## PROJECT OVERVIEW

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| Age of study population | Other: 16-24 |
| 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 |
| Project Goal - For a general audience as well as your peers, explain the goals of the project in clear and compelling language. | Musicians show enhanced inhibitory control (IC), the ability to inhibit interference to attend to needed task. IC matures into early adulthood and declines in aging or pathologies such as depression. The neural mechanism of enhanced IC is unclear. We use neurostimulation combined with neural recording in youth musicians and non-musicians to identify mechanism of enhanced IC in youth. This can lead to discovering novel IC enhancing therapies. |
| Research Category | Neuroscience |
| Identify the governing body that would be responsible for overseeing the proposed research if it involves human participants. | Research Ethic Board at [redacted] |

## COLLECTION OVERVIEW

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| Please indicate if there have been any changes to the project or information submitted since the letter of inquiry. | We modified the date for initiation of study from April 1, 2016 to March 15, 2016. Small adjustments were made in the budget following precise calculation of costs. |

## PROJECT NARRATIVE

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| Project Narrative: 9,500 characters with spaces maximum. Please create in a Word document and copy and paste into this field. Number sections per the guidelines and add spaces in between sections to improve readability. | 1. Project Description<br>Music literature has shown enhancement of inhibitory control (IC) in musicians and music training across age [1-3]. It is suggested [3,4] that this enhancement may underlie the general cognitive advantage repeatedly observed in this population[5-9]. IC is a core cognitive function that 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[10]. IC is involved in numerous cognitive processes and pathologies such as youth depression[11-14], a debilitating condition that impairs mood and cognition. IC matures well into young adulthood rending youth more vulnerable to IC impairments. IC impairment in youth also underlies substance abuse[15] and completed suicide[16]. Understanding the exact neural mechanism that underlies IC enhancement in youth musicians will provide novel |

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| | opportunities for developing targeted therapies to enhance this cognitive function across pathologies.<br><br>Recent evidence using event related potential (ERP) electroencephalography (EEG) showed modifications of frontal cortex function in Go/NoGO IC task in musicians[1], a task that showed impairment in depression[17,18]. In this task, participants answer as fast and as accurately as they can to a target stimuli (Go trials: 80%) or withhold answering (NoGo trials: 20%). EEG in NoGO trials reflects an early positive potential by 200ms (P2), a negative deflection by 400ms (N2), and a late positivity after 400ms (P3). In musicians, potentiation of P2 and reduction of N2 are reported[1]. However, the exact neural mechanism underlying this finding is unclear. Evidence suggests that gamma-aminobutyric acid (GABA)ergic mechanisms may underlie IC function. Lateral prefrontal cortex (PFC) is involved in IC functions[3]. Development of IC is linked with GABA maturation in the PFC[19,20]. The GABAergic neurotransmission regulates information flow and is critically implicated in cognition and pathologies, including youth depression[13,21]. Also, lower frontal GABA levels in youth is linked with impulsivity and poorer performance in Go/NoGo IC task[20]. Therefore, GABA mediated inhibition may underlie IC enhancement in musicians.<br><br>How GABA neurotransmission can be measured? In the past decade, we advanced combination of transcranial magnetic stimulation with electroencephalography (TMS-EEG) to reliably quantify GABA mediated inhibition across brain regions in a cause (TMS) and effect (EEG) manner in humans (CHART Fig1A). Simultaneous EEG recording during TMS was previously unattainable due to various TMS-induced artifact[22]. We addressed these challenges, produced data processing standards[22], and developed markers of GABA mediated inhibition[23-27]. We achieve this by activating GABAergic mechanisms with TMS and concurrently recording response with EEG. Application of single TMS pulse to the frontal cortex generates multiple TMS evoked potentials (TEP)s post TMS pulse (CHART Fig1B). We identified that a negative TEP at 100ms (N100) reflects activation of GABAB mediated inhibition[25] as replicated by several studies including pharmacological interventions[28]. When single pulse TMS is followed by a second pulse within 100ms in protocol long interval cortical inhibition (LICI), TEP is inhibited due to GABAB activation by the first pulse (CHART Fig1C). We established LICI and its reliability in frontal cortex[24,29] and for the first time showed a selective association between LICI in dorsolateral PFC (absent in motor cortex) and performance in working memory[30], recently replicated for N100[31]. We also showed that N100 and LICI in PFC (but not motor cortex) predict reduction in suicide[32]. Therefore, |

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| | TMS-EEG offers a novel, precise and reliable method to delineate brain-behavior relationship in humans.<br><br>2. Research Question<br>We take a unique multidisciplinary approach and combine TMS-EEG, ERP, and behavioral response in IC tasks to discover the neural mechanism that underlies enhanced IC in youth musicians. We investigate the question whether enhancement of GABA mediated inhibition in PFC underlies the enhanced IC in youth with music expertise.<br><br>Objective 1: Assess magnitude of GABA mediated inhibition in motor cortex and PFC in youth musicians compared to non-musicians.<br>Hypothesis 1: N100 and LICI are significantly potentiated in motor cortex and PFC in musicians.<br><br>Objective 2: Assess the association between IC and magnitude of GABA mediated inhibition in motor cortex and PFC.<br>Hypothesis 2: Performance and ERP profile in Go/NoGo are positively associated with enhancement of N100 and LICI in the PFC. Weaker or no association is found in motor cortex.<br><br>Objective 3: Assess if magnitude of GABA mediated inhibition predicts enhanced IC.<br>Hypothesis 3: N100 and LICI in PFC classify subjects with high and low Go/NoGo performance and ERP profile with high accuracy.<br><br>3. Research Applications<br>IC matures into young adulthood, is impaired in pathologies such as depression and substance use, and potentiates by music training. Depression alone is leading cause of disability affecting 350 million people worldwide[33]. The prevalence of depression (13%) peaks in youth (15-24 y)[34-36] while current treatments are inadequate or cause side effects in up to 50% of youth[37-40]. TMS-EEG markers of IC enhancement in musicians have tremendous potentials for guiding new IC enhancing therapies that precisely target underlying biological impairments. Importantly both daily music training[2,41-45] and repetitive TMS[46-49] can be tailored to potentiate these mechanisms in youth depression and across multiple pathologies.<br><br>4. Methodology<br>Participants. Thirty healthy musicians and thirty controls will be recruited. Inclusion criteria for musicians are: (1) right handed between the ages of 16 and 24; (2) competent to consent; (3) started training younger than age 10; (4) actively practicing on a weekly basis; and (5) a minimum 8 years of formal training. The control groups are right handed age- and sex-matched non-musicians, also controlled for intelligence and education. The exclusion criteria are: (1) not eligible to |

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| | receive TMS or MRI; (2) history of a neuropsychiatric illness or a first degree relative with psychiatric illness; (3) history of substance dependence or abuse within the last 3 months; (4) a concomitant major unstable medical illness.<br><br>Study Design. The study has 3 visits:<br>Visit 1: (1) eligibility is determined and consent obtained; (2) 64-channel EEG is recorded during basic and emotional Go/NoGo tasks (~15min); In basic Go/NoGo, participants are presented with two alternating neutral stimuli (e.g., geometrical shapes). In emotional version, the geometrical shapes are superimposed by human faces depicting sad, neutral or fearful expressions; (3) two cognitive batteries are obtained: (a) Raven Matrices to control for IQ; and (b) standardized IC tasks by [redacted] toolbox for cross-study comparisons.<br><br>Visit 2: Structural MRI is done at [redacted] on a 3.0 Tesla General Electric research scanner to obtain a T1 anatomical scan (sagittal 3D FSPGR: echo time 3ms; repetition time 8.2ms; time to inversion 650; flip angle 8; FOV 24cm). MRI is used to navigate TMS coil placement in visit 3. Visit 3: EEG is acquired by 64-channel Synamps2[24,25,29] as single and paired pulse (LICI) TMS are administered according to previous methods to left and right motor cortex and dorsolateral PFC[24]. In each condition, 100 trials are applied separated by 5 to 6s (<10min/condition). TMS is administered with a 7cm figure-of-eight coil, and two Magstim 200 stimulators (Magstim, UK) connected via Bistim module. TMS coil localization is MRI-guided (BrainSight Roch, Canada.)<br><br>Primary Outcomes include (1) the TMS-EEG indices of GABAB mediated inhibition: (a) magnitude of single pulse N100 TEP as published[25,28] which reflects the magnitude of GABAB activation; and (b) the ratio of TEPs in LICI as published[26] which reflects the effect of GABAB mediated inhibition; (2) the behavioral scores (reaction time and accuracy) in Go/NoGo tasks; and (3) ERP components in NoGO trials.<br><br>Sample Size. We previously compared IC between adult musicians and non-musicians revealing significant group differences in ERP with partial eta squared of 0.15[1]. Calculating Cohen's f (f=.42), using G*Power, 2 groups, approximately 8 conditions, alpha of 0.05, power of 80%, and 10% unusable data, 30 subjects per group are needed.<br><br>Pilot Data. We have successfully recorded and analyzed N100 maker in 2 musicians and 3 non-musicians youth in the motor cortex. As hypothesized, data shows an increase in N100 in the musicians (CHART Fig2). |

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| | 5. Key Personnel<br>(1) A graduate student enrolled in [redacted] assists data collection, leads data analysis, and contributes to manuscripts and conference presentation under Dr. [redacted]'s supervision. (2) A research analyst (employee at [redacted]) working in Dr. [redacted]'s lab assists subject recruitment, obtaining consent, and data collection. (3) Dr. [redacted] (Co-PI) (researcher at [redacted]) oversees recruitment, ERP analysis, and drafting and editing the manuscripts. (4) Dr. [redacted] (PI), researcher at [redacted] and [redacted], is responsible for all aspects of the study coordinating team meetings and ensuring successful dissemination of results. |
| Access and dissemination plan (please refer to guidelines for details) 2,000 character with spaces maximum with spaces: | We anticipate that our study will lead to several peer-reviewed publications. If all three hypotheses are true we will consider a publication in Nature or Science. If Hypotheses 1 and/or 2 are true, we will consider publication in [redacted], Neuroscience, or Neuron.<br><br>We will consider an opinion publication related to the clinical application of our study outcomes in [redacted], [redacted] or [redacted]. Furthermore, Dr. [redacted] has ongoing studies in youth depression in whom similar IC and TMS-EEG indices are collected. Upon completion of both studies, we will consider data sharing between studies. Such collective data integration and analyses have a high potential to lead to ground breaking findings and major publications in journals such as [redacted].<br><br>Our data also provides opportunities for secondary analyses related to integrity of other markers of brain health also considered to be potentiated in musicians (e.g., neural connectivity). Specifically, TMS-EEG markers of effective connectivity can be captured from our data sets using the single pulse TMS condition. Alternative hypotheses and secondary data analyses that are based on strong scientific rationale will be considered. Findings from these types of analyses can also lead to important findings which all will be published.<br><br>At least once per year, we will present our interim and then final findings at international conferences. We will consider attending two or more international conferences including [redacted], and importantly. |

## Brief biographies and roles of key personnel: 3,000 character with spaces maximum

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| Brief biography of key personnel: 3,000 character with spaces maximum | [redacted] (PI)<br>Dr. [redacted] is Assistant Professor of Psychiatry at [redacted] and Scientist at [redacted], [redacted]'s largest and leading mental health research hospital. She obtained her Bachelor from [redacted] and her PhD from [redacted] in [redacted], and her Postdoctoral Training from [redacted] in [redacted]. Dr. [redacted]'s research is in neuroengineering with application in medical diagnosis and neurotherapeutics. Her work has focused on developing experimental modalities for diagnosis and treatment of neuropsychiatric disorders such as schizophrenia and depression. She is leading this work through multidisciplinary collaboration and combining clinical trials, neuroimaging, neuromodulation, and behavioral assessments. Despite being a young investigator, Dr. [redacted] has over 40 publications in high impact factor journals (H-index = 19, i10-index = 26, 1053 citations), numerous international invited talks, and several media interviews.<br><br>Role: Dr. [redacted] is well known for her contribution in developing TMS-EEG to investigate integrity of human brain circuitries. She will be responsible for overseeing all aspects of the study from obtaining ethic approval, implementation of the study design and overseeing the study visits, student supervision, organizing team meetings, and final dissemination of the study outcomes, and approval of manuscripts.<br><br>[redacted] (Co-PI)<br>Dr. [redacted] is Director of the [redacted] ([redacted]), and a research 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 centers of excellence (NCE): [redacted] and [redacted]. The mandate of NCE is to develop national applied research projects on youth and senior populations. Dr. [redacted]'s research program focuses on brain plasticity and its implications for neuroeducation and neurorehabilitation. He investigates 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. He has developed several software training based on music and published several findings showing their benefits for cognition. 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.<br><br>Role: Dr. [redacted]'s leadership and expertise in investigation of the |

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| | neuromodulatory effects of music training will guide the project in two areas: overseeing recruitment of musicians and assisting interpretation of study outcomes. He will also provide guidance in EEG ERP analyses, and significantly contribute to draft and edit of the manuscripts. |

## SUPPORTING DOCUMENTS

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| Project Timelime: One page only. | [redacted] |
| Budget Sheet: Only the GRAMMY Foundation formatted budget will be accepted. | [redacted] |
| Chart or Other Graphic Representation of the Project: One page only, if needed, for charts or other graphic representation of the project. | [redacted] |
| Letter of Support #1: | [redacted] |
| Letter of Support #2: | [redacted] |
| Citations or References: Reference previous research or any research cited in the narrative. | [redacted] |