Executive function as an ADHD endophenotype

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In an ever-changing world, a vital skill for survival is the preparation of possible actions, the monitoring of a selected action and the termination of an inappropriate action. Therefore, preparation, selection, monitoring and inhibition are all core aspects of executive function; they are also some of the key deficits in attention deficit hyperactivity disorder (ADHD).

Psychometric measurements of executive function tend to capture only the behaviours, not the core symptoms of these deficits. Event-based electrophysiological brain measures can reveal the neural mechanisms of executive function and can distinguish subtypes of ADHD. The combination of the neurological and behavioural markers of executive dysfunction in ADHD can give an endophenotype diagnosis of condition and inform more personalised treatment plans.

Executive function

Executive function is an umbrella construct referring to the functions necessary to plan activities and see them through efficiently. The qualities needed for this are accurate goal selection, action planning, monitoring, judgement, self-awareness, anticipation, organisation, flexibility and decision-making. Emotional control is also often seen as a necessary part of good executive functioning. The negative effects of executive dysfunction are seen in weak academic and occupational performance, even when the individual has a high IQ. Recalling facts, getting started on projects, maintaining sustained attention, controlling frustration, thinking before speaking or acting and analysing a problem systematically are all compromised. The same deficits affect social relationships. Impulsivity, distractibility, forgetfulness, emotional volatility and a low boredom threshold can be problematic when looking for expressions of relationship depth and stability.

Psychometric measurement of executive function

Executive function has been proposed as the central core deficit in ADHD and has been measured in a variety of ways. These include questionnaires such as the Behaviour Rating Inventory of Executive Function (BRIEF)[1] and the Delis-Kaplan Executive Function System (D-KEFS);[2] tasks such as the Wisconsin Card Sorting Test,[3] the Stroop test[4] and the Rey-Osterrieth Complex Figure Test;[5] and the computer-based continuous performance tests of commission and omission, such as the Test of Variables of Attention[6] and the Intermediate Visual and Auditory Continuous Performance Test.[7] All of these are suggested to show some frontal lobe involvement, and to be a reflection of frontostriatal brain activity, which mediates executive functioning. A more detailed outline of the full executive system of the brain, which includes connections from the cortex to the basal ganglia, including the striatum and globus pallidus as well as the thalamus, can be found in Kropotov *et al*.[8]

ADHD and executive dysfunction

ADHD symptoms overlap with executive dysfunction. Despite expectations, the *Diagnostic and Statistical Manual of Mental Disorders-5* has not substantially changed the criteria of hyperactivity, impulsiveness and inattention measured psychometrically, although the whole diagnostic category of ADHD has at least been placed in the neurodevelopmental disorders chapter.

However, since electrophysiological brain-based measures can distinguish individuals with ADHD from those without ADHD,[9] the combination of behavioural symptoms and brain-based measures would fulfil the criteria for an endophenotype. At its simplest level, an endophenotype is defined as a biologically based trait that has been shaped by the environment, including genetic and behavioural aspects of ADHD. It also holds promise for more objective and accurate diagnosis.

Measuring executive function by interview or observation of various behaviours such as 'frequently interrupts' or 'difficulty in organising a project' are isolated pieces of behaviour simply totalled. The measurement of executive function by electrophysiological means, however, can encapsulate the whole of executive function, since all human behaviour is a set of sensory, motor, affective and cognitive actions. The sequence of any task is as follows:

- Prepare for action
- Select an appropriate action and/or suppress an inappropriate one
- Evaluate the outcome
- Store the results of the action – successful or not
- Manipulate this information for the next action and predict the outcome.

An example of this would be crossing the road: cross on green; this is inhibited if green changes to red; if the light is amber you may be tempted to cross. In this instance, you would think of the consequences and decide whether to launch the action. This is a major difficulty in ADHD, at least in adults, according to Boonstra *et al*,[10] who tested adults diagnosed with ADHD on five domains of executive functioning. They concluded that ADHD was mainly a disorder of one of the executive functions – inhibition or stopping an action.

Event-related potentials

Event-related potentials (ERPs) are a non-invasive measure of the electrical activity or electroencephalography (EEG) of the brain while a subject is performing a task. The use of EEG and ERPs to measure brain function is called neurometrics. The ERPs have low amplitudes compared with the background EEG, so hundreds of trials must be averaged by 'time locking' each to the stimuli onset. This generates a set of positive and negative waves at different latencies from the beginning of the trial. A single cognitive task will have a collection of waves called components, related to the different actions in the task. The P300 wave, for example, is a positive wave that peaks at around 300 milliseconds (ms) after the start of the trial and signifies a synchronisation of neural activity (see Figure 1). A well-known ERP measure is the Go/NoGo task (see Figure 2).

ERPs trace the passage and rate of information flow through the brain in response to a particular task in time windows of 500 ms or more. The components reflect basic sensory perceptual and cognitive processing stages as the brain perceives, classifies and acts on the stimuli. The location of any deviation of latency (time lag) or amplitude (excess synchronisation or desynchronisation) suggests which brain network is compromised.

Over the last 70 years, research has yielded much empirical knowledge about the functional meaning of the extracted waves. The P300, in particular, has been implicated in several neurodevelopmental disorders, including ADHD, autistic spectrum disorders, Alzheimer's disease, Parkinson's disease, cognitive decline, alcoholism and traumatic brain injury, among others.[12] This correlates with lower grey matter volume in the prefrontal cortex. Some researchers think the P300 represents the transfer of information to consciousness.[13]

More recently, the P300 has been divided into two different parts,[14] the P3a and P3b, each having different neurotransmitter involvement. The P3a reflects attention to a stimulus, followed by the P3b over the parietal cortex, which is elicited when the stimulus or event is improbable, such as an odd picture, number or word in a sequence.

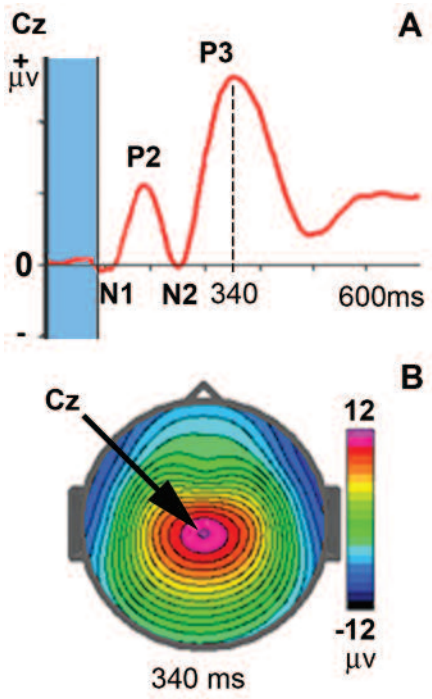

Figure 1. Figure 1A shows an event-related potential (ERP) with time in milliseconds (ms) on the X-axis. The Y-axis shows the change in brain response to the stimuli, with the plus sign being an increase in microvolts (µV) in relation to a baseline recorded just before the beginning of each trial. The blue shaded area shows the first 100 ms where the picture is displayed. The waveform has several peaks and troughs at different times; for example, the N1 is a 'negative' trough at 100 ms and the P3 (also called the P300) is a 'positive' peak at around 300 ms. The activity was measured at the location called Cz in the international 10–20 system and is at the centre (top) of the head
Figure 1B is a 'head map' showing the topology of the brain response at 340 ms from the beginning of the trial. The 'hot' colours show an increase in activity, with pink showing 12 µV, while 'cold' colours show a decrease in activity, with dark blue showing -12 µV. Green indicates no change

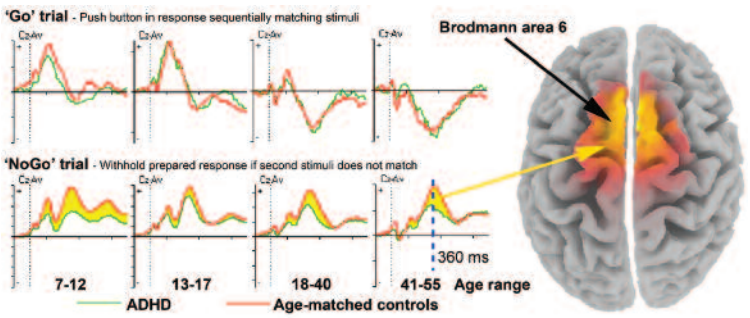

Figure 2. Reduction of the action inhibition component in ADHD subjects.[9] The Go/NoGo task is to push a button as quickly as possible when an image of an animal is followed by a second animal 1,100 milliseconds later – this is the 'Go' trial. The subject is instructed to withhold the planned motor response if the second image is not an animal – this is the 'NoGo' trial. The top row of four event-related potentials (ERPs) in the different age ranges are elicited in the 'Go' trial and the bottom row shows ERPs from the 'NoGo' trial, with ADHD subjects shown in green and age-matched controls in red. The yellow shaded area is the difference between ADHD subjects and controls. It shows no significant difference in the 'motor engagement component' in the top row, but demonstrates a significant difference across all ages in the 'P300 action inhibition NoGo' component on the bottom row; that is, impulsive responding. The image of the brain on the right shows the source of this activity (by sLORETA[11]) to be the Brodmann area 6, the supplementary motor area of the frontal lobe

Many factors that influence cognition, such as age, disease, mental illness, and alcoholism or drug abuse, affect the amplitude of the P3b, since working memory is at least one factor in these conditions. In order to judge improbability, one needs to have an idea of what is expected.

A further complexity in ERP research is that there are several types of tasks designed to measure different sensory, motor or cognitive activities. Because slight changes in the task design – such as the time between stimuli, or the loudness or brightness of the stimuli – will change the ERP components, comparisons cannot be made between components from different tasks and it is essential to have norms of each task to ensure their clinical utility.

ERPs of executive function

Differences in the particular sequence of executive function activated make a difference to the individual's functioning and not all ERP components will be abnormal. However, there are consistencies in ADHD. The main abnormality noted in ADHD is the reduction in amplitude of the 'P300 motor suppression' component when recorded in the NoGo 'action inhibition' paradigm. The 'NoGo' is the waveform elicited when the subject suppresses the prepared action of pushing a button in response to a non-target stimulus and is an index of difficulty in inhibiting behavioural responses. Kropotov *et al* found that this wave was reduced in 252 subjects diagnosed with ADHD aged between seven and 55, compared with 333 controls of the same age.[9] This shows the physiological link to the psychological observation of Barkley that the core ADHD deficit is an impairment of inhibition.[15] The inhibition measured in Barkley's research was the degree to which the subject could stop or inhibit an ongoing behavioural response – such as interrupting others in conversation – and was gleaned from interviews and questionnaires from teachers and parents. This reflects the same sequence of cognitive control exerted in everyday life.

Impulsivity of motor responses may be connected with other types of impulsivity such as choice – the basis of delay aversion; where ADHD subjects will choose a smaller immediate reward rather than wait for a bigger one. An ERP study of this[16] showed enhanced amplitude in the late positive components when subjects escaped delay, but reflected ventral prefrontal cortex activity. Emotional impulsivity where the subject was motivated to avoid waiting (delay aversion) was shown to activate the amygdala.[17] These behavioural types of impulsivity are unlikely to show relatedness in the brain and ADHD understanding could be enhanced by the study of ERPs of impulsivity types.

Conclusion

The combination of ERPs and psychometric measures of executive function can provide a specificity, identify co-morbidities and predict likely medication response, as well as help titrate medication.[18] Measuring this endophenotype would be of value in distinguishing the children exhibiting ADHD symptoms who may have only a developmental lag of the executive function[19] and will catch up in time. Other misdiagnoses are likely when the individual is under extreme stress, has a high degree of anxiety or other developmental problems such as autism or pathological demand syndrome.

Recently, as the EEG hardware has become cheaper, better and easier to use, and with the development of normative databases, EEG and ERPs have started to move out of the research lab and into clinical practice. Organisations such as the British Neuroscience Association and the Society of Applied Neuroscience organise conferences and courses for psychologists and other healthcare professionals wishing to add this diagnostic tool to their clinical practice. Not only are ERPs a promising, precise and objective means for diagnosing ADHD, but they can aid in the treatment by knowing the precise endophenotype. Neurofeedback[20] or transcranial stimulation can normalise the aberrant electrophysiology and is an efficient adjunct to the standard psychological treatment ■

Declaration of interest
The authors declare that there are no conflicts of interest.

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Key points

- Executive dysfunction is a core aspect of attention deficit hyperactivity disorder (ADHD).
- Psychometric measurements tend to only capture the behaviours, rather than the symptoms of the deficits in executive dysfunction. Event-based electrophysiological brain measures can reveal the neural mechanisms of executive function.
- A combination of both neurological and behavioural markers can give an endophenotype of ADHD and inform treatment plans.