PhD Proposal
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Do you still know all the words to the songs on your favourite CD from high school? Have you ever heard part of a song and immediately remembered where you were the last time you heard it? These are just some examples that anecdotally show how robust memory for music can be. The robust nature of musical memory is especially apparent in patients with Alzheimer's disease, a disease that results in memory deterioration. Even when other memories are lost, long-term familiarity for melody and music lyrics can be present in severe Alzheimer's disease (Cuddy et al., 2012). What makes memory for music so special? It is this question that I aim to answer with my PhD research. With my first project, I will more clearly define the brain areas involved in music memory. Based on the results of the first experiment, I will explore what makes musical memory distinct from other forms of memory and why it is selectively spared in patients with Alzheimer's.

The initial evidence for a distinct memory for music comes from a number of case studies. In 1996, Peretz described patient CN who suffered bilateral temporal lobe damage leading to a severe, music specific agnosia. CN could recognize lyrics from songs, but did not recognize previously familiar melodies. Her normal performance on tests of music perception (melody or tone discrimination) indicated that her agnosia was in fact music-specific and was not a deficit in the processing of melodic information. In contrast, Patient PM (Finke, Esfahani, & Ploner, 2012), who had been a professional cellist until he contracted encephalitis, had severe semantic and episodic memory deficits but performed like a healthy musician on a music recognition test. PM could not recognize family or friends but he could differentiate between famous and non-famous musical pieces. These case studies indicate that memory for music can be dissociated from other types of memory. In fact, Peretz & Coltheart (2003) proposed that humans have a 'musical lexicon' that contains representations of all the musical phrases one has ever heard, and that this musical lexicon is separate from the verbal lexicon, where representations of phonological sounds are stored.

Neuroimaging techniques have allowed researchers to uncover the neural basis for the separate musical lexicon described by Peretz and Coltheart. Using PET, Groussard et al. (2009) showed that the musical lexicon, and musical semantic memory in general, is sustained by a temporo-prefrontal cortical network. This network showed greater activity during a task where participants rated their level of familiarity with a series of melodies than in a task where participants determined whether two unknown melodies were the same or different. Groussard et al. (2009) hypothesized that the right-sided regions within this network are mainly responsible for holding the melodic traces of familiar tunes, whereas the left-sided regions are responsible for the semantic and associative memories involved in recognizing a

musical piece as familiar. The left-sided activation occurred in areas common to those classically shown to be involved in verbal semantic memory (Groussard et al., 2009). In 2010, Groussard et al. conducted a follow-up study using fMRI and showed a clear dissociation between the neural patterns elicited by musical and verbal stimuli. These neuroimaging results supported the theory of Baird and Samson (2009) who suggested that musical memory in Alzheimer's patients is spared because of the intact functioning of the necessary and specific brain regions that are relatively unaffected by the disease. They suggest that explicit musical memory, that relies on the temporal lobes, is affected by Alzheimer's disease, but other types of musical memory such as procedural musical memory rely on frontal areas and therefore are relatively preserved in Alzheimer's. In 2015, Jacobsen, Fritz, Stelzer, and Turner showed that the caudal anterior cingulate and the ventral pre-supplementary motor areas are involved in the processing of both unknown and known music and that these areas, responsible for encoding musical memory, were relatively spared in a sample of patients with Alzheimer's disease. Together, theses results indicate that not only is memory for music separate from other types of memory, but this dissociation can be seen with neuroimaging techniques.

Study 1: Neural Correlates of Music Recognition

Will begin collecting data in July 2017

In previous studies, the dissociation of memory for music has been shown using familiar music chosen by the researchers. There is little control for the amount of exposure participants have had to each song during their lifetime. In Study 1, I will train participants to become familiar with a set of musical stimuli, and therefore I will be able to track each participant's exposure to the stimuli and more accurately determine the neural correlates of musical memory. Tracking stimulus exposure will allow for control over the musical memory being formed without extraneous variables such as associations with events or emotions that may differ from person to person.

Participants will undergo an fMRI scan while listening to 16 unfamiliar musical pieces. They will then listen to half of the music (8 pieces) regularly over the course of two to three weeks. Listening will be done through an online music player that will track the number of times the song was played. Throughout the training period, participants will come to the lab for intermittent behavioural testing to track how familiar they are becoming with the stimuli. This will be done using a forced-choice paradigm that asks participants to identify a correct lyric out of a pair of lyrics where one is correct and one lyric has been modified. Once participants reach a particular threshold of familiarity with the stimuli (assessed by performance on the lyric recognition task) they will undergo a second fMRI scan

while listening to all 16 musical pieces. At the second scan, participants will now be familiar with half of the stimuli. No other study to date has explored the neural correlates of music recognition by training participants on a set of stimuli. The stimuli used in this study are 16 unfamiliar songs that fall into four groups: instrumental music only (no lyrics), a cappella singing (no instruments), lyrics and instrumental music, and spoken word. Varying the stimuli within the lyric and music categories will allow me to identify how the presence of lyrics interacts with the music to affect recognition. It is possible that the presence of lyrics aids recognition of music because of the involvement of both music and lyric networks.

The BOLD contrasts between the first and second scans will allow me to identify which brain areas are involved in music recognition. I hope to replicate the results from previous papers (Groussard et al., 2010; Jacobsen et al., 2015). A PCA analysis applied to the fMRI data collected during music listening may be able to identify a network of brain areas that are critical for music recognition. I would like to compare how these networks differ for known and unknown music and how the networks change or differ as exposure to the music increases and as a function of the presence of lyrics.

Potential Next Steps

Follow up study. My first experiment will explore the neural correlates for musical memory during an intense listening period of 2-3 weeks. One striking characteristic of musical memory is a person's ability to remember a song many years after they last listened to it. I would like to bring back some of the participants from the first experiment 12-18 months after their second scan for a third scan. Comparing the active brain areas between scan two and scan three may give insight into why music can be clearly remembered for so long.

Musical background. In the first experiment, I will collect musical background information from participants. This includes whether participants play any instruments, how long they have been playing, and whether they have had formal training. It is possible that the amount of musical training a person has had affects the way they listen to music and subsequently the way they remember music. It will be interesting to see if there are differences in the music recognition networks isolated in the first experiment as a function of musical training. Musicians may have a larger music recognition network because of the amount of music they learn and memorize during their training. Any differences could then be related to the work on neural correlates of musical memory in Alzheimer's in order to determine whether musical training early in life affects a patient's ability to remember music.

Marker of consciousness. Previous work has found that brain networks activated by suspense-filled audio clips can be used to assess consciousness, but musical stimuli did not produce a robust enough signal to elicit activation in a similar network (Sinai, 2015). In this experiment, participants listened to theme songs from popular television programs. Familiar music may result in a more robust signal allowing music to be used as a marker of consciousness. The brain areas that are active in response to familiar music include areas beyond primary auditory cortex. These areas are active because a participant is engaging with the music and the music is triggering a memory or sense of recognition. Presumably, the participant has to be conscious to recognize the music. If a robust network of brain areas that responds to familiar music can be identified in healthy participants, then maybe such a network could be used as a diagnostic tool for minimally conscious patients. Families could supply music that is well known to the patient. If the patient shows activation in the music familiarity brain networks then perhaps this is an indicator of their consciousness.

Before bringing such a paradigm to patients, the effects of differing levels of consciousness on the musical familiarity network could be investigated using healthy participants under anesthetic. Data from anesthetized patients would help us to understand how auditory information is processed at varying levels of consciousness and how it differs as that auditory information becomes familiar. These data will also help us understand if it is possible for the music recognition network to be activated when a participant is not conscious. Similar to studies that have investigated speech processing under various levels of anesthetic (Davis et al., 2007) we may find that lyric comprehension is reduced. No work to date has investigated how processing of music changes with reduced consciousness.

Alzheimer's patients. Postdoc Dr. Lucy McGarry is interested in collecting data from the first experiment that will allow us to determine whether there is inter-subject synchronization (ISS) while participants listen to the musical stimuli. The ISS analysis will show whether the timecourse of activation in brain areas is similar, or synchronized, across listeners. We will be able to compare whether synchrony increases as familiarity increases or as a function of lyric presence. Based on the results from the experiment in healthy participants, I will explore whether similar synchrony patterns are present in patients with Alzheimer's disease. Understanding how the synchrony patterns change (or do not change) as the disease progresses may provide insight into why these patients still remember music when other areas of memory are disturbed. If the brain compensates for deterioration in other memory areas then there may be greater activation in the music recognition network in patients with Alzheimer's than in healthy controls.

Summary

Through my PhD research I will more clearly define the brain areas that are responsible for musical memory. No study to date has controlled music exposure during an experiment to determine the neural correlates of musical memory. With my first experiment I will investigate how characteristics like lyrics, degree of familiarity with the music, and participant's musical experience affect musical memory. Based on the results from my initial experiment, I would like to explore the feasibility of using known music as a diagnostic marker of consciousness in patients with disorders of consciousness and in healthy anesthetized participants. While investigating musical memory there is the potential to learn about memory related diseases such as Alzheimer's and to understand why musical memory seems to be spared even at late stages in the disease. My central objective is therefore to better understand how memory for music occurs in the brain and how it is dissociated from other forms of memory.

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