Identifying Patterns of Executive Functions in children and adolescents with suspected Attention-Deficit-Hyperactive-Disorder using a novel computerized system: the E*f*A system[1]

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Background

Attention Deficit Hyperactive Disorder (i.e. ADHD) is a developmental disorder, characterized by inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013). It affects 3% to 8% of school-aged children (AACAP, 2007) and may persist into adulthood (Swanson , et al., 1998) (Kaplan & Sadock, 2009).

ADHD is considered to be a common referral to the paediatric primary care services, whether it is to psychiatry, neurology or paediatric clinics. As such it creates a sizable clinical and economic burden on those services, whether it is clinical resources needed for diagnosis or those required for the treatment (Matza, et al., 2005) (Jensen & et al, 2001) . The diagnosis itself of ADHD is still considered to be a clinical-based diagnosis as a gold standard (Kaplan & Sadock, 2009). To-date there is no known test that has been proven to be valid or sensitive enough in order to replace the physician's clinical judgment (AACAP, 2007)

So far, several tools have been developed to assist in the diagnostic process, such as: the Connor's Rating Scale (= a screening tool), Continuous Performance Tests (which may offer some valid insights but never proved its value as independent diagnostic tools for themselves), DSM-based checklists, etc. But even with all of those supportive tools there has been no single tool that was identified and/or proven to be more reliable than the gold-standard clinical assessment.

The diagnosis of ADHD may be straightforward, but at times, as part of a broader complex/syndrome, the differential diagnosis can be quite confusing. Cases such as Learning Disorders mixed with ADHD often lead to confusion as they may mask each other. And in severe cases - ADHD might be mistaken for autistic traits (Mayes & Calhoun, 2007) (Geurts, et al., 2008).
Hence it is crucial to find a way to assess the core impairments that cause ADHD, thus allowing for a better and more precise diagnosis and subsequent appropriate treatment.

Current diagnosis methodology and the NIMH

Over the years it has been repeatedly observed that there is a wide gap between the DSM's criteria[2] and the suspected underlying biology (Rapin, 2014). Even before the recent publication of the DSM-V, the American National Institution of Mental Health (a sub-division of the NIH) has started forming its own diagnostic manual, called Research Domain Criteria (RDoC). The development by itself serves as a statement, calling for clinicians to progress from the phenomenological approach used in the DSM to a more neuro-cognitive /measurable approach. Or in other words: modern times call for a more exact, quantifiable and measurable parameters, rather than clinical observation which

[1] E*f*A System = Executive Functions Assessment System
[2] DSM = Diagnostic Statistical Manual used in psychiatry

may not be sufficiently accurate at times. In its press release (Insel & Lieberman, 2013), the NIMH representatives has stated the following: "*...Looking forward, laying the groundwork for a future diagnostic system that more directly reflects modern brain science will require openness to rethinking traditional categories. It is increasingly evident that mental illness will be best understood as disorders of brain structure and function that implicate specific domains of cognition, emotion, and behaviour*".

Since ADHD is traditionally presented as a cluster of multiple possible items, it has been criticised more than once for its vagueness and lack of specificity. As mentioned above – many diagnoses can be masked by and/or mistaken for ADHD. For example: children with severe PTSD or anxiety might be positive for most of the inattentive/hyperactive item; ASD clients are also a well-known group to be baffling clinicians on the question of co-morbid ADHD.

It may be that the time has come to abandon the phenomenological approach and rethink the diagnostic approach which emphasises the proposed underlying neurology of ADHD.

Literature review: Executive Functions and ADHD

In 1994, Posner and Raichle developed a comprehensive, multi-component theory of attention, called the "neuro-anatomic network theory of attention" (Posner & Raichle, 1994). In their research, Posner and Raichle identified 3 attention networks: the networks of alerting, orienting, and executive control. While the first two domains were interesting for themselves, it was the executive control concept that has been broaden with the years. These days the concept encompasses a broader array of functions, used by the brain to manage and prioritize stimulus and responses, via a set of skills which include: attention, timing, planning, prioritizing, modulation of responses, etc. This cluster/array of functions is known today as the *Executive Functions*. Several studies were aimed at identifying and describing ADHD via the Executive Functions paradigm (Nigg, et al., 2002).
A rather good way to visualize part of this array of functions is presented in Figure 1, taken from the book: "A New Understanding of ADHD in Children and Adults" (Brown, 2013). It shows how various resources and skills clustered into various functions.

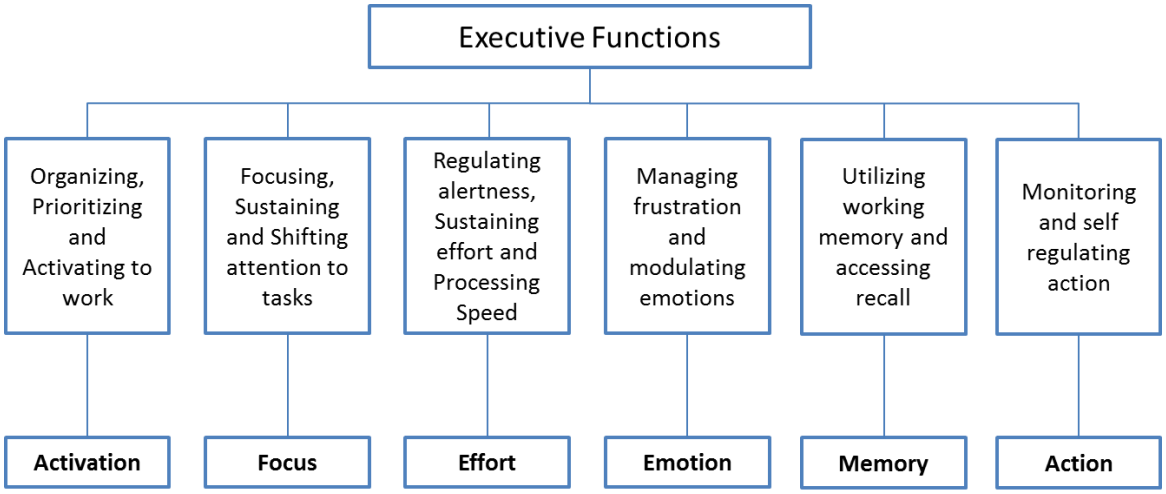


Figure 1

The neuro-anatomy and physiology of those functions is no yet fully understood. It is believed to be related mainly to the right pre-frontal lobe's functions, and considered to be mediated mainly via the dopaminergic system and various circuits.

To better understand how ADHD represents a primary deficit in executive control, we can define executive function as comprising of at least four factors: (1) response inhibition and execution, (2) working memory and updating, (3) set-shifting and task-switching and (4) interference control

(Wilcutt, et al., 2005). The literature shows significant differences between children with and without ADHD on tasks assessing executive function. The most consistent effects were observed in measures of response inhibition, vigilance, and planning; children with combined and inattentive types of ADHD differed from controls and did not differ from each other, whereas children with hyperactive-impulsive ADHD had minimal executive function impairment, suggesting that executive function weaknesses are primarily associated with inattention, rather than hyperactivity-impulsivity symptoms. Six of eight studies assessing working memory found impaired working memory in children with ADHD. On the other hand, the observation that fewer than half of the children with ADHD had significant impairment of any specific task of executive function, and that the correlation, while significant, tended to be small in magnitude, led the authors to conclude that their findings "do not support the hypothesis that executive functions deficits are the single necessary and sufficient cause of ADHD in all individuals with the disorder. Instead executive function difficulties appear to be one of several important weaknesses that comprise the overall neuropsychological etiology of ADHD".

The literature also documents lifelong executive function deficits in ADHD (Seidman, 2006) , with the most consistent results found in planning, working memory, and inhibition, followed by set-shifting (Pennington & Ozonoff, 1996), with greater reductions in Visio-Spatial than verbal working memory. Furthermore, impaired executive functions in ADHD are more apparent with increased task demands (Gau, et al., 2009) (Castellanos, et al., 2006).

Current valid testing tool

As Executive Functions been recognized as the proposed "smoking gun" in the case of ADHD, several approaches were found to be valid in the assessment of those functions. One of the tools which is prevalent in New Zealand to date is the *Test of Everyday Attention for Children* (otherwise known as the TEA-Ch).
The TEA-Ch has been previously validated as a sensitive tool which may support the diagnosis of ADHD in candidate clients (Manly, et al., 2001). The various sub-tests are measures of auditory and visual detection, of counting, of response speed, and so forth. Separable attention processes are inferred constructs believed to contribute significantly to differences in the efficiency of performance on these tasks. Clients who were previously diagnosed with ADHD showed significant deficits across sustained attention and attentional control subtests of the TEA-Ch.

During 2001, another research was published, which looked into patterns of Executive Functions performance in clients with ADHD versus non ADHD clients (Shelley, et al., 2001). It was found that children with ADHD performed significantly worse on the TEA-Ch than the controls on subtests of sustained attention and attentional control. The groups did not differ, however, on subtests of selective attention. These findings were suggested that the TEA-Ch is a sensitive tool in attentional deficits unique to ADHD.

There is however a major drawback with the TEA-Ch. The test itself does not measure or quantify any of the hyperactive symptoms. Contrary to the inattentive component, the measurement of the hyperactive component in the TEA-Ch is still very much based on the psychologist's observation of the client, rather than on objective measurements. The TEA-Ch cannot measure processing speed as well, which is yet another major component in the assessment of the Executive Functions.

Current proposed system

In Taranaki, as much as in the rest of New Zealand, children and adolescents are referred query ADHD to three possible specialists-types: Psychiatrists, Paediatricians and Child Neurologists. The various groups and/or specific clinicians may differ in their approach, whether it is mainly relying on their clinical judgment vs. mainly relying on aiding tools in order to substantiate their diagnosis (i.e. screen questioners and psychological tests such as the TEA-Ch and others). Or in other words: while the gold standard according to current literature is the clinical assessment, some physicians tend to rely heavily on additional tests. Those tests consume substantial time and resources, and lead to less than favourable results in terms of clinical accuracy and resource management. It also makes the client's experience lengthy and cumbersome.

On the other hand, while relying mainly on clinical judgment is the advised approach, still, at times, it could be confusing and less than accurate, especially when a complex case is. Hence relying on diagnostic tools is not always avoidable.

Hence – a cost-effective unified tool may solve some of these issues, providing a more *objective and measurable approach*, while relying on up-to-date understanding of underlying mechanisms. With this in mind, and with the proposed approach by the NIMH (i.e. the RDoC) we are proposing the use of a newly developed system which focuses on the cognitive and functional construct underlying the ADHD presentation: the Executive Functions Assessment System (aka – the E*f*A System).

The E*f*A system is a computer based testing module. It holds seven tests, which aim at assessing 7 different domains/executive functions. Some of the tests were designed as variations on existing psychological tests (such as the Tower Of London, Stroop, trail making), while others are original. The 7 tests are administered as a bulk, while the computer captures in the background numerous data items relevant for the clinician. Some of the tests' results overlap with others, allowing for inner-reliability. The end result is presented graphically, in a relatively easy way to read and interpret by the physician. The 7 tests are as follows:

Test	Main functions assessed
Tower of London	Planning, impulsivity
Simple Response Test	Attention, Sustaining of Attention
STROOP	Splitting of attention
Visual Scan	Visual scanning, visual attention
Trail Making	Sustaining of attention, parallel processing
Digit Span	Working memory
Go/No-Go	Response inhibition over time, sustaining of attention

The current TEA-Ch, while being considered to be valid and sensitive enough, is not free of limitations. First of all it requires an experienced and qualified psychologist (supervised trainee or a senior one) to administer the test and interpret its results. Secondly – the TEA-Ch is time consuming as the administration, interpretation and report production require the psychologist's attention and time. Third – as a pen-and-paper based test – it requires its own logistics and on-going admin which in turn, translates to more resources.

Progressing into a computer-based platform makes the entire process much more efficient and cost effective. The test is designed to be carried out by the child and a staff member, who does not have to be a psychologist. The test is relatively short and the report is produced automatically within minutes. The data is then automatically collected into an electronic data base which can be used in the future as a framework for producing NZ norms and other data-driven insights.
In current times, where staff and resources are becoming scarcer, progressing into a more efficient testing paradigm has plenty of benefits.

Combining the scientific up-to-date approach with the cost-effective aspects of the E*f*A system would allow Taranaki's CAMHS to better manage and diagnose ADHD-query referrals.

Proposed research

Goal: Demonstrate the effectiveness and sensitivity of the E*f*A system, as a support-tool for the process of diagnosing ADHD.

Hypothesis: The E*f*A system is as valid as the TEA-Ch and/or clinical assessment in capturing and quantifying Executive Functions.

Basic Design/Concept:

- The proposed research will be a *prospective case-double-control* study, comparing the E*f*A system with both the TEA-Ch assessment and a clinical/physician assessment (hence the double-control).
- The participants will be recruited from both CAMHS and Paediatric community clinics, ages 6-18 years and from the group who was referred to either of the clinics query ADHD.
- The research is designed to be a national one, hence the CAMHS and Paediatric clinics will be chosen from various DHBs across New Zealand, who will choose to participate in the research. Having said that – the first phase of the research will be conducted solely in the Taranaki District, aiming (among other things) at testing the IT infrastructure.

Consent:

- The research's objectives and methods will be presented and explained to the clients and their parents, in a suitable and appropriate fashion.
- A copy of the consent form will be given to the family, allowing them to read it carefully before making their decision.
- Informed consent will be obtained from both the clients and their parents, as long as the client is cognitively capable of making this decision by himself/herself.
- In case of a single parent – the main caregiver's consent will be obtained.

Inclusion criteria:

- Age 6-18 years
- Referred query ADHD
- Both the client and his/her parent/legal guardian have given their consent (when applicable)
- Both the client and the legal guardian are cognitively able to give an informed consent

Exclusion criteria:

- Known intellectual impairment
- Known major neurological disorder (such as: Epilepsy, CNS disease, head trauma, CP, etc)
- Sensory impairment (deafness, blindness)
- Other major mental health diagnosis (Psychosis, Major depression, Severe anxiety/OCD, etc)

Methodology

- Once a client is enrolled, he/she will be going through three different assessments (not necessarily in the same day):

1. A clinical assessment done by a consultant, either a Paediatrician or a Child Psychiatrist.
2. A full TEA-Ch assessment (done by a qualified psychologist, trained in administering the TEA-Ch, as per the DHBs' regulations).
3. A full E*f*A assessment - will be supervised by the client's key worker or any other person designated by the clinic. This person will be trained in administering the E*f*A system.

- The E*f*A system is an application which is stored on the Taranaki DHB's server farm. The accompanying database is stored in the same location, and is maintained and protected by the TDHB's IT department, complying with the latest regulations and methods.
- Clinicians who will join the research from various DHBs will have their unique Username and Password which will allow them to log in and complete the E*f*A assessment with their clients.
- The E*f*A's results will be produced and delivered to the designated clinician in a secure way, complying with the IT department's regulations, methods and guidelines.

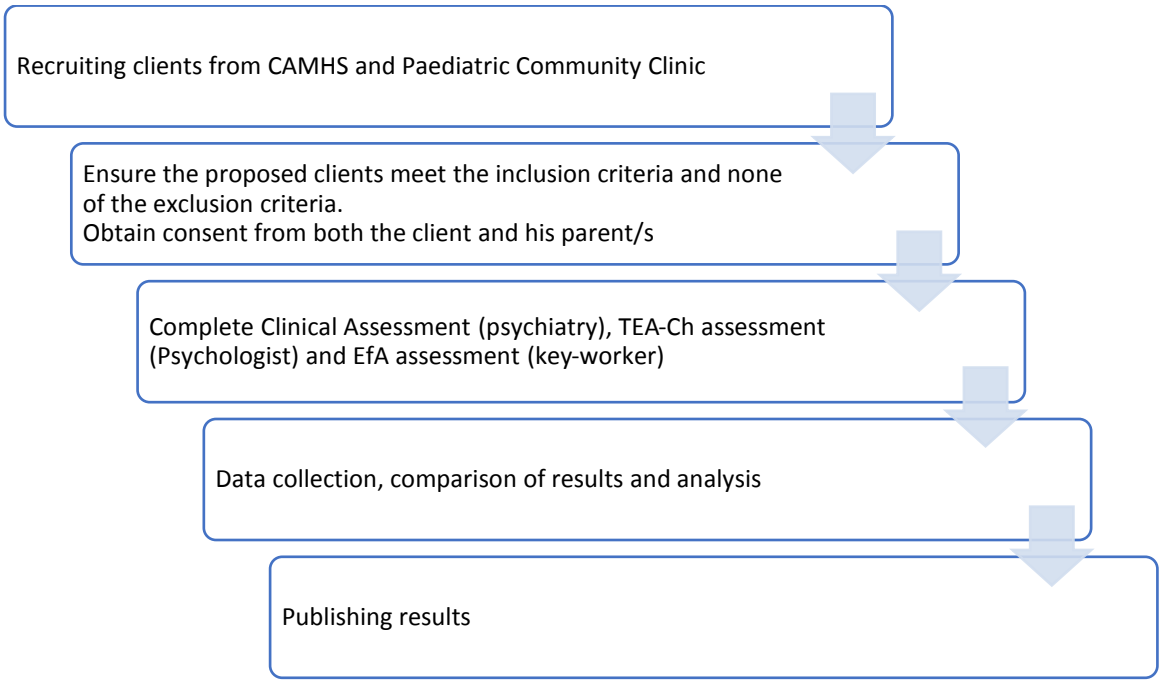
Data collection and processing

Data will be documented via expected route for the specific assessment, i.e.: clinical notes for psychiatric assessment accompanied by a DSM-Checklist, psychological report for the TEA-Ch assessment and an automated report for the E*f*A system.

Assessments results will then be processed and compared on two levels:

1. The macro level (i.e. whether ADHD was eventually diagnosed or ruled out)
2. The micro level: sub-tests and sub-domains (i.e. Attention span, working memory, planning, etc.) will be compared between the various tests' results (when applicable).

Data will be then processed statistically with commonly used tools and approaches, in order to establish sensitivity, specificity, validity and significance of the results and the comparison.



Ethical considerations:

1. Each client and guardian will be presented with information sheets and consent forms, as required by the ethical committee.
2. To ensure that no client will be diagnosed by a single tool only (which in turn may bias the diagnosis, resulting in an inappropriate treatment plan), we have designed the study in a way that every client will be assessed by all three tools, from which two have been already previously validated (i.e.: clinical assessment by a senior consultant and the TEA-Ch). No client will be diagnosed only by the E*f*A system.
3. To ensure the integrity of the clinical process and outcomes, all diagnosis and subsequent treatment plans will be based solely on the clinical assessment as per the New Zealand relevant guidelines (New Zealand Ministry of Health, 2001). Should there be a conflict between the various tests, the clinical assessment will the one who determines the treatment plan and course, overriding any conflict.
4. Should a client show additional suspected diagnosis other than ADHD, he/she will be further referred accordingly to an appropriate clinical/diagnostic process.
5. Should a client be diagnosed with ADHD, the parents and the client will be advised regarding the recommended therapy.
6. Once the client has finished his/her part of the study, he/she will remain under the clinic's care for the entire period of his/hers treatment. The enrolment in the study will not affect any other procedure and diagnostic/treatment approach that would have been implemented otherwise.
7. Should any client or guardian feel that they have been harmed in any way during the research, they will have the option to contact the main researcher in order to amend any alleged wrong.
8. No fees will be charged from the enrolled clients and/or their families for their participation in the study.

Cultural and Gender aspect

1. As far as the lead researcher is aware of – there is no component in the tests that may be considered offensive or discriminative to any culture or gender.
2. The tests/research will be offered to Pākehā and Māori alike, as well as any other culture or demographic origin which will be referred to the participating clinics.

Funding:

At the moment – all the work that has been done so far was funded via personal route: Initial programming and software design and testing were done by the main researcher.
Dedicated computer and literature were purchased from CME resources.

Additional Web adaptations and web-based database design will be completed by the Taranaki DHB's IT department.

It is the main researcher intent to pursue further external funding for the research, for purposes of: additional computers, research assistance, TEA-Ch forms, statistical analysis, etc..
The proposed funding resources will be sought from local venues (Taranaki's Medical Foundation, TSB Bank community trust, etc.).

There is no other commercial venue or resource that is being pursued for the purpose of financing this research.

Possible implications and/or application of the study

1. Should the E*f*A system be deemed valid as per the study's results, we intend to put it into daily use in the various DHB's clinics, complementing and supporting the clinical assessments.
2. The E*f*A system would allow for a fast, cost-effective method of augmenting the ADHD-diagnosis process, producing a "map" of strength and weaknesses of the proposed clients, in terms of their Executive Functions.
3. All clinicians will be able to converse in the same fashion regarding their clients' diagnosis, strength and weaknesses.
4. A growing electronic database would serve in the future for the purposes of additional studies and for the production of New-Zealand based norms.
5. This test / platform will also allow for a set of multi-cultural norms to be developed, as data could be spliced per origin, culture, gender, etc. Hence eventually will allow for a more precise and appropriate set of norms, rather than relying on the average-Caucasian-western-client's norms as we usually do.
6. Freeing psychologists from hours of administrating the TEA-Ch will allow them to provide yet a better service for our clients, as they will be available for additional psychotherapy and advanced testing.
7. Clinically speaking – as the E*f*A system is easy to use and re-use, we could aim at administrating the test before and after intervention, thus measuring/documenting the effectiveness of the treatment. This option might be useful when discharge-timing is in question; relapse is being queried, etc.
8. It should also be helpful in the clinical decision making when it comes to complex cases where DHD is suspected alongside ASD, Learning Disorder, etc.

But perhaps the most important implication would be the forward move towards a more neuro-functional-based framework of diagnosis rather than relying on old nosology.

Conflict of interests

The study is not funded by any pharmaceutical company or any other commercial company as such.

To the best of my knowledge, no one of the researchers in the study is affiliated with any commercial/business endeavour of such.

Should additional funding will be given via any commercial resource, it will be clearly disclosed in the subsequent paper.

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