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Analysis of acute naproxen administration on memory in young adults: A randomized, double-blind, placebo-controlled study

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Abstract

Nonsteroidal anti-inflammatory drugs work by non-selectively inhibiting cyclooxygenase enzymes. Evidence indicates that metabolites of the cyclooxygenase pathway play a critical role in the process of learning and memory. We evaluated whether acute naproxen treatment impairs short-term working memory, episodic memory, or semantic memory in a young, healthy adult population. Participants received a single dose of placebo or naproxen (750 mg) in random order separated by 7–10 days. Two hours following administration, participants completed five memory tasks. The administration of acute high-dose naproxen had no effect on memory in healthy young adults.

Keywords

Naproxen, NSAID, memory, working memory, episodic memory, young adults

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed and available over the counter to reduce pain and inflammation. NSAIDs inhibit the activity of cyclooxygenase (COX) enzymes. Constitutive COX-2 protein is detected in neurons of the hippocampus and cortex, structures essential for memory (Adams et al., 1996). NSAIDs have been shown to suppress long-term potentiation and antagonize long-term depression (Murray and O'Connor, 2003), suggesting that they could have adverse effects on memory. Multiple studies using different animal models have shown memory impairments associated with NSAIDs (Hölscher, 1995; Rall et al., 2003).

The relationship between NSAIDs and behavioral measures of human memory is unclear. Correlational studies on the chronic administration of NSAIDs and measures of cognitive abilities in in elderly humans have been published. The results of these studies are highly variable – from NSAID-associated deficits (Goodwin and Regan, 1982), to no-association (Hanlon et al., 1997), to NSAID-associated benefits (Jonker et al., 2003). Experimental paradigms have shown no effect of NSAIDs or suggest potential cognitive decline with long-term use (Price et al., 2008).

Whether the acute administration of NSAIDs affects cognition in young adults is unknown as neither experimental nor correlational studies have been reported. We evaluated acute naproxen administration on a range of memory tasks optimized to assess long-term episodic memory, semantic memory, and short-term working memory.

Methods

The protocol was approved by Syracuse University and SUNY Upstate Medical University IRBs (# 367423). The experiment was a placebo-controlled, randomized, double-blind study. Data from 49 younger adults (82% female, ages 18–26) with no self-reported health problems and no contraindicated health history are reported. Each participant received a single dose of placebo or naproxen (750 mg) in random order separated by 7–10 days. Two hours following administration, participants completed five memory tasks (Figure 1). Three were long-term tasks, two measuring episodic memory (single-item recognition and associative recognition) and one measuring semantic memory (lexical decision). Two were short-term tasks measuring verbal span (operation span) and visual-spatial (multiple update). Full methodological details and data analyses are reported in the supplementary material (https://osf.io/dzmby/).

Results

There was no difference in performance under naproxen and placebo for any of the memory tasks (Table 1). Meta-cognition, as measured by confidence in the episodic memory tasks, was not affected by naproxen.

Discussion

This is the first randomized, placebo-controlled, double-blind, within-subject study to test whether acute naproxen administration alters memory in healthy young adults. We chose naproxen because it is an over-the-counter and clinically useful NSAID that

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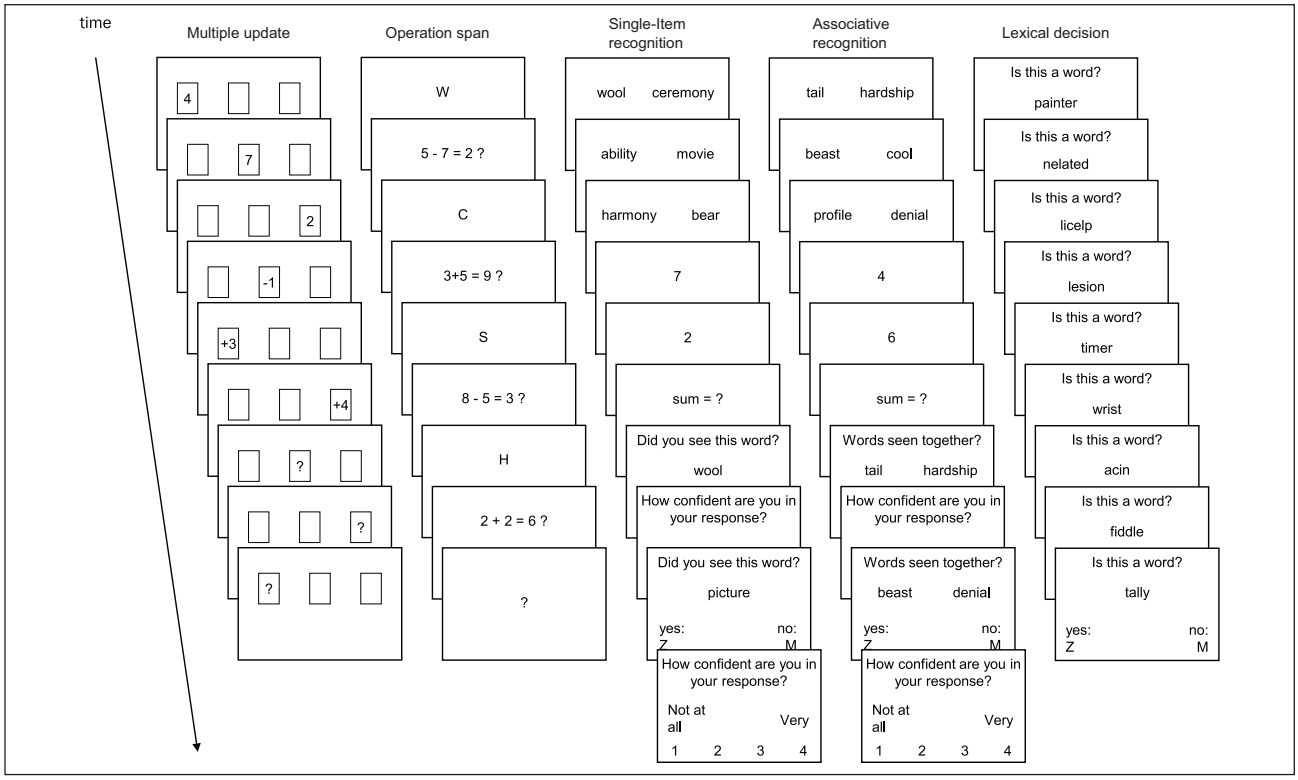

Figure 1. A schematic of the flow of each of the five memory tasks. Each box represents a successive display on the computer screen. In the multiple update task, participants track the sum of digits presented in each box and report the sum when a question mark appears (as in the last three example trials). In the operation span task, participants report between 4 and 8 consonants (as in the last panel), separated by math equations, which they judge to be true or false. In single-item recognition, participants are asked to endorse studied targets (wool) and reject unstudied foils (picture) following a series of encoding trials and a distractor task (summation of a series of digits). In associative recognition, participants are asked to endorse studied pairs (tail hardship) and reject rearranged foils (beast denial) following a series of encoding trials and a distractor task (summation of a series of digits). In lexical decision, participants are asked to endorse words and reject pseudo-words.

Table 1. Performance on all cognitive tasks.

Task	Measure	Placebo		Naproxen		Statistics			
		Mean	(SEM)	Mean	(SEM)	*df*	|*t*|	*p*	BF_{01}
Long-term episodic memory									
Single-item recognition	Hit rate	0.763	(0.017)	0.754	(0.019)	48	0.472	.64	5.792
	False alarm rate	0.265	(0.025)	0.288	(0.022)	48	1.413	.16	2.538
	Confidence	3.078	(0.056)	3.011	(0.060)	48	1.560	.12	2.082
Associative recognition	Hit rate	0.752	(0.020)	0.744	(0.022)	48	0.401	.69	5.964
	False alarm rate	0.149	(0.019)	0.146	(0.017)	48	0.174	.86	6.346
	Confidence	3.216	(0.058)	3.235	(0.052)	48	0.388	.70	5.993
Semantic memory / lexical decision									
Word trials	Pr(correct)	0.858	(0.008)	0.852	(0.012)	48	0.610	.55	5.398
	RT	0.587	(0.011)	0.596	(0.014)	48	0.991	.33	4.055
Non-word trials	Pr(correct)	0.936	(0.009)	0.939	(0.008)	48	0.427	.67	5.905
	RT	0.626	(0.013)	0.651	(0.019)	48	1.506	.14	2.242
Short-term / working memory									
Multiple update	Pr(correct)	0.634	(0.024)	0.644	(0.028)	46	1.498	.69	2.232
Operation span	Pr(correct)	0.699	(0.024)	0.725	(0.023)	46	0.400	.14	5.854

Note: Mean accuracy and standard error of the mean (SEM) for all conditions. Pr indicates proportion correct. RT indicates median response time in seconds. Paired samples *t*-tests were used to compare naproxen to placebo for each dependent measure. Bayes Factors (BF) indicate the relative evidence for competing models. In this case BF_{01} indicates the evidence in favor of the null hypothesis versus a model with an effect (using the default prior of a Cauchy with $r = .707$ in JASP, JASP Team, 2017). Values above 1 indicate the ratio of evidence favoring the null hypothesis. For example, $BF_{01} = 5$ means the data are 5 times more likely under the null hypothesis than the alternative hypothesis.

is rapidly absorbed. Based on these data, the acute administration of naproxen does not adversely affect episodic, semantic, or short-term working memory in healthy young adults. We assessed a broad set of memory classes, including episodic memory, for items in a specific event and the capacity to bind memories from an event together; semantic memory, specifically lexical knowledge; and verbal and spatial short-term working memory.

The absence of naproxen-related deficits across any of these tasks is interesting in light of data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) Research Group (Martin et al., 2008). In initial reports, the ADAPT group suggested that chronic NSAID administration (either celecoxib or naproxen) was associated with greater general cognitive decline (compared to placebo) in healthy older adults. Over three years, participants administered with either celecoxib or naproxen experienced a significantly greater decline in global cognitive performance versus the placebo. An exploratory analysis found that subgroups who had the greatest rates of decline in the mini-mental state measure were harmed most by naproxen administration. A follow-up study found that treatment condition was unrelated to cognitive decline in the years following treatment.

There are some reports of changes to memory associated with NSAIDs, in contrast with the null effects of naproxen we report. Two differences in methodology are clear. First, published studies recruited older adults with a family history of Alzheimer's Disease (AD)**[AQ: 1]** or who displayed cognitive symptoms of clinical or pre-clinical AD, whereas we sampled healthy younger adults. Second, published studies considered the chronic administration of NSAIDs, whereas we considered the acute effects. One potential explanation is that some aspect of aging, healthy or otherwise, leads older adults to be more susceptible to acute or chronic (or both) effects of NSAIDs on cognitive performance. The possibility that naproxen has no measurable effect on cognitive performance or general cognitive decline in either older or younger adults without underlying disease must also be considered, especially given the mixed results of correlational and experimental studies reported in the literature.

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Declaration of conflicting interests

None declared.

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