Daily oral intake of AC-11® results in a cognitive boost: A randomized double-blind cross-over placebo controlled human experiment.

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ABSTRACT

Background: AC-11® is a widely used commercially available dietary supplement that exhibit health benefits that include, improved DNA repair, reduced inflammation and increased bioavailability of aromatic amino acids. These health benefits may theoretically improve cognitive outcomes, however, the role of AC-11® on neuropsychological functions is unresolved. ***Hypothesis:*** The current research test the hypothesis that daily oral intake of AC-11® will improve neuropsychological functions. ***Research Design:*** To test the hypothesis a randomized double-blind cross-over placebo controlled pilot experiment was pursued. Standardized unsupervised neuropsychological assessments served as the main methodology. These assessments included individual tests that measure attention, memory, executive function, and social cognition. A total of 18 individuals participated in the study and each individual was relatively healthy with normal cognition at baseline. ***Results:*** The results revealed that daily oral intake of AC-11® resulted in statistically significant ($t = 2.4$, $p < 0.05$) improvement in attention, memory, and executive function. Additionally, 64% of the participants evidenced improvement in social cognition. Improvement in attention was the most resilient and persistent. ***Conclusion:*** Heathy individuals with normal cognition may use AC-11® to provide a "cognitive boost" when needed.

INTRODUCTION

Cognition is a nebulous construct. However, one reasonable conception of cognition is the coordinated response of multiple brain regions in order to execute a particular function. Such functions can range from the detection of a stimulus to complex behavioral and emotional tasks. Throughout history, healthy individuals have sought to improve their cognition to provide a competitive advantage in educational, occupational, recreational and social endeavors (Greely et al., 2008; Smith and Farah, 2011). For instance, up to 25% of university students in the United States have misused prescription stimulants to improve their cognition for educational gains (McCabe et al., 2005). Among a wider demographic, up to 62% of individuals have misused prescription drugs to enhance cognition (Maher, 2008). Survey data suggest that one in five respondents may consume drugs to improve their cognitive performance (Maher, 2008). There appears to be a need/desire among the general population to increase cognitive functions when needed (before taking an exam, completing a work-related task, etc.). However, the misuse of prescription drugs to achieve cognitive improvement can be illegal and risky due to the development of side effects such as psychosis, insomnia and irritability (Nicholson and Wilson, 2017; Woźniak-Karczewska et al., 2018). Furthermore, it is unknown whether misused prescription drugs can actually improve cognition among heathy individuals who already have normal cognition. Therefore, the perception of cognitive enhancement from the misuse of prescription drugs might be dubious at best.

The perception of cognitive enhancement can be achieved in at least three ways. One is the placebo effect, where the act of taking a drug with presumed benefits, can lead to positive cognitive outcomes when in fact the drug imbues no real effect on cognition. A second is the self-appraisal effect, where the drug alters one's perception of a given task (e.g., the amount of

work to be done and the quality of the work) without improving cognitive performance of the task (Hurst et al., 1967). A third in the arousal effect, where the drug potentiates energy, wakefulness or motivation which increases task performance yet cognition remains unchanged. Due to these confounding variables, randomized double-blind placebo-controlled experiments that employ quantitative measures of cognition are needed. Therefore, the current study was design to determine whether a dietary supplement, AC-11®, could increase cognitive performance among relatively healthy individuals with normal cognition.

MATERIALS AND METHODS

Participants

Participants were recruited for the study via digital and print announcements in Northern Arizona USA. These announcements directed prospective participants to make an appointment for an initial intake interview. Prior to this initial interview each subject was randomly assigned to a drug-then-placebo (DP) group or a placebo-then-drug (PD) group (drug = AC-11®). During the initial interview, the subjects were screened for cognitive deficiency by taking and passing the mini-mental status examination (MME) (Folstein et al., 1975). The MME is a widely used (e.g., doctor's office, hospitals or clinical settings) tool for assessing orientation in time, orientation to place, immediate recall (memory), dyscalculia, attention, delayed verbal recall (delayed memory), language repetition, language 3-stage commands, reading, and motor functions. A score ≤ 20 indicates less than ideal cognition. Each participant in the current study exhibited extremely high scores of ≥ 30. An indication that each participant was already functioning at high cognitive levels. Each participant was also queried to ascertain general health and neurologic status. All participants presented with relatively normal health and no

neurologic deficiencies. Additionally, participants were probed for eligibility for the study and basic demographic data (sex, age, educational level, etc.) were collected from each participant. A total of 18 healthy individuals with high cognitive status completed the entire study. Both adult females (N = 11) and males (N = 7) participated in the study. The participants ranged in age from 19 to 66 years old. They exhibited a range of educational achievements from high school to doctoral degrees. These participants self-identified as Caucasian, Asian, and Hispanic. All participants submitted informed written consent to participate in the study and the study received institutional review board (IRB) approval and oversight.

Neuropsychological assessments

In the current study neurocognitive functions were evaluated with unsupervised computer automated assessments from the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB is published in over 2000 peer reviewed articles and is widely used in clinical, academic and pharmacologic research (Backx et al., 2020; Barnett et al., 2016; Wild et al., 2008). The CANTAB assessments are fully automated (from testing to scoring and data tabulations) with visual on-screen and auditory voice-over guidance from training to final assessments. Each assessment began with a training paradigm to get participants familiar with the intended tasks. Once a given participant is fully trained, then the assessment commences. The training, assessments and the transition between them (and between assessments) are all unsupervised and artificial intelligence (AI) driven to remove bias induced by the interference of study staff (researchers). A total of four neuropsychological assessments (rapid visual information processing; paired associate learning; spatial working memory; and emotional bias task) were pursued in the current study. Each assessment is design to limit learning effects, therefore each assessment can be administered to the same participants over time (Backx et al.,

2020). For instance, for each test session, test stimuli are presented at random from a large pool of stimuli or alternate test stimuli were selected which limits the possibility that a given participant will complete the same stimulus induced task more than once. This adaptive paradigm ensures little or no practice effects from taking the same assessment multiple times. Figure 1 provides instantaneous screenshots of each assessment.

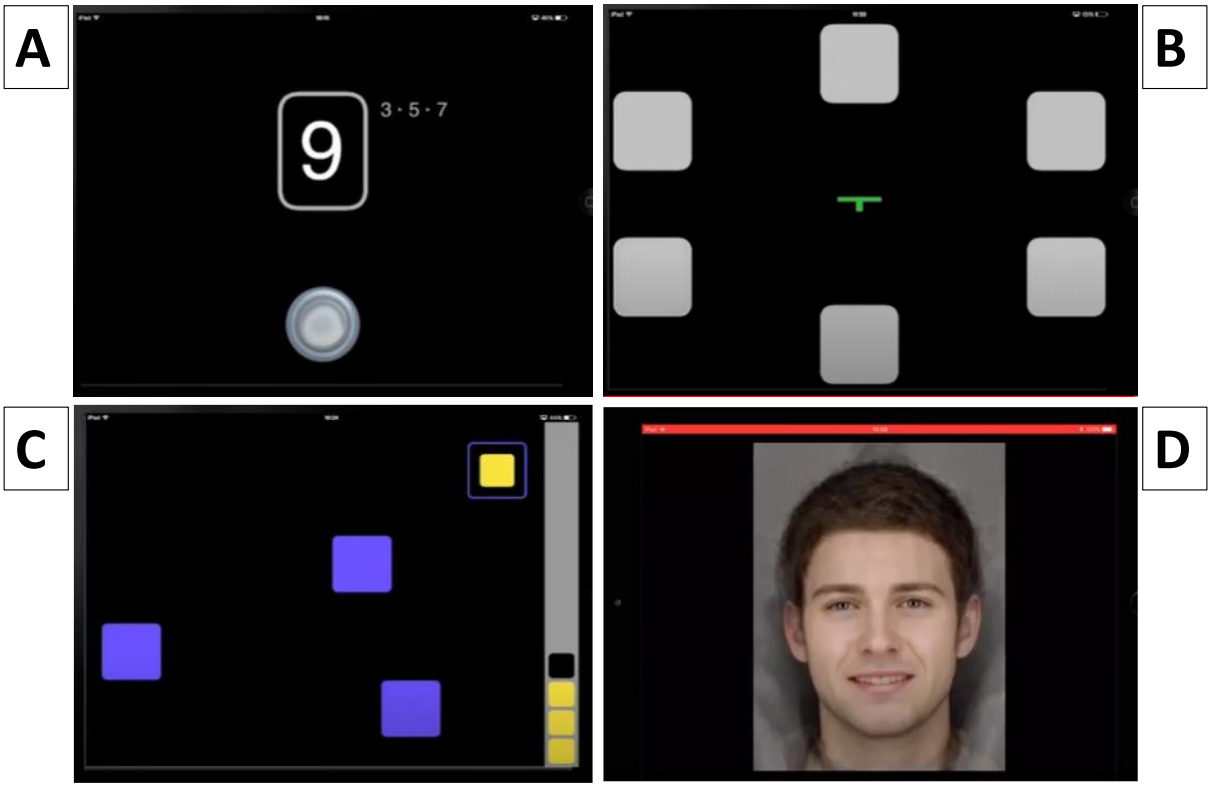

Figure 1. Computer screenshots of the neuropsychological assessments deployed in the current study. **(A)** *Attention*: rapid visual information processing. **(B)** *Memory*: paired associate learning. **(C)** *Executive function*: spatial working memory. **(D)** *Social cognition*: emotional bias task.

Rapid Visual Information Processing (RVP):

This assessment evaluates sustained attention (Backx et al., 2020; Sahakian et al., 1989). At a rate of 100 digits per minute, 1 to 9 digits are presented successively in pseudorandom order. Participants are tasked with motor responses to target sequences, such as three

consecutive odd or three even digits (3-5-7, 2-4-6, 4-6-8, etc.) as quickly as possible. Stimulus duration was 600 millisecond (ms) with no interstimulus intervals. Target sequences may be one or multiple simultaneous sequences. Outcomes measures include the mean latency (in ms) of responses to targets.

Paired Associate Learning (PAL):

This assessment evaluates visual episodic memory (Barnett et al., 2016). A number of boxes are displayed and for some boxes their unique patterns (contents) randomly appear then disappear briefly. A given pattern (content within a specific box) is then presented in the middle of the computer screen and the participant is task with remembering which of the original set of boxes contained the pattern and where the box was localized. The difficulty of this task increases with each successful trial. Outcomes measures include errors in task completion (memory errors).

Spatial Working Memory (SWM):

This assessment evaluates executive function via retention and manipulation of visuospatial information (Owen et al., 1990; Rabbitt and Lowe, 2000). The test involves the presentation of a number of colored squares (boxes). Participants are tasked with selecting the boxes and using a process of elimination, the participants should find one yellow 'token' in each of a number of boxes and use them to fill up an empty column on the right-hand side of the computer screen. The number of boxes can be gradually increased until a maximum of 12 boxes are shown for the participant to search. The color and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. Outcomes measures include errors in selecting boxes that have already been found to be empty and revisiting boxes which have already been found to contain a token (executive function errors).

Emotional Bias task (EBT):

This assessment evaluates social cognition via detection of perceptual biases in facial emotions, using images of faces displaying magnitudes between happy and disgust emotions (Kelaiditis et al., 2021; Tristão et al., 2022). Faces are present at a rate of 150 ms, followed by a two-alternative forced choice where participants must select one of the two emotions. Outcome measures include the percentage of bias towards happy or disgust emotions.

Experimental research design

The current study deployed a randomized double-blind placebo cross-over research design. Participants were randomized to one of two groups (DP or PD) before the initial intake interview. No attempt was made to equalize the number of participants in each group, therefore random allocation resulted in 11 participants in the DP group and seven participants in the PD group. The DP group started the study by taking the neuropsychological assessments at baseline then they consumed AC-11® for 1-month. AC-11® consumption included oral intake of one 350 mg capsule twice daily (total of 700 mg/day) for 30 days. At the end of this month, participants took the neuropsychological assessments again in order to determine whether AC-11® induced an improvement in scores from baseline. These same participants then experienced a washout period, where they did not take AC-11® or placebo for 1-month. At the end of this washout period, the same participants took the neuropsychological assessments again. They then consumed the placebo (350 mg capsule twice daily, total of 700 mg/day) for 1-month and at the end of this month they took the neuropsychological assessments for the final time. This particular experimental research design allows for within-group comparisons. For instance, within the same group of subjects, one can determine whether AC-11® had an effect on cognitive function and one can determine whether or not the placebo had similar or no effects.

Therefore, the research question pursued in the current study can be answered with this cross-over design on the DP group. However, to further interrogate the research question the PD group was also investigated.

The PD group started the study by taking the neuropsychological assessments at baseline then they consumed placebo for 1-month. At the end of this month, they took the neuropsychological assessments again in order to determine whether the placebo had any positive effects relative to baseline. These same participants then experienced a washout period, where they did not take placebo or AC-11® for 1-month. At the end of this washout period, the same participants took the neuropsychological assessments again. They then consumed AC-11® for 1-month and at the end of this month they took the neuropsychological assessments for the final time. This particular experimental research design allows for within-group comparisons. Therefore, one can determine whether placebo or AC-11® had an effect on cognitive function with just the PD group. Combining the two cross-over designs (that of the DP and PD groups) provide a rigorous, confirmative and powerful experimental approach for determining and evaluating efficacy of AC-11® in cognitive improvements. Additionally, all study staff (researchers) were blinded to the scoring of each neuropsychological assessment and tabulation of test results from each participant. Unblinding occurred after test scoring and data tabulations. Similarly, each participant was blinded to whether they were consuming AC-11® or the placebo. The AC-11® and placebo capsules were identical in appearance. The AC-11® capsules contained carboxy alkyl esters (CAE; active ingredient) and Manioc Maltodextrin (starch). The placebo capsules were composed of Manioc Maltodextrin. The capsule materials were composed of titanium dioxide (food coloring).

Statistical analysis

The aim of the current study was to determine whether AC-11® can improve cognitive functions among individuals with normal cognition functions. Statistical comparisons between baseline cognitive functions and cognitive functions after AC-11® consumption provides data to directly address the aim. Therefore, paired-samples *t*-tests were deployed to detect statistically significant differences relative to baseline. Two experimental groups (DP and PD) were deployed and each group served as its own within-group control, therefore, the specific aim could be evaluated with anyone of the groups (DP or PD). A *p-value* of < 0.05 was used as the significance criterion. A professional graphing and statistical software suite (GraphPad Software, Inc., La Jolla, CA. USA) was deployed for all graphing and statistical computations.

RESULTS

The purpose of the current study was to determine whether or not daily oral intake of AC-11® would improve cognitive functions among relatively heathy individuals with normal cognition. Therefore, the results from cognitive assessments after daily oral intake of AC-11® was compared to the results from cognitive assessments at baseline (at the start of the study). If AC-11® treatment resulted in cognitive test results that were better than the test results at baseline then this was interpreted as AC-11® induced improvement in a particular cognitive function. To increase the rigor of the experimental research design and to further qualify interpretations of the results, a placebo treatment condition was also included. Therefore, the results from cognitive assessments after daily oral intake of the placebo was compared to the results from cognitive assessments at baseline (at the start of the study). Four cognitive domains

were assessed in the current study and they included, attention, memory, executive function and social cognition.

Attention:

Figure 2 reveals that oral intake of AC-11® improved attention above baseline (beginning of the study) levels. Furthermore, this improvement was maintained for two months (second month of the study). Figure 2A reveals baseline attention scores, as well as attention score after 1-month oral intake of AC-11® and 1-month intake of placebo. The group who consumed AC-11® showed an improvement in attention compared to baseline while the group who consumed the placebo showed no improvement. This suggest that 1-month oral intake of AC-11® was sufficient to improve attention among normal/heathy individuals. Figure 2B shows that this positive AC-11® effect was persistent out to two months (1-month after cessation of AC-11®). Therefore, AC-11® intake enhanced attention and this enhancement was consistent across two months.

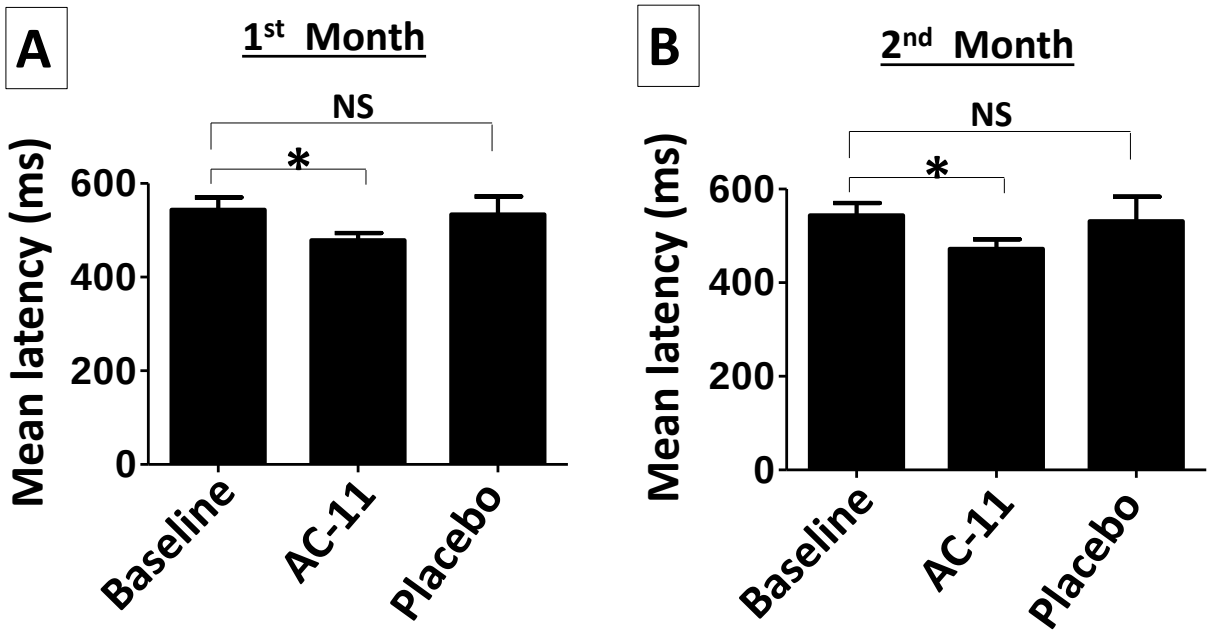

Figure 2. AC-11® improved attention within one month. **Panel A** shows that after one month of daily oral intake of AC-11® there was a statistically significant improvement in mean latency (lower scores equal better performance) compared to baseline (at the beginning of the study). Note that one month of oral intake of the placebo resulted in no statistically significant improvement compared to baseline. **Panel B** shows that the statistically significant improvement in attention that was induced by AC-11® was stable for a second month (one month after cessation of AC-11®). Note that the placebo continued to have no effect. Bars = mean ± S.E.; ms = millisecond; NS = not statistically significant; * = $p < 0.05$ or statistically significant.

Statistical computations were conducted and the results confirmed the conclusion that AC-11® improved attention. Comparing baseline attention scores to attention scores after 1-month (1-month into the study) of AC-11® intake resulted in statistically significant improvement ($t[10] = 2.376$, $p = 0.0389$; two-tailed). One month after AC-11® cessation (2-months into the study), this statistically significant effect was still maintained ($t[9] = 2.388$, $p = 0.0407$; two-tailed). However, comparing baseline attention scores to attention scores after 1-month (1-month into the study) placebo intake resulted in no statistically significant improvement ($t[6] = 0.9216$, $p = 0.3926$; two-tailed). One month after placebo cessation (2-

months into the study), there was still no statistically significant placebo effect ($t[5] = 1.563$, $p = 0.1787$; two-tailed). Therefore, only the AC-11® treatment improved attention.

Figure 3 reveals additional data that confirmed the positive effect of AC-11® on attention. Figure 3A show the results for a group of participants who received placebo the first month of the study and their attention scores were similar to their scores at baseline. This indicates that placebo had no effect on attention. These same participants then went through a month long washout period (break or rest period). After this washout period their scores did not change and remained the same as that at baseline. However, when AC-11® was introduced and the same participants consumed AC-11® for 1-month, there was a significant improvement in their attention scores compared to baseline scores. This suggest that the introduction of AC-11® to the placebo group resulted in the improvement of their attention scores. Figure 3B further interrogates this conclusion by showing the results for a group of participants who received AC-11® the first month of the study and their attention scores were improved relative to their scores at baseline. This indicates that AC-11® had a positive effect on attention. These same participants then went through a month long washout period (break or rest period). After this washout period their scores remained improved relative to baseline. Interestingly, when placebo was introduced and the same participants consumed the placebo for 1-month, there scores continued to be better than that at baseline. This further confirmed that the introduction of AC-11® improved attention and this improvement may last months after cessation of AC-11® intake.

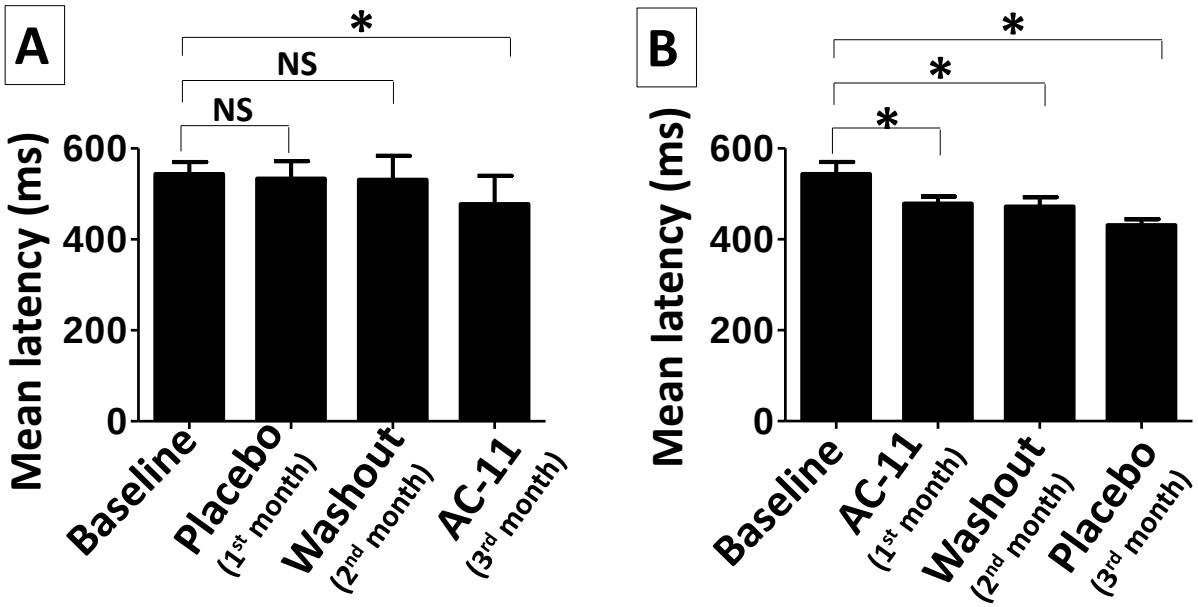

Figure 3. Late-stage oral intake of AC-11® improved attention. **Panel A** shows the participants who experienced daily (1st month) oral intake of the placebo, then they experienced 30 days of no treatment (washout period: 2nd month) and lastly, these same participants took AC-11® for 30 days (3rd month). Note that the only statistically significant improvement in attention occurred at 3 months due to AC-11® treatment (lower scores equal better performance). **Panel B** shows the participants who experienced daily (1st month) oral intake of AC-11®, then they experienced 30 days of no treatment (washout period: 2nd month) and lastly, these same participants took the placebo for 30 days (3rd month). Note that AC-11® treatment improved attention after one month of treatment and this improvement continued out to 3 months. Furthermore, placebo intake did not prevent this positive effect of time. Bars = mean ± S.E.; ms = milliseconds; NS = not statistically significant; * = $p < 0.05$ or statistically significant.

Statistical computations were conducted on the data in Figure 3. There was no statistically significant ($t[6] = 0.9216$, $p = 0.3923$; two-tailed) difference between baseline attention scores and attention scores following placebo treatment. Similarly, there was no statistically significant difference ($t[5] = 1.563$, $p = 0.1787$; two-tailed) between baseline attention scores and attention scores following the washout period. However, there was a statistically significant difference ($t[8] = 3.468$, $p = 0.0085$; two-tailed) between baseline attention scores and attention scores following AC-11® intake. This suggest that AC-11® was

successful at improving attention among the group of participants who consumed the placebo first then AC-11® second. Interestingly, AC-11® was also success at improving attention among the group of participants who consumed AC-11® first then placebo second. For instance, there was a statistically significant ($t[10] = 2.376$, $p = 0.0389$; two-tailed) difference between baseline attention scores and attention scores following AC-11® intake. Similarly, there was a statistically significant difference ($t[9] = 2.388$, $p = 0.0407$; two-tailed) between baseline attention scores and attention scores following the washout period. Lastly, there was a statistically significant difference ($t[8] = 3.468$, $p = 0.0085$; two-tailed) between baseline attention scores and attention scores following placebo intake. Therefore, it appears that the AC-11® induced improvement in attention was sustained beyond the washout period and even after placebo intake.

Memory:

Figure 4 reveals that daily oral intake of AC-11® may improve memory. The group of participants who were treated with placebo evidenced no improvement in memory compared to their baseline memory scores. This suggest that placebo intake did not increase or decrease their memory performance. Interestingly, these same participants showed improvement in memory after the 1-month washout period. It is unknown why the participants would exhibit improvement in memory at this stage of the study since the washout period is a period where they refrained from both placebo and AC-11® intake. When these same participants consumed AC-11® their memory scores continued to improve. This suggest that AC-11® intake does not impede improvements in memory and may contribute to better memory.

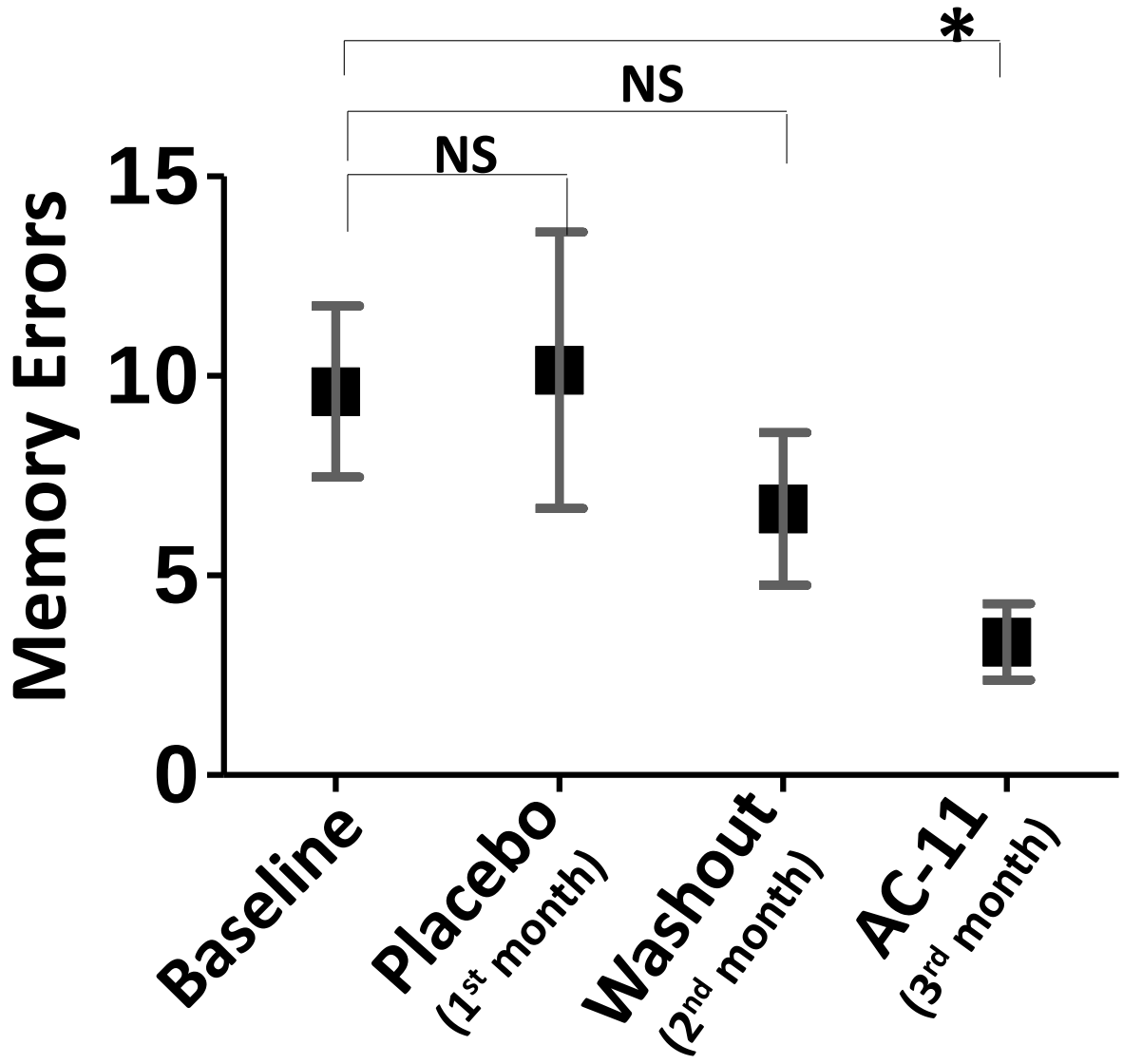

Figure 4. Oral intake of AC-11® improved memory. The figure shows quantification of memory errors for participants at baseline (the beginning of the study). These participants first experienced 1-month of placebo by oral intake. Note that their memory errors did not improve after 1-month of placebo intake. Next, the participants experienced a 1-month washout period (rest period). Their memory errors were reduced but still not statistically different from baseline. Lastly, the participants experienced 1-month of oral intake of AC-11®. Note that their memory errors now showed a statistically significant improvement (lowest scores) compared to their scores at baseline. Boxes = mean ± S.E.; NS = not statistically significant; * = $p < 0.05$ or statistically significant.

Statistical computations revealed that there were no significant difference between memory scores at baseline and memory scores after placebo intake ($t[6] = 0.7101$, $p = 0.5043$; two-tailed). This is an indication that the placebo had no effect on memory. Additionally, there was no statistically significant difference ($t[5] = 1.736$, $p = 0.1431$; two-tailed) between memory scores at baseline and memory scores after 1-month of washout. This suggest that although memory scores showed some level of improvement, this effect was not significantly difference from chance. However, statistical computations revealed that there was a significant difference ($t[5] = 2.951$, $p = 0.0318$; two-tailed) between memory scores at baseline and memory scores after AC-11® intake. This suggest that the AC-11® induced improvement in memory scores was not due to chance.

Executive Function:

Figure 5 reveals that daily oral intake of AC-11® may improve executive function among healthy individuals with normal cognitive functions. One month after AC-11® intake there was a noticeable improvement in executive function. This improvement continued and even became more pronounced after a 1-month washout period. It is possible that AC-11® may provide both short and long-term benefits to executive function and the long-term benefits may be the most prominent. However, placebo intake reversed this trend by creating worse scores among the same participants. It is not clear why the participants would produce poor scores after placebo, but the data suggest that the positive effect of AC-11® on executive function may only last for 2-months. After this 2-month time point, executive function may return to more baseline levels.

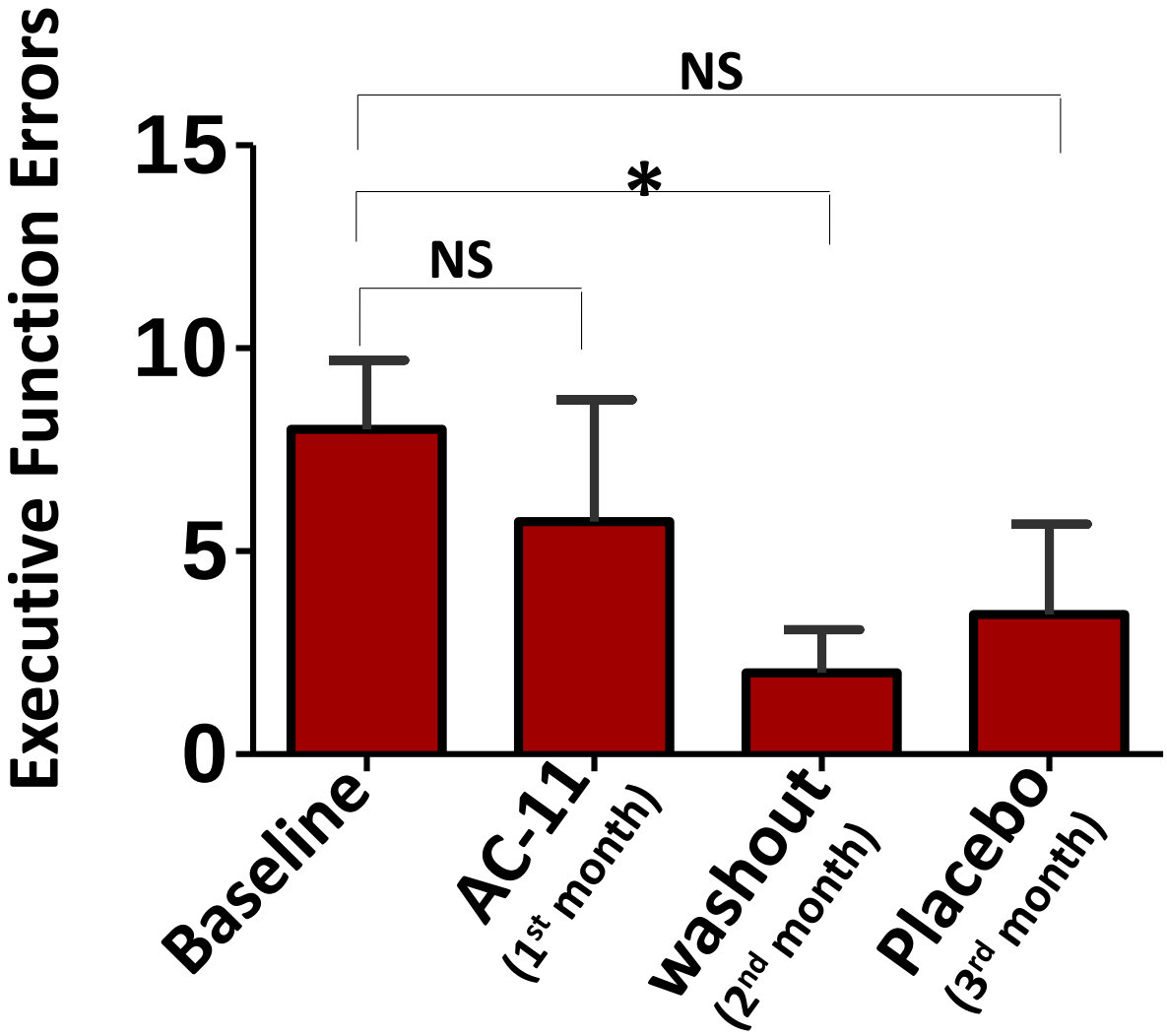

Figure 5. Oral intake of AC-11® improved executive function (e.g., retention and manipulation of visuospatial information). The figure shows quantification of executive function errors for participants at baseline (the beginning of the study). These participants first experienced 1-month of AC-11® by oral intake. Note that their executive function errors did not improve after 1-month of AC-11® intake. Next, the participants experienced a 1-month washout period (rest period). Their executive function errors were significantly reduced and statistically different from baseline. This suggest that the AC-11® intake had a delayed effect on improving their executive function. This was confirmed by the fact that placebo treatment caused an increase in executive function errors. Bars = mean ± S.E.; NS = not statistically significant; * = $p < 0.05$ or statistically significant.

Statistical computations further confirmed the positive effect of AC-11® intake. At 1-month after AC-11® treatment the mean scores were better than that at baseline but did not reach statistical significance ($t[10] = 1.656$, $p = 0.1287$; two-tailed). However, after an additional month (2-month study duration) there was a statistically significant improvement ($t[9] = 3.712$, $p = 0.0048$; two-tailed) in executive function. This indicates that it may take 2-months after the cessation of AC-11® intake to observe a significant improvement in executive function. In contrast, other cognitive domains, such as attention showed improvement as early as 1-month following cessation of AC-11® intake. Statistical computations also showed that executive function may return to baseline levels ($t[8] = 2.253$, $p = 0.0543$; two-tailed) after 3-months. A further indication that AC-11® induced improvement in executive function may only extent out to 2-months.

Social Cognition:

Figure 6 reveals that daily oral intake of AC-11® results in a positive social disposition. Figure 6A shows that the majority (64%) of participants who consumed AC-11® exhibited social scores that were consistent with a happy disposition. This was confirmed in Figure 6B, where only a small proportion (36%) of participants who consumed AC-11® exhibited social scores that were consistent with a disgust disposition. In contrast, only 14% of participants who consumed the placebo evidenced social scores that were consistent with a happy disposition. Furthermore, 86% of participants who consumed the placebo demonstrated social scores that were consistent with a disgust disposition.

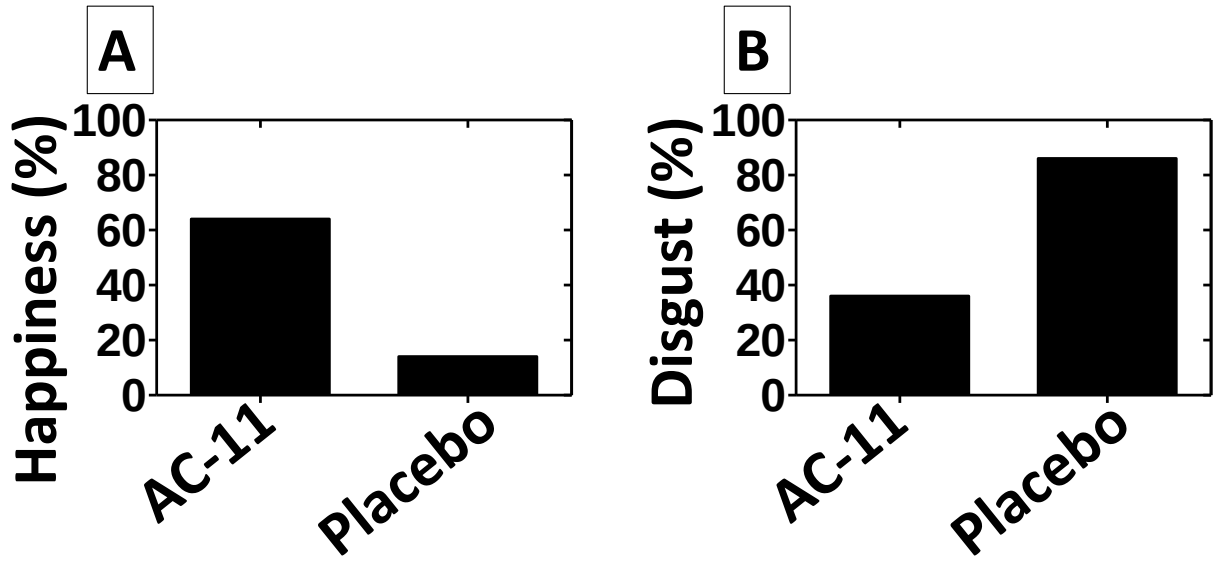

Figure 6. Oral intake of AC-11® improved social cognition. **Panel A** shows the percentage (%) of participants who exhibited a preference towards "happiness" after taking AC-11® or placebo for 1 month. Note that AC-11® treatment resulted in more happy facial interpretations. **Panel B** shows the percentage (%) of participants who exhibited a preference towards "disgust" after taking AC-11® or placebo for 1 month. AC-11® treatment resulted in less disgust facial interpretations.

CONCLUSION

The purpose of the current exploratory pilot study was to determine whether or not daily oral intake of AC-11® would improve the cognitive performance of healthy individuals with normal cognition. Given that the participants were healthy and already possess normal cognition, the task of improving their cognition was particularly challenging because they were already operating at a relatively high level (e.g., the ceiling effect). Nonetheless, the results from the current study suggest that AC-11® intake can significantly improve cognition. AC-11® intake was effective at enhancing cognition in four cognitive domains: attention, executive function, memory and social cognition. The results for attention appears to be more significant and sustained relative to the results from the other domains. For instance, AC-11® improved

attention for participants who were initially randomized to receive AC-11® for the first month of the study then placebo for the last month of the study. AC-11® also improved attention for participants who were initially randomized to receive placebo for the first month of the study then AC-11® for the last month of the study. In both scenarios, AC-11® showed statistically significant improvements in attention. Although AC-11® also showed improvements in executive function, memory and social cognition, it is possible that these improvements may be due to the improvement in attention. Primary improvement in attention could secondarily enhance a variety of other cognitive functions. Alternatively, AC-11® may act to independently improve performance within each cognitive domain, with attention receiving the greatest impact. In this situation, it is possible that prolonged use of AC-11® (e.g., additional months of AC-11® intake) or an increase in AC-11® concentration may yield improvements in other neurocognitive domains that meet or exceed the improvements in attention. Given the novelty of the current research, the underlying neurobiology is unknown and further research is needed.

Gain effects:

An important outcome from the current research is the fact that cognitive test results at baseline were able to improve after consuming AC-11®. This is suggestive of a gain effect, where the participants gained by taking AC-11®. This gain was evidenced as early as 1-month after AC-11® consumption and could also be observed two and three months later. For instance, attention scores improved after 1-month of AC-11® and this improvement continued out to three month. Given that the study ended after three months, it is possible that this gain effect may have persisted longer. Memory, executive function and social cognition also evidenced gain effects following AC-11® consumption. However, these gain effects were less persistent relative to that of attention. Therefore, consumption of AC-11® may result in long-

term improve in attention but improvements in other cognitive domains requires appropriate planning. For instance, improvement in executive function occurs after 2-month of AC-11® consumption, while improvement in memory occurs after 3-months of AC-11® consumption.

Cohort Effect:

An important outcome from the current research is the fact that the AC-11® group demonstrated cognitive improvement while the placebo group did not. This is suggestive of a cohort effect, where one cohort (group) outperforms another. A cohort effect was most prominent for attention. For instance, the group that received AC-11® consistently showed improved attention across all time points. The group that received placebo failed to exhibit an improvement in attention yet this same group could be improved when they received AC-11®. For memory, only the placebo cohort showed improvement with AC-11® intake. In this cohort, the participants started with placebo consumption then they experienced a washout period followed by AC-11® consumption. It is possible that AC-11® consumption improved their memory scores but it is equally possible that improvements in their memory scores were due to a placebo effect. Support for a placebo effect is the fact that their scores were already improving before AC-11® intake. However, support for an AC-11® effect is the fact that the placebo effect failed to achieve statistical significance while the AC-11® effect achieved statistical significance. With regard to executive function, there was a clear AC-11® induced effect among the AC-11® cohort. These participants received AC-11® then experienced a washout period followed by placebo intake. AC-11® induced an improvement in executive function that started at 1 month and continued to improve after this one month period. Interestingly, consumption of the placebo reversed this positive improvement. An indication that unlike attention, improvement in executive function is less resilient. Interestingly, AC-11®

outperformed placebo in the area of social cognition across both cohorts. Therefore, a prominent conclusion from the current study is that different cohorts can benefit in different ways from AC-11® induced cognitive improvements.

Implications:

The results from the current exploratory pilot study are supportive of five implications. *First*, daily oral intake of AC-11® can improve cognition among heathy individuals who already have normal cognitive functions. This is evidenced by the improvement in attention scores relative to that at baseline. Therefore, individuals who require a "cognitive boost" before occupational, recreational, educational or social encounters may benefit from daily oral intake of AC-11®. *Second*, beneficial effects of AC-11® on specific neurocognitive domains is time dependent. For instance, improvement in attention may occur within 1-month, while improvement in executive function may occur in 2-months and 3-months for memory. With appropriate planning, individuals may consume AC-11® to achieve the desired neurocognitive outcome at the necessary time. *Third*, AC-11® induced improvement in attention was significant across cohorts/groups. However, AC-11® induced improvement in other cognitive domains were group dependent. These findings suggest that AC-11® may more directly target the neural substrates that underlie attention. Therefore, consuming AC-11® to improve attention might be a general/global outcome for most individuals. However, improvement in other neurocognitive domains might only be specific to some individuals. *Fourth*, daily oral intake of AC-11® may improve social cognitive. This is a neurocognitive domain that is rarely assessed yet it is the foundation of normal human social interactions and when perturbed may serve as a marker for a variety of abnormal psychiatric/psychologic conditions (Adolphs, 2009; Cotter et al., 2018). Therefore, individuals may consume AC-11® in order to improve their

social cognition. *Fifth*, given that daily oral intake of AC-11® improved cognitive performance among individuals who already have normal cognitive function, then it might be possible for AC-11® to improve cognitive function among individuals who suffer with cognitive decline. However, additional studies are need to confirm the results of the present study and to explore whether or not AC-11® would be efficacious among individuals who suffer with cognitive decline.

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