UBC BEST MINT

NeuroTechX Open Challenge Proposal

1. Summary

Measurements of psychological states can add an objective layer to diagnosis and treatment. In the case of ADD/ADHD the low reliability of single-sitting tests makes diagnostics subjective, which results in an overdiagnosis epidemic. UBC MINT proposes an accessible biomarker measurement that allows for multiple sittings (longitudinal test) thus improving reliability and empowering patients. For the NTX 2018 Open Challenge, we developed an ADD/ADHD biomarker testing app to be used with a MUSE headset. The Flanker test is used to measure Alpha and Beta suppression as biomarkers for the user's neural connectivity, which is impaired in ADD/ADHD patients.

2. Introduction

The nature of ADHD diagnosis is imperfect. Diagnosis of ADHD often begins with a parent, teacher, or clinician presenting concerns about academic performance in school. The next step involves a standard medical history and physical examination, followed by a neurological exam where the clinician looks for behavioural symptoms associated with ADHD such as hyperactivity, impulsivity, inattention, daydreaming, lack of concentration and behavioural problems. Then, family and school assessments are conducted to seek more evidence of ADHD symptoms and impaired functioning. Next, the clinician compiles the information from the medical exams, neurological assessment, family assessment and school assessment to see if the exhibiting symptoms meet the criteria for DSM-5 diagnosis for ADHD and rule out other conditions that have similar symptoms. Possible comorbid disorders are also considered. If an ADHD diagnosis is made, treatment options are considered, and parents and teachers are educated.

While ADHD is often considered a neurodevelopmental disorder, current assessment and diagnosis methods do not involve biomarkers (biological based indicators of ADHD, such as brainwave tests). Potential biomarkers for ADHD are being researched and many have been consistent in finding abnormalities in the frontal cortex, a trait seen as universal in those who experience ADHD. The main issue facing ADHD diagnosis is subjectivity, stemming from the diagnostic process, growing expectations from parents and teachers, and an overlap of behavioural and attention symptoms with other clinical disorders. These complications result is an

ongoing overdiagnosis crisis, in which expected immaturity is confused for a neurodevelopmental delay (Sanford, 2015).

The introduction of an electroencephalographic (EEG) biomarker to address subjective nature of diagnosis would be vital to increase the accuracy of ADHD diagnosis. Using a biomarker in conjunction with the current standard of assessment and diagnosis of ADHD would increase the efficiency of the diagnostic process because it would assist in showing a more homogenous phenotype of ADHD, which may lead to more specific etiology, course, treatment and response.

EEG is one of the most promising ways to introduce the use of a biomarker in ADHD assessment and diagnosis, since it is relatively inexpensive and non-invasive. There are also no real safety restrictions involved in EEG compared to other neuroimaging techniques such as positron-emission technology or transcranial magnetic stimulation. It is also much easier to administer with less specialized training, this means that doctors can learn how to integrate it into the diagnostic process of ADHD.

3. Current Methods

When using an EEG to investigate the potential of ADHD, the most consistent biomarker is the presence of increased absolute power in the theta band. This is a marker of slow EEG activity in frontal central areas of the brain, a phenomena shared by many individuals experiencing ADHD. The Theta/Beta ratio is also linked to hypoarousal, one of the first signs of ADHD. Research has also shown decreased activity in the beta EEG band in individuals with EEG. However, this has more mixed findings than the presence of increased power in the theta band. The theta beta ratio is represented through elevated power of slow waves (4-7 Hz "theta") and/or decreased power of fast waves (14-30 Hz "beta"). Based on the findings of an increased theta and decreased beta, the theta/beta ratio has become a measure used to help discriminate those suffering from ADHD from those who don't.

3.1. Problems with theta/beta ratio

Despite it being one the preferred biomarkers to investigate the presence of ADHD, the Theta/Beta ratio, has some significant problems. In a meta- analysis done by Snyder SM, Quintana H, Sexson SB, et al, it was found that a strong theta/beta ratio identifies a majority of people with ADHD, however, there was also moderate percentage of people (18%) with ADHD that have a normal theta beta ratio that would not be detected. This 18% rate of a type 2 error, or a false negative means that the Theta/Beta ratio marker is not good enough to be used a clinical diagnostic tool, and this may be one of the reasons why EEG is not used as a part of ADHD

diagnosis and assessment. Another study by Magee CA, Clarke AR, Barry RJ, McCarthy R and Selikowitz M (2005), found that the Theta/Beta ratio marker only had an accuracy rate of 58% in detecting patients with ADHD. It is difficult to know whether the inconsistent results of using the theta/beta in detecting ADHD is due to methodological issues such as variations in sampling, behavioral variations (L. Cummings, 2000), instrumentation, data processing and analysis, or if due to EEG diversenesses within the ADHD population.

Brainwave measurements vary within a single day (L. Cummings, 2000), and behavioral traits show weekly and monthly cycles, (K. Hirschenhauser, 2002). Thus, we believe that single-sitting tests must be significantly affected by individuals' behavioral variability and their corresponding EEG biomarkers. If so, these current tests available must be tuned to capture fixed aspects of brain functioning, which are less likely to accurately identify psychological patterns. Perhaps this contributes to the low sensitivity and specificity reported.

3.2. Advantage of Longitudinal Tests

Longitudinal tests consist of taking the same measurements over a longer period of time, as opposed to single-sitting tests, which collect one or more measurements only once. Longitudinal testing can mitigate variability over time, which is especially pronounced for behavioral and psychological traits.

Currently, EEG testing is not done longitudinally because of high demand of specialists, which creates an accessibility dimension to the problem. We propose that an accessible measurement tool can be applied for longitudinal testing of EEG spectral biomarkers, thus mitigating the time variation of measurements and allowing for more accurate results.

Furthermore, when users own their testing equipment, they show more engagement with their health and are empowered to experiment objectively with different habits and coping tools (M. Bauman, 2015). Perhaps this impact can be promoted with psychological conditions once testing becomes accessible.

4. Our Proposed Solution

As discussed before, we intend to improve the accessibility of EEG testing for psychological illnesses, with the goal of creating longitudinal testing tools that have an acceptable sensitivity and specificity. If our research is correct, a less accurate measurement taken longitudinally could lead to more accurate predictions, so we hope to improve upon current single-sitting measurements such as Theta-Beta Ratios.

To make a hyper accessible EEG test, we developed an MVP phone app that obtains data from a MUSE headset. Since the MUSE was designed for

hyperaccessibility, users could have their own units and test themselves consistently. The analysis that would normally require a specialist is done computationally by the app, and results over time are stored for comparison. This eliminates the costs of specialized clinical EEG amplifiers as well as specialist facetime.

The biomarker collected is the Alpha and Beta suppression measured by the Flanker Test, meant to indicate neural functional connectivity. Since the Flanker Test is an active measurement (requires user participation) we expect it to be less sensitive to mood and attention variability over time, at least compared to passive measurements such as the Theta-Beta Ratio.

4.1. Flanker Test

We chose to use a cued version of the Eriksen flanker test as our paradigm for the app. Our analysis is based mostly on the results found using this same test in Mazaheri et. al. (2014). They conducted experiments on 57 pre-screened adolescents aged 12-17. The participants were split into three groups: typically developing (TD), ADHD/ADD inattentive type (IA) and combine IA and hyperactive/impulsive (CB) type. By using a cue-based paradigm, we can eliminate some elements of ambiguity as we are measuring a response to a known stimulus.

The study measured oscillatory EEG response in the theta (3-5 Hz), alpha (8-12 Hz), and beta (22-25 Hz) frequencies during multiple stages of the flanker test. At the beginning of the test, one of blue or yellow would be chosen as the colour to indicate action. The test begins with a cue categorized as one of three types: response preparation (RP), Null, and Warning. The RP cue would show an image of a right hand and left hand, with one of them in the "action" colour. This cue would accurately predict the hand that will be used to perform the flanker task 84% of the time. The Null cue would not give any predictive information (both hands the same colour). The Warning cue would warn the participant that the following trial would be incongruent.

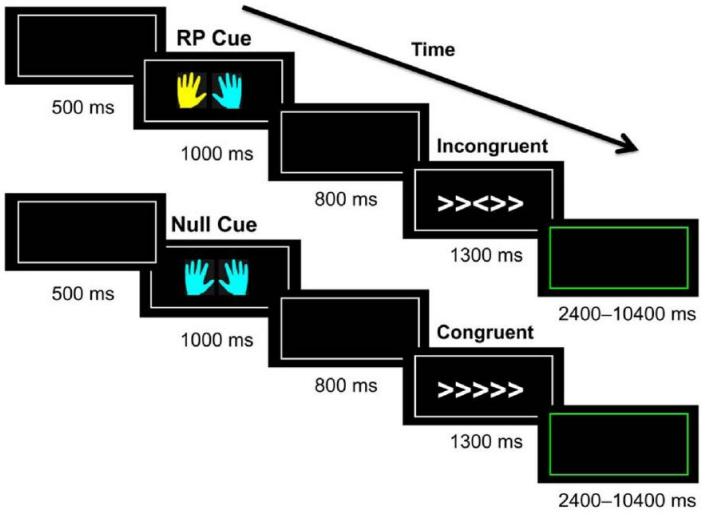


Figure1: depiction of series of screens in flanker task. Credit: Mazaheri et. al.

A congruent trial would show five arrows pointing in the same direction, while an incongruent trial would have the middle arrow pointing in the opposite direction from it's "flanking" arrows. The participant then has to press a button with their right or left hand depending on the direction of the middle arrow. More details about the implementation in Mazaheri et. al. (2014) can be found in their paper.

The key differences between TD and ADHD groups found were:

1) TD participants had a significantly higher alpha suppression during RP cues, but no significant differences were found between any of the groups during null cues
2) Beta suppression is diminished in the CB group
3) Beta activity is correlated with behavior in TD group
4) IA group had most significantly diminished alpha suppression
5) Frontal theta/posterior alpha coupling was absent in both ADHD subtypes
6) Beta levels were correlated to reaction time for all groups

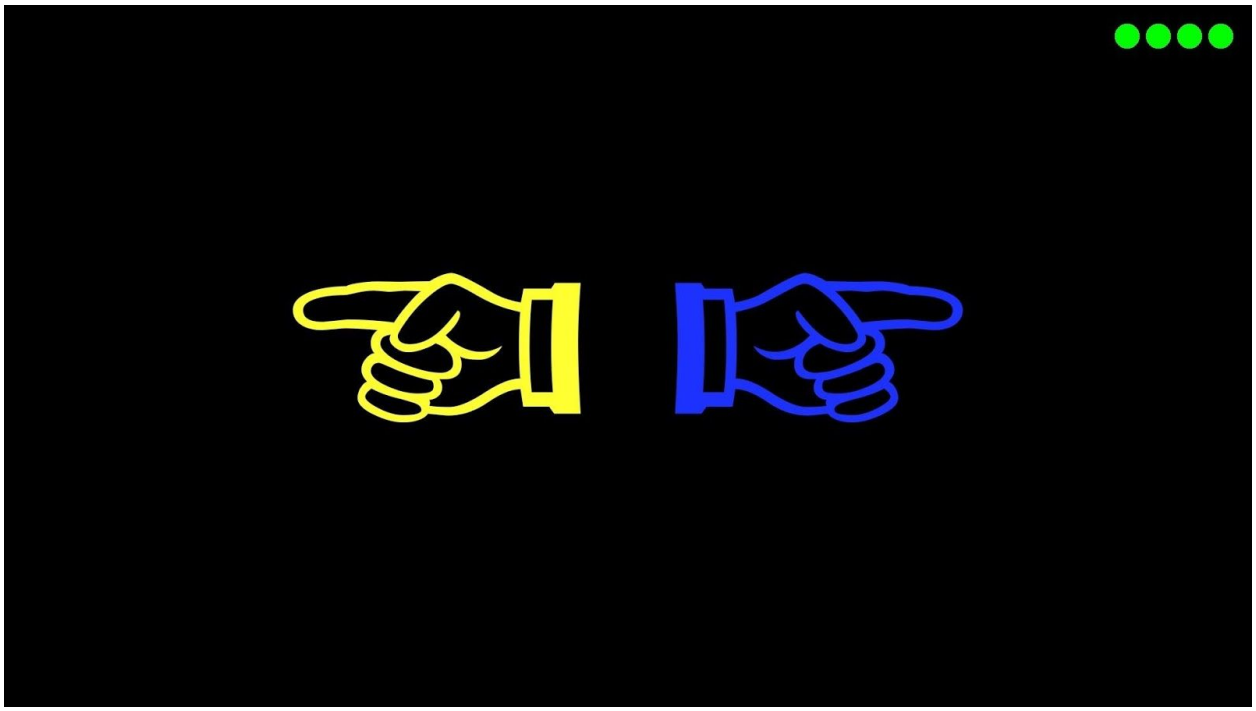
These results together form a group of biomarkers that we will use in our app to help our users identify signs of ADHD/ADD. We are aware, however, that this is not clinically validated and thus must not be used for clinical decision-making at this stage.

Some limitations in this paradigm are the fact that the subtypes of ADHD/ADD are widely debated, as well as the fact that this study was done on a relatively small group of subjects. Subjects from different groups had different levels of exposure to

medication. While it did not seem to have a significant effect on their performance, and all participants went through a 24-hour "cleanse" prior to the experiment, long-term effects of ADHD medication are not well-documented and may have skewed the results.

5. App Implementation

We envisioned the app to be something people could easily interact with throughout their day. Below is a snapshot of the opening screen and the screen during data collection:



All of the source code for our app is available at github.com. We wanted to design for the MUSE EEG headset because it is a commercially available product that has already been designed for comfort and usability. Furthermore, a kind gift of 2 MUSE headsets from the NTX community allowed us to start testing right away. The user is able to start a testing session whenever they want and collect and view the their recorded data.

Our implementation of the flanker test on this app is very similar to that in Mazaheri et. all (2014). We chose to implement in Android because a large portion of our developers owned Android devices, it is easy and free to set up the app, and MUSE has a library for communicating with android. We also wished to use android data binding toolkit for live data viewing.

As there is no standard explicit threshold for healthy alpha and beta suppresion, our app can only give relative information i.e., it would allow the user to see their normal brain activity and view in real-time how it changed throughout the flanker test. For now, we do not intend to distribute or promote our MVP as a diagnostic device, since it would not be clinically tested and thus ethically inadequate for clinical decision-making. This is reflected in the UX and UI we designed.

Future improvements include incorporating a clear explanation page which will tell the user what to look for. We are also thinking of creating a calibration test for the user to periodically set their own baseline neural activity. This would allow for more quantitative results when they use our app. We would also like to improve the UI by incorporating Android Material Design principles and allowing for smoother transitions between displays.

6. Legality of Development

From current Health Canada standards, rule 10 of "Risk-based Classification System for Non-In Vitro Diagnostic Devices (non-IVDDs)" (Ministry of Health, 2015) our app would be considered an active device of Class II, since it is potentially depended upon for a diagnostic decision. Thus, it would require an MDR (Medical Device Regulations) for development, as well as an MDEL (Medical Device Establishment Licence) for distribution. Considering the reach of our student team, this would likely require that we obtain a patent and then sell our MVP to a more established company.

Furthermore, if the tool is not suitable for diagnosis and clinical empowerment, it may still hold value as a neurohacker tool for tracking attention and focus, as long as the UX and UI is redesigned to stress that it is not sufficiently effective to be a clinical product, and must not be trusted in medical decision-making.

7. Impact

An unfortunate reality of the medical field is the lack of patient engagement. Clinicians and health institutions show a concern for increasing engagement (CPSI, 2016), and the patients themselves have an incredible vested interest in their own bodies, so what is holding us back? Perhaps it is the sheer complexity of clinical issues, which require lengthy specializations and thorough investigation for any broad understanding to be formed. Furthermore, clinical technology is (understandably) designed, distributed and marketed to the health sector, leaving a vacuum of technical capacity for users and patients to be active and informed decision makers for their own health.

Our project is not a clinical tool, but it intends to operate within a clinical problem. We understand the ethical and practical difficulties in bringing clinical decision-making to the user, however, we are developing a hyper accessible tool in order to suggest an alternative approach, fulfilling this vacuum. The recent affordability of computation allows us to develop effective and accessible tools that may empower individuals over their own bodies. Perhaps psychology, the grey zone between neurology and behavior, can be a door to exploring clinical empowerment solutions.

8. References

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