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MAO-A and the EEG Recognition Memory Signal in Left Parietal Cortex

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Abstract

A key part of episodic memory, or memory for the events of our lives, is recognition memory. Recognition memory is the ability to remember previously encountered stimuli. Studies have linked recognition memory to the old/new effect, an EEG indicator of stimulus familiarity. Monoamine oxidase A (MAO-A) is an enzyme that catalyzes monoamines, leading to the depletion of norepinephrine, epinephrine, serotonin, and dopamine. MAO-A is more efficiently transcribed in individuals with a 4 repeating sequence variation (4R) of the MAO-A gene leading to less monoamine availability. As many of these monoamines have been linked to episodic memory, we hypothesized that individuals homozygous for the 4R MAO-A polymorphism would show differences in mean EEG signal amplitudes during recognition memory. EEG data was recorded as participants viewed both new words and words that had been previously presented. Our results show that mean peak amplitudes over the left parietal cortex 500-800 ms post-stimulus presentation for hits were greater than those for correct rejections, indicating the old/new effect. Critically, our results revealed an interaction between mean hit and correct rejection amplitude over the left parietal cortex and MAO-A group. Individuals homozygous for the 4R variation (the High MAO-A group) do not show an old/new effect due to increased correct rejection amplitudes. These results suggest that less monoamine availability leads to new stimuli being identified as old by the left parietal cortex.

Introduction

A major type of memory essential to the processes of recollection and recognition is episodic memory, or memory for 'contextual details' relating to a particular event or item (Cycowicz & Friedman, 2003). Recognition memory - a component of episodic memory - is a virtually automatic judgment of whether a stimulus has been experienced previously (Rugg & Curran, 2007). Importantly, recognition memory depends on two key processes, the first of which is familiarity - has a sense that they have seen a recognition target in the past during their re-encoding of the target (Montaldi *et al.,* 2006). Familiarity-based recognition is a fast, automatic process and does not give qualitative information about the study session (Rugg & Curran, 2007). The second process is recollection, which is accurate source memory with recognition (Rugg & Curran, 2007). Recollection involves a subject recalling contextual information via a recognition target (Montaldi *et al.,* 2006).

Furthermore, recollection is generally categorized as a slower process that involves effort to consciously access information about the previous occurrence of the test item as well as the context of said occurrence (Rugg & Curran, 2007). Familiarity and recollection both serve major functions in item and source memory tasks. Item memory is linked to familiarity: whether an item has been seen before, whereas source memory is more strongly associated with recollection because subjects are asked to retrieve the memory for contextual, specific details (Rugg & Curran, 2007).

As individuals strive to remember contextual (source) details of their previous experiences, the effects of episodic memory in event-related brain potentials (ERP) are evidenced (Cycowicz & Friedman, 2003). ERPs are electrical signals in the brain that are influenced by stimuli, and may be positive or negative. Previous studies have shown that ERP signals are influenced by whether a stimulus has previously been experienced. Stimuli that have previously been encountered evoke more positive-going ERPs than signals evoked by novel stimuli. This distinct signal, which is seen around the 400-500 ms post-stimulus onset, is known as the "ERP Old-New effect" (Rugg & Curran, 2007). A link has been established between recognition and the old/new effect. The parietal old/new effect is modulated based on whether the items presented are 'remembered' or 'known,' as well as whether items are associated with unsuccessful or successful source judgments (Rugg & Curran, 2007). Those test items that are assigned 'remember' or 'know' judgments produce old/new effects with differing topographies for familiarity and recollection across the scalp (Duzel *et al.,* 1997).

A second effect, called the 'mid-frontal' effect, (also known as the FN400 old/new effect) is seen over the frontal scalp in the same 300-500 ms time frame, and is brought about when studied items are incorrectly identified as old, and is related to recognition as a function of familiarity (Rugg & Curran, 2007). The mid-frontal effect is also maximal over the parietal scalp, and is elicited by all studied items, regardless recognition accuracy or study task (Rugg & Curran, 2007). Mean left anterior superior frontal (LAS) and right anterior superior frontal (RAS) region amplitudes in the 300-500 ms timeframe showed new items having more negative

amplitudes than old items (Curan & Dien, 2003). Rugg *et al.* (1998) propose that the mid-frontal old/new effect shows implicit memory acting separately from explicit memory, as well as being based off of recognition from familiarity.

A third effect - the 1000-1500 ms late frontal effect – involves old items having more positive amplitudes than new items. The late frontal effect is often seen in ERP studies relating to recognition memory (Curran & Dien, 2003). Additionally, the late frontal effect is thought to relate to activity of evaluation processes post-retrieval (Allan, Wilding, & Rugg, 1998).

Previous studies using human neuroimaging have indicated that the parietal cortex, as well as the prefrontal and medial temporal cortices, is involved in recognition memory (Yonelinas *et al.,* 2005). There are two functionally distinct lateral parietal regions that have been found to be important to recognition memory. The first of which is the inferior lateral parietal cortex, which has been implicated in the process of correctly identifying old versus new items. The second region is the superior lateral parietal cortex, which is sensitive to the ratio between new and old test list items (Yonelinas *et al.,* 2005). Furthermore, the medial parietal cortex has been found to have two regions of activity that are functionally distinct: a superior region that responds to familiarity confidence, and an inferior region that responds to recollection (Yonelinas *et al.,* 2005). Studies have suggested that the parietal cortex provides input as to whether an item is old or new, and the input is used in conjunction with signals from the hippocampus and prefrontal cortex to make a decision.

Monoamine Oxidase A

Polymorphisms of the gene that codes for monoamine oxidase A (MAO-A), can have drastic implications for cognition and memory function, as individual genetic differences can contribute to differences in attentional processes as well as neuromodulator availability and efficiency (Fan *et al.,* 2003). MAO-A is an enzyme that catalyzes the degradation of the monoamines norepinephrine, serotonin, and dopamine. The depletion of these neurotransmitters is exacerbated in individuals with the 4R variable number tandem repeat (VNTR) upstream of the gene that codes for MAO-A (Sabol *et al.,* 1998). The depletion of neurotransmitters is thought to be due to the polymorphism having an effect on the transcriptional activity of the gene promotor region for MAO-A. Individuals may have the 30 base pair repeated sequence in either 3, 3.5, 4, or 5 copies, but those alleles with 4 copies of the repeat sequence have been shown to be transcribed as much as 10 times more efficiently (Sabol *et al.,* 1998) leading to less norepinephrine, epinephrine, dopamine, and serotonin availability. Therefore, we separated our subjects into two groups. One group was comprised of individuals homozygous for the 4R variation (High MAO-A) with the second group incorporating all other subjects (Low MAO-A), including those with one 4R allele in combination any other variation.

The monoamines have been linked to episodic memory in numerous studies, and have been found to be important in long-term potentiation, thereby influencing encoding and recall of episodic memory (Lisman & Grace, 2005). A recent study

found that administering pharmaceuticals that blocked the reuptake of monoamines contributed to improvements in episodic memory, as well as working memory (Herrera-Guzmán *et al.,* 2009). Included in the wide body of evidence suggesting that monoamines are important in the proper functioning of episodic memory is a recent study done by Lisman and Grace. They found that dopamine plays a key role in learning reinforcement, as well as in the formation of episodic memory (Lisman & Grace, 2005). The monoamines have also been studied in both human and animal models, and results indicate the key role they play in long-term potentiation during episodic memory formation and retention (Schott *et al.,* 2006).

As many of these monoamines have been linked to episodic memory, we hypothesized that individuals homozygous for the 4R MAO-A polymorphism would show differences in mean EEG signal amplitudes during recognition memory. A recent study by Schulze *et al.,* (2000) found that increased MAO-A gene promotor alleles lead to higher MAO-A activity, and was found to be a contributing factor to risk of major depressive disorder in females, suggesting a possible link between memory function, MAO-A, and depression.

Overall, studies generally agree that the monoamines are a vital component of the efficiency and performance of episodic memory in daily life. We therefore hypothesize that there will be a difference between mean hit and correct rejection amplitudes over the ROIs and timeframes during item and source tasks.

Methods

Participants

The experiment and data collection were performed as part of a dissertation by Erika Nyhus in Boulder, Colorado. The fifty-nine right-handed participants (thirty-three males and twenty-seven females) all gave informed consent, and were given monetary compensation for their participation. Thirty-seven were in the High MAO-A group, and twenty-two were in the Low MAO-A group. Participants had an average age of 20.7 years, and an age range of 18-29.

Procedure

Eight hundred adjectives were used as experimental stimuli, with an additional 15 adjectives used for practice. Words used were common English adjectives (e.g. happy, dirty) approximately equated for word frequency (M=34.86, SD=86.96, range 0:1171) based on the Kucera and Francis (1967) word norms. Adjectives were presented on an LCD computer in white upper case letters, and appeared on a black background subtending a visual angle of 2.3 degrees (Nyhus, 2010).

Subjects performed an item and source memory task. Encoding task and memory status were manipulated within subjects, and word lists were randomized across encoding tasks. For the source retrieval condition, subjects encoded stimuli as they carried out both a Place task and a Pleasant task (Dobbins & Wagner, 2005).

Subjects were presented with instructions and then a short practice study block, (consisting of 10 study words) per session. Once the practice study blocks were completed, subjects then moved on to the study block, viewing 204 words per block. Primary and recency buffers were provided in the form of two words at the beginning and end of the list. Subjects were instructed to picture a mental image of a spatial scene described by the adjective to encode half of the study words (for example, in the Place task, for "LARGE," an elephant might be imagined). Half of the study words were encoded in association with the pleasantness of the word (for example, in this Pleasant task, "SAD" might be imagined by the subject as not very pleasant).

After the encoding task subjects were asked to rate how successfully they performed each task, in order to strengthen the memory trace (Figure 1). Subjects pressed one of four buttons using their index and middle fingers on both hands. They could select 1 (unsuccessful), 2 (partially), 3 (with effort), or 4 (with ease). Before each word, a 500 ms cue (Place/Pleasant) was presented to indicate which encoding task the subject was to perform, followed by the presentation of a 200 ms blank screen. Next the adjective was presented and displayed for 500 ms, after which the encoding task was performed during a 4000 ms fixation.

Following the study block, subjects were presented with a short practice test block of 15 test words while wearing the EEG sensor net. Approximately 30 minutes after the study list, subjects began the test block.

Genotyping

Saliva samples were collected from subjects using a commercial product (Oragene™, DNAgenotek, Ottawa, Ontario, Canada), in order to obtain genomic DNA (Bornstein & Badre, 2011). Subjects were then genotyped and separated on the basis of the 4R variation of the gene coding for MAO-A. Those that were homozygous for the 4R variation were assigned to the High MAO-A group, while all other subjects (those with one 4R allele and any other allele combination other than a second 4R allele) were assigned to the Low MAO-A group. The 4R/4R variation of the polymorphism is the more efficient MAO-A enhancer, transcribing MAO-A 2-10 times more efficiently than other variations of the polymorphism (Sabol *et al.,* 1998).

EEG Analysis

A 128-channel HydroCel Geodesic Sensor NetTM connected to an AC-coupled, 128-channel, high-input impedance amplifier (200MΩ, Net Amps TM, Electrical Geodesics Inc., Eugene, OR) was used to collect scalp voltages from participants during the testing phase of the experiment. Individual sensors were adjusted until impedances were less than 50kΩ, and amplified analog voltages (0.1-100 Hz bandpass) were digitized at 250 Hz.

ERP Lab (Lopez-Calderon, J., & Luck, S.J., 2014) was used to pre-process all subjects. The data was filtered from 0.1 to 40 Hz and re-referenced to average. Then the data was epoched using settings of -800 ms to 1500 ms in order to separate Correct Rejections, Hits, Misses, and False Alarms. The data was re-referenced to

average, and baselined from -800 ms to 0 ms. Afterwards, subject data was put through moving window rejection (with channel wavelengths registering above 100 mV being rejected in 50 ms windows) and manual inspection of channels in EEG Lab.

We analyzed the item and source data using groupings of electrodes for different brain regions (regions of interest) within specific timeframes (Figure 2). We examined three regions of interest (ROIs) and three timeframes. The ROIs were the left anterior superior (LAS), the right anterior superior (RAS), and the left parietal superior (LPS). The three time points analyzed were 300-500 ms, 500-800 ms, and 1000-1500 ms. We ran three repeated measures ANOVAs to assess differences in ERP amplitudes on our collected data, using SPSS software. For the early (300-500 ms) effect , a 2 (condition; hits vs correct rejections) x 2 (hemisphere; LAS vs RAS) x 2 (group; 4R/0 and 4R/4R) repeated measures ANOVA was run. For the mid parietal effect (500-800 ms in LPS) a 2 x 2 repeated measures ANOVA was run with condition (hits and correct rejections) and group as variables. The third test was same test but for RAS 1000-1500 ms

Behavioral Analysis

Reaction times and proportion accurately identified were calculated for subjects under both the hit and correct rejection conditions. Using a significance of $p > 0.05$, 2x2 repeated measures ANOVAs were performed for item and source memory tasks, in order to determine any differences between genotype groups.

These were done in both the reaction time analysis and proportion accurately identified analysis

Results

Parietal Effects

A main effect of condition was found in the item task ($F_{(1, 57)} = 4.892$, $p = 0.031$), as well as a condition by group interaction ($F_{(1, 57)} = 4.197$, $p = 0.045$). Paired sample t-tests within each group show a significant difference between mean hit (mean hit amplitude = 0.8462, +/- 0.2608) and correct rejection (mean correct rejection amplitude = 1.2906, +/- 0.2752) amplitudes in the Low MAO-A group ($t_{(21)} = 3.28$, $p = 0.004$), but not the High MAO-A group (mean hit amplitude = 1.1075, +/- 0.3060 : mean correct rejection amplitude = 1.7095, +/- 0.2810, $t_{(21)} = 1.804$, $p = 0.076$). This illustrated the old/new effect, and importantly, it was seen in the Low MAO-A group but not in the High MAO-A group (the group homozygous for the 4R variation; see Figures 3 and 4). Independent t-tests directly comparing mean amplitudes of hits and correct rejections between the Low MAO-A and High MAO-A groups were not significant for the High MAO-A group ($t_{(36)} = 0.122$, $p = 0.903$) , but were significant for the Low MAO-A group ($t_{(21)} = 3.278$, $df = 21$, $p = 0.004$). The results of the paired and independent t-tests suggest the condition x group interaction in LPS was caused by an increase in correct rejection amplitudes in the high MAO-A group.

For the source task we also found a main effect of condition ($F_{(1,57)} = 6.514$, $p = 0.013$), and an interaction of hemisphere by group ($F_{(1,57)} = 4.631$, $p = 0.036$). We saw no between subject effects, but did see a main effect of condition within-subjects for the source task ($F_{(1,57)} = 57.044$, $p < 0.000$). We saw no significant condition by group interaction in the source task or for the High MAO-A group.

Early Frontal Effects

We saw no significant condition by group interactions in the 300-500 ms time frame in LAS for item task ($F_{(1,57)} = 0485$, $p = 0.489$), and saw no significant condition by group interaction for source task ($F_{(1,57)} = 0.001$, $p = 0.976$).

Late Frontal Effects

In the RAS ROI 1000-1500 ms post-stimulus during the item task, we found a main effect of condition ($F_{(1, 57)} = 6.587$, $p = 0.013$), meaning that hit amplitudes were greater than correct rejection amplitudes. We also found a main effect of condition in the source task ($F_{(1,57)} = 11.269$, $p = 0.001$).

Behavioral Effects

No significant results were found in our behavioral data analysis.. However, if we were to have used a wider age range of participants it is possible that we would have had significant results here (Figure 5).

Discussion

We found that there was an old/new effect over the left parietal cortex 500-800 ms after stimulus was presented, indicated by mean peak amplitudes in this ROI and timeframe being greater for hits than correct rejections. Our results showed that there was an interaction between mean hit and correct rejection amplitude over the left parietal cortex and MAO-A group. Those individuals in the low MAO-A group showed the old/new effect. Critically, our results show that the High MAO-A group did not show an old/new effect because of higher correct rejection amplitudes. Elevated MAO-A levels result in decreased availability of monoamines due to degradation (Meyer *et al.,* 2006). These results suggest that new stimuli are identified as old by the left parietal cortex due to decreased monoamine availability.

I hypothesize that the parietal cortex signal is identifying new items as old items, and that it is only part of a larger system. Because we saw no significant results in our behavioral data, this suggests that the parietal cortex is not making the final decision on whether an item is old or new. Therefore the parietal cortex is most likely being overridden by the prefrontal cortex, as well as being influenced by possible input from the hippocampus. Functional imaging studies suggest that the parietal cortex contributes to the retrieval and encoding of episodic memory (Wagner *et al.,* 2005).

MAO-A and Depression

A recent study by MacBeth and colleagues (2008) indicated that changes in monoamine levels in the brain may play a role in alterations of observed behavior. Higher monoamine activity was correlated with better performance on recognition memory tasks (MacBeth, *et al.,* 2008). The difference in MAO-A levels potentially resulted in no differentiation between hits and correct rejections in their ERP signals during the task, as well as their lack of old/new effect in the item task. Therefore, subjects that had impaired performance on recollection memory tasks may have done so because their genetic polymorphism of the gene coding for MAO-A results in much more efficient than normal degradation of monoamines. Schulze *et al.,* (2000) also found that the long copy of the allele (4R) is more functionally active than the short allele (3R). This in turn may lead those individuals homozygous for the 4R variation to have less available monoamines.

There may be a potential link between risk of depression and a reduction in MAO-A levels, since depression has been found to affect the distribution of not only attention, but all aspects of working memory (Christopher & MacDonald, 2005). The monoamine theory of depression proposes that monoamine systems in the brain have an important, direct role in depression (Heninger *et al.,* 1996). Furthermore, Meyer *et al.,* (2006) found a significant elevation in MAO-A levels (34% on average) in all brain regions in individuals afflicted with major depressive disorder, compared to a healthy control group. Research suggests that elevated MAO-A activity results in greater susceptibility for major depressive disorder in

female rats, as well as evidence for a positive association between recurrent major depression and the MAO-A polymorphism (Schulze *et al.,* 2000).

Decreases in serotonin, dopamine, and norepinephrine have been attributed to depression and depressive illness (Youdim & Buccafusco, 2005). Giller *et al.,* (1982) examined the efficacy of MAO inhibitors in the treatment of depressed patients, and found that patients with mild to moderate depression an anxiety responded well to MAO inhibitors, despite not being responsive to other antidepressants. This suggests that the level of monoamines available in the brain is a key factor in depression and its treatment.

Depression and Memory

Recent studies have stated that impairments in memory to be associated with depression. Brand, Jolles, and Gispen-de Wied (1992) found that depressed individuals exhibited impairments when encoding information, as well as showing impairments in retrieval processes. The depressed subjects recalled fewer words on average than the control subjects, and despite demonstrating deficits in retrieval; the depressed subjects had no encoding deficit (Brand, Jolles, & Gispen-de Weid, 1992).

It has also been argued that depression is associated with impairments in cognitive function relating to numerous memory processes, including episodic memory, selective attention, and working memory (Dillon & Pizzagalli, 2007). Ilsley, Moffoot, and O'Carroll (1995) also found that depressed subjects exhibited deficits

in memory retrieval but not in encoding, suggesting that individuals with depression are impaired in search and retrieval processes of encoded information.

In summary, our results showed an interaction between mean hit and correct rejection amplitude over the left parietal cortex and MAO-A group. However, individuals homozygous for the 4R variation did not show an old/new effect, due to increased correct rejection amplitudes. These results indicate that less availability of monoamines leads to new stimuli being identified as old by the left parietal cortex.

Future research on depression may be well served by examining the function and properties of monoamines, and developing treatments that regulate monoamine levels in the brain. Because the monoamines are thought to be important components of numerous cognitive processes, any impact on these neurotransmitters has the potential to result in various cognitive impairments, in particular those evidenced in depression. Due to the multitude of research implicating a correlation between depression and memory deficits – and citing the importance of monoamines in memory function – further study into the relationships among monoamine and memory performance may be beneficial in gaining a better understanding of the mechanisms and causes of depression.

Figures

Figure 1: Design of training and testing blocks used in the item and source tasks.

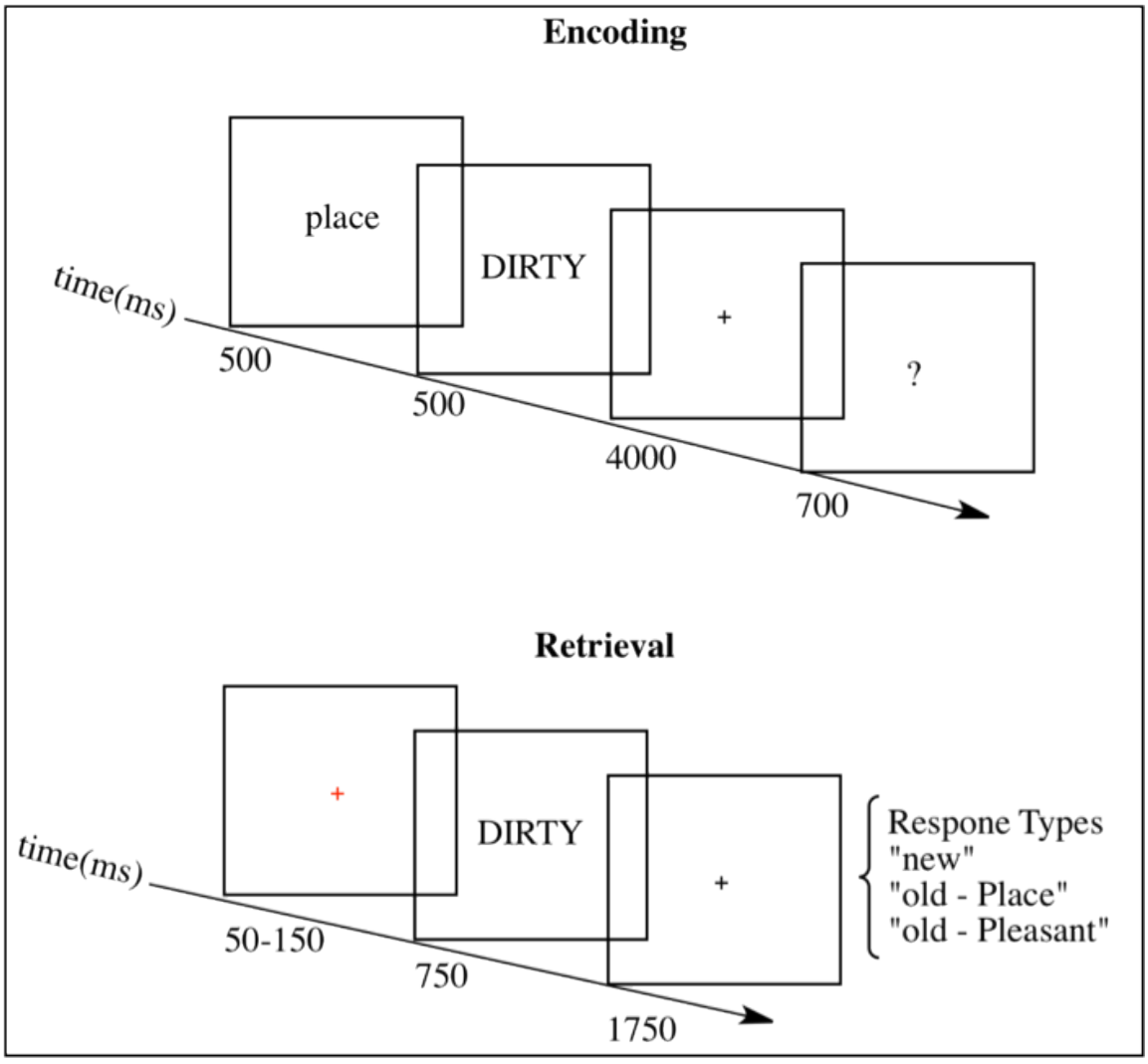
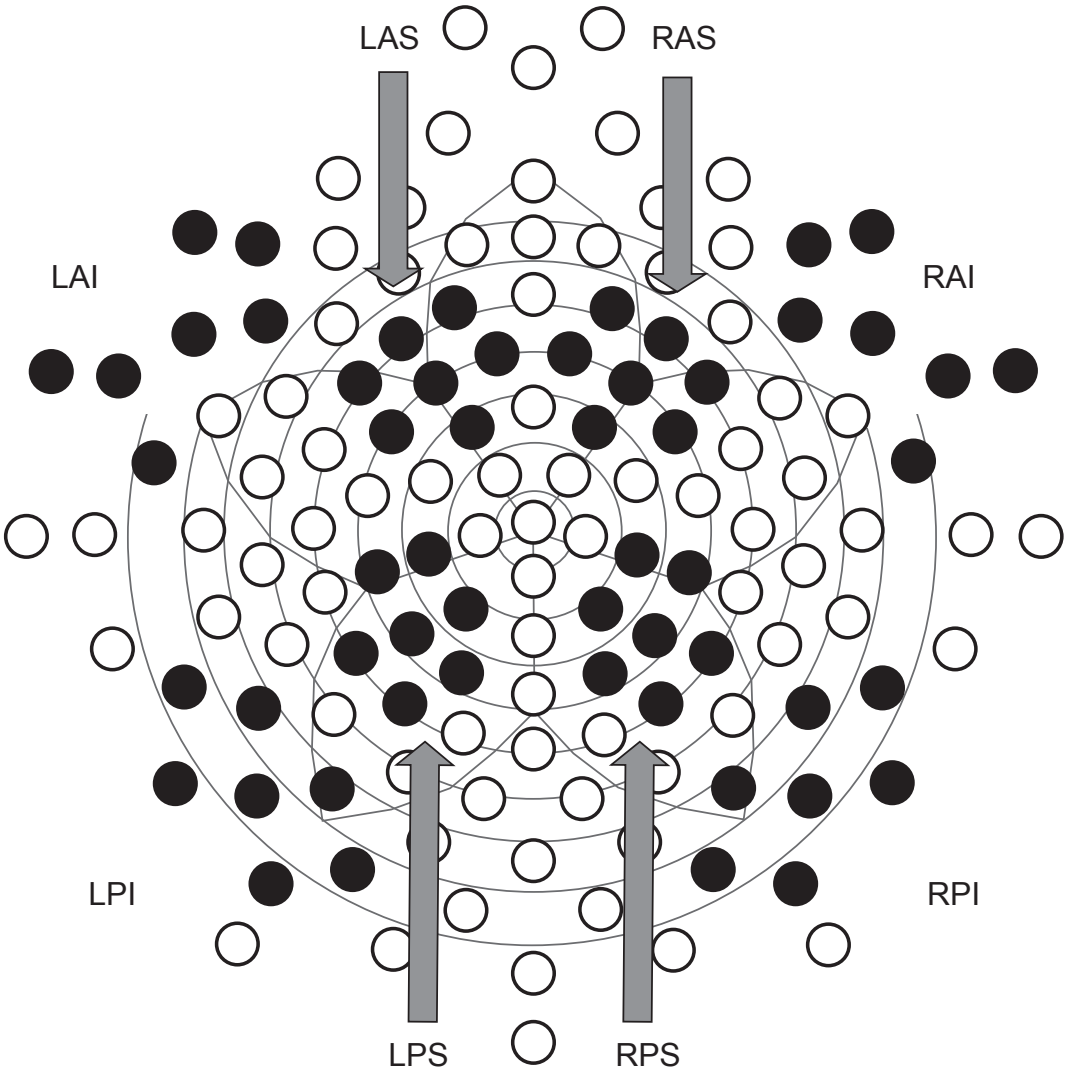


Figure 2: Electrode groupings on the scalp for the regions of interest.



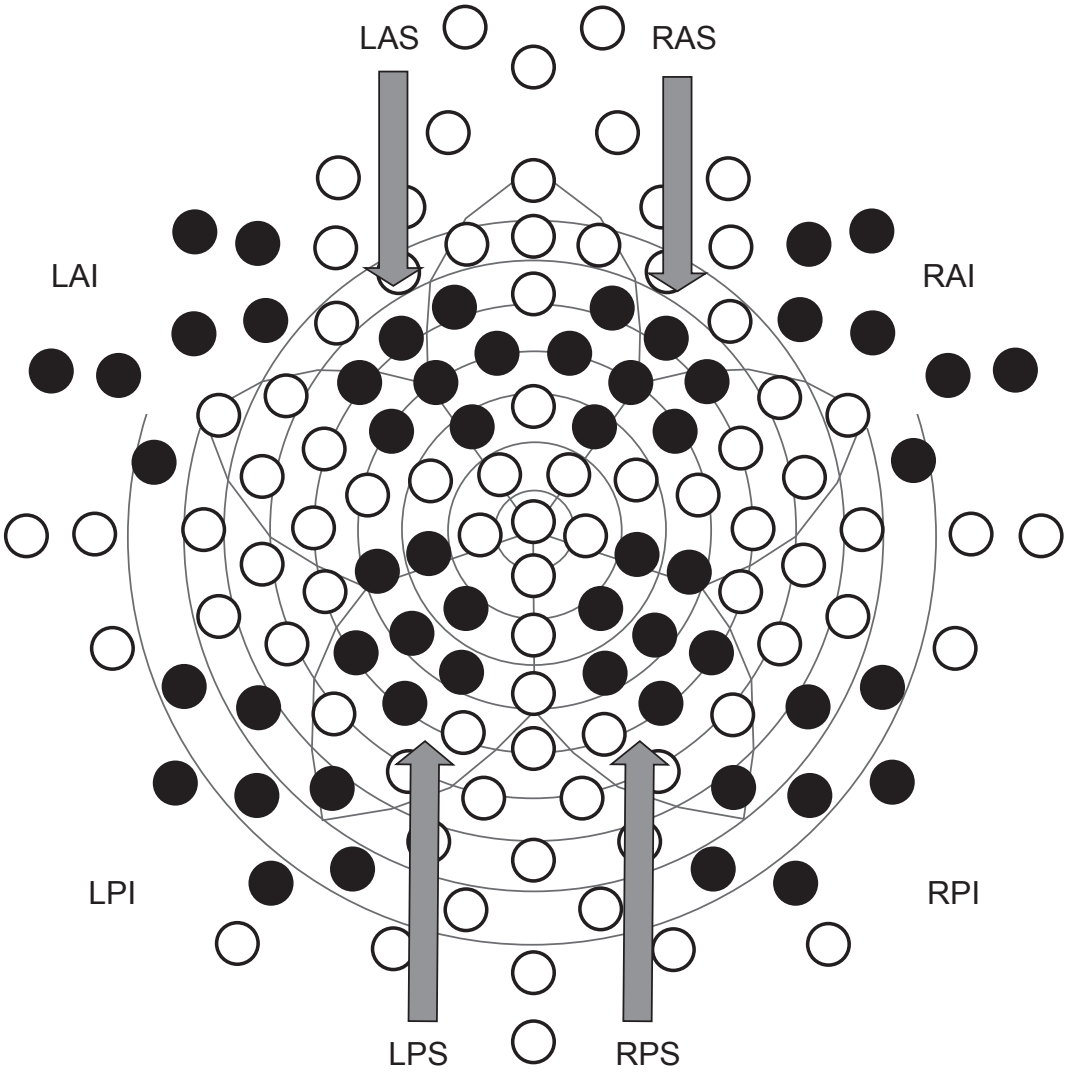


Figure 3: ERP waveforms during item memory in LPS. Differences by MAO-A group are seen (High MAO-A group is blue, low MAO-A group is orange). There was a significant difference in amplitudes for the Low MAO-A group but not for the High MAO-A group.

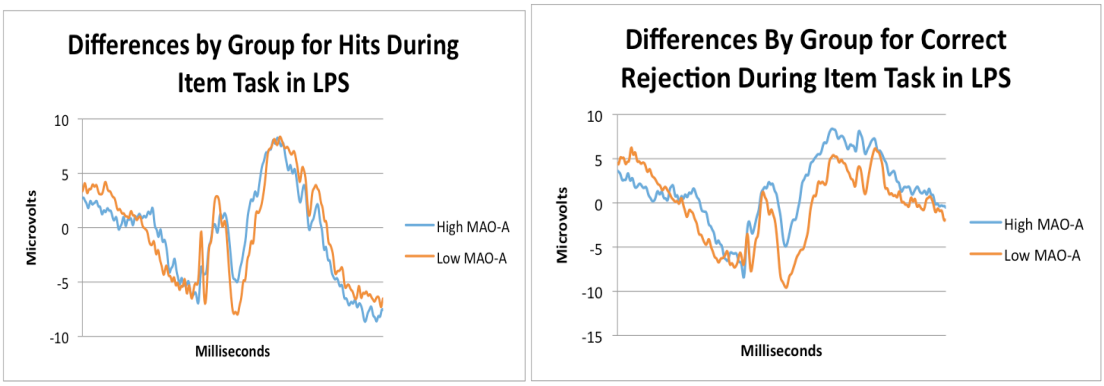
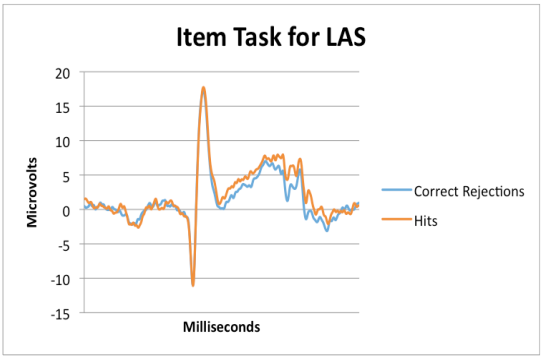
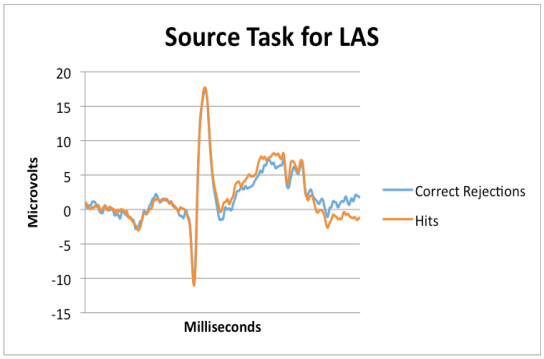
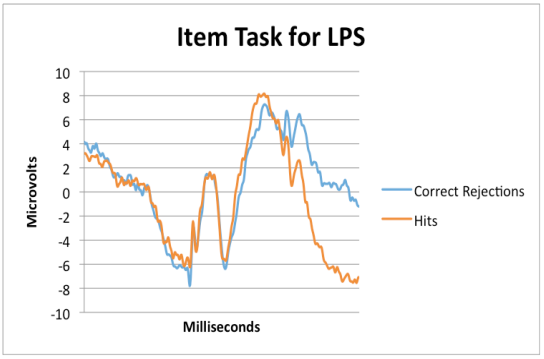
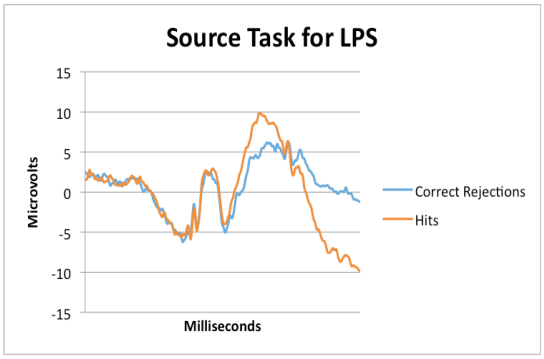


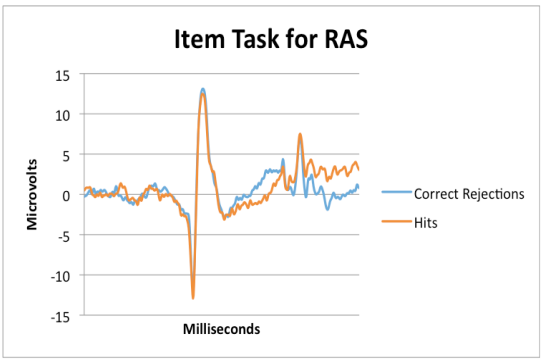
Figure 4: ERP waveforms for LAS, LPS, and RAS over all subjects.











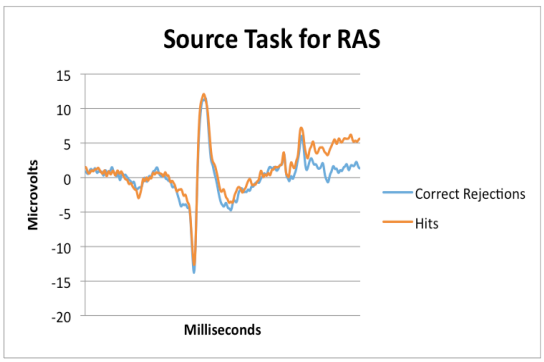
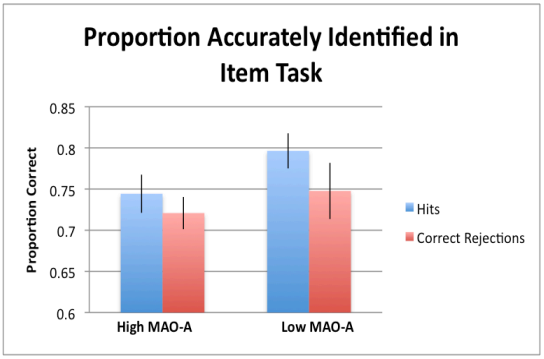
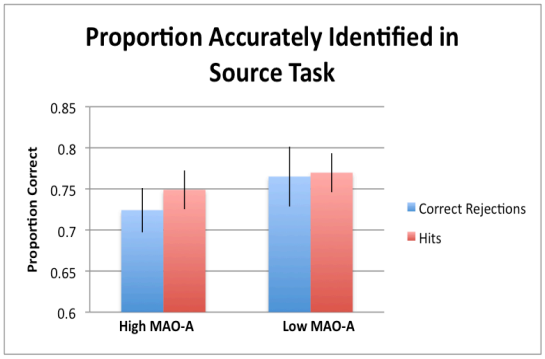
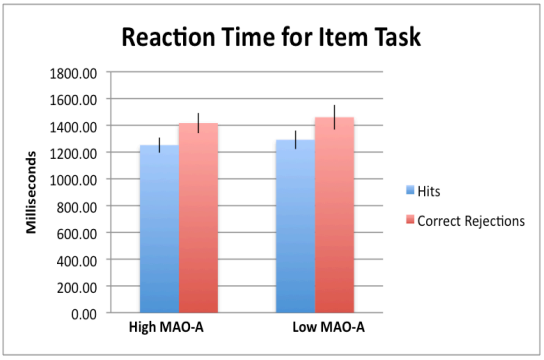
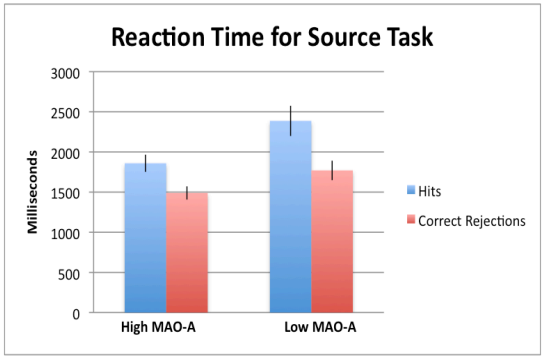


Figure 5: Behavioral data analysis results - proportion accurately identified and reaction time for both item and source tasks.









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