Date: 22/06/18

Study code: 55C2

Study title: The acute and chronic cognitive effects of a sage extract: a randomized, placebo controlled study in healthy humans

Ethics code: 8970

STUDY DESIGN AND PLAN

The study will follow a randomised, double-blind, placebo-controlled, parallel groups design.

STUDY PROCEDURES

Testing will take place in a suite of testing facilities with participants visually isolated from each other. Participants will attend the laboratory on 3 separate occasions, an introductory visit between 1 and 14 days before the first day of treatment, and two testing days (Day 1 and Day 29):

The Introductory visit to the laboratory will comprise: briefing on requirements of the study, obtaining of informed consent, health screening, completion of the Caffeine Consumption Questionnaire (CCQ) and State-Trait Anxiety Inventory (STAI) trait subscale, training on the cognitive and mood measures and collection of demographic data.

For the two ensuing laboratory-based testing sessions (Day 1, Day 29) participants will attend the laboratory before 8.00 am having consumed a standardised breakfast of cereal and/ or toast at home no later than an hour before arrival. They must have refrained from alcohol for 24 hours and caffeine for 18 hours. On arrival on each day participants will complete the State-Trait Anxiety Inventory (STAI) state subscale and the computerised cognitive assessment (as per Figure 1) followed by measurements of blood-pressure and heart rate. Immediately following this they will consume their treatment for that day. Two further cognitive assessments (plus BP and HR), identical to the pre-dose assessment will commence at 120- (~11:00 am) and 240 (~02:00 pm) minutes post-dose; the latter in order to take advantage of natural declines in performance during the day. Participants will be given a standardised lunch at approximately 12:10 pm. This lunch will comprise a white bread cheese sandwich, packet of ready salted crisps and custard pot.

Cognim^{app} mobile phone assessments will take also place outside of the laboratory before the treatment period begins (Day -6 to -1) and at intervals of 7 (+/- 1 day) days (e.g. Day 7, 14, 21, 28) with the final assessment taking place the day before the final laboratory visit. Assessments will take place in the morning (pre-dose) and evening on each day. Participants will be prompted by text messaging. Additionally, on Day 24, participants will complete the learning phase of the location-learning task. On day 28 the Cognim^{app} assessment will include completion of the retrieval phase of the location-learning task.

Figures 2 and 3 depict the laboratory-based testing session timeline and chronic study overview respectively.

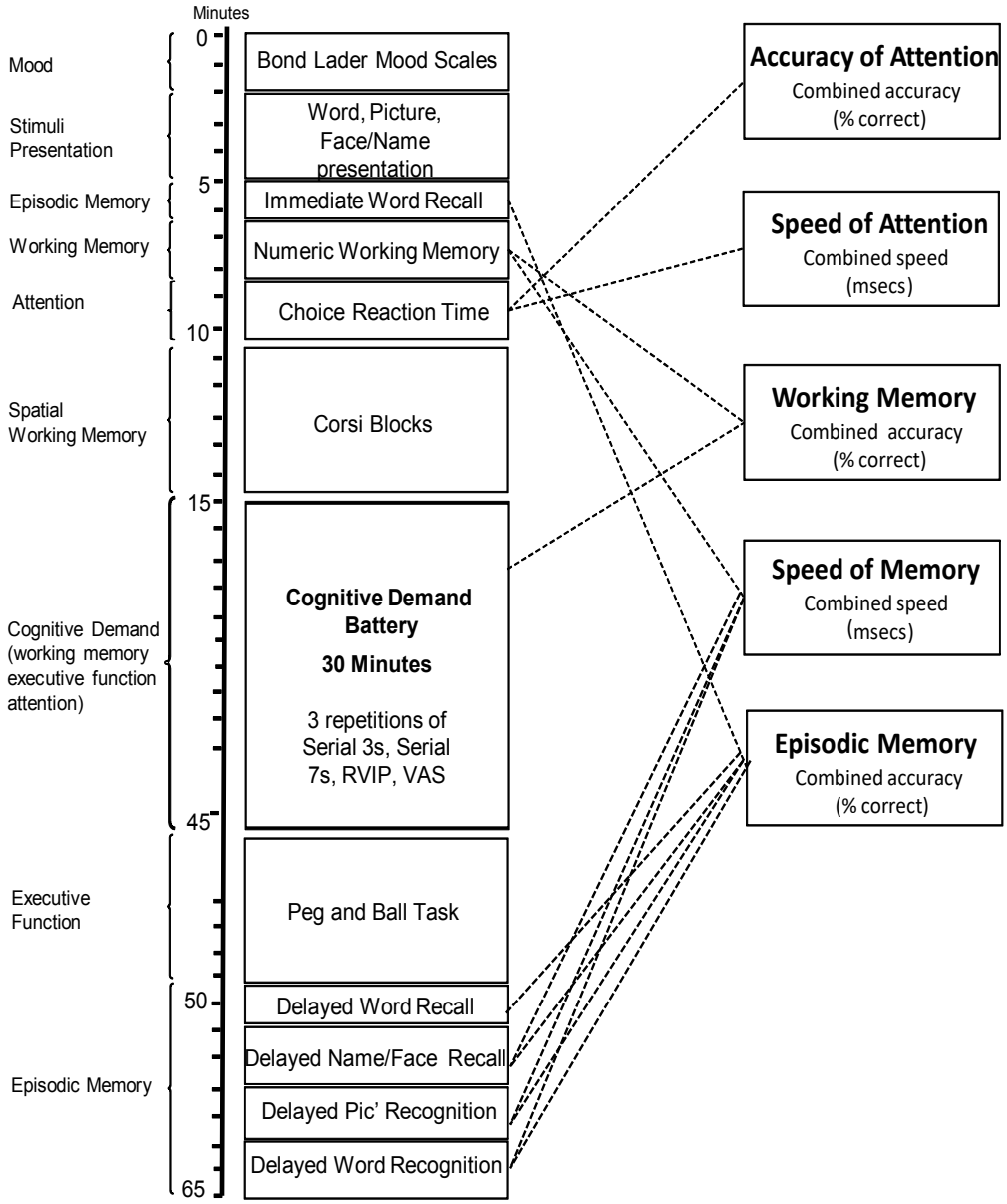

Figure 1. The running order of the individual cognitive assessments. Tasks are shown in order of completion with approximate timings. On the left the 'cognitive domain' assessed by the task is shown and the boxes to the right show potential global measures into which data from several tasks can be collapsed.

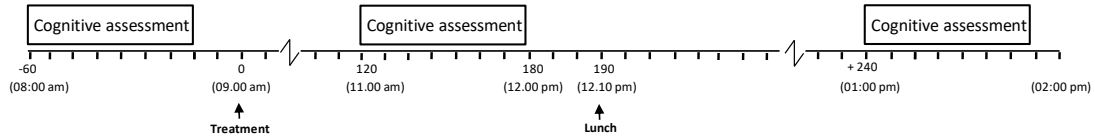

Figure 2. Testing session timeline on both the acute and chronic visit. participants complete a full cognitive assessment pre-dose and at 120 and 240 mins post-dose. Lunch is provided at approximately 12:10 pm.

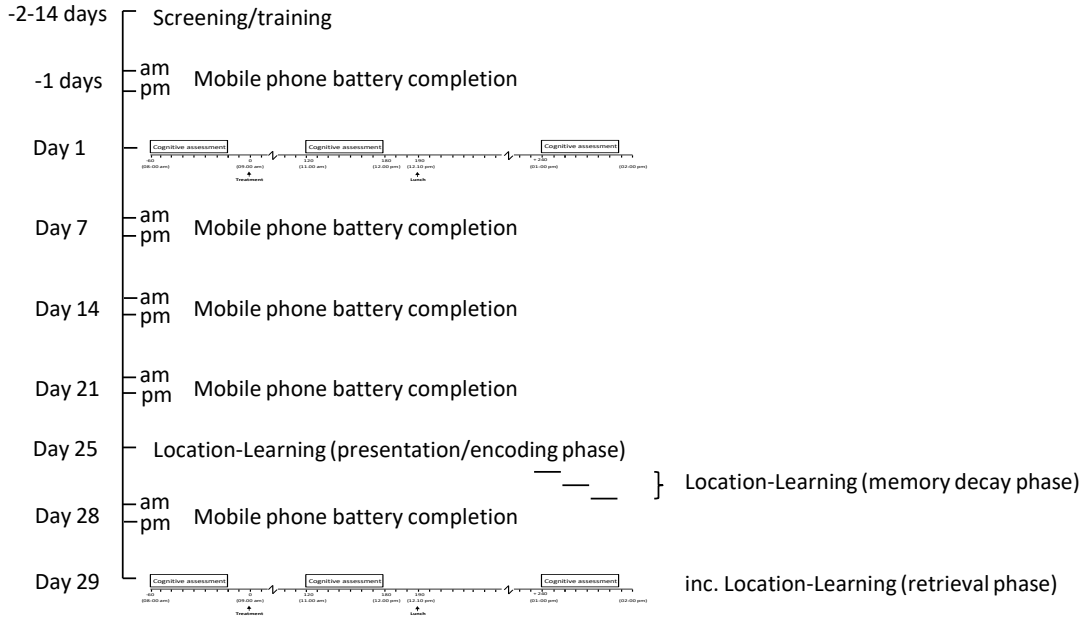

Figure 3. Overall trial diagram. Diagram includes screening/ training and main acute (day 1) and chronic (day 29) lab visit sessions. Weekly (day -6 to -1, 7, 14, 21 and 28) completion of the mobile phone battery and location-learning task completion (presented during day 25 and retrieved during day 29; with the intervening 3 days representing the memory decay phase) is also depicted.

Treatment schedule across the study

Participants will be provided with at least 30 days supply of the study's investigational products (sage or placebo) for consumption daily between testing visits Day1 and Day 29 and will undergo the cognitive/mood assessment on the first day (Day 1) and the last day (Day 29) of the active treatment period. The allocation to treatments will be undertaken via a randomly generated treatment schedule.

Details of the mood assessments, COMPASS battery, CDB battery and mobile phone battery are presented in Appendices I, II, III and IV.

PLANNED ANALYSES

Cognitive task data, mood scale and Blood Pressure (BP) analysis

The cognitive task, mood and BP measures produce data that can be analysed to assess both acute (potential treatment effects within day 1 and day 29), pure-chronic (chronic treatment-related effects which have taken place across the 29 day supplementation period but prior to taking the day 29 treatment) and superimposed acute/chronic (the difference in 'acute' effects between day 1 and day 29 or the difference in effects pre and post-dose on day 29) effects of treatment. In order to adequately analyse the 'acute', 'pure chronic' and 'superimposed acute/chronic' effects of the treatments the following proposed analyses will be conducted:

1.Pure acute effects

To ascertain if any acute treatment effects have taken place, post-dose data from day 1 and day 29 will be baseline adjusted with regards the pre-dose baseline data collected on day 1 and entered into a two way (treatment x assessment [120/240 min]) ANOVA.

2. Pure chronic effects

To ascertain if any pure chronic treatment effects have taken place, pre-dose data on day 29 will be baseline adjusted with respect to day 1 pre-dose baseline data and analysed via ANOVA to compare performance between treatments.

3. Acute, and superimposed effects

i) To ascertain if any acute effects on day 1 have increased or attenuated over the 29 day treatment period, data from day 1 and day 29 will be baseline adjusted with respect to the respective day's baseline assessment and entered into a three way (day x assessment x treatment) ANOVA.
ii) To ascertain if there are differential chronic effects pre and post-dose on day 29, pre and post dose data from day 29 will be baseline adjusted with respect to the pre-dose baseline on day 1 and subjected to a two way ANOVA (treatment x assessment.

The proposed a priori and post-hoc comparisons between treatment means to be utilised will be specified in the Statistical Analysis Plan

Mobile phone battery analysis

Data will be baseline adjusted and analysed by ANOVA (treatment (placebo and active) by day (7, 14, 21 and 28) by time (am and pm).

State Trait Anxiety Inventory (STAI)
Trate anxiety scores, collected during the screening/training visit will be compared between the treatment condictions to ensure that no differences exist between groups on this stable anxiety factor.

State anxiety scores, collected prior to pre-dose cognitive tasks on day 1 and on day 29, will be converted into a change score (day 29 score minus day 1) and compared between treatments via ANOVA.