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CLINICAL TRIALS

The Relationship Between Mental Health and Cognitive Health

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Introduction

Mental health refers to our emotional, psychological, social well-being and cognitive function. It encompasses our thoughts, feelings, and behaviours, how we act and react, and how we perceive and interact with the world. This dynamic status and can change acutely, or over longer periods of time and can be in flux throughout the lifespan, depending on life experience (trauma, abuse, loss, major life changes, stress, sleep), age and life stage (early-life, adolescence, menopause, elderly), medical status (illness and disorders) and genetics amongst others. There are a number of mental health disorders that can range from mild to severe including anxiety disorders (e.g. general anxiety disorder, panic disorders, phobias), mood disorders (e.g. depression, bipolar disorder), obsessive-compulsive disorder and related disorders, post-traumatic stress disorder, psychotic disorders (e.g. schizophrenia), eating disorders (e.g. anorexia nervosa, bulimia) and neurodevelopmental (e.g. autism spectrum disorder, ADHD) and neurodegenerative disorders (e.g. Parkinson's disease and Alzheimer's) [1].

Our mental health impacts our ability to cope with stress, handle challenges, and maintain healthy relationships. Emotional wellbeing entails our perception and appropriate management of emotions in response to life experiences. Psychological wellbeing includes our cognitive health, self-esteem, resilience and overall satisfaction with life; while social wellbeing refers to our relationships and social interactions and sense of belonging. Not surprisingly, mental health and cognitive health are intertwined with one impacting the other. If one is unhappy, distracted or feeling isolated this can negatively impact on cognitive performance, while this in turn can impact emotional sense of reward, self-esteem and social inclusion.

Cognition is an overarching term covering many complex and interactive mental processes that occur in the brain, and refers to the status of our brain's functionality and the processes that enable us to acquire, process, store, retrieve and appropriately utilise information [2, 3]. The status of our cognitive health affects our ability to think, learn, reason, remember, concentrate, make decisions, and complete tasks. Critically, these functions include memory, attention, processing speed, visual-spatial skills, executive function, sensory perception, language and social cognition. Thus, cognitive health is crucial for our daily functioning, learning, memory, problem-solving, communication and decision-making; and it is these factors that are crucial in both diagnosing and treating cognitive impairment, as well as in prognosis for healthy cognitive ageing across the lifespan. In the current climate, much of the areas of concern for consumers is in stress management, learning and memory, and focus and attention; and where dietary supplements and interventions can support these areas.

Cognition Across the Lifespan

Cognition changes throughout the lifespan from birth to old age, and several factors influence how our cognitive abilities evolve over time. These factors can vary widely and include both biological and environmental elements. For example, genetics play a significant role in shaping our cognitive abilities with inherited traits influencing intelligence, memory, brain development, and susceptibility to cognitive decline or disorders associated with cognitive health.

In early life, the brain undergoes rapid development, with the cells in our brains (neurons) forming synaptic connections and undergoing pruning and maturation. From infancy, cognitive abilities like communication and motor skills emerge affecting learning, memory, attention, and problem-solving abilities, while in later life many synaptic connections are lost and the efficiency of synaptic neurotransmission can deteriorate, and cognitive decline can occur [4-6]. Proper nutrition in early life is crucial for cognitive development with deficiencies in key nutrients like iodine, iron, or omega-3 fatty acids potentially leading to developmental delays or cognitive impairments, while diets rich in antioxidants, vitamins, and omega-3 fatty acids have been linked to better brain health in the ageing population[5].

However, genetics and diet are not the only determinants of cognitive health. Environmental factors such as education, social relationships, early-life experiences, hormonal changes, exercise, sleep, mental health status, lifelong learning and mental stimulation (reading, puzzles, music) are all critical contributors to cognitive health in the development, maturation and maintenance of healthy cognitive function.

In reality, there is little we one can do about their genetic make-up, and it difficult to control early life experiences such as performance in school, social interactions in early life as this is unique to each individual. However, one key aspect that is controllable is our diet and supplementary support, that along with stress management, exercise, continual learning and development, and sleep lead to a better prognosis for healthy cognitive ageing.

Dietary Supplements in Cognitive Health

Several dietary supplements have been researched for their potential to improve cognition, memory, and mental clarity. While the evidence can vary, some supplements have shown promise, particularly for individuals experiencing age□related cognitive decline or mild cognitive impairment. Many of these observations are correlative in nature e.g. cognitive decline being associated with lower levels of certain minerals and vitamins and causality has not been confirmed. However, supplements including omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EHA), flavonoids and other antioxidants, phosphatidylserine, choline, curcumin, amino acids, vitamins (B12 and D3 particularly) and minerals such as magnesium are associated with overall brain health and healthy development [7].

In order to understand how these various molecules improve cognitive health we must take a holistic approach. As we grow our brains are concomitantly undergoing growth and development with the formation of new synaptic connections and pruning. These processes require metabolic support and the cells involved require metabolites from the diet.

Many factors can impact normal neurodevelopment and maturation, and physiological processes such as availability of cellular metabolites, immunological and neuroinflammatory molecules as well as reactive oxygen molecules can all impact the healthy growth, maturation and maintenance of neurons in the brain. Macronutrients, minerals and vitamins from our diet all play a role in healthy brain aging ultimately impacting on cognitive health

Microbiome-Gut-Brain Communication

The microbiota-gut-brain connection is an emerging area of research that explores how the gut microbiota (the community of microorganisms living in the digestive system) can influence brain function, cognition, mood, and behaviour. Factors that impact this first early seeding of our gut microbes are whether we are vaginally delivered getting vertical transmission of vaginal microbes from our mothers or whether we undergo caesarean section getting exposure to skin microbes in the first instance.

Shortly after delivery, another important contributing factor to gut microbiota development is whether we are breastfed or bottle fed, as there are many nutrients present (including distinct human milk oligosaccharides) in our mother's milk that may be absent in bottle feeding that act like prebiotics nourishing different families of microbes. Next comes the weaning period, where we first start getting exposure to solid foods, and the reduction of breastmilk or bottle milk, and thereafter the exposure to different food-types profoundly impacts our gut microbe development. As such, the microbiota of each individual is unique, like a fingerprint that has developed as we get exposed to microbes in our environment [5].

Along our gastrointestinal tract we have millions of microbes that communicate with the lining of the gut and can influence the bi-directional communication between the gut and brain. The mechanism by which they influence this connection can be crudely broken down into four main methods; by influencing vagal innervation that runs from the intestines directly to the brain, through the immune system and inflammatory markers, hormones and neurotransmitters, and microbial by-products (including short chain fatty acids (SCFAs) and peptidoglycans and bacterial cell fragments (amongst others) [5].

Interestingly, there are many aspects of our diet that we humans as a host cannot metabolise, and are reliant on the microbes that reside in our gut to breakdown by enzymatic means. Examples include digestion-resistant fibres that get metabolised in the large intestine into molecules (e.g. short chain fatty acids, and branched chain fatty acids) [8] that we as hosts can then utilise in metabolism. Similarly, gut microbes can impact the pharmacodynamics and pharmacokinetics of pharmacological agents; and vice versa, the gut microbes can be altered by various drug types (e.g. antibiotics, antidepressants, antipsychotics amongst others), and this fascinating area of research (pharmacomicrobiomics) is currently gaining much more interest.

Microbiome-Gut-Brain Communication (Continued)

Several studies (both preclinical and clinical) have looked into the microbiome to determine if any imbalances are associated with disease-related states or cognitive health, but there is no clear correlation for any keystone gut bacteria or probiotic or prebiotic or minerals or vitamins for improved cognitive health. Psychobiotics is a term used for probiotics that have been developed for effects on mental health, and there is some evidence for some probiotics in cognitive health mostly lactobacilli, bifidobacteria and bacteriodes species but further evidence is required to clearly demonstrate an improvement in cognitive health [5, 9].

Some interesting studies in germ-free mice have demonstrated that they exhibit decreased memory as compare to wild-type mice and that this effect was reversible with the addition of gut microbes back into these germ-free mice, suggesting a role for gut microbes in improved memory. Further work also demonstrated changes in the microglia in the brain of germ-free mice upon restoration of gut microbes further implicating gut microbes in brain development, maturation and maintenance. While further work is required, the evidence strongly suggests a role for gut microbes, and their modulation of and by the diet, probiotics, prebiotics, minerals and vitamins in brain development, maturation

Biomarkers to Assess Cognitive Health

There are no true biomarkers to assess cognitive health status, however several markers have been identified from animal studies or that are altered in disease state that can be used as diagnostic tools. Such biomarkers include amyloid beta (Aβ) plaques that form abnormal clumps of proteins or plaques, that are considered hallmark indices of Alzheimer's disease and other neurodegenerative disorders. Similarly, Aβ42 can be measured in cerebrospinal fluid and has been reported to correlate with Aβ plaque deposits in the brain. Tau protein, YKL40, neurofibrillary tangles and neurofilament light chains have also been associated with neurodegenerative disorders and can be identified in the brain and in CSF. Other biomarkers that have been associated with cognitive impairment in disease states include BDNF and synaptic proteins such as synaptophysin and vesicular acetylcholine transporter [11-13]. Alterations in cytokines, microglia, myelin and other markers of neuronal health are also associated with cognitive decline, although much further work needs to be conducted in this research area establishing causality.

Much of this information on biomarkers has been attained from post-mortem assessment of brain tissue or from invasive biopsies in disease state individuals, or from animal studies and it is unclear whether these biomarkers are causative or occur as a result of other physiological events

Pharmaceuticals in Cognitive Health

Several drugs have been investigated for their potential to improve certain aspects of cognition, particularly in individuals experiencing cognitive decline, such as those with Alzheimer's disease or other forms of dementia. While no drug has been clinically proven to significantly boost cognition in healthy individuals, some medications have shown promise for improving cognitive function in those with cognitive impairments or neurological conditions.

For example cholinesterase inhibitors such as Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne), and NMDA receptor antagonists Memantine (Namenda) have been used in the treatment of cognitive decline in Alzheimers and Parkinson's disease although the mechanism of action of these types of compounds on cognitive health is not fully elucidated [3, 14]. Other compounds such as modafinil (Provigil), methylphenidate (Ritalin), amphetamines (Adderall) and other psychostimulants have been used to increase alertness, attention and higher executive function [3] Much of this information on biomarkers has been attained from post-mortem assessment of brain tissue or from invasive biopsies in disease state individuals, or from animal studies and it is unclear whether these biomarkers are causative or occur as a result of other physiological events.

Clinical Practices in Cognitive Assessment

In clinical practice, it is important to assess an individual's cognitive strengths and weaknesses at a baseline level and then to track this over time, which can then allow clinicians to guide treatment or rehabilitation efforts or to determine positive effects of any treatment. A multidisciplinary approach is often recommended, involving neurologists, psychologists, occupational therapists, and other healthcare professionals to provide a comprehensive assessment.

In designing a clinical study to assess cognitive performance, a number of factors need to be considered [15, 16]. At the initial screening a thorough assessment should be completed to gather details about the patient's history, lifestyle, any cognitive impairment or injuries, family medical history related with conditions such as Alzheimer's disease, Parkinson's disease, dementia, stroke or psychiatric disorders [16]. Useful tools in the assessment of cognitive status include neuropsychological tests including, but not limited to, the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trail Making Test (TST), continuous performance test (CPT) and Digit Span Test (DST), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Stroop test, and verbal learning test. Other disease-focussed questionnaires to assess cognitive function include the Alzheimer's disease assessment scale – cognitive subscale (ADAS-Cog), the Neuropsychiatric inventory (NPI), Rowland Universal Dementia Assessment Scale (RUDAS), AD8 Dementia Screening Interview, MATRICS Consensus Cognitive Battery (MCCB) for schizophrenia and Subjective cognitive decline (SCD) questionnaire amongst others.

Computerised cognitive assessment tools such as Cambridge Neuropsychological Test Automated Battery (CANTAB), cognigram and Cogstate are also useful for assessing cognitive performance in healthy and disease-state population and allow for a more objective assessment of cognitive performance on memory, attention, processing speed and executive function.

Neuropsychological testing has uncovered a wealth of data on cognitive performance and incorporates a number of assessments including memory, language, problem-solving, attention, impulsivity, decision making, and executive functions like planning, flexibility and inhibition. Some standard test batteries include the Wechsler Adult Intelligent Scale (WAIS) and Halstead-Reitan Neuropsychological Battery to provide a baseline cognitive profile, which retain validity for subsequent testing over time.

Clinical Practices in Cognitive Assessment (Continued)

Neuroimaging techniques such as magnetic resonance imaging (MRI), CT scans and positron emission topography (PET) are powerful tools that can assess changes in blood flow in the brain, or injuries or changes in the volume or shape of the brain. These techniques can be used in real time to assess what is actually happening in the brain when one is recognising faces for example, or in response to different facial expressions of emotions to assess their cognition of social cues.

Electrophysiological methods such as electroencephalopathy (EEG) and magnetoencephalography (MEG) can provide readouts on electrical activity in the brain. Such methods facilitate real-time insights into brain activity and are useful in studying attention, memory processes, impulsivity and response to social cues. EEG in particular has been used for detecting altered brain wave patterns associated with certain cognitive disorders such as ADHD or epilepsy, while MEG measures the magnetic fields generated by neuronal activity and can be useful in assessing brain response in higher cognitive functions including language and executive control.

With the advent of digital tools there are several technologies available that can help support and improve cognitive health. Several apps have been designed to boost brain function including memory, language skills, executive function, processing speed, attention, puzzles and problem solving, as well as mindfulness apps for stress management, and techniques to improve sleep, focus and overall mental wellbeing. Similarly, there are apps for tracking fitness, exercise, relaxation, and nutrition, and wearable devices to track sleep, heart rate, stress levels, and physical activity that all contribute to mental wellbeing. More recently there have been advances in virtual headsets that can be used for cognitive improvement including higher executive function, hand-eye co-ordination and spatial navigation tasks.

Designing a Clinical Study to Assess Cognitive

In terms of clinical study design it is critical that one considers a number of factors. In the first instance, the sponsors must decide whether the study in a 'healthy' population, a 'mild to moderate/subclinical' population, or a disease state; and at what stage of disease (e.g. early onset versus full-blown dementia). Depending on the objectives, it should be decided whether the study is a parallel or crossover study design, is there a control group(s), and whether the study is blinded. Careful consideration must be given to the criteria for inclusion and exclusion, and this should be done with clear understanding of what criteria are accepted by different regulatory bodies in different territories. Another key consideration is what aspect of cognition the trial should be focussed on. Important co-factors include gender (for some disorders, there is a bias towards gender), age and age range, educational background, role of the caregiver (if in a disease population) and baseline cognitive scoring at this point.

Cognition encompasses memory, attention, processing speed, visual-spatial skills, executive function, sensory perception, language and social cognition amongst others, so the sponsor should clearly identify what is the primary endpoint for assessment based off what is known about the treatment or intervention from preclinical assessments and/or information in the literature. For example, should the study objective be to assess a specific cognitive domain (e.g., memory, executive function perhaps by using CANTAB or questionnaire or battery-based approach) or a global cognitive score (e.g., MMSE, ADAS-Cog). The sponsor should also determine what secondary or exploratory endpoints are they going to target, and whether methodologies such as wearable devices, apps, MRI, PET, CT scans, EEGs, MEGs, questionnaires, skillset batteries will be employed, as well as deciding whether any biomarkers are going to be assessed and from what sample types (e.g. blood, stool, urine, biopsies).

To improve participant retention would could consider the number of timepoints and whether the study can be conducted remotely, with prompts from the study co-ordinator. Once the target demographic and study duration has been decided and the primary endpoint (and secondary or exploratory endpoints) have been identified, a power analysis should be conducted to determine the number of participants to be included in the study. Thereafter a statistical analysis plan should be identified, after which ethics approval needs to be sought and the trial should be registered on a relevant database (e.g. clinicaltrials.gov) prior to commencement of the study.

The study should also be registered with a database such as Cochrane Dementia and Cognitive Improvement Group's (CDCIG's) register of all dementia trials, ALOIS. ALOIS is a freely accessible electronic database whose aim is to collate information on all trials with a dementia or cognition focus

Conclusion

In conclusion, there is an ever-increasing interest in cognitive health across the lifespan. Certain factors that are critical in cognitive health including genetics and previous life experience cannot be changed. However, dietary interventions represent a realistic way to positively impact brain functions that support cognitive health throughout the lifespan namely memory, attention, processing speed, visual-spatial skills, executive function, sensory perception, stress management, language and social cognition. From a consumer perspective the main areas of interest include memory, attention, stress management, mood, energy and mental wellbeing. In terms of dietary supplements, one must also consider the impact of the gut microbiota which is unique to every individual. However, dietary interventions alone may not result in immediate improvements in any of the aforementioned functions.

Future treatment strategies should consider a multi-targeted approach involving sleep monitoring, exercise regime, stress-reduction (possibly using apps or wearables) and a balanced diet (or supplementation if the diet is restrictive). This combined approach represents the approach with the most likelihood for success in healthy cognitive health throughout the lifespan.

About the Author

Dr. Kieran Rea, Scientific Director at Atlantia Clinical Trials, holds a Biochemistry degree and a Master's in Neuropharmacology from N.U.I. Galway. His PhD in Neuropharmacology, completed between RijksUniversiteit Groningen and Lundbeck A/S, focused on antidepressant augmentation. He later researched cannabinoids' effects on cognition, pain, and anxiety before managing APC Microbiome Ireland's Microbiota-Gut-Brain Axis lab. Transitioning to industry, he held leadership roles at Eli Lilly, Deerland Probiotics & Enzymes, and ADM, overseeing clinical trials and R&D.

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