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Food Interventions for Stress and Cognitive Performance:

Measurement Methods & Trial Design

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1 INTRODUCTION

Stress is a part of daily life. Every individual regularly encounters stressful experiences which may range from minor short-lived annoyances such as being stuck in traffic, to chronic unrelenting challenges such as caring for a loved one suffering from a serious illness. Although there are differences in how a person appraises, manages and responds to stress (Allen *et al.*, 2013), by and large, an individual who experiences chronic and persistent stress in their day to day life is at much greater risk of developing a range of physical and mental health conditions. The World Health Organisation estimates that stress-related mental health problems will be will be the leading cause of Global Burden of Disease by 2030 (WHO, 2004). Chronic stress can lead to cognitive problems in young and middle aged adults whilst accelerating cognitive decline in the elderly (Prenderville *et al.*, 2015). There is thus an imperative to develop and test novel interventions, such as food products with potential pro-cognitive and stress reducing properties.

In this white paper we provide a brief literature review on the biological stress response and the impact of stress on cognitive performance, an outline of the standard means of measuring stress and cognitive performance in clinical intervention trails, and some key considerations for trial design.

2 STRESS

A '*stressor*' is defined as any real or imagined event, condition, situation, or stimulus that instigates the onset of the human stress response process within an individual (Everly Jr and Lating, 2012). The hypothalamic-pituitary-adrenal (HPA) axis is the core neuroendocrine response system in humans (McEwen, 1998). Activation of the HPA axis can occur in response to a range of external or internal physical and psychosocial stressors (McEwen and Wingfield, 2003).

In response to stress, a co-ordinated hormonal cascade is initiated wherein corticotropin-releasing factor released from the paraventricular nucleus (PVN) of the hypothalamus, stimulates the anterior pituitary gland to release adrenocorticotropin releasing hormone (ACTH). ACTH reaches the adrenal glands via the blood stream to stimulate the systemic release of cortisol (Dinan, 2001, Dinan, 1994, Dinan *et al.*, 2006, Dinan and Scott, 2005, McEwen, 2007, McEwen and Wingfield, 2003). Subsequent deactivation of the HPA axis occurs via a negative feedback loop, where cortisol released from the adrenal glands acts on glucocorticoid and mineralocorticoid receptors at the level of the pituitary, hypothalamus and higher cognitive brain regions including the hippocampus, amygdala and prefrontal cortex, to inhibit further cortisol release (Dinan, 2001, Dinan, 1994, Dinan *et al.*, 2006, Dinan and Scott, 2005, McEwen, 2007, McEwen and Wingfield, 2003). Glucocorticoid receptors are widely expressed and as such, stress leads to a range of physiological effects. Short-term acute stress constitutes an adaptive response where the release of glucocorticoids and noradrenaline from the adrenal cortex has many physiological functions such as energy metabolism, increased cardiovascular tone and suppression of the immune system (Sapolsky *et al.*, 1986, Sapolsky *et al.*, 2000). However, persistent and chronic stress is predominantly maladaptive and has numerous negative consequences. With regards to brain function and behaviour, numerous rodent studies have shown that structural and functional changes of the hippocampus, such as neuronal atrophy and reduced long-term potentiation, occur due to chronic stress, and chronically elevated glucocorticoid levels (Bellani *et al.*, 2006, Li *et al.*, 2008, Wright and Conrad, 2005, Yu *et al.*, 2010). In addition, pre-clinical studies have shown that chronic stress can also alter the integrity and function of frontal brain regions (Cerqueira *et al.*, 2007, Lapiz-Bluhm *et al.*, 2009). Although determining causal relationships in human studies is inherently difficult it is clear that chronic stress in adulthood can lead to HPA axis dysfunction (Kang and Marks, 2014), heightened immune activity (Glaser and Kiecolt-Glaser, 2005), and altered grey matter volume in several brain regions (Gianaros *et al.*, 2007).

3 Impact of Chronic Stress on Cognitive Performance

Cross-sectional, retrospective and prospective studies assessing how self-reported stress, or cortisol levels measured in blood or saliva relate to cognitive performance have documented that chronic stress can impair cognitive function in humans (Jonsdottir *et al.*, 2013, Lupien *et al.*, 2007, Lupien *et al.*, 2009, Wilding *et al.*, 2007). For example, individuals who are primary caregivers to debilitated family members experience high levels of chronic stress and have been shown to exhibit hippocampal mediated episodic memory and frontal mediated working memory impairments (Mackenzie *et al.*, 2009).

Studies in elderly populations have documented a relationship between elevated cortisol levels and a decline in hippocampal-mediated episodic memory performance (Lupien *et al.*, 1994, Seeman *et al.*, 2004), and hippocampal atrophy (Lupien *et al.*, 1998). In addition, elderly adults self-reporting greater levels of perceived stress (Aggarwal *et al.*, 2014) or perceived social isolation (Tilvis *et al.*, 2004) exhibit accelerated cognitive decline.

Stress-related disorders such as depression and anxiety are also associated with cognitive impairments. In depression, which is characterised by HPA axis dysfunction, decreases in hippocampal volume and deficits in episodic memory performance have been documented (Videbech and Ravnkilde, 2004). Irritable bowel syndrome (IBS) is a stress-related brain-gut axis disorder associated with both functional bowel symptoms and high prevalence of psychiatric co-morbidity (Kennedy *et al.*, 2012). Patients with IBS have been shown to exhibit an exaggerated HPA axis response to acute psychological stress (Kennedy *et al.*, 2014c) and a stress-related impairment in episodic memory performance (Kennedy *et al.*, 2014b).

4 Measuring Stress

Physiological Measures

Cortisol Awakening Response

The cortisol awakening response (CAR) is a commonly used measure of HPA axis function in clinical studies (Kennedy *et al.*, 2014b). The CAR is a naturally occurring increase in cortisol levels (up to 70% increase) which occurs upon wakening (Fries *et al.*, 2009). The CAR can be simply determined by asking study participants to collect repeat morning saliva samples. Salivary cortisol is relatively stable when refrigerated prior to processing and correlates well with blood levels of cortisol. As such, measuring the CAR is a straightforward and relatively non-invasive means of determining HPA axis function.

Validated Self-Report Measures

To ensure that study groups are similar in baseline characteristics that may affect stress and cognitive performance, self-report measures should be included in the study design. As stress can affect a number of aspects of normal functioning separate from cognitive performance, it is also important to include psychological scales which measure not only subjective stress but also a range behavioural and mood components. Commonly used measures which are well validated and have published psychometric properties are briefly described below.

Perceived Stress Scale (PSS)

The PSS is a self-report measure in which participants rate, on a 5 point scale ranging from 0 (never) to 4 (very often), how often they have particular thoughts or feelings described by each of the 10 items (Cohen *et al.*, 1983). Scores range from 0-40 with higher scores indicating greater stress over the previous month.

Beck Depression Inventory (BDI)-II

The BDI-II is a self-report measure consisting of 21 items rated on a 4-point scale from 0 (absence of symptom) to 3 (severe manifestation of symptom (Beck *et al.*, 1996). Scores range from 0-63. Cut-off scores indicating clinically relevant levels of depression have been determined as 0-13 (minimal); 14-19 (mild); 20-28 (moderate); 29-63 (severe).

State Trait Anxiety Inventory (STAI)

The STAI is a self-report measure consisting of two subscales each with 20 items, one measuring trait anxiety and the other measuring state anxiety (Spielberger *et al.*, 1983). Participants rate how they feel either *right now* (state) or *generally* (trait), in response to each item on a 4-point scale from 'not at all' to 'very much.' The range of scores for each sub-scale is 20-80 with higher scores indicating greater anxiety.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI assess sleep quality over the prior month (Buysse *et al.*, 1989). The PSQI is a self-report measure comprised of 19 items which are designed to measure seven key components indicating problematic or non-problematic sleep; sleep latency, sleep duration, sleep efficiency, sleep disturbances, subjective sleep quality, use of sleep medication, and daytime dysfunction due to sleep disturbance. Scores on each component are combined to give a global score with >5 indicating significant disturbance of sleep quality during the prior month.

5 MEASURING COGNITIVE PERFORMANCE

There are a vast number of cognitive/ neuropsychological tests and test batteries used by researchers and clinicians that are designed to assess functioning in one or in most cases a combination, of cognitive domains (see **Table 1** for description of cognitive domains). When choosing the appropriate test and test battery the aim should be to combine information across a range of cognitive domains (Mapou and Spector, 1995). The depth of assessment in a particular cognitive domain will vary dependent on the available information in the scientific literature regarding the known, or potential, cognitive deficits in the study population. If the data indicating a target cognitive domain are currently inconsistent or sparse for a particular population, or indeed there is no pre-specified target cognitive domain, a test battery should aim to measure at least one aspect of each of the core cognitive domains outlined in **Table 1** (Strauss *et al.*, 2006).

Table 1. Core cognitive domains that can be assessed by a range of tests

Cognitive Domain	Description	Reference
Executive Function	Executive function(s) is an umbrella term encompassing a number cognitive processes including; problem solving, planning, sustaining attention, feeback utilization, cognitive flexibility, verbal reasoning and the inhibition of prepotent responses. Prefrontal regions are key in mediating most of these processes.	(Chan *et al.*, 2008, Spreen and Strauss, 1998)
Working Memory	Working memory refers to the short-term limited capacity store for information (e.g. list of digits) which can be held from seconds to minutes and in which information held can be operated upon and manipulated. The dorsolateral PFC is a fundamental brain region in mediating working memory performance.	(Strauss *et al.*, 2006)
Attention	Attention refers to mechanism through which an individual actively processess a select amount of information from the vast amount of information recieved by the brain. Numerous tests are available to assess various attentional processes. Prefrontal regions, in particular, regions of the ACC, are intricately involved in attentional functioning.	(De Weerd, 2003a)
Declarative Memory	Declarative and episodic memory are sometimes used interchangeably, however, strictly speaking, declarative memory refers to 'explicit' memory, and incorporates both episodic memory and semantic memory	(Schacter and Tulving, 1994a, Tulving and Schacter, 1990)
Episodic Memory	The storage and recollection of personally experienced events, specifically with reference to the temporal context, location and content of such events. The hippocampus is the key region involved in the formation of episodic memories.	(Dere *et al.*, 2008).
Semantic Memory	The storage and recollection of general knowledge and facts such as the name of objects and the meaning of words, all of which are not unique to the individual and are not temporally or contextually specific. Similar to episodic memory, the hippocampus and other regions of the temporal lobes are involved in semantic memory processes	(Martin and Chao, 2001, Sternberg, 2009).

The American Psychological Association has outlined guidelines when making a decision on which test(s) or test battery to use clinically or for research purposes. They state; "Knowledge of test characteristics such as psychometric properties, basis in theory and research, and normative data....should influence test selection" (Turner *et al.*, 2001).

Traditionally, cognitive assessments have been carried out using pen and paper tests which are still mainly used in clinical neuropsychological practice (Strauss *et al.*, 2006). However, computerised assessments are a popular choice in research settings for a number of reasons. Computerised assessments offer much greater accuracy and sensitivity for tests in which the primary outcome measure is response speed or response latency. They allow for complete standardisation of how the test is presented to each study participant/patient and, they reduce experimenter error when the number of trails in a particular test is being recorded or when a time limit is imposed (Strauss *et al.*, 2006). In addition, they also reduce the impact that negative self-evaluation, due to a participant having difficulty completing a task, can have on test results (Green *et al.*, 1984).

Nevertheless, in study populations where cognitive function is significantly impaired, and particularly in elderly participants, one to one assessment using pen and paper assessments may be necessary to engage the participant and provide accurate results. Cognitive test batteries and assessments commonly used in clinical studies are briefly outlined below.

Young and Elderly Adults with Normal Cognitive Function

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is one of the most widely utilized test batteries in research settings. CANTAB is a computerised touch-screen based test battery which currently offers 25 tests covering aspects of visual memory; working memory; executive function; attention; semantic/ verbal memory; decision making and response control and emotion related cognition (http://www.camcog.com/).

There is quite extensive data detailing relationships between scores on specific tests of the CANTAB battery and clinical evidence of damage to specific brain structures of the temporal and frontal lobes (Owen *et al.*, 1996, Owen *et al.*, 1995) and brain imaging techniques have been employed to identify the specfic neural substrates engaged while participants are performing some CANTAB tasks**.**

CANTAB has been extensively used for the assessment of cognitive function in a wide variety of neurological and psychiatric disorders such as bipolar disorder (Roiser *et al.*, 2009), depression (Taylor Tavares *et al.*, 2007), obsessive compulsive disorder (Fenger *et al.*, 2005), anxiety disorders (Castaneda *et al.*, 2008), schizophrenia (Cummings *et al.*, 2013, Donohoe *et al.*, 2009, Leeson *et al.*, 2009) and stress-related disorders such as irritable bowel syndrome (Kennedy *et al.*, 2014a, Kennedy *et al.*, 2014b). CANTAB has also been used to assess the cognitive effects of a range psychopharmacological agents (Deakin *et al.*, 2004, Nielen and Den Boer, 2003), and dietary interventions (File *et al.*, 2005, Hartley *et al.*, 2004, Nolan *et al.*, 2014, Yurko-Mauro *et al.*, 2010).

The CANTAB is thus an extremely effective tool for determining the potential pro-cognitive effects of food interventions in adults.

There are a number of other computerised test batteries (see **Table 2**) which may also be considered for interventional studies whilst be cognisant of the test characteristics and available data indicating the psychometric properties of the tests within the battery.

Table 2. Commercially available computerised cognitive test batteries

Test Battery	Age-range	Website
CNS Vital Signs	7-90	http://www.cnsvs.com/
Cogstate	18-82	https://cogstate.com/
MicroCog™	18-89	http://pearsonclinical.com/
NeuroTrax™	-	http://www.neurotrax.com/
Automated Neuropsychological Assessment Metrics (ANAM)	-	http://www.vistalifesciences.com/
Cognitive Drug Research (CDR) System	-	http://www.bracketglobal.com/services/cognition

Elderly Adults with Cognitive Impairment

Quick mild cognitive impairment screen (Qmci)

The Qmci is a short cognitive screen that measures orientation, working memory (registration), visuospatial/executive function, semantic memory and two episodic memory domains. The Qmci is scored out of 100 points, can be completed in 3–5 min, and is specifically designed to discriminate normal, mild cognitive impairment and dementia (O'caoimh *et al.*, 2013, O'caoimh *et al.*, 2012). The Qmci is a valid outcome measure for use in clinical trials (O'caoimh *et al.*, 2013, O'caoimh *et al.*, 2012, O'Caoimh *et al.*, 2014).

Montreal Cognitive Assessment (MoCA)

The MoCA is a freely available screening measure to detect mild-cognitive impairment. It is short to administer, taking around 10 minutes and assesses visuospatial abilities, verbal abstraction, executive function, attentional function, language and orientation (Nasreddine *et al.*, 2005).

Standardized Mini-Mental state Examination (SMMSE)

The SMMSE is a widely used instrument that tests orientation, registration, concentration, short-term memory, language and visuospatial ability. It takes approximately 10 minutes to administer. The SMMSE has been shown to be responsive to change and correlates well with other cognitive screening instruments (Molloy and Standish, 1997, Standish *et al.*, 1996).

6 Considerations in Trial Design

Expertise & Facilities

The cognitive assessments outlined above can be administered by appropriately trained study personnel. However, interpretation of test results should be carried out by an academic/clinician with sufficient expertise in cognitive assessment (e.g. psychologist, psychiatrist, and geriatrician). Similarly, the validated self-report measures can be scored to compile data for analysis by any team member trained in scoring each measure, but interpretation of measures such as the Beck Depression Inventory should be by a mental health professional.

Analysis of salivary cortisol requires access to wet lab facilities in which Enzyme-Linked Immunosorbent Assay (ELISA) analysis can be conducted.

Controlling for Practice Effects in Repeat Testing of Cognitive Performance

A major consideration when conducting an intervention study to assess the pro-cognitive potential of a food product is the effect of repeat cognitive testing. '*Practice effects,'* meaning participant performance will improve by virtue of being more familiar with the test and developing performance enhancing strategies, are common in repeat cognitive testing. This is particularly problematic in younger cognitively intact adults. Tests of executive function show greater practice effects than other cognitive domains. As such, the choice of test or test battery should be in part guided by the availability of parallel/alternate versions of a specific test for repeat testing. It is also good practice to have an introductory session which can be carried out at a screening visit, where participants are administered some or all of the tests, prior to a full study session to familiarise them with the test battery, testing environment and test administrator. This will reduce variability in the study data collected at subsequent testing sessions.

Controlling for Order & Carryover Effects in Cognitive Testing

A comprehensive test battery in an interventional study may take up to 1-2 hours to administer. As such, mental fatigue is likely to occur in study participants. To reduce the influence of fatigue or *'order effects'* on data, it is common practice to counterbalance the order of tests. This also serves to reduce *'carryover effects'* in which performance on one test is influenced by the test preceding it. Counterbalancing the order of tests can be achieved using a Latin Square design. **Table 3** shows an example of a test battery consisting of 8 tests (**Test 1-8**) with 8 test battery orders (**Order A-H**). Study participants can be sequentially assigned to each test battery order as they enter the study.

Table 3. Example Latin Square design for counterbalancing cognitive test order

Order A	**Test 1**	**Test 2**	**Test 3**	**Test 4**	**Test 5**	**Test 6**	**Test 7**	**Test 8**
Order B	Test 2	Test 4	Test 1	Test 6	Test 3	Test 8	Test 5	Test 7
Order C	Test 4	Test 6	Test 2	Test 8	Test 1	Test 7	Test 3	Test 5
Order D	Test 6	Test 8	Test 4	Test 7	Test 2	Test 5	Test 1	Test 3
Order E	Test 8	Test 7	Test 6	Test 5	Test 4	Test 3	Test 2	Test 1
Order F	Test 7	Test 5	Test 8	Test 3	Test 6	Test 1	Test 4	Test 2
Order G	Test 5	Test 3	Test 7	Test 1	Test 8	Test 2	Test 6	Test 4
Order H	Test 3	Test 1	Test 5	Test 2	Test 7	Test 4	Test 8	Test 6

7 CONCLUSIONS

There is huge scope for developing food based products with potential pro-cognitive and stress reducing effects that may hold great promise in thwarting an increasing societal problem. Chronic stress has a plethora of negative outcomes for the brain and body across the lifespan. The impact of stress becomes particularly apparent in aged adults where stress accelerates age-related cognitive decline. In order to demonstrate the pro-cognitive and stress reducing effect of a food product, well designed studies which account for numerous physiological factors such as HPA axis function, and a range of psychological components including depression and anxiety, are crucial. The choice of cognitive test or test battery should be guided by the known psychometric characteristics and availability of parallel/alternate test versions for repeat testing. In addition, consideration should be given to the flexibility of the software as regards to the ability to pre-program test battery orders to reduce the impact of *order* and *carryover* effects. The scientific literature should be consulted to gather information on target cognitive domains in the study population, if available, or the assessment should be broad enough to capture effects across a range of cognitive domains.

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