Project Title	Mapping Neural Mechanisms of Inhibitory Control in Musician and Non-Musician Youth
Please indicate if the project involves basic research or applied research:	Basic research
Age of study population	Other: 16-24
Project Goal - For a general audience as well as your peers, explain the goals of the project in clear and compelling language.	It is shown that inhibitory control (IC), the ability to suppress interfering thoughts to attend to what is needed, is impaired in youth depression and enhanced by music training. We will use transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) to identify neural mechanisms that underlie IC improvements in youth musicians. Discovering the mechanisms of enhanced IC will guide designing new therapies for youth depression.
Research Category	Neuroscience Cognition and/or emotion
Identify the governing body that would be responsible for overseeing the proposed research if it involves human participants.	Research Ethic Board at [redacted]
Project Start Date	03/15/2016
Project End Date	03/15/2017
Grant Request	20000
Total Project Budget	55000
A brief description of the project: 5,000 character maximum, including spaces	Evidence suggests that individuals with music expertise perform better in tasks of attention and memory. We have showed that this advantage is linked to enhancement in a core cognitive function, inhibitory control (IC). IC involves being able to control one's attention, emotions, and thoughts in order to suppress irrelevant internal or external interference and attend to what is needed or appropriate. IC matures well into young adulthood rending youth more vulnerable to IC impairments. IC has causal roles in etiology of depression, a debilitating condition that impairs mood and cognition. IC impairment underlies depressive symptoms and serious co-morbidities in youth - importantly, substance abuse and completed suicide. We have shown that IC is enhanced in individuals with musical training and following a course of daily cognitive training based on music. However, the mechanisms subserving this improvement remain poorly understood. Identifying the exact neural mechanisms underlying the enhanced IC has tremendous potentials as targets of novel treatments in youth depression. Our study will investigate the question if enhancement of the gamma-aminobutyric acid (GABA)ergic mechanisms underlies the enhanced IC

	in youth with music expertise? Development of IC functions is associated with maturation of GABA in the prefrontal cortex(PFC). Normal brain functions and behavior depend critically on the precise interplay between the excitatory and inhibitory neurotransmissions. Excitation is mediated by glutamate and regulated by GABAergic inhibition. The GABAergic neurotransmission regulates information flow across brain networks and is critically implicated in cognition and IC functions and depression. Lower GABA in the PFC is associated with impulsivity and poorer IC performance(e.g., Go/NoGo task) in youth. How to measure GABAergic mechanisms in humans? We have advanced a brain mapping technology that involves concurrent combination of transcranial magnetic stimulation (TMS) and EEG (TMS-EEG) and permits transferring investigation of brain circuitries from brain slices to non-invasive investigation from the intact cortex. Employing TMS-EEG, we designed novel paradigms and extracted markers of inhibitory neurotransmission across brain regions such as PFC. We achieved this by delivering one or two TMS pulses to the PFC to activate GABAergic mechanisms, while concurrently recording responses by EEG. We have confirmed the reliability of this technique, and integrated it with imaging to guide TMS localization. Therefore, for the first time we will use TMS-EEG and assess inhibitory neurotransmission in youth with and without music expertise. We hypothesize that improvement in IC are associated with enhancement of GABAergic neurotransmissions in regions activated in IC, in particular lateral PFC. Method. Subject: We will recruit 30 healthy musician youth (age: 16-24 y) with at least 8 years of formal music training who started training younger than 10 years of age. The control group is age- and sex-matched non-musicians, also matched for intelligence and education. Study Design: TMS-EEG protocols that assess GABAA and GABAB receptor mediated neurotransmission will be administered to brain regions in frontal and parietal cortices during rest and IC task (e.g., Go/NoGo). MRI-guided neuronavigation will be used to precisely target brain regions. Data Analysis: Metrics of GABAergic inhibition will be extracted according to our published methods. Sample Size: We previously compared IC between adult musicians and non-musicians revealing significant group differences in Go/NoGo task with partial eta squared of 0.15. Calculating Cohen's f (f=.42), using G*Power, 2 groups, 8 conditions, alpha of 0.05, power of 80%, and 10% unusable data, 30 subjects per group are needed.

	Impact. IC matures in early adulthood, is impaired in neuropsychiatric conditions such as depression and potentiates by musical training. Depression is leading cause of disability affecting 350 million people worldwide. The prevalence of depression (13%) peaks in youth (15-24 y) and severely impacts an individual's function in school, work and relationships. Current treatments are inadequate or cause serious side effects in up to 50% of youth. Recent efforts are focused on designing treatments that precisely target and modulate underlying biological impairments. Characterizing mechanisms of IC improvement using TMS-EEG has important potentials, as repetitive TMS therapy can then be guided to selectively modulate these mechanisms. This study will also provide evidence in support of utility of music training in treatment of IC impairments. Existing support ($35k). The cost of testing non-musician youths will be offset by funding from [redacted] that involves using TMS-EEG to map neural circuitries at rest and during cognition across the lifespan. This grant also provides personnel and infrastructure.
Please give a brief description of the dissemination plan	We anticipate that our study will lead to several peer-reviewed publications. If our main hypothesis is true (e.g., integrity of GABAergic neurotransmissions predict IC), we will consider a publication in a high impact neuroscience journal such as Neuron, Cell, or Science. We will consider a publication in Biological Psychiatry or Brain related to the clinical application of our study outcome in designing novel treatments. Our data also provides opportunities for secondary analyses related to characteristics of other neural mechanisms between musicians and non-musicians. These will be considered for publications in neuroscience, biomedical engineering and physiology journals. We will present our findings at several international conferences, such as [redacted], brain stimulation conferences, and importantly [redacted]
Brief biographies and roles of key personnel: 5,000 character maximum, including spaces. Please indicate whether each person is a full-time employee or a hired	Dr [redacted] is Assistant Professor of Psychiatry at [redacted] and an Independent Scientist at Centre for [redacted], [redacted]'s largest and leading mental health research institute. Dr. [redacted] obtained her Bachelor in Biomedical Engineering and Psychology from [redacted]. She subsequently obtained her PhD in collaborative program of Biomedical Engineering and Medical Sciences from [redacted]. She completed her

contractor	postdoctoral training at [redacted] in Cognitive Neurology. Dr. [redacted]'s research focus is in neuroengineering with application in medical diagnosis and neurotherapeutics. Her work to date has focused on designing new experimental strategies for diagnosis, and treatment of neuropsychiatric disorders such as schizophrenia and recently youth depression. She is leading this work through multidisciplinary collaboration and combining basic electrophysiology, neuroimaging, neuromodulation, and behavioral training. Dr. [redacted] is well known for her contribution in developing TMS-EEG as a brain mapping technique to investigate integrity of brain circuitries, in particular plasticity and integrity of cortical inhibitory processes. She has led and collaborated on several clinical trials designing and investigating the efficacy of repetitive TMS therapy for schizophrenia and depression. Through these works, Dr. [redacted]'s research aims to address three important challenges for the implementation and adoption of neurotechnology in clinical and translational research: (1) Development of novel experimental strategies to safely and reliably assess neural processes in humans to discover brain-behavior relationship; (2) Identification of novel strategies to facilitate discovery of biomarkers of brain health and impairments; and (3) Translation of the gained knowledge into clinical practice, and guiding the design of novel diagnosis and treatments for neuropsychiatric conditions such as youth depression. Dr. [redacted] is Director of the [redacted], faculty in the school of engineering at [redacted]. [redacted] is a premier center of applied research focusing on human behavior and digital solutions research. The center is hosting two large [redacted] national center of excellences (NCE), [redacted]. The mandate of those NCEs is to develop national applied research projects on youth and senior populations. Dr. [redacted]'s research program focuses specifically on brain plasticity and its implications for neuroeducation and neurorehabilitation. He is especially interested in how different forms of training, specifically training in music, can improve cognitive functioning and stimulate transfer of skills to other cognitive domains such as executive function, attention, and intelligence. During his career, he developed several software training based on music and published several findings showing their benefits for cognition. Finally, Dr. [redacted] has been the recipient of many awards from national and international organizations. His work has received widespread press in various media outlets including newspaper, magazine, and television. Dr. [redacted] and [redacted] are full-time employees.