scrambled pictures, and each one presented for 2s. Participants were asked to press both buttons when they saw the scrambled pictures. The DMST memory trials and the scrambled picture blocks were presented alternatively.

Key Figures/Results:



Regions showing activation (in red) and deactivation (in blue) during repetition in NC and MCI group ($p<0.05$, corrected).

- Generally, both NCs and MCIs displayed activation (i.e., distracter>baseline) in the occipital cortex and the left middle frontal gyrus (Fig. 3, Red).
- Both groups displayed deactivation (i.e., distracter<baseline) in the medial frontal gyrus, the middle temporal gyrus, and the inferior parietal lobule (Fig. 3, Blue).
- Specifically, along with the repetition, NC group exhibited reliable activations in the middle occipital gyrus (MOG), fusiform, inferior frontal gyrus and middle frontal gyrus; and deactivations in inferior/medial frontal gyrus, superior temporal gyrus, and inferior parietal lobule



Mean activations (a & b) or deactivations (c) within the ROIs from (a) the middle occipital gyrus (MOG), (b) middle frontal gyrus (MFG), and (c) inferior frontal gyrus (IFG) for the D1, D2, and D3&4.

- Significant activations occurred in the MOG and middle frontal areas with the repetition (D1 versus D2 versus D3&4) × group (NC versus MCI) interaction. The repetition-associated activations in the MOG were decreasing during repetitions in the NC group , while the activations first decreased in D2 but increased to the similar extent in D3&4 compared with D1 in the MCI group (a).
- The activations in the middle frontal areas were decreasing in the NC group while the activations first decreased in D2 but increased to the similar extent in D3&4 compared with D1 in the MCI group during repetitions (b).

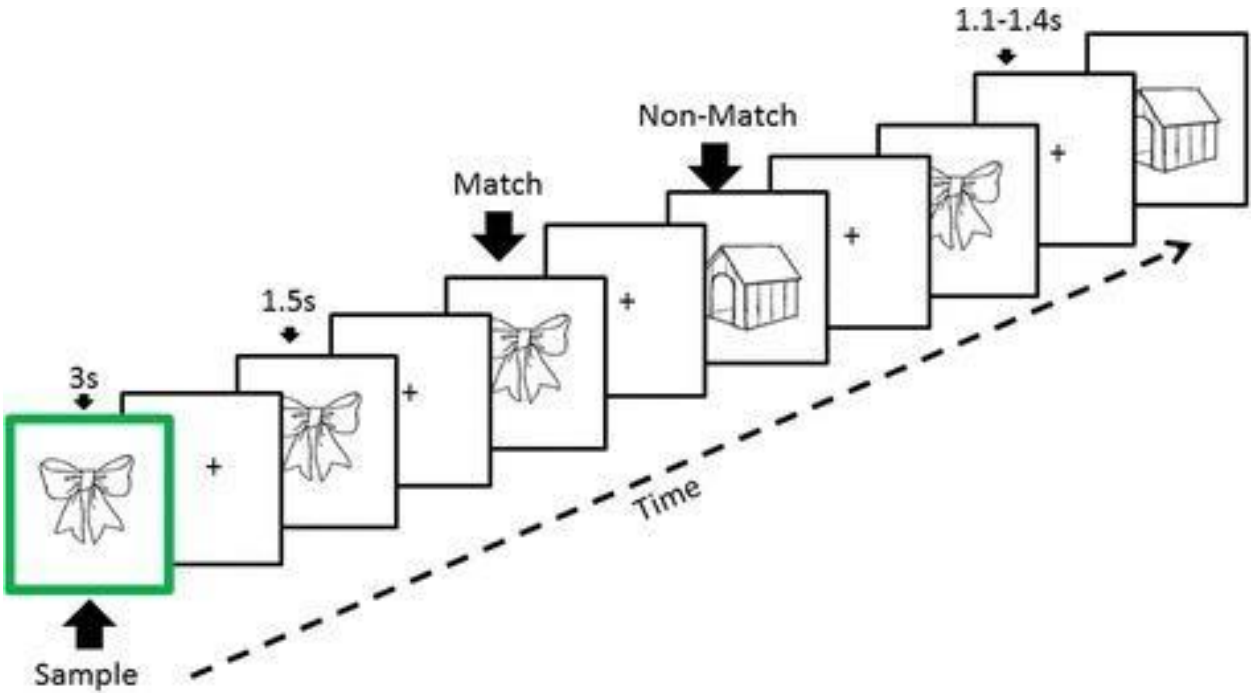
Old, Cognitive Normal, MCI, AD, EEG, Cognitive ERP (2017)

A cognitive electrophysiological signature differentiates amnestic mild cognitive impairment from normal aging

Li, J., Broster, L. S., Jicha, G. A., Munro, N. B., Schmitt, F. A., Abner, E., … Jiang, Y. (2017). A cognitive electrophysiological signature differentiates amnestic mild cognitive impairment from normal aging. Alzheimer's Research & Therapy, 9(1), 3. doi: 10.1186/s13195-016-0229-3

Link: https://doi.org/10.1186/s13195-016-0229-3

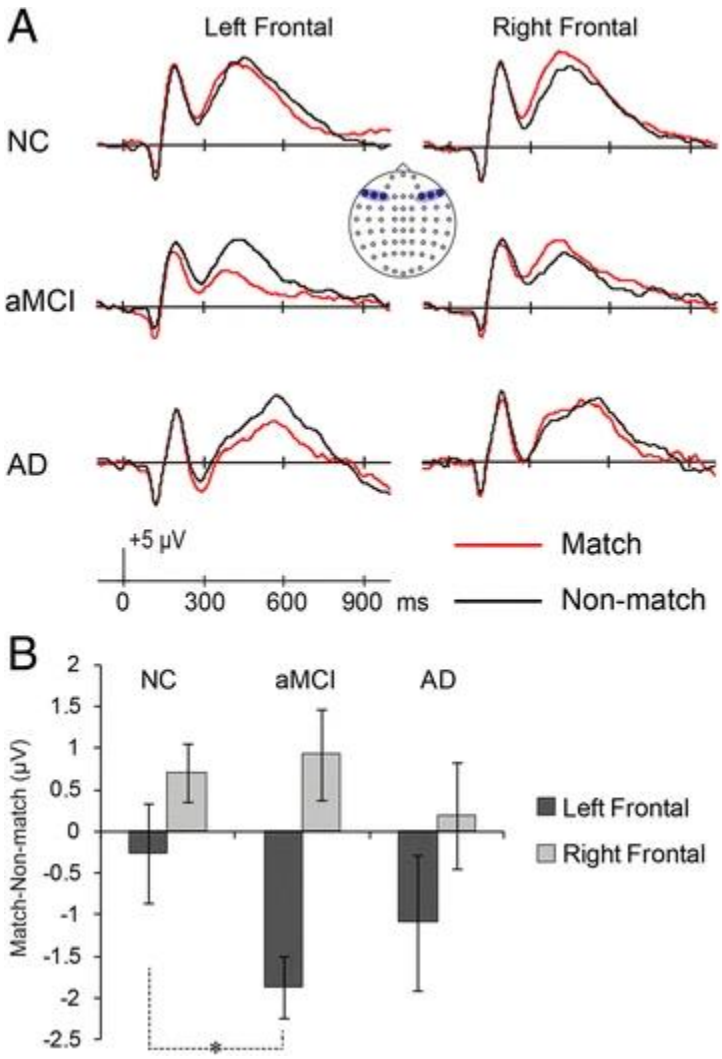
Abstract: Noninvasive and effective biomarkers for early detection of amnestic mild cognitive impairment (aMCI) before measurable changes in behavioral performance remain scarce. Cognitive event-related potentials (ERPs) measure synchronized synaptic neural activity associated with a cognitive event. Loss of synapses is a hallmark of the neuropathology of early Alzheimer's disease (AD). In the present study, we tested the hypothesis that ERP responses during working memory retrieval discriminate aMCI from cognitively normal controls (NC) matched in age and education. Eighteen NC, 17 subjects with aMCI, and 13 subjects with AD performed a delayed match-to-sample task specially designed not only to be easy enough for impaired participants to complete but also to generate comparable performance between subjects with NC and those with aMCI. Scalp electroencephalography, memory accuracy, and reaction times were measured. Whereas memory performance separated the AD group from the others, the performance of NC and subjects with aMCI was similar. In contrast, left frontal cognitive ERP patterns differentiated subjects with aMCI from NC. Enhanced P3 responses at left frontal sites were associated with nonmatching relative to matching stimuli during working memory tasks in patients with aMCI and AD, but not in NC. The accuracy of discriminating aMCI from NC was 85% by using left frontal match/nonmatch effect combined with nonmatch reaction time. The left frontal cognitive ERP indicator holds promise as a sensitive, simple, affordable, and noninvasive biomarker for detection of early cognitive impairment.



Method: A sample image with a green border was initially presented for 3 seconds. After a jittered delay (1.1–1.4 seconds), the participant indicated whether each of five successive test images matched or did not match the sample. A new sample image was used in each trial. Individual images (either matching or nonmatching) were tested two or three times per trial. Each working memory (WM) trial lasted approximately 16 seconds. Altogether, 60 trials were performed in 2 blocks of 30 trials each, with a short break between blocks. The working memory task lasted approximately 18 minutes overall.

Participants were instructed to memorize a sample image and then indicate whether each of five serially presented objects matched the sample image. Stimuli consisted of 120 two-dimensional common objects taken from Snodgrass and Vanderwart. Each picture was presented with a black background and within an area of 8.3 cm × 5.8 cm. All stimuli were presented on a high-resolution color monitor using E-Prime software (Psychology Software Tools, Sharpsburg, PA, USA). Stimuli were presented at a 65-cm visual distance and a visual angle of approximately 7 degrees. Test images were normalized across retrieval status (i.e., matching or nonmatching) for image familiarity and image complexity.

Key Figure/Results:



Group comparisons on grand average waveforms and mean amplitudes of match/nonmatch effects at frontal region are shown

❖ The NC group showed the typical P3 match enhancement seen in previous studies [10–12], maximal at right central areas. In addition to the typical P3 match enhancement, a unique and striking feature shown in the aMCI and AD groups was at the left frontal sites, where the nonmatch condition elicited a larger P3.

❖ The accuracy of discriminating aMCI from NC was 85% by using left frontal match/nonmatch effect combined with nonmatch reaction time.

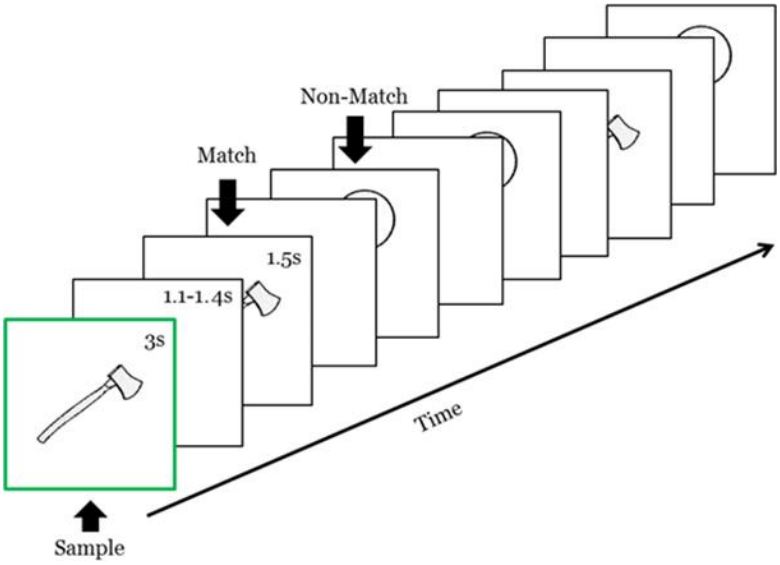
Older, Cognitive Normal, MCI, & AD (2018)

Spared behavioral repetition effects in Alzheimer's disease linked to an altered neural mechanism at posterior cortex

Broster, SL, Li, J, Smith, C, Jicha, G, Schmitt, F, Munro, N, Haney, R, & Jiang, Y (2018). Spared behavioral repetition effects in Alzheimer's disease linked to an altered neural mechanism at posterior cortex, Journal of Clinical and Experimental Neuropsychology,40 (8): 1-16. doi:10.1080/13803395.2018.1430230

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397625/

Abstract: Individuals with dementia of the Alzheimer type (AD) classically show disproportionate impairment in measures of working memory, but repetition learning effects are relatively preserved. As AD affects brain regions implicated in both working memory and repetition effects, the neural basis of this discrepancy is poorly understood. We hypothesized that the posterior repetition effect could account for this discrepancy due to the milder effects of AD at visual cortex. Participants with early AD, amnestic mild cognitive impairment (MCI), and healthy controls performed a working memory task with superimposed repetition effects while electroencephalography was collected to identify possible neural mechanisms of preserved repetition effects. Participants with AD showed preserved behavioral repetition effects and a change in the posterior repetition effect, suggesting that visual cortex may play a role in maintained repetition effects in persons with early AD.



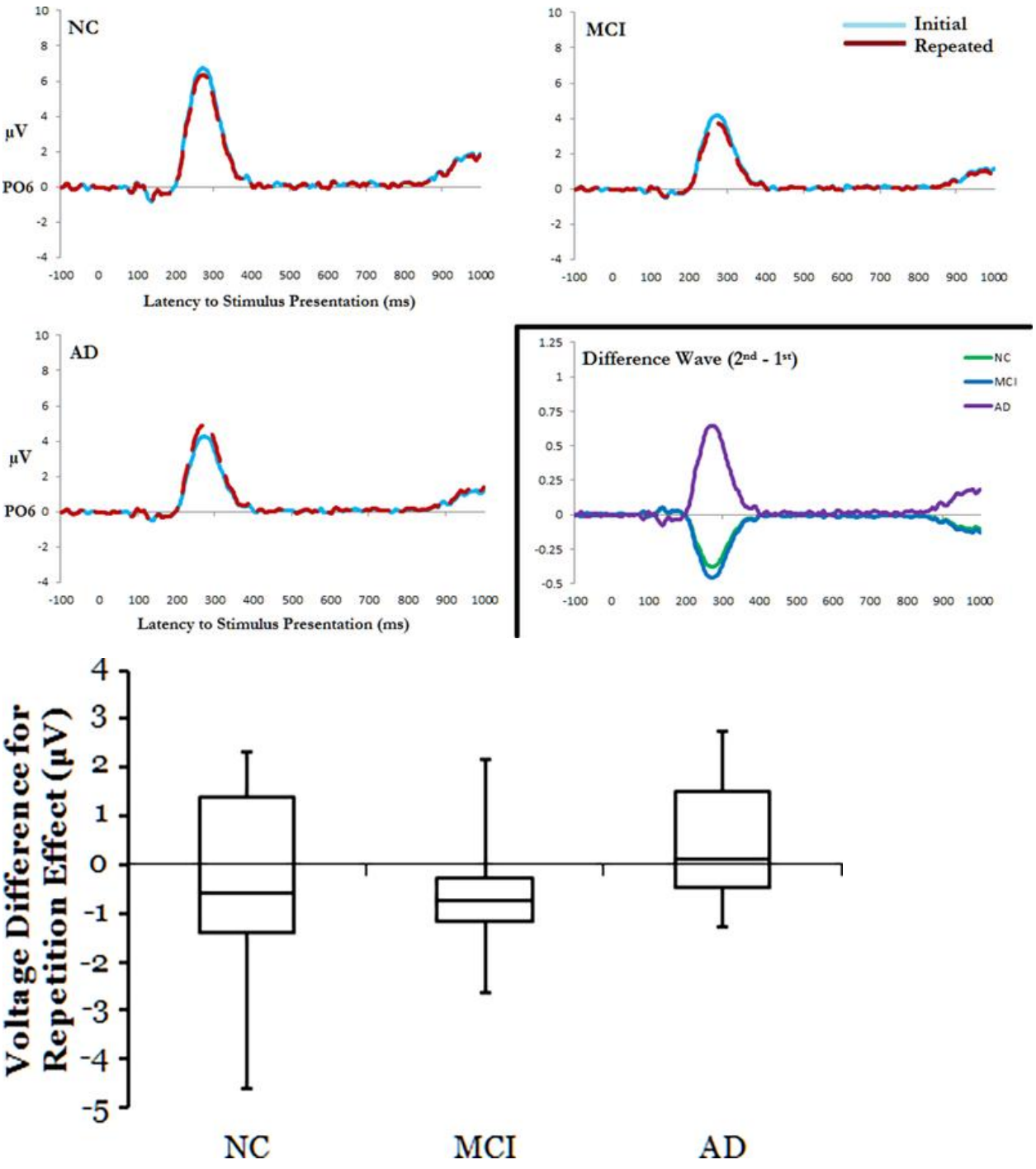
Method: The schematic represents a typical empirical trial. The z-axis represents time. First, a sample image with a green border was shown to the participant. After a jittered delay, the participant indicated whether each of a series of images matched or did not match the sample. Individual images were tested 2–3 times per trial. A new sample image and new distractor image were used in each trial.

Participants performed a hybrid delayed-match-to-sample/repetition (DMS-R) task that has been validated in human and nonhuman primate physiological studies while neurophysiological data was collected (Guo et al., 2007; Jiang, Haxby, Martin, Ungerleider, & Parasuraman, 2000; Miller & Desimone, 1994; Miller, Erickson, & Desimone, 1996). Incorporating both working memory

and repetition effects into a single paradigm, as in the hybrid paradigm used in the current study, facilitates the interpretation of any interaction effects observed (Kennedy, Rodrigue, Head, Gunning-Dixon, & Raz, 2009; Voss & Paller, 2008, 2009). Participants memorized a sample cartoon image at the beginning of each trial and then indicated whether or not each of 5 serially presented objects matched the sample image via response box with the left or right hand, counterbalanced between participants (Snodgrass & Vanderwart, 1980). One image matching the sample and exactly one nonmatching image were each tested exactly 2 or 3 times per trial, respectively, for 5 total test stimuli per trial (Howard, Howard, Dennis, & Kelly, 2008). A consequence of this design is that subjects could never infer the identity of the final tested image, ensuring that the cognitive task upon test image presentation was uniform. Because this design also meant that there were half as many 3rd presentations as 1st or 2nd presentations, 2nd and 3rd presentations were aggregated before analysis. Images were presented in a pseudorandom order. The detail that each trial would test the matching stimulus at least twice and the nonmatching stimulus at least twice was not made explicit to participants. The differential working memory retrieval status of a given stimulus (i.e., whether each stimulus was a match or a nonmatch) was used as a probe of working memory while repetition of a given stimulus (i.e., initial test or subsequent test) was a probe of repetition effects. Each image was used in exactly one trial. 60 trials were performed altogether in two blocks of 30 trials each; as described previously, each trial consisted of 5 test stimuli. Each block lasted 5 minutes and 30 seconds. Participants took a short, self-paced break between blocks that typically lasted about 60 seconds. During this time researchers confirmed the comfort of participants and provided encouragement to participants. Pilot data suggested that persons with AD responded poorly to negative accuracy feedback during experimental protocols. Consequently, the protocol was modified so that participants would not receive accuracy feedback.

A 5-minute practice period preceded the entire experiment to ensure that participants were comfortable with the cognitive and motor components of the task. This practice period was also designed to reduce or eliminate the influence of motor learning confounds on any repetition effects. During the practice period a researcher remained in the experimental room with the participant and provided oral feedback related to performance. As in the 2 blocks of formal experimentation, computerized feedback was not provided.

Key Figure/Results:



(a) This graph summarizes the unique posterior effect in the Alzheimer's disease (AD) group. The separate event-related potentials to the initial and subsequent presentation of stimuli are graphed for the normal control (NC), mild cognitive impairment (MCI), and AD groups, and the difference waves between those conditions (subsequent – initial) are shown together in the bottom-right quadrant. Individuals with AD uniquely showed repetition enhancement. (b) This box-and-whiskers graph shows the five-point summary of the unique posterior effect. Positive values indicate that the secondary

presentations of an image were associated with a larger amplitude than the initial presentation (i.e., 2nd > 1st). The boxes depict the first quartile,median, and third quartile for the NC, MCI, and AD groups, respectively, while the error bars depict the minimum and maximum values for each group. Individuals with AD showed a more positive mean amplitude difference than the other groups.

- Our results implicate an AD-related difference in an early, posterior repetition effect mechanism whereas repetition was associated with a reduced effect at this site in participants without AD, it co-occurred with an enhanced behavioral repetition effects in participants with AD.
- The sensitivity of the posterior mechanism to pathological cognitive aging (i.e., in the context of clinical dementia due to AD) departs somewhat from previous findings that the posterior repetition effect mechanism is robust to cognitive aging.

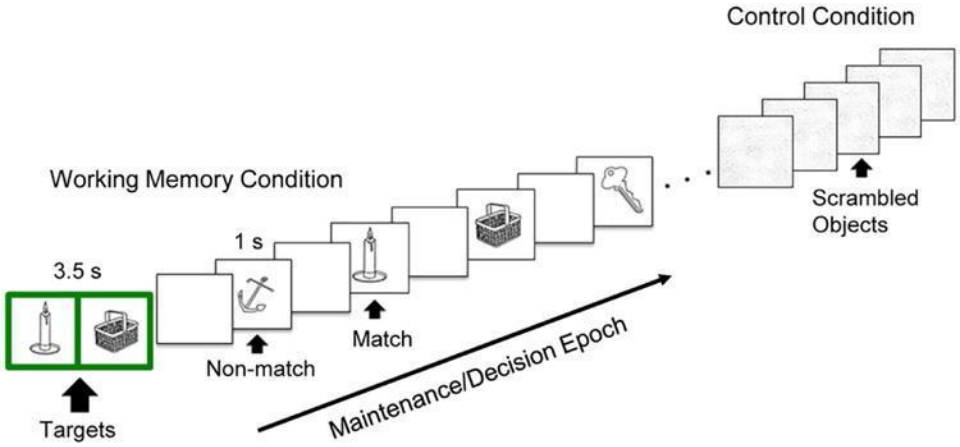
Young, Old, Cognitive Normal, preclinical AD, fMRI, DTI (2018)

Age and Alzheimer's pathology disrupt default mode network functioning via alterations in white matter microstructure but not hyperintensities

Brown, CA, Jiang, Y, Smith, CD, & Gold, BT (2018). Age and Alzheimer's pathology disrupt default mode network functioning via alterations in white matter microstructure but not hyperintensities, Cortex, 104:58-74. doi: 10.1016/j.cortex.2018.04.006

Link:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6008234/

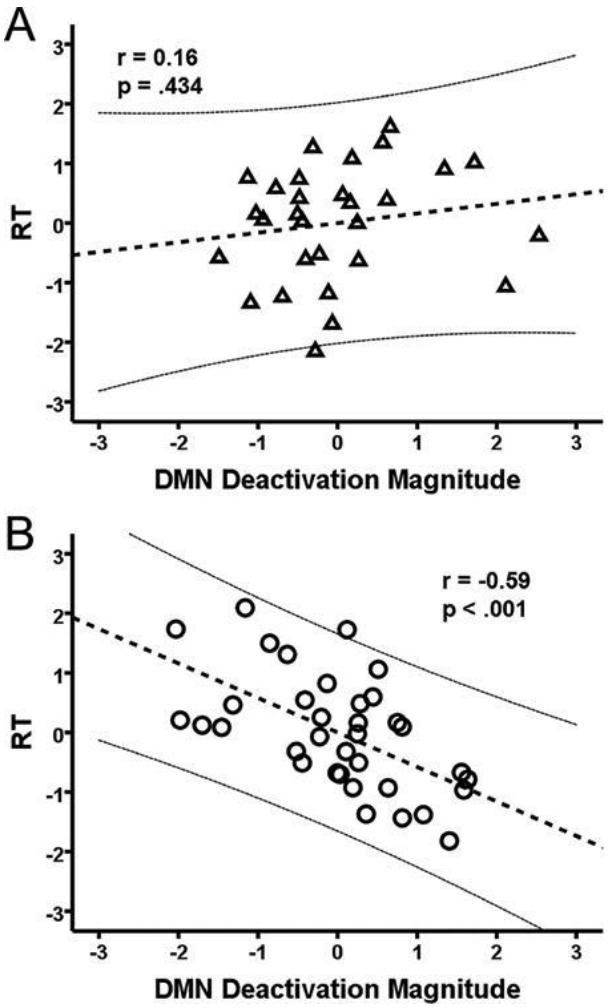
Abstract: The default mode network (DMN) comprises defined brain regions contributing to internally-directed thought processes. Reductions in task-induced deactivation in the DMN have been associated with increasing age and poorer executive task performance, but factors underlying these functional changes remain unclear. We investigated contributions of white matter (WM) microstructure, WM hyperintensities (WMH) and Alzheimer's pathology to age-related alterations in DMN function. Thirty-five cognitively normal older adults and 29 younger adults underwent working memory task fMRI and diffusion tensor imaging. In the older adults, we measured cerebrospinal fluid tau and $A\beta_{42}$ (markers of AD pathology), and WMH on FLAIR imaging (marker of cerebrovascular disease). We identified a set of regions showing DMN deactivation and a set of inter-connecting WM tracts (DMN-WM) common to both age groups. There were negative associations between DMN deactivation and task performance in older adults, consistent with previous studies. Decreased DMN deactivation was associated with AD pathology and WM microstructure but not with WMH volume. Mediation analyses showed that WM microstructure mediated declines in DMN deactivation associated with both aging and AD pathology. Together these results suggest that AD pathology may exert a "second-hit" on WM microstructure, over-and-above the effects of age, both contributing to diminished DMN deactivation in older adults.



Methods: Task blocks involved presentation of two target images surrounded by a green border followed by 12 single 'test' images (match or non-match). Participants were asked to hold 'in mind' the target images and decide whether each single test image represented a match, or a non-match, with either of the target images. Blank screens between images represent temporal jittering. The control condition involved viewing 5 sequentially-presented scrambled images. Analyses compared BOLD signal during a portion of the maintenance/decision epoch with BOLD signal during a portion of the control condition (baseline block).

Participants performed a visual working memory paradigm during fMRI scanning. The paradigm was a modified delayed-match-to-sample task (Figure 1) with multiple targets and repeating intervening distractors, which increases demands on executive processes (Jiang, 2000; Kane & Engle, 2002). The task stimuli were two-dimensional pictures of common objects selected from Snodgrass and Vanderwart (Snodgrass & Vanderwart, 1980). During task blocks, participants were asked to 'hold in mind' the two target images and indicate (via button press) whether or not each of 12 serially presented single samples represented a match with either target image. Sample images were either one of the two target (match) images presented at the beginning of the task block or distractor (non-match) images, which were repeated between 2-4 times in a block. The ratio of targets to distractors in each block ranged from 5:7 to 7:5. During baseline blocks, participants viewed scrambled versions of object images (created by Fast Fourier transform algorithms).

Key Figure/Results:



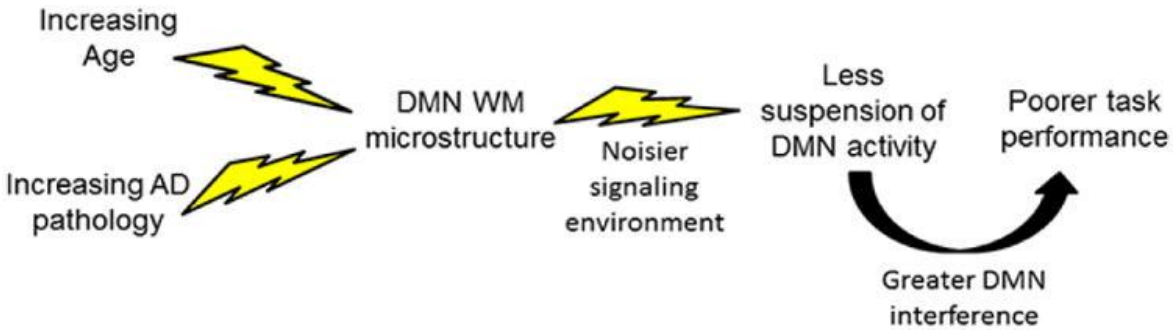
Relationship between DMN deactivation and working memory performance
Scatter plots of RT against DMN deactivation show no relationship within younger adults **(A)** and a significant inverse relationship within older adults **(B)**. Values are standardized residuals after regressing out the effects of age, sex, and education. The r- and p-values are for the linear best fit (thick dashed line).

- Partial correlations demonstrated that lower DMN deactivation magnitude was significantly associated with slower task RT within older adults (r = -0.59, df = 30, p < .001), but not in younger adults

- Lower DMN deactivation was uniquely associated with poorer task performance in cognitively normal (cognitively normal) older adults.

- Within older adults, lower deactivation was linked with higher AD pathology and lower FA in DMN-WM, but not WMH burden.

- Further, WM microstructure mediated the effects of age and AD pathology on DMN deactivation.



DMN-WM microstructure as common pathway contributing to diminished DMN deactivation

- Schematic of the proposed role of DMN-WM microstructure as a common pathway by which age and AD pathology contribute to diminished DMN deactivation.

- Decline in WM microstructural properties creates a noisier signaling environment, which leads to less suspension of DMN activity (and default-mode processes) during the working memory task. This results in greater interference from the DMN that impairs performance. Reduced DMN deactivation may only become severe enough to impact working memory once WM microstructure is significantly impacted by both age and AD pathology.

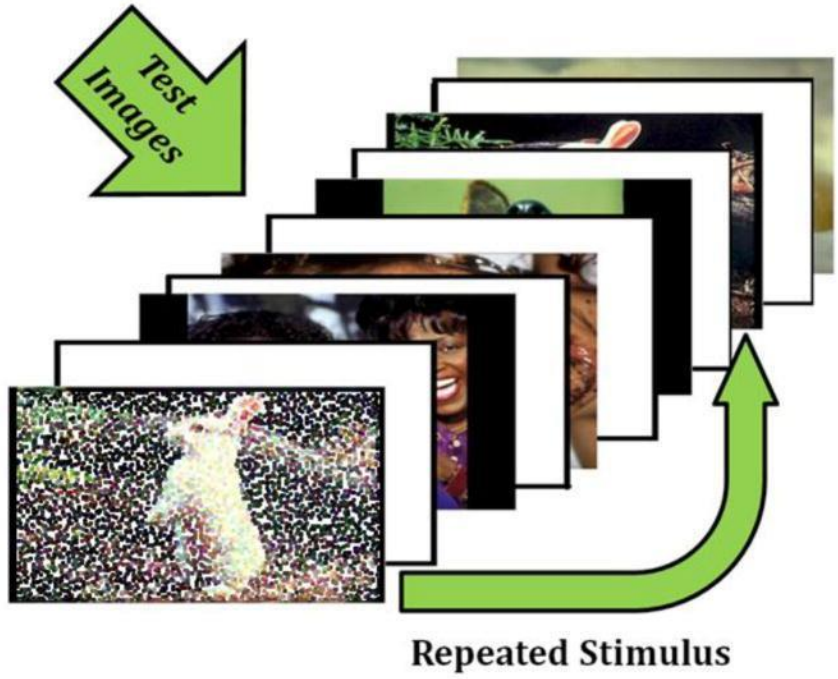
Older, Cognitive Normal, AD, MCI, EEG, ERP (2018)

Electrophysiological repetition effects in persons with mild cognitive impairment depend upon working memory demand

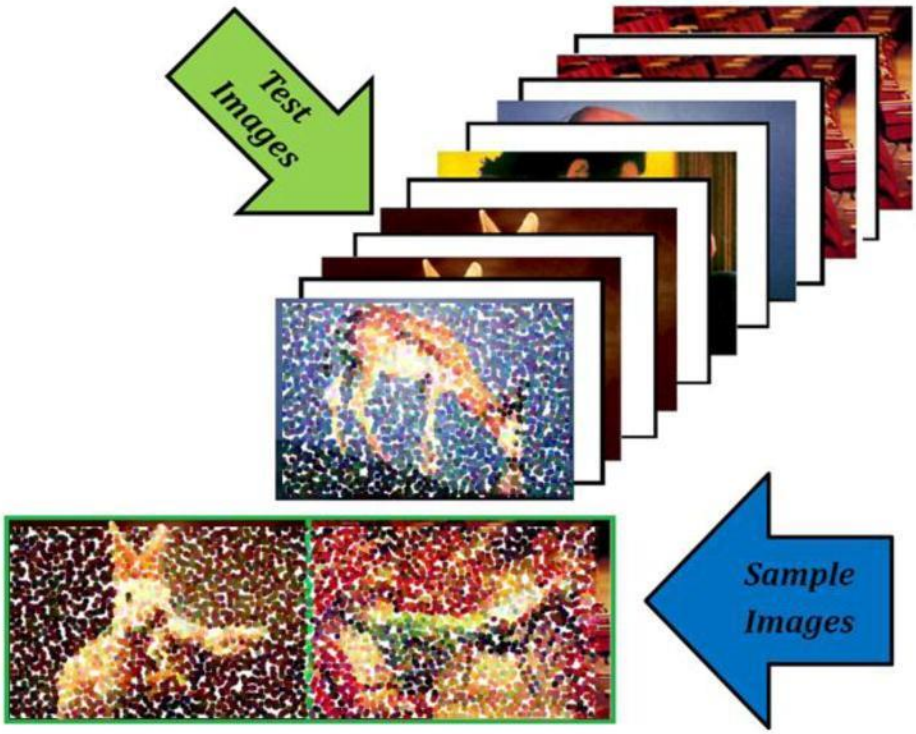
Broster, LS, Jenkins, SL, Holmes, SD, Edwards, MG, Jicha, GA, Jiang, Y (2018). Electrophysiological repetition effects in persons with mild cognitive impairment depend upon working memory demand, *Neuropsychologia*, 117, 13-25.doi: 10.1016/j.neuropsychologia.2018.05.001

Link:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6086740/

Abstract: Forms of implicit memory, including repetition effects, are preserved relative to explicit memory in clinical Alzheimer's disease. Consequently, cognitive interventions for persons with Alzheimer's disease have been developed that leverage this fact. However, despite the clinical robustness of behavioral repetition effects, altered neural mechanisms of repetition effects are studied as biomarkers of both clinical Alzheimer's disease and pre-morbid Alzheimer's changes in the brain. We hypothesized that the clinical preservation of behavioral repetition effects results in part from concurrent operation of discrete memory systems. We developed two experiments that included probes of emotional repetition effects differing in that one included an embedded working memory task. We found that neural repetition effects manifested in patients with amnestic mild cognitive impairment, the earliest form of clinical Alzheimer's disease, during emotional working memory tasks, but they did not manifest during the task that lacked the embedded working memory manipulation. Specifically, the working memory task evoked neural repetition effects in the P600 time-window, but the same neural mechanism was only minimally implicated in the task without a working memory component. We also found that group differences in behavioral repetition effects were smaller in the experiment with a working memory task. We suggest that cross-domain cognitive challenge can expose "defunct" neural capabilities of individuals with amnestic mild cognitive impairment.

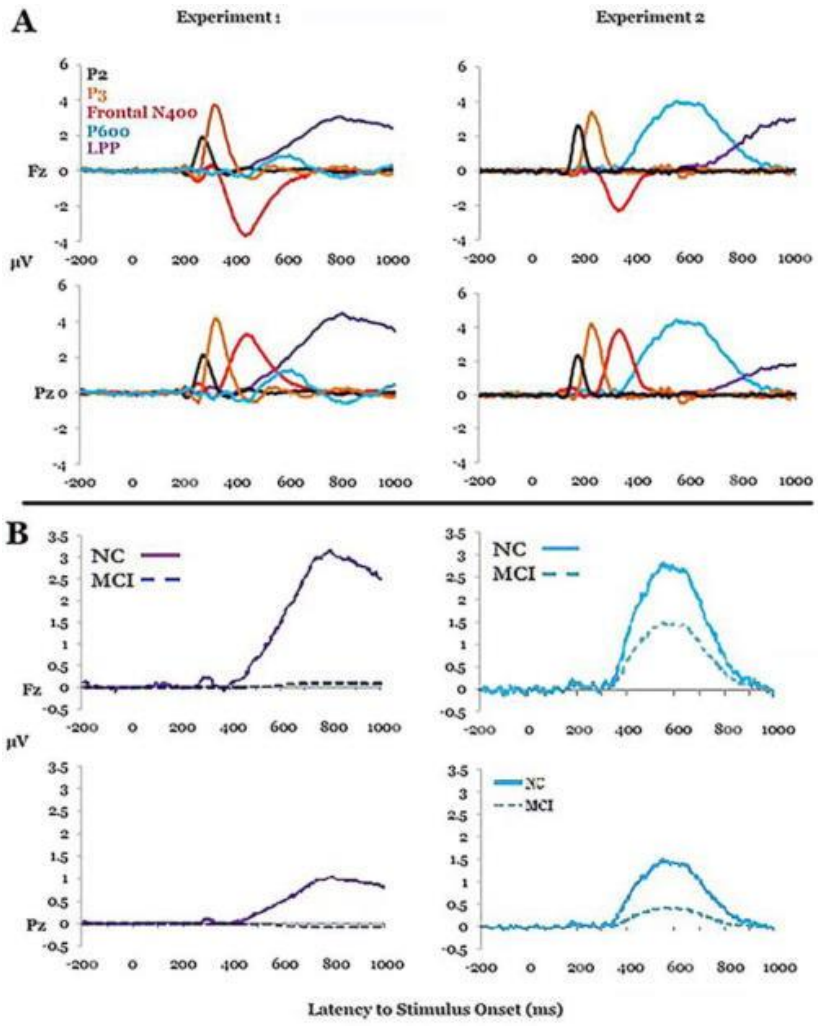


Method: Participants indicate whether the content of each image includes humans or human parts, and individual images are all repeated exactly twice after variable lag. Individual images differed in their hedonic valence and arousal levels (i.e., low arousal positive, LAP, or high arousal negative, HAN). The non-occluded image has been graphically blurred in keeping with publication standards for IAPS images; the blurring is not intended to imply that IAPS images were blurred during experimentation.



Method: First, two sample images are displayed with a green border, and participants are directed to commit these images to memory. Then, text images are displayed one-by-one, and participants indicate whether each image was among the sample images from that trial by keyboard press. The non-occluded images have been graphically blurred in keeping with publication standards for IAPS images; the blurring is not intended to imply that IAPS images were blurred during experimentation.

Key Figure/Results:



Components in Experiments 1 & 2 and repetition effect difference waves. A) These graphs depict the temporal PCA solution of Experiment 1 (first column) and Experiment 2 (second column) at a frontal (first row) and posterior (second row) electrode. Notable is the stark contrast in the size of the P600 between experiments; the component is prominent for the working memory task, but almost negligible in the simple repetition task. B) These graphs show difference waves between the 1st and 2nd presentations of stimuli (2nd minus 1st; positive values indicate larger amplitudes with repetition). Individuals with MCI did not show a repetition effect at the LPP (first column), but at the large P600 that was only apparent in the working memory study, persons with MCI showed a repetition effect, albeit an attenuated one (second column). The first and second rows show the effect at a frontal (Fz) and posterior (Pz) electrode, respectively. LPP = late positive potential

- We found that persons with MCI and persons without impairment showed a late positive potential (LPP) repetition effect difference

- For Experiment 2, a task that required patients to engage working memory, a repetition effect persisted during a distinct but temporally-overlapping component (P600). Interestingly, the P600 component was of very small magnitude in Experiment 1, and the P600 and LPP were difficult to distinguish visually without the benefit of PCA in both experiments.

- In our opinion, these findings indicate that a neural mechanism evoked by working memory is sensitive to repetition effects and maintains relatively intact repetition effects in MCI. This finding may account for why experimental repetition effects have manifested disparately in AD.

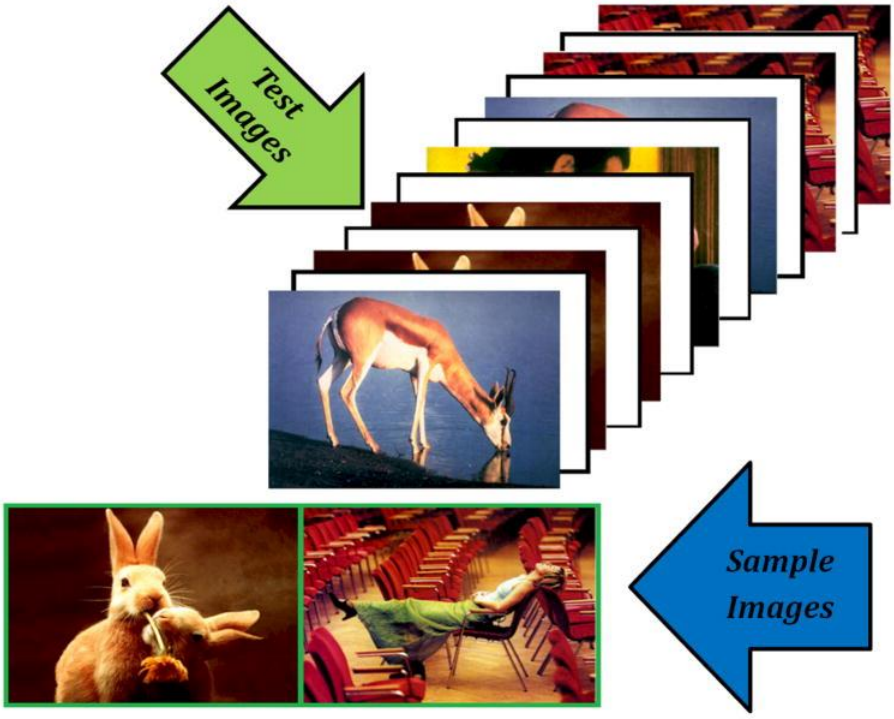
Older, Cognitive Normal, MCI, EEG, ERP (2017)

Low Arousal Positive Emotional Stimuli Attenuate Aberrant Working Memory Processing in Persons with Mild Cognitive Impairment

Broster, LS, Jenkins, SL, Holmes, SD, Jicha, GA, Jiang, Y (2017). Low Arousal Positive Emotional Stimuli Attenuate Aberrant Working Memory Processing in Persons with Mild Cognitive Impairment, *Journal of Alzheimer's Disease*, 60, 1222-1349. doi: 10.3233/JAD-170233

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5929098/

Abstract: Emotional enhancement effects on memory have been reported to mitigate the pathophysiology of Alzheimer's disease (AD). However, relative to their manifestation in persons without pathologic aging, these effects may be reduced in magnitude or even deleterious, especially in tasks that more closely model ecologic memory performance. Based upon a synthesis of such reports, we hypothesized that in persons with AD low arousal positive stimuli would evoke relatively intact emotional enhancement effects, but that high arousal negative stimuli would evoke disordered emotional enhancement effects. To assess this, participants with and without mild cognitive impairment (MCI) presumed to be due to AD performed an emotionally-valenced short-term memory task while encephalography was recorded. Results indicated that for persons with MCI, high arousal negative stimuli led to working memory processing patterns previously associated with MCI presumed due to AD and dementia of the Alzheimer-type. In contrast, low arousal positive stimuli evoked a processing pattern similar to MCI participants' unaffected spouses. Our current findings suggest that low arousal positive stimuli attenuate working memory deficits of MCI due to AD.



Method: First, two sample images are displayed with a green border, and participants are directed to commit these images to memory. Then, text images are displayed one-by-one, and participants indicate whether each image was among the sample images from that trial by keyboard press.

During each trial of the working memory task, participants were first shown two sample images surrounded by a green border and were subsequently directed to indicate whether sequentially-presented images matched a sample image. For each 10–12 s trial, the sample image and each tested image were either uniformly low arousal positive (LAP) or high arousal negative (HAN) to prevent within-trial emotional level from being correlated to stimulus working memory status. Participants pressed the “A” and “L” keys on a keyboard to indicate matching or nonmatching responses.

Key Figure/Results:

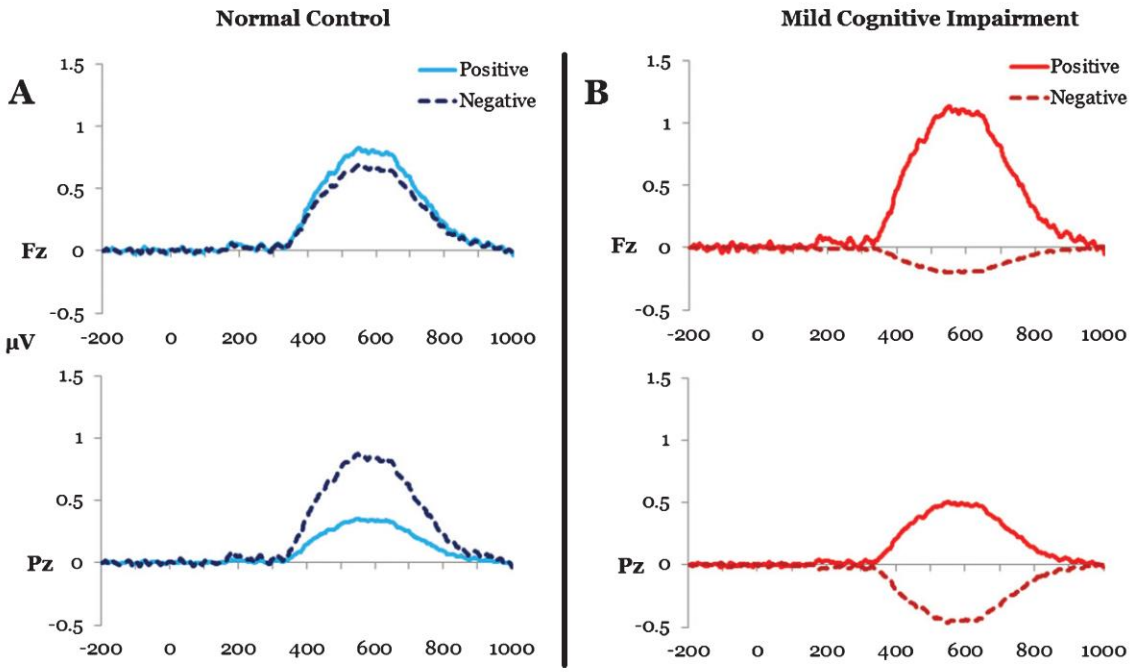


Fig. 5. **Summary of the group differences at the P600 as difference waves**. Each line depicts the difference in P600 activity between matching and non-matching stimuli for stimuli that were either positive (solid line) or negative (dashed line). Individuals without impairment (A) and individuals with MCI (B) showed similar brain responses for positive stimuli, but very different responses for negative stimuli. Data have been graphed at a frontal (Fz) and posterior (Pz) electrode in the first and second rows, respectively, to provide a general sense of differences in this effect at frontal and posterior sites.

- ❖ We found that persons with MCI showed AD-like ERPs when performing working memory with high arousal negative (HAN) emotional stimuli, but showed ERPs similar to persons without impairment for low arousal positive (LAP) stimuli.

- ❖ Persons with MCI were also slower and less accurate than persons without impairment.

- Put together, these findings support the idea that stressful circumstances disrupt the normal effects of emotional enhancement on working memory, but they stop short of suggesting that emotional enhancement effects disrupt cognition in the context of MCI in general.

- The current results suggest that LAP environments maintain the ability to facilitate normal working memory processing in persons with MCI.

Contact and Support

Author:
Soheil Borhani, <sborhani@vols.utk.edu>,
PhD Candidate, Mechanical, Aerospace, and Biomedical Engineering, University of Tennessee, Knoxville

Collaborator(s):
Joshua Dunkley, < jdunkley@vols.utk.edu>,
Bachelor's, Computer Science, University of Tennessee, Knoxville

Michael O'neil, <moneil8@vols.utk.edu>,
Bachelor's, Computer Science, University of Tennessee, Knoxville

Research labs:
Professor Xiaopeng Zhao's Brain-computer interface lab, University of Tennessee, Knoxville
Dr. Yang Jiang's ABC lab, University of Kentucky, Lexington
Bluegrass Short-term Memory paradigm has been developed by Dr. Yang Jiang