# Neuroimaging Studies on Familiarity of Music in Children with Autism Spectrum Disorder

by

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## Abstract

The field of music neuroscience allows us to use music to investigate human cognition in vivo. Examining how brain processes familiar and unfamiliar music can elucidate underlying neural mechanisms of several cognitive processes. To date, familiarity in music listening and its neural correlates in typical adults have been investigated using a variety of neuroimaging techniques, yet the results are inconsistent. In addition, these correlates and respective functional connectivity related to music familiarity in typically developing (TD) children and children with autism spectrum disorder (ASD) are unknown. The present work consists of two studies. The first one reviews and qualitatively synthesizes relevant literature on the neural correlates of music familiarity, in healthy adult populations, using different neuroimaging methods. Then it estimates the brain areas most active when listening to familiar and unfamiliar musical excerpts using a coordinate-based meta-analyses technique of neuroimaging data. We established that motor brain structures were consistently active during familiar music listening. The activation of these motor-related areas could reflect audio-motor synchronization to elements of the music, such as rhythm and melody, so that one can tap, dance and “covert” sing along with a known song. Results from this research guided our second study. This work investigated the familiarity effect in music listening in both TD and ASD children, using magnetoencephalography (MEG).

This technique enabled us to study brain connectivity and characterize the networks and frequency bands involved while listening to familiar and unfamiliar songs. TD children recruited a similar brain network as those in typical adults during familiar music listening, in the gamma frequency band. Compared to TD, children with ASD showed relatively intact processing of familiar songs but atypical processing of unfamiliar songs in theta and beta-bands. Atypical functional connectivity of other unfamiliar stimuli has been reported in ASD. Our findings reinforced that processing novelty is a challenge. Overall, this work contributes to the advancement of both fields of music neuroscience and brain connectivity in ASD.

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# Contributions

I, Carina Freitas, was primarily responsible for all aspects of each study in this thesis including planning, execution, analysis and writing of all original research and preparation of manuscripts for publication. The following contributions by other individuals are acknowledged below:

Dr. Evdokia Anagnostou served as my primary supervisor and appear as co-author on all studies presented here. Roles included: mentorship, laboratory resources, guidance and assistance in planning, execution, analysis and interpretation of experiments as well as manuscript and thesis preparation.

Dr. Jason P. Lerch and Dr. Margot Taylor served as members of my thesis committee and co-authors for Chapter 4 and Chapter 5. Roles included: mentorship, laboratory resources, guidance in planning, execution, analysis, interpretation in addition to manuscript and thesis preparation.

Dr. Russell Schachar and Dr. Joyce Chen served as members of my thesis committee and co-authors for Chapter 5. Roles included: mentorship, guidance in planning and in interpretation of results as well as manuscript and thesis preparation. Dr. Benjamin Dunkley and Dr. Benjamin Hunt also served as co-authors for chapter 5 and provided assistance in the MEG data analysis, interpretation of results and manuscript preparation.

Enrica Manzatto and Alessandra Burini served as co-authors for Chapter 4 for their contribution in the literature selection, data analysis and results interpretation. Simeon Wong served as a co-author for Chapter 5 for his contribution in programming for MEG data analysis.

Dr. Alana Iaboni, Leanne Ristic, Susan Fragiadakis, Stephanie Chow contributed as co-authors for Chapter 5. Their role was to recruit participants and behavioural testing and scoring.

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# List of Abbreviations

| | |
|---|---|
| AAC | Anterior cingulate cortex |
| AAL | Automated anatomical labeling |
| ADI-R | Autism diagnostic Interview-Revised |
| ADOS | Autism diagnostic observation schedule |
| AEC | Amplitude envelope correlation |
| ALE | Activation likelihood estimation |
| ANOVA | Analysis of variance |
| AP | Absolute pitch |
| ASD | Autism spectrum disorder |
| BA | Brodmann area |
| BOLD | Blood-oxygen-level-dependent |
| BPM | Beats per minute |
| CSS | Calibrated severity score |
| DICS | Dynamic imaging of coherent sources |
| DSLM | Developmental Speech and Language training through Music |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders – 5th edition |
| DTI | Diffusion tensor imaging |
| ECD | Equivalent current dipole |
| EEG | Electroencephalography |
| EPF | Enhanced Perceptual Functioning |
| ERP | Event related potential |
| FD | Familiar disliked |
| FDR | False discovery rate |
| FL | Familiar liked |
| fMRI | Functional magnetic resonance imaging |
| FWE | Family-wise error |
| FWHM | Full width at half-maximum |
| ICA | Independent component analysis |
| IQ | Intelligence quotient |
| IS | Insistence on sameness |
| LCMV | Linearly constrained minimum variance |
| LFP | Local Field Potentials |
| LORETA | low resolution electromagnetic tomography |
| LPC | Late positive complex |
| MA | Activation map |
| MEG | Magnetoencephalography |
| MNI | Montreal neurological institute |
| MPFC | Medial prefrontal cortex |
| MPRAGE | Magnetization-prepared rapid gradient echo |
| MRI | Magnetic resonance imaging |
| MSI | Magnetic source imaging |
| MUSAD | Music-based Scale for Autism Diagnosis |
| NA | Neural adaptation |
| NAcc | Nucleus Accumbens |
| NBS | Network-based statistic |

| | |
|---|---|
| NMT | Neurologic music therapy |
| PAC | Phase-amplitude coupling |
| PET | Position emission tomography |
| PLI | Phase lag index |
| PLV | Phase Locking Value |
| POND | Province of Ontario Neurodevelopmental Disorders |
| PSP | Post-synaptic potentials |
| RBS-R | Repetitive Behavior Scale Revised |
| ROI | Region of interest |
| RRB | Restricted and repetitive behaviors |
| SAM | Synthetic Aperture Magnetometry |
| SCQ | Social Communication Questionnaire |
| SL | Synchronization likelihood |
| SMA | Supplementary motor area |
| SQUID | Superconducting Quantum Interference Device |
| STS | Superior Temporal Sulcus |
| TD | Typically developing |
| ToM | Theory of Mind |
| UF | Unfamiliar |
| VL | Ventral lateral nucleus of the thalamus |
| WASI | Wechsler abbreviated scale of intelligence |
| WCC | Weak Central Coherence |
| wPLI | weighted phase lag index |

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# Chapter 1

# General Introduction

## 1.1 Concepts and Ideas

"The ear tends to be lazy, craves the familiar and is shocked by the unexpected; the eye, on the other hand, tends to be impatient, craves the novel and is bored with repetition"

Wystan Hugh Auden

Music is universal and present in every culture since the beginning of recorded history (Conard et al., 2009; Mehr et al., 2018, 2019). Advances in neuroimaging techniques in the last three decades allowed the development of the scientific study of the neurobiology of music. More than any art form or cultural artefact, music has the ability to induce significant changes in the structural and functional organization of the brain (Sarkamo et al., 2013; Schlaug, 2001). As such, music can be a tool to investigate human cognition in vivo. Listening to familiar or repeated music is a pleasurable experience that makes one feel good (Salimpoor et al., 2011). Mothers soothe their babies singing well known lullabies and Alzheimer's patients evoke autobiographic memories while listening to familiar songs (Haj et al., 2012; Trehub and Trainor, 1998). Consequently, music and its features have potential therapeutic value that scientists and clinicians are starting to unravel and validate.

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by great phenotypic heterogeneity (Masi et al., 2017). Although its pathophysiology remains unclear, altered brain connectivity has been reported and linked to socio-emotional and cognitive impairments (Ha et al., 2015). Understanding these neural mechanisms would bring clarity on patterns of brain organization in this disorder. Since Kanner's original description of ASD in 1943, music has been reported as an auditory stimulus that interests and motivates many individuals within the spectrum (Kanner, 1943). However, little is known on the neurobiology of music function in this population. The few available neuroimaging studies in ASD have suggested altered brain functional connectivity when listening to different types of music.

Functional connectivity, originally defined as the temporal correlations between remote neurophysiological events (Friston et al., 1993) can be investigated using techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), event-related potentials (ERP) and magnetoencephalography (MEG). The latter has the advantage of high spatial and temporal resolution to investigate neural oscillations and their sources at different frequency bands. Further information on oscillatory synchrony among brain areas during cognitive processes can expand our knowledge of network topology and dynamics underlying brain functions.

Neuroimaging studies on familiarity in music listening using different modalities have shed light on the neural substrates of this auditory experience. Either to evoke aesthetic emotions or to facilitate neurorehabilitation, examining how brain processes familiar and unfamiliar music can transcend boundaries and help us to understand not only our nature but also the nature of atypicalities with developmental consequences such as those seen in neurodevelopmental disorders / autism.

## 1.2 Thesis structure

This dissertation is dedicated to the study of the neural correlates of familiarity in music listening and to the underlying functional connectivity of oscillatory networks in typically developing children and children with ASD. Chapter 2, Literature Review, will give an overview of the music components and its processing by the human brain. This chapter will also clarify the construct of familiarity and its application to the music field. Next, it will review core concepts in ASD as well as familiarity and music research in this disorder. Another section of this chapter will introduce the principles of neural oscillations and functional connectivity. Chapter 2 will finalize describing magnetoencephalography techniques and relating previous concepts to atypical brain connectivity in ASD.

The aims of the thesis will be presented in Chapter 3. Specific hypotheses for each study will be presented in the Chapter of the study. Chapter 4 will systematically and quantitatively review and summarize the literature on the neural correlates of familiarity in music listening in typical adults using different neuroimaging methods (fMRI, PET, ERP) (Study 1). Chapter 5 will examine the neural synchronization during a music familiarity task in typically developing and ASD children using magnetoencephalography (MEG) (Study 2). Patterns of connectivity while listening to familiar and unfamiliar songs will be reported. Chapter 6 discusses the key findings and explores potential directions for future research related to familiar music. Other musical features and their relations to brain rhythms will also be taken into consideration for the development of therapeutic applications within the ASD spectrum and beyond.

# Chapter 2

# Literature Review

## 2.1 Music and the brain

### 2.1.1 Historical perspectives on neuroscience of music

Over the last two decades, the scientific field of music neuroscience has grown tremendously, offering us a multitude of ways to understand the brain's structure and function (Sarkamo et al., 2013). This breakthrough was mainly possible due to two concurrent reasons. One was the growing interest in musical behaviours, competence and its clinical applications by the music related disciplines (music psychology, music education, musicology, music performance and music therapy). The other reason was the rapid development of sophisticated brain imaging technology and respective analysis software, such as electroencephalography (EEG), event-related potentials (ERP), functional magnetic resonance imaging (fMRI), position emission tomography (PET) and magnetoencephalography (MEG).

The new field of neuromusic enables us to better understand the brain mechanisms underlying specific components of music (such as pitch or acoustic frequency, rhythm, timbre, sound intensity or imagery) and musical behaviours such as listening, performing, remembering, learning and composing music. We can now study the time course and spatial location of the neural correlates of music processing during different types of musical activities, knowledge that is valuable to understand human cognition and emotion (Koelsch, 2005b).

Since, there are significant differences between listening, producing and performing music (Collins, 2013), in this dissertation I will focus on understanding the brain processes during music listening, more specifically for familiar and unfamiliar music.

### 2.1.2 How the brain processes music listening

There is consensus that there is no 'centre for music' in the brain, but several neural networks linking the different components of music perception (e.g. pitch, timbre, duration and loudness). According to Zatorre (2005) listening to and producing music involves practically every human cognitive function. Listening to music recruits a widespread, bilateral areas of the brain (Hyde et al., 2009) which control for auditory, cognitive, sensorimotor and emotional functions (see Figure 2-1).

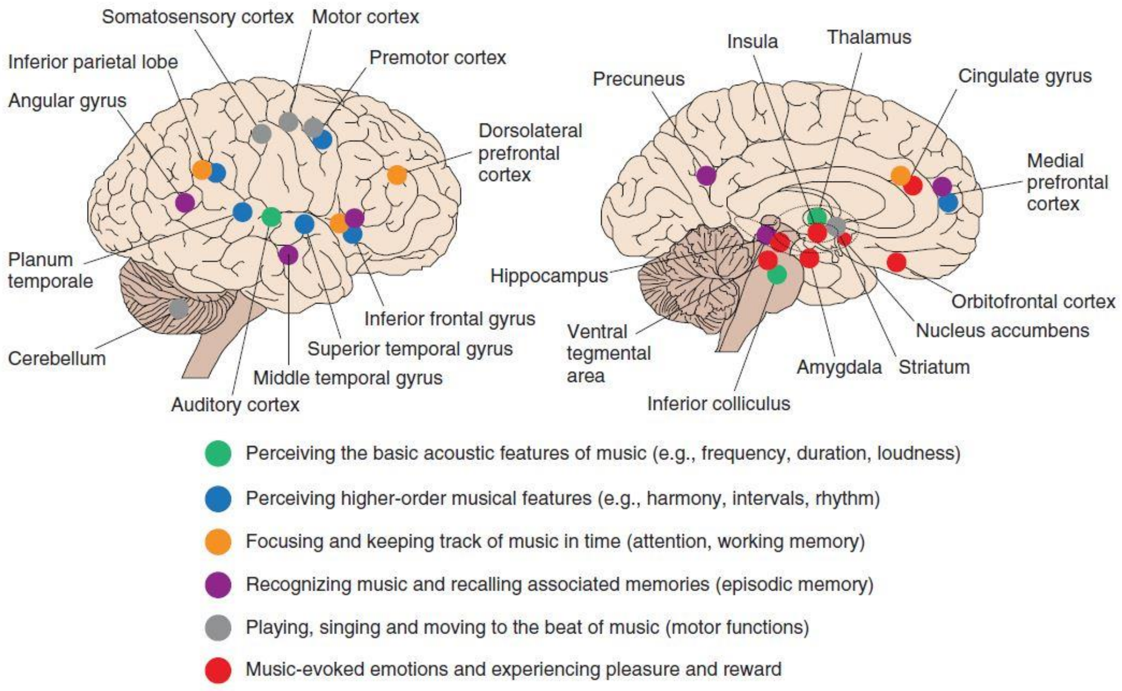

Figure 2-1: Schematic illustration of key brain areas associated with music processing based on neuroimaging studies of healthy adults (Reprinted from Wiley Interdisciplinary Reviews: Cognitive Science, 4, Sarkamo et al., Music perception and cognition: development, neural basis, and rehabilitative use of music, pages 441-451, copyright (2013) with permission from John Wiley and Sons: Licence # 4683790384189.

Even though, music elicits activation in bilateral brain areas, evidence has demonstrated a hemispheric specialization for music processing. Listening to music seems to put more emphasis on the right hemisphere, as pitch and melody information are predominantly processed in the right primary auditory cortex (Patterson et al., 2002; Stewart et al., 2006; Zatorre, 2005). Studies have shown that the left auditory cortex has higher resolution for temporal information, such as rhythm (Meyer et al., 2004) while the right has a higher resolution of spectral resolution, like pitch (Hyde et al., 2008; Zatorre et al., 2002). Moreover, this hemispheric specialization develops with age (Overy et al., 2004).

### 2.1.2.1 Brain models of music processing

Initially, neuroscientists investigated the brain processing of individual elements of music such as pitch and rhythm. Then they studied the processing of multiple musical components until they finally proposed complete explanatory models for how the brain processes music. Koelsch (2011; Koelsch and Siebel, 2005) and Peretz (2009; Peretz and Coltheart, 2003) created models of music perception which have been reviewed and updated across time. Both models examine how the brain processes the different musical elements from songs, individually and as part of a whole.

Peretz' model explains how the brain processes and recognizes a familiar tune (see Figure 2-2). For this reason, this is the theoretical framework of music processing used in this dissertation. Peretz proposed a modular model of brain processing for music (for review about modularity of cognitive functions see Fodor, 1983).

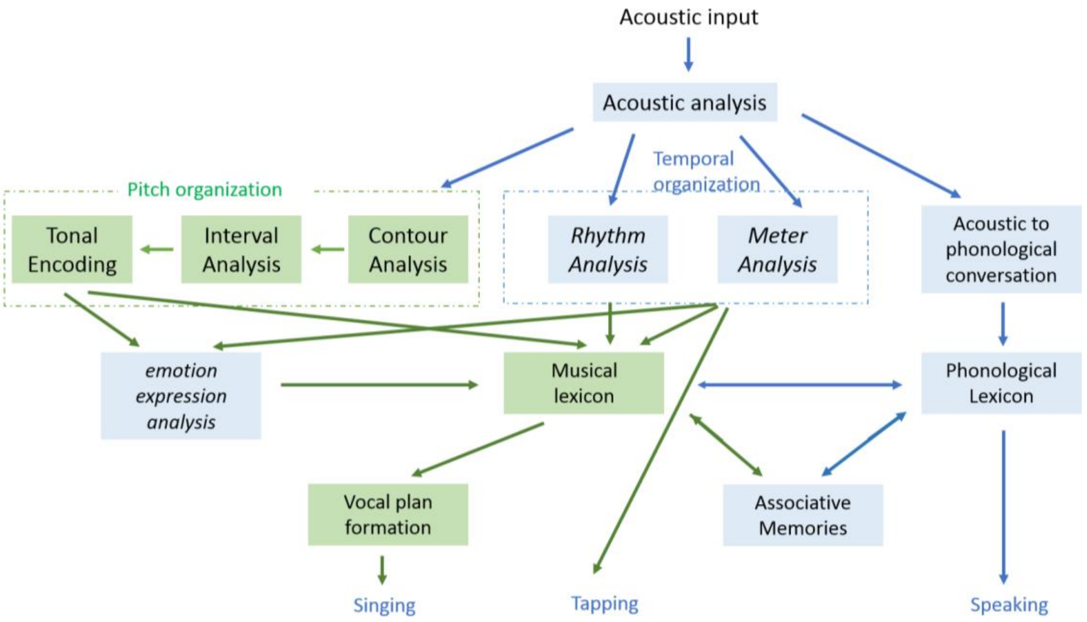

Figure 2-2: Schematic representation of the modular components involved in the recognition of a tune. Each box represents a processing component, and the arrows are pathways between processing components. All components whose domains seem to be specific to music are in green. Others that are in common with language processing are in blue. Components whose specificity to music are unknown are in italics. Figure adapted from Peretz and Coltheart (2003).

This modular functional model was derived from case studies of neurological patients with brain injuries with specific impairments or preservation of particular musical abilities. It proposes various music-processing modules (or music components), each of which is responsible for specific musical information. Central in this framework, are two parallel and independent subsystems for pitch and temporal content, as melody (pattern of pitch over time) and rhythm form the basis of musical organization (Krumhansl, 2000). The pitch content deals with melodic contour, interval analysis and tonal encoding, and the temporal content specifies rhythm and meter analysis. Both pitch and temporal pathways send their outputs to the "musical lexicon" or to the "emotion expression analysis" (Peretz and Coltheart, 2003). The musical lexicon system contains all the representations of the specific musical stimuli to which one has been exposed during one's lifetime. Recognizing familiar music depends on selection procedure from the musical lexicon. This procedure consists of three stages (access, selection and integration) (Peretz et al., 2009). After music recognition, if the aim is to sing along, covert singing or singing from memory, then the melody will be paired with associated lyrics stored in the phonological lexicon component, which will be integrated and prepared for vocal production. If the task is to name the tune or to retrieve an associated experience, this knowledge will be invoked from the "associative memories" component.

The ability to recognize familiar melodies is present from infancy to old age (Saffran et al., 2000; Trainor et al., 2004) and appears to be dependent on the integrity of pitch and rhythm perception (Peretz and Coltheart, 2003; Volkova et al., 2014). Of these two factors, the former is thought to play a more important role (Peretz et al., 1998a).

#### 2.1.2.2 How musical expertise can modulate music processing

The brain has the capacity to adapt to new experiences and recover lost skills during rehabilitation (Nudo, 2013). Music is a powerful stimulus for brain plasticity (Wan and Schlaug, 2010) and music training and practice has been demonstrated to induce structural and functional brain changes. Structural brain changes have been found in children learning to play a musical instrument (Hyde et al., 2009; Schlaug et al., 2005) and both structural and functional plasticity has been demonstrated in adult musicians (Bangert and Altenmüller, 2003; Schlaug, 2001).

Musicians, compared to non-musicians have better auditory skills, such as larger auditory working memory (Parbery-Clark et al., 2009), enhanced auditory attention (Strait et al., 2010), faster and more robust response to sounds (Musacchia et al., 2007) and facilitated pitch processing (Magne et al., 2006; Schön et al., 2004). It should be highlighted that cognitive and perceptual advantages of music training correlate with the intensity and duration of musical practice (Barrett et al., 2013).

### 2.1.3 Functions of music listening

Music is not only seen as a form of art (for entertainment and pleasure), but also as a means of communication of cognitive states and internal states, including emotion. During music listening, we can extract meaning through the interpretation of musical information (Koelsch, 2011). Moreover, music seems to serve a biological purpose for emotional regulation. Although music does not have obvious survival benefits, it has an adaptive value as a reward system for the enjoyment it promotes (Brown, 2003; Wallin et al., 2000) and may have therapeutic applications. Individuals often report that they listen to music to change or enhance their emotions, and listening to familiar songs makes them “feel good” (Salimpoor et al., 2011).

#### 2.1.3.1 Listening to familiar music as a rewarding experience

During the past few years, cognitive neuroscience research has demonstrated that listening to music can induce pleasure and strong emotions (Blood et al., 1999). It has also been empirically demonstrated that music can elicit highly pleasurable emotional responses, such as “shiver down the spine” when listening to favourite (familiar) pieces of music (Blood and Zatorre, 2001). Neuroimaging studies have implicated emotion and reward circuits of the brain during listening to pleasurable music (particularly the nucleus accumbens of the ventral striatum, suggesting the possible involvement of dopaminergic mechanisms). When listening to familiar music, especially recorded music that can be repeated in the same way, listeners can mentally predict what follows in music, resulting in anticipatory arousal (Omar Ali and Peynircioğlu, 2010; Salimpoor et al., 2013). Salimpoor et al. (2011) investigated the temporal dynamics of dopaminergic activity during music listening and found a functional dissociation (anticipation versus peak emotional experience). They reported that dopamine was released from the caudate nucleus during the anticipation of reward and released from the nucleus accumbens during the experience of peak emotional responses to music. Overall, results indicated that the intense pleasure in response to music can lead to dopamine release in the striatal system (Salimpoor et al., 2011; Zatorre and Salimpoor, 2013). Dopaminergic activity in the nucleus accumbens is also the common mechanism underlying reward response to biologically adaptive behaviours (e.g. food and sex) and psychoactive drugs.

#### 2.1.3.2 Listening to familiar music as a therapeutic experience

The power of music and sound to restore the harmony of the human body and spirit has been used since ancient times. Hippocrates, the father of medicine, used music for his patients with mental problems in the healing temples of Greece (400 B.C.). Throughout the history of human societies, music has shown measurable benefits on both physiological (vital signs: heart rate, blood pressure, respiratory rate, oxygen saturation) and psychological (pain and anxiety) outcomes in infants, children and adults. The therapeutic use of music is being applied as a complementary intervention in clinical and educational settings. In clinical care, music interventions can be classified as music therapy or as music medicine (Bradt et al., 2015). While music therapy is a structured psychotherapeutic practice offered by a trained music therapist, music medicine is pre-recorded music offered by medical personnel. These interventions can be conducted in both acute and chronic settings, as a rehabilitation treatment. Familiar music has been proposed to be preferred by its listeners and may boost treatment effectiveness, and satisfaction compared to music in general (Suhartini, 2011). Listening to familiar music offers an atmosphere of familiarity and comfort that may decrease fear. Some examples of therapeutic use of passive listening of familiar music in clinical settings are:

- As “audio-analgesia” for post-operative pain management, in patients after nasal (Tse et al., 2008) and open heart surgery (Jafari et al., 2012; Özer et al., 2013);

- For pain and anxiety reduction in children during invasive procedures in an emergency department (Berlin, 1998):
- In neurological rehabilitation:
    - To enhance autobiographical memories in: healthy adults (Janata, 2009), mild Alzheimer´s dementia patients (Haj et al., 2012) and acquired brain injury patients (Baird and Samson, 2014);
    - To improve aspects of self-awareness in patients with Alzheimer disease (Arroyo-Anlló et al., 2013);
    - To enhance cognitive recovery during the early post-stroke stage (Sarkamo et al., 2008);
    - To increase walking speed in gait rehabilitation in Parkinson disease, using the rhythmic auditory cueing method (Leow et al., 2015);

Surprisingly, familiar music is also being used as a pain alleviator and positive distraction from the difficult effort of athletic training in competitive sports (Brooks and Brooks, 2010). Listening to familiar (self-selected) music during athletic performance as a motivational tool was demonstrated to be more ergogenic and analgesic than unfamiliar music in a rowing study (Sudar et al., 2012).

### 2.1.4 Music listening as a musical competence

In the western culture, there is a misperception that music competence is a characteristic of only expert musicians, such as professional instrumentalists. Music, as language, is a complex form of human communication and can be conceptualized as an ability with two dimensions: expressive (production) and receptive (perception). If one is competent in language production, he or she has the ability to speak, whereas production competence in music, means ability to sing or perform, which requires years of formal training. But receptive competence is widespread for language and music (Margulis, 2014). Most people are competent music listeners even with no formal training, as melodic, pitch and rhythm structures are acquired through implicit (unconscious) learning. The process of acquiring complex music theoretical features is effortless and develops with exposure and interaction with a large number of musical compositions

(Rohrmeier and Rebuschat, 2012). These findings lead to the notion that our brain is naturally musical (Koelsch, 2011).

### 2.1.5 Music as an important factor for human development

Individuals are born with the capacity to internalize the musical structure of their own culture (Hannon and Trehub, 2005) except for 4% percent of the population affected by congenital amusia, also called “tone deafness”, a disorder of musical development in which individuals are unable to recognize a familiar tune (Peretz et al., 2002). Babies are born with musical abilities that facilitate the acquisition and the processing of language, especially learning to decode pitch information. Babies can detect different features in sounds and recognize familiar melodies and rhythms (Trehub, 2003). Infants are also sensitive to prosody (patterns of stress and intonation in a language) which is used by parents to convey emotions. Caregivers speak to infants in a musical or sing-song manner that incorporates musical elements (such as melody contour and repetitive melodic line) reflecting emotional expressiveness (high pitch, slow tempo and an emotive voice quality). When singing, parents use a special repertoire for infants that is limited to lullabies and play songs. This genre of music has common features across cultures, such as repetition, simple pitch contours and narrow pitch change which is needed for the infant to learn the structure of speech (Trehub and Trainor, 1998). Besides being a cognitive and motor stimulus for language development in prelinguistic infants, these parent-child musical interactions and communication are important for the regulation of the emotional and attentional state of the infant. The repetitive property of the lullabies facilitates infant engagement and fosters interpersonal ties (Nakata and Trehub, 2004; Trehub, 2003).

Overall, infants are responsive to musical elements present in parent-child interactions before they have developed the ability to process language (Trevarthen and Aitken, 2001). This musical responsiveness suggests that at an early age, music and language are not processed as separate domains by the human brain and that language is considered a special case of music (Koelsch, 2011). There is an ongoing debate on the evolutionary relationship between music and language with four hypothesis: music evolved from speech or speech evolved from music, both evolved from a common ancestor or they evolved independently (Besson et al., 2011). Both Rousseau and Charles Darwin were in favour that music and speech may have evolved from a musical protolanguage (Brown, 2000).

### 2.1.6 Music cognition research in neurodevelopmental disorders

Music is a useful tool to study auditory, motor, affective and cognitive processing throughout the lifespan (development, adulthood and ageing). In the field of neurodevelopmental disorders, or disabilities, music perception and cognition have been studied by different scientific disciplines (studies of music, disability and cognitive neuroscience). Investigating music processing in clinical populations such as Down´s Syndrome, Autism Spectrum Disorder and Williams Syndrome is an opportunity to learn about specific aspects of cognitive functions. Previous studies have investigated musical interest, musicality, auditory processing, cognitive abilities, emotion in music, modularity of brain function and independence of mental faculties (for a review see Lense and Dykens (2011). However, no study has ever investigated the effects of familiarity in music in the ASD population. Future research could build on this knowledge to help design training and intervention programs for these individuals.

## 2.2 Familiarity

### 2.2.1 Origin, definition and principles of familiarity

The word familiarity has a Latin origin (*familiaritatem; nominative familiaritas*) dating from the late 14 century and means family, domestic, intimate and well-known. Although a large number of studies on familiarity have been conducted since the late nineteenth century, the familiarity principle, also known as the “mere exposure effect”, was first described by Zajonc in 1968 (Bornstein, 1989). It is a psychological phenomenon which suggests that “the repeated exposure of the individual to a stimulus is a sufficient condition for the enhancement of his attitude toward it” (Zajonc, 1968). In other words, we prefer something because it is familiar. According to King and Prior (2013) familiarity is a complex and unconscious process that can be considered as a dichotomous variable (something or someone is familiar or not), or be interpreted on a “bipolar” continuous scale: we are more familiar with our families members than our friends; more familiar with music that we have listened many times than the one we have just heard on a single occasion as background music.

The familiarity effect is pervasive and has been demonstrated using different stimulus modalities (e.g. visual, auditory, olfactory and gustatory) and experimental paradigms (controlled presentations to real-world settings) (Houston-Price et al., 2009).

### 2.2.2 Familiarity in music listening

The concept of familiarity has been investigated across various scientific disciplines, including music-related fields (e.g., music psychology, musicology and music education). It should be noted that the largest body of research on music familiarity is mostly focused on music listening, as opposed to music learning or music performance (King and Prior, 2013).

Even though the "mere exposure effect" was introduced by Zajonc in 1968, the familiarity principle had been known for a long time by social psychologists and applied to the music field. Meyer (1903), an experimental psychologist, documented it in 1903. Over the course of time, other music studies confirmed the reliability, and robustness of the familiarity concept. For instance, in 1928, Buhler and his colleagues observed and described that "human infants reacted to a strange sound by crying out with fear. Upon the second exposure of the sound stimulus, movement and vocalization, that indicated displeasure, were observed. On the third exposure, the infants listened to the sound showing some signs of attention but did not show any displeasure. On the fourth exposure, they looked in the direction of the sound with detectable interest" (Buhler et al., 1928).

Several music neuroscientists have developed overlapping constructs that facilitate our understanding of familiarity. Peretz et al. (1998a) reported that familiarity is best conceptualized as an "implicit memory phenomenon", in which previous experience aids the performance of a task without conscious awareness of these previous episodes. Snyder (2000), in his book "Music and memory: an introduction", refers to a type of implicit memory and defined it as *priming*, in which the exposure to one stimulus influences a response to another stimulus. A musical example of priming would be a feeling of familiarity about a musical phrase that is similar to what we have heard earlier in the same piece.

### 2.2.3 Relationship between familiarity and likeability

Zajonc (1968) suggested a causal relationship between the frequency of exposure of a stimulus and a positive attitude or enjoyment toward it. Later, Jakobovits (1966) proposed an inverted-U shaped relationship between exposure and popularity or liking of a song. His hypothesis for a non-linear correlation was that “repeated exposure to an unfamiliar stimulus would result in its increase in meaningfulness up to a point where further exposure no longer adds meaningfulness”. Figure 2-3 shows the liking as a function of familiarity (exposure), and a decrease in liking with too much exposure.

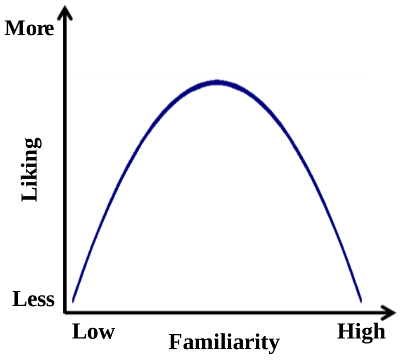

Figure 2-3: Relationship between liking and familiarity with a stimulus.

There are various explanations for the inverted U-shape preference response. One is the perceptual fluency theory (Bornstein and D’Agostino, 1994), which posits that the number of times a person has been exposed to a stimulus is positively correlated to the ease which it is comprehended, leading people to like it more because it is easier to process. However, pleasure decreases when one understands that liking was due to repetition effects rather than to the positive misattribution of the experience of perceptual fluency. The other model was proposed by Berlyne (1971). It is explained as an “interaction of two impulses:” the ascending part of the inverted U is due to an evolutionary preference for familiar stimuli and the descending favors novelty seeking to avoid boredom.

Usually, this effect of familiarity is maximal after a few presentations and reaches a plateau after about ten presentations (Bornstein, 1989). The complexity of a musical stimulus has also been found to have a great impact upon exposure and satiation effects (Szpunar et al., 2004). Highly complex stimuli have produced increased liking with exposure, moderate complexity has produced an inverted-U shaped relationship and very simple stimuli have produced decreased liking with exposure (Brentar et al., 2009). Overall, familiarity in music deepens our understanding and engagement with it.

### 2.2.4 Familiarity as a memory process

Familiarity has also been described as a memory process or type of memory, distinct from recollection (see Yonelinas, 2002, for a review). These two memory components have been discussed since the time of Aristotle by different theorists. While familiarity can be described as a general sense of “knowing” (“quantitative” memory strength), recollection relates to determining detailed information, such as the spatial-temporal context, about a remembered event (“qualitative” information). Both have been proposed as retrieval processes or memory assessment mechanisms that structure the recognition memory performance, in a dual-process framework. Cognitive, neuropsychological and neuroimaging studies have contributed to the characterization and disentanglement of these two distinct forms of memory, which seem to differ in speed of response, type of information and underlying neural correlates. Familiarity is a faster process than recollection and supports memory for perceptual information, while recollection assists semantic (or meaning-based) information (Yonelinas, 2002).

Familiarity is related to semantic memory, which is a category of long-term memory proposed by Tulving (1972), who initially presented two types of long-term memory which he coined as episodic and semantic. Later on, he added another category called procedural memory. The episodic and semantic memory make up the category of declarative knowledge (e.g. words, colours, faces or music). The semantic memory is a structured record of information acquired over a lifetime, and it relates to the feeling of familiarity. Episodic memory is responsible for storing information about events (i.e., episodes) experienced in our lives. It is remembering and thus relates to recollection. The procedural memory is responsible for knowing how to do things (riding a bicycle, tying shoelaces) and it is unconscious.

Musical semantic memory is defined as the long-term storage of music related information, such as melodic content and progression of tones, which enables us to have a strong feeling of familiarity when we listen to music (Groussard et al., 2010a; Platel, 2005). This type of musical memory organizes familiar songs along with conceptual lines clustered by similar non-musical factors into thematic groupings, such as by artist, age of acquisition, music category (Christmas, patriotic, commercial jingle, musicals, etc.) (Halpern, 1984; Johnson and Halpern, 2012).

#### 2.2.4.1 Neural mechanisms underlying the familiarity effect

The underlying neural mechanisms of the behavioural familiarity enhancement effect remain unknown. There are two main hypotheses, the bottom-up and the top-down theories. This enigma has been investigated in face perception studies as well, as it is currently accepted that subjects process familiar faces more efficiently than unfamiliar ones (Jenkins et al., 2011; Young and Burton, 2018). The bottom-up theory of familiarity enhancement predicts that the visual experience with repeated faces enhances representation of familiar faces by adjusting the bottom-up perceptual filters for face features (Di Oleggio Castello and Gobbini, 2015). Alternatively, the top-down hypothesis posits that activation of associated memories would lead to enhanced perceptual representations and consequently to the familiarity effect, but requires time for feedback from high-level areas (Schwartz and Yovel, 2016). Dobs et al. (2019) investigated and clarified the familiarity effect using familiar and unfamiliar celebrities’ faces and concluded that familiarity effect was found to arise very early in the visual processing most likely supporting the bottom-up theory. No comparable study is published for familiar and unfamiliar music.

### 2.2.5 Neural correlates of familiarity (all modalities)

Different authors have investigated the neural correlates of familiarity and recollection as memory recognition processes using the dual-process model (Aggleton and Brown, 1999; Nyberg et al., 1996; Yonelinas et al., 1998). While, there was consistency among researchers in assuming that recollection is dependent on the hippocampus and medial temporal lobes, there was less agreement about familiarity neural correlates. All agreed that familiarity is processed by the surrounding structures of hippocampal region, but Aggleton and Brown (1999) were more specific, mentioning the inferior temporal lobes (e.g. the parahippocampal gyri) and also suggesting a circuit linking the perirhinal cortices (anterior part of the parahippocampal gyri) to the medial dorsal thalamus and direct projections from the thalamus to the frontal lobes. Nyberg et al. (1996) added that the frontal regions more specifically the left prefrontal region was also important for familiarity processing. Plailly et al. (2007) investigated the neural bases of familiarity processing evoked by stimuli of two modalities: music and odours. Findings revealed a bimodal neural system activation in left frontal and parieto-occipital areas, more specifically the superior and inferior frontal gyri, the precuneus, the angular gyrus, the parahippocampal gyrus, and the hippocampus. According to the authors, parts of these neural systems were shown to be active to the processing of familiar faces, voices, pictures and verbal items (presented visually). The overlap between the neural correlates involved in familiarity of items from different modalities led Plailly et al. (2007) to claim a multimodal, rather than a bimodal, neural system underlying the feeling of familiarity. The neural correlates of the feeling of unfamiliarity (impression of novelty) of odors and music have also been investigated and findings showed activation of the right anterior insula (Plailly et al., 2007).

### 2.2.6 Neural correlates of familiarity in music

Familiarity is a complex construct with different conceptualizations and the neural mechanisms underlying this memory phenomenon toward music listening are still not very clear or consistent.

Recognizing a familiar song needs selection and retrieval from the *musical lexicon*, which contains all the representations of musical stimuli that one has been exposed to during one’s lifetime (Peretz and Coltheart, 2003). Pioneer work of Penfield and Perot (1963) identified that the left or right superior temporal gyrus were the neural substrates of the musical lexicon, in which electrical stimulation in those regions could elicit music memories in the form of a musical hallucination. Other early brain lesion studies reported the involvement of both temporal gyri or left superior temporal area and left frontal areas (Platel et al., 1997, 2003) in music familiarity. These regions' involvement may be attributed to extra-musical events associated with the familiar songs, such as lyrics and memories. Also, it has been reported that left lateralization could relate to acoustic factors (Plailly et al., 2007; Platel et al., 2003).

Plailly et al. (2007) reported music-specific and odour-specific activations. For music, modality-specific activation included the left superior frontal gyrus (Brodmann area (BA) 47) and medial frontal gyrus, the superior temporal sulcus (STS), the posterior part of the central gyrus, the right angular gyrus, and the left supramarginal gyrus. Peretz et al. (2009) showed that recognition of a familiar instrumental piece activated a network including the right and left STS, the left planum temporale, the left supplementary motor area (SMA) and the left frontal inferior gyrus. The authors highlighted the apparent importance of STS to music recognition. Janata (2009) studied the neural correlates of music-evoked autobiographical memories in healthy individuals and those with Alzheimer disease. His findings showed that familiar songs from one's past can trigger emotionally salient episodic memories and that this process is mediated by the medial prefrontal cortex (mPFC). In the same study, hearing familiar tunes also activated the pre-supplementary motor area, left inferior frontal gyrus, bilateral thalamus, and the right cerebellar hemisphere (Janata, 2009). Groussard and her co-workers investigated music semantic memory and found activation of the superior temporal gyri (BA 22). The right superior temporal gyrus was mostly involved in the retrieval of perceptual memory traces (information about rhythm and pitch), which are useful for deciding whether a melody is familiar or not. The left superior temporal gyrus seemed to be involved in distinguishing between familiar and unfamiliar melodies (Groussard et al., 2010a).

An additional method to access to memory representations in the musical lexicon is studying musical imagery, which consists of imaging familiar music in the absence of real sound input (Halpern, 1988). Zatorre and Halpern (1993) found that imagery deficits were found after damage to the right auditory cortex. Other studies showed that thinking about a familiar tune engaged inferior frontal regions (Halpern and Zatorre, 1999) and the supplementary motor area (SMA) (Halpern et al., 2004; Halpern and Zatorre, 1999), which could relate to covert or inner singing.

Recently, Pereira et al. (2011), in an fMRI study, investigated familiarity and music preference effects in determining the emotional involvement of the listeners and showed that familiarity with the music contributed more to the recruitment of the limbic and reward centres of the brain. Previous neuroimaging studies in the neurobiology of reward during listening of preferred (familiar) music had demonstrated the involvement of mesolimbic striatal areas, especially the nucleus accumbens (NAcc) in the ventral striatum.  In section 2.1.3.1- Listening to familiar music as a rewarding experience, we have already explored the relationship between music familiarity and reward activation in further detail.

Overall, the neural correlates of music familiarity are not consistent across studies, due to the use of different modalities, experimental paradigms and music stimuli (melodies, songs with and without lyrics), although the superior temporal gyrus, left frontal areas and supplementary motor areas are often mentioned as associated with memory for familiar music.

## 2.3 Autism spectrum disorder

### 2.3.1 Epidemiology and clinical presentation

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that affects approximately 1% of the population. In Canada, 1 in 66 children and youth between 5-17 years of age have been diagnosed with ASD (Ofner et al., 2018). It is characterized by persistent difficulties in social interaction and social communication, and restricted, repetitive patterns of behaviours, interests and activities (American Psychiatric Association, 2013). These two subsets of symptoms are the core criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The second subset about repetitive patterns of behaviour is of relevance in this thesis, as repetitive behaviours seem to indicate a preference for the familiar and aversion to novelty in ASD (Esler et al., 2018).

In this disorder clinical heterogeneity and comorbid psychiatric and medical diseases are a hallmark (Masi et al., 2017). As such, there is a wide variety of clinical presentations with a range of severity levels. Cognitive skills, especially intellectual quotient (IQ) and language abilities have been reported as predictors of social outcome in ASD (Billstedt et al., 2005). Regarding IQ, the ASD population is often stratified into “low and “high” functioning ASD to reflect individuals with IQ in at least the average range versus individuals with intellectual disability (ID) (Siegel et al., 1996). We highlight this as individuals without ID are more often selected for enrollment in research studies since they have greater ability to comply with instructions and successful completion of neuroimaging studies, including in Study 2 in this thesis. This recruitment bias limits neuroimaging results to high-functioning participants and consequently cannot be generalized to all individuals with ASD. As for gender, there is a male bias in ASD prevalence, a ratio of around 4 males to 1 female (Masi et al., 2017) and this is also reflected in published neuroimaging literature limiting generalization of findings to females with ASD. As a heterogeneous condition with multiple aetiologies, developmental trajectories and phenotype it is normal to expect that children with ASD present different behavioural and neural responses to stimuli. This inter-individual and also intra-individual variability in ASD may contribute to inconsistent literature in ASD and to the observation of larger variation around the mean compared to controls (David et al., 2016; Otto-Meyer et al., 2018).

The domain of restricted, repetitive interests and behaviours in ASD is relevant to understand familiarity, as repeated exposure to a stimulus establishes familiarization. Since the first description of autism as a disorder Kanner (1943) described two key features present in all 11 of his original cases of children with autism. These were extreme aloneness and “an anxiously desire for the maintenance of sameness” or “resistance to change”. The autistic child wishes a static world, with no changes and insists that aspects of the environment stay the same. This need for preservation leads to various forms of restricted and repetitive behaviours (RRBs), with varying intensity. It includes rigorous adherence to routines or rituals, insistence on specific interests and resistance to change in the surroundings (such as placement of toys, bath towels). This subgroup of RRBs is currently referred to as insistence on sameness (IS) (Bishop et al., 2013; Szatmari et al., 2006).

Insistence on sameness behaviours are also present in typical development (Evans et al., 1997), especially at times of transition (Evans and Gray, 2000). Many young children around 30-36 months ask to hear the same bedtime story (McGraw et al., 1974) or to watch the same TV program repeatedly (Evans et al., 1997). These behaviours are transient and adaptive in nature. Researchers have speculated that other ritualistic or obsessive-compulsive disorder (OCD)-like behaviours serve as compensatory mechanisms in fearful situations (Evans et al., 1999) and help individuals to establish predictability and control in a perceived chaotic environment (Fiske and Haslam, 1997). On the other hand, in ASD children repetitive behaviours may be intense and persistent (Bishop et al., 2013; Szatmari et al., 2006). This desire for sameness and resistance to change may relate to familiarity, as stimuli, when repeatedly presented, become familiar.

Restrictive and repetitive behaviours can also be manifested by sensory symptoms (American Psychiatric Association, 2013). There are three patterns of sensory features: hyperresponsiveness (i.e., behavioural over-reactivity to sensory stimuli); hypo responsiveness (i.e. behavioural under-reactivity to sensory stimuli) and sensory seeking (i.e., craving/fascination with certain stimuli) (Ben-Sasson et al., 2009; Miller et al., 2007). It has been suggested that some restricted and repetitive behaviours help individuals with ASD to manage their unusual sensory processing (Baker et al., 2008). One example is hyperresponsiveness to sound (atypical sensory processing) and avoidance of certain environments (restricted behaviour). However, little is yet known about the association between patterns of sensory features and repetitive behaviours. One study has suggested that the co-occurrence and association of hyperresponsive sensory features and repetitive behaviours may be related to shared neurobiological mechanisms (Boyd et al., 2010). It has also been suggested that due to detail-focused style of processing, individuals with ASD may have impairments in filtering out environmental sensory information. As such, heightened sensitivity to novel stimuli may underlie preference for sameness (Baron-Cohen and Belmonte, 2005; Happe, 1999).

### 2.3.2 Theories of autism

Various cognitive theories have emerged to explain strengths and impairments in autism, including the repetitive interests and behaviours described in this disorder. The most prevalent theories are the Weak Central Coherence (WCC), the Enhanced Perceptual Functioning (EPF) model, the Theory of Mind (ToM) and the Deficit of Executive Function. The WCC theory was proposed by Uta Frith (1989) to explain both the deficits and strengths (amazing talents) of individuals with ASD. It states that these individuals excel at focusing on extreme detail, being able to extract a tiny element from a mass of complex data or objects. A person has enhanced local processing, but with diminished global processing. It is a "detail-focused cognitive style" The Enhanced Perceptual Functioning (EPF) model was proposed by Mottron and Burack in 2001 and updated in 2006 (Mottron et al., 2006; Mottron and Burack, 2001). This theory was conceptualized as an alternative to the WCC model, the prevailing model at the time. It attempted to account for superior performance in visual and auditory modalities emphasizing that individuals with autism are biased to detect and discriminate specific local features (locally oriented ''default setting'') but with intact global processing. The theory of mind hypothesis was formulated by Simon Baron-Cohen in his book Mindblindness (Baron-Cohen, 1995). It posits that children with autism are unable to conceive and attribute mental states of oneself and others (beliefs, intents, desires, perceptions and emotions). This theory tries to account for socio-cognitive deficits in autism and was proposed in the beginning of ToM research in the field of developmental psychology (Baron-Cohen et al., 1985). Regarding the Deficit of Executive Function theory, this was proposed by Ozonoff et al. (1991) and attributes autistic symptomatology to deficits in broader, domain-general, executive control processes. These executive functions include planning, inhibition, mental flexibility, organized search and working memory. People with autism do not seem to anticipate long-term consequences of behaviour well, have difficulties in self-reflecting, and appear impulsive, unable to inhibit responses. Deficits in these executive control processes were also proposed as a cause for the rigid, inflexible and repetitive behaviour patterns in children with autism, who would present stereotyped and ritualistic avoidance strategies and "preservation" (repetition of a particular response, such as word, phrase, or gesture) as patients with prefrontal cortical dysfunction (Damasio and Maurer, 1978).

### 2.3.3 Autism, familiarity and novelty

#### 2.3.3.1 Studies investigating familiarity

Individuals with autism have been described as having a stronger preference for familiar stimuli and novelty aversion (Croonenberghs et al., 2002; Gustafsson and Papliński, 2004; Kanner, 1943). Parents and researchers have described this familiarity preference, including Happé and Frith (2009) who suggested that "sameness is what people with ASD would prefer, even over decades". Also, Dawson and Lewy (1989) hypothesized that aversion to novelty is more salient for social stimuli, which are dynamic and unpredictable. In addition, research findings showed decreased exploratory behaviour in children with ASD in unstructured novel environments (Pierce and Courchesne, 2001).

Despite its relevance and social impact, the concept and the effect of familiarity in individuals with ASD has been poorly investigated. One study explored the examiner familiarity on standardized test performance in preschool and elementary school-age children with ASD which demonstrated a procedure bias. Being familiar with the examiner had positive effects on test performance (Szarko et al., 2013). Other studies exploring the effect of familiarity used visual stimuli, such as faces. Most of these studies were on face processing, as understanding socio-emotional difficulties is relevant in this disorder. Faces are salient stimuli critical for social interaction and communication (Jack and Schyns, 2015). In fact, atypical processing of faces related to poorer recognition skills in the ASD population has been reported through different neuroimaging modalities, such as ERPs (Dawson et al., 2002; Webb et al., 2006, 2010) and fMRI (Grelotti et al., 2005; Pierce et al., 2004; Pierce and Redcay, 2008). The most consistent finding is that face recognition impairments apply to the processing of unfamiliar but not familiar faces (Simmons et al., 2009), although some authors suggest delayed development of the processing of familiar faces (Batty et al., 2011; Webb et al., 2011). Unfamiliar faces have been preferred stimuli to investigate the altered emotional face processing in ASD individuals, using different neuroimaging techniques. Some of these studies have been completed using MEG which revealed specific frequency bands associated with these emotional impairments (Leung et al., 2014, 2018; Mennella et al., 2017; Safar et al., 2018).

#### 2.3.3.2 Studies investigating novelty

Due to the unusual behaviour when processing novel sensory stimuli and how it underlies the "need for sameness", there have been investigations on the neural basis of novelty. This research topic is relevant as it mimics many aspects of life in which we continuously adapt to unpredictable and changing events. These studies use the "novelty oddball" paradigm. The oddball paradigm is an experimental design in which repetitive stimuli are presented and are infrequently interrupted by a deviant or oddball stimulus. The reaction to the oddball stimulus is recorded. The "novelty oddball" paradigm used by Gomot et al (2008) presented three classes of auditory stimuli (standard, deviant and novel) and participants were required to detect and respond to the target (novel) stimuli (Gomot et al., 2008). Many ERP studies have shown atypical responses associated with the processing of auditory oddball stimuli in individuals with autism, but the neural correlates remain unknown (Courchesne et al., 1985; Novick et al., 1980).

There have been few fMRI studies investigating auditory novel target detection in individuals with ASD. Gomot et al. (2006) found hypo-activation (lower brain activation) in children with autism during passive listening of deviant and novel stimuli. The authors suggested the findings could reflect reduced orientation toward novelty, possibly related to attentional mechanisms. A subsequent study, also in children with ASD, showed atypical brain activation associated with novelty detection when compared with typically developing children. The prefrontal and inferior parietal cortices showed stronger activation in children with ASD than controls, both regions well known for being involved in selective attention (Gomot et al., 2008).

### 2.3.4 Autism and neural adaptation

Every familiar stimulus was once a novelty (unfamiliar). Neural adaptation (NA), also referred to as sensory adaptation or repetition suppression, can be described as a gradual decreasing sensitivity to a stimulus after repeated exposure to it (Kohn, 2007; Webster, 2012). An example applied to the sense of touch is when we put on a new piece of clothing, we instantly notice its texture, but after it has been worn for a while, we are no longer consciously aware of it. In ASD, neural adaptation on average is reported to be attenuated in the sensory domains, at multiple levels in time and space, from short time to long scales, and multiple sensory pathways, from the level of neurons, through to the macroscopic BOLD signal, with reduced cortical adaptation effects to sensory stimuli (Noel et al., 2017; Turi et al., 2015), including the auditory domain (Millin et al., 2018). In other words, the ASD brain on average processes novelty differently compared to the typical brain, likely due to maladaptive neural adaptation and deficits in the dynamic range of neural responsiveness.

### 2.3.5 Autism and music research

The history of ASD has shown that many individuals with this disorder give increased attention to music and have musical abilities. Leo Kanner, the doctor who first described the term “infantile autism” in 1943, reported that 6 out of 11 children in his clinical group exhibited “extraordinary music memory”, given their developmental levels. An exceptional example was case number 9, a boy of 18 months of age who could discriminate between 18 symphonies and identify their composers (Kanner, 1943). Since this time, music perception and abilities are seen as relative strengths associated with ASD (Heaton, 2009). Moreover, there is a history of 50 years of music-therapy interventions in ASD (Reschke-Hernández, 2011), as well as work by Bergmann et al. (2015, 2016) who developed the Music-based Scale for Autism Diagnosis (MUSAD). This observational instrument (using music-based interactions as the source of information) was designed to be a musical equivalent of the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012) to identify ASD in adults with intellectual disability (ID) and limited speech (Bergmann et al., 2019).

Extensive work has already been done to understand perceptual features as well as high order characteristics of music in ASD, summarized below:

#### 2.3.5.1 Pitch discrimination ability

Despite Kanner´s interesting reports in 1943, musical skills in non-savant children with autism just started to be investigated in 1979, 36 years later. Pitch and melody have been the elements of music most studied so far in this population. Applebaum and his colleagues observed in a very small sample that children with autism had superior performance on reproducing atonal melodies than children with typical development and who had higher levels of musical experience (Applebaum et al., 1979). Heaton et al. (1998) examined the absolute pitch (AP) ability (the ability to produce or identify specific pitches without reference to an external standard) in musically naive children with autism and found superior recall in the autism group relative to IQ matched, typical controls (Heaton et al., 1998). Subsequent studies in pitch perception have also been consistent in indicating that short and long term pitch memory and labelling are superior in autism (Bonnel et al., 2003, 2010; Heaton, 2003, 2009; Stanutz et al., 2014). According to Brown et al. (2003), the incidence of AP among individuals with autism is estimated to be 1 in 20 whereas the prevalence in the general population is 1 per 10,000 (Profita and Bidder, 1988). It is of interest to note that enhanced pitch perception in this population exists especially in those individuals with a history of delayed speech onset. Nevertheless, the causal relationship between language impairment and superior pitch perception is unclear (Bonnel et al., 2010). On the other hand, Jones et al. (2009) suggest that not all individuals with ASD have enhanced auditory discrimination, but just 20% of ASD population have this ability. A recent study by Jamey et al. (2019) found that children with ASD performed similarly to TD children on melodic pitch perception and melody memory. This could explain mixed results often seen in studies with small sample sizes (Quintin, 2019). Since successful recognition of familiar songs builds on melody (pitch) and rhythm identification (Peretz and Coltheart, 2003; Volkova et al., 2014) assessing pitch discrimination ability is relevant for this thesis.

#### 2.3.5.2 Timing and rhythmic discrimination ability

Regarding rhythm, it has been established that children with ASD are able to synchronize auditory-motor rhythm just as well as their typically developed counterparts (Tryfon et al., 2017). These findings are consistent with intact rhythmic perception found by Jamey et al. (2019) but in conflict with previous work showing deficits in rhythm processing in ASD, particularly in meter categorization (DePape et al., 2012).

#### 2.3.5.3 Intensity or loudness perception

With respect to the perception of other low-order music features such as loudness, individuals with ASD are hypersensitive to sudden and unexpected loud sounds, causing them great distress and aversive responses. In fact, few studies have explored loudness processing in ASD, but typically, results indicated enhanced loudness sensitivity which declines with age and also typical performance on intensity discrimination tasks (O’Connor, 2012).

#### 2.3.5.4 Perceiving emotions in music

Regarding the processing of music´s higher order characteristics, such as emotion, despite the fact that the individuals with autism are often impaired in social domains (as in face processing recognition; Rump et al., 2009), research has shown that they can recognize emotion in music in childhood and adulthood. In 1999, Heaton et al. were the first to report that children with autism could understand music´s emotional connotation, by examining perception of music mode. In their study, children with autism were as likely to pair fragments of major mode music with happy faces and fragments of minor mode music with sad faces as controls were (Heaton et al., 1999). More recently, Molnar-Szakacs and his colleagues also showed that children with autism identified the emotional musical excerpts as well as the typical developing control participants (Molnar-Szakacs et al., 2012).

However, this is not applicable to all individuals with autism. Temple Grandin, a well-known high-functioning woman with autism, self-reported insensitivity to the affective aspects of music (Heaton and Allen, 2009). This finding may be due to type II alexithymia, a disorder that has been observed in some adults with high functioning autism and is characterized by difficulties in identifying and describing one’s own feelings (Molnar-Szakacs and Heaton, 2012). It has been estimated that this disorder affects up to 85% of high-functioning adults with ASD, while a much lower prevalence of 10% has been observed in the general population (Bermond, 1997; Berthoz and Hill, 2005; Hill et al., 2004; Rieffe et al., 2007).

### 2.3.5.5 Motivation to music listening

ASD individuals present the same motivational reasons to listen to music as typically developing controls, such as “feeling of belonging and satisfying emotional needs” which generally suggest that the individuals with autism have intact musical appreciation (Allen et al., 2009; Heaton and Allen, 2009). They also spend as many hours per week listening to music as their peers (Bhatara et al., 2013). These preserved musical functions support the hypothesis that musical elaboration in autism presents specific cerebral mechanisms that seem relatively preserved.

### 2.3.5.6 Neuroimaging studies on music in ASD population

Over the last three decades the field of music cognition in autism has been growing. The advancement of neuroimaging techniques allowed the development of the scientific study of the neurobiology of music. In the ASD population, the first fMRI studies examined the emotional processing of (happy and sad) music in autistic adults (Caria et al., 2011; Gebauer et al., 2014). As expected, music activated reward and emotion processing systems but with mixed findings. While Caria et al. (2011) found hypo-activation of the left insula, Gebauer et al. (2014) found hyper-activation. One interpretation for this discrepancy was the fact that Caria et al. (2011) presented well-known (familiar) and self-selected music while Gebauer et al. (2014) used novel music. The insula is a brain area associated with detection of novel stimuli, awareness and cognitive processing of emotional states. Other neuroimaging studies completed in children with ASD have compared music and language without an emphasis on emotions (Lai et al., 2012; Sharda et al., 2015). Both studies used song and speech to investigate the processing of these stimuli in ASD children, capitalizing on shared perceptual and neural mechanisms for music and language (Fedorenko et al., 2009; Rogalsky et al., 2011; Schön et al., 2010). Lai et al. (2012) and Sharda et al. (2015) used the same multimodal imaging method, a combination of fMRI and diffusion tensor imaging (DTI) while participants completed a passive listening paradigm. Lai et al. (2012) explored the effect of familiar speech and each participant’s favorite song in a group of low-functioning children with ASD compared to controls. Sharda et al. (2015) built upon previous research with an improved design paradigm, controlling for stimulus and familiarity effects. The sample consisted of ASD children with varying levels of functioning. The two studies showed reduced inferior frontal gyrus (IFG) activity in the speech/spoken word condition, while also identifying increased fronto-temporal connectivity in the sung-word listening condition compared to the spoken-word condition. The studies investigated brain connectivity in both music and speech processing using fMRI and DTI, however, no study has ever studied brain networks involved in music processing using MEG, nor compared familiar to unfamiliar songs processing. Based on Gebauer et al. (2014) studies, insula connectivity would be predicted to be involved in processing of unfamiliar music.

#### 2.3.5.7 The potential for music interventions

Music therapy programs have been used in individuals with ASD since 1969 (Reschke-Hernández, 2011). The application of music therapy in this clinical group was due to the musical interest and abilities described in many children with ASD. Two Cochrane reviews of music therapy in the treatment of children with ASD have been published (Geretsegger et al., 2014; Gold et al., 2006). The first review (Gold et al., 2006) included three small studies with a total of 24 participants and were considered of limited applicability to clinical practice as they only assessed short-term effect of music therapy. Findings showed that music therapy was superior to placebo therapy in improving verbal and gestural communicative skills, but better research was needed to clarify if effects of music therapy were enduring. The latest review (consisting 10 studies with a total of 165 participants) (Geretsegger et al., 2014) examined the short and medium-term effects of music therapy interventions (one week to seven months). The evidence was moderate for social interaction outside the therapy context, initiating behaviour, social adaptation, and the quality of the parent-child relationship. Evidence was low for the other three main outcomes (nonverbal communicative skills outside the therapy context, verbal communicative skills outside of the therapy context, and social-emotional reciprocity). The small number of participants in the included studies and concerns with study design were reported as limitations to the quality of the evidence. Nevertheless, another study (international multicentre clinical trial) did not find effects of improvisational music therapy on symptom severity based on the ADOS social affect domain among children with ASD (Bieleninik et al., 2017). The pragmatic approach with broad inclusion criteria, representing 9 countries, with different languages, musical traditions, cultural expectations about child development, and cognitive abilities may have introduced too much heterogeneity to treatment response.

More recently, Sharda et al. (2018) reported that music-therapy in children could improve communication and quality of life and demonstrated that these communication improvements were associated with increased auditory-subcortical and decreased auditory-visual functional brain connectivity. This was the first neuroimaging study to provide evidence that 8-12 weeks of individual music intervention could improve social communication and functional brain connectivity.

It is important to characterize which brain networks are engaged in children with ASD during familiar and unfamiliar music listening to help design suitable clinical and educational intervention programs. Usually, the primary target domains of the intervention are social communication, language and speech impairments. However, there are proposals suggesting an expansion of the clinical scope of music-therapy in autism, addressing motor control and attentional deficits using Neurologic Music Therapy (NMT) techniques (Janzen and Thaut, 2018), such as the developmental speech and language training through music (DSLM) (Thaut and Hoemberg, 2014).

ASD is also a disorder of brain connectivity (Belmonte, 2004). Considering that the aim of Study 2 of this thesis is to investigate functional connectivity during a music familiarity task using magnetoencephalography (MEG), the following sections (2.4 and 2.5) will introduce the concepts of functional connectivity and MEG, respectively.

## 2.4 Functional connectivity

### 2.4.1 Neural oscillations

Neural oscillations are rhythmic or repetitive patterns of activity generated by neural tissue. This activity can be intracellular voltage in single neurons and/or local field potentials (LFPs) generated by populations of synchronized cells (Koepsell et al., 2010). Oscillations are fluctuations in the excitability of neurons, that may arise due to a variety of physiological mechanisms: i) interplay between excitatory pyramidal cells and inhibitory (GABAergic) interneurons; ii) purely excitatory networks and iii) purely inhibitory networks (Klausberger et al., 2003; Wang and Rinzel, 1992, 1993). Other sources of oscillations are pacemaker cells, resonance or subthreshold membrane oscillations (Pevzner et al., 2016).

Oscillations can be described by three different pieces of information: frequency, power and phase (Cohen, 2014)(Figure 2-4). Frequency is the speed of the oscillation, which refers to the number of cycles per second and it is measured in Hertz (Hz). Power is the amount of energy in a frequency band and is the squared amplitude of the oscillation. Phase is the position along the sine wave at any given time point and is measured in radians or degrees (Cohen, 2014).

Neural oscillations can be stratified into microscale (activity of a single neuron), mesoscale (activity of a local group of neurons) and macroscale (neural activity from different brain regions or networks) (Idris et al., 2014).

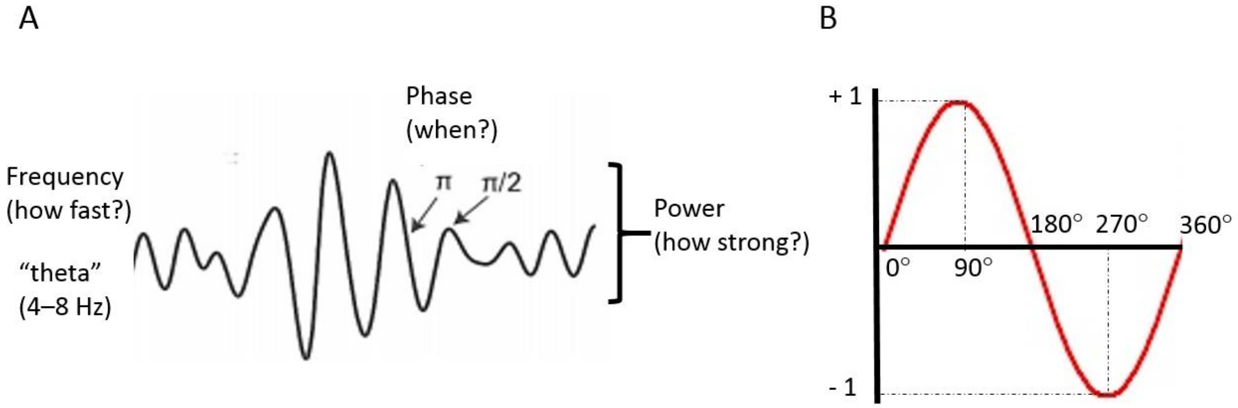

Figure 2-4: A:Illustration of frequency, phase and power of an oscillation; B: graphical representation of phases or angles of a brain wave adapted from Cohen (2014).

### 2.4.2 Rhythms of the brain

Human neurons can exhibit a wide range of oscillations (~0.05 to 500 Hz) which can enter into precise synchrony over a limited period of time (millisecond scale) (Buzsáki and Draguhn, 2004). These oscillations produce rhythms at different frequencies. Hans Berger (1897-1941) who described the first human EEG pattern, which he termed “alpha rhythm” introduced the nomenclature of the different rhythms by Greek letters (Berger, 1929). Neural oscillations have been divided into different bands: delta (1-4 Hz), theta (4-7 Hz), alpha (8-14 Hz), beta (15- 30 Hz), gamma (> 30 Hz) and high-frequency oscillations (HFO) (>80 Hz). Most of the neuronal connections are recruited through high frequency oscillations which reflect local communication. On the other hand, slow rhythms reflect long-range communication between distant brain regions (Buzsáki and Draguhn, 2004; Engel et al., 2001).

### 2.4.3 Functional properties of neural oscillations

The oscillatory activity in our brain is vital for normal brain functions and many studies have investigated the function of neuronal oscillations. Even though the role of most oscillations depends on the function of the brain system that generates it, some oscillations are independent of the brain structure underneath it (Buzsáki and Draguhn, 2004). The sources that generate oscillations can be specific to sensory modality and brain region (Koepsell et al., 2010). Different neural generators are involved in the generation of brain oscillations at different frequencies. Oscillations can originate through different mechanisms: by the temporal structure of the stimulus (as in auditory system), from periodic movements of mechanical sensors or generated by electrical resonances of individual cells. These mechanisms can operate cooperatively (Koepsell et al., 2010).

Regarding the functional role of neural oscillations, each frequency band (delta, theta, alpha, beta and gamma) is linked to a variety of perceptual, sensorimotor and cognitive operations (Engel and Fries, 2010; Harmony, 2013). Delta oscillations are considered to be involved in many cognitive processes, such as mental calculation, working memory, semantic processing and meditation (Başar et al., 2001; Harmony, 2013). They are the most prevalent during deep sleep and thus are considered a characteristic of sleep (Huber et al., 2004). Delta oscillations have also been implicated in behavioural inhibition (Kamarajan et al., 2004), in motivational and emotional processes (Knyazev, 2007).

Theta oscillations are associated with hippocampal functions (temporal coding and decoding and modification of synaptic weights) (Buzsáki, 2002) and long-range cognitive integration. Alpha rhythms have been implicated in the inhibition/suppression of task-irrelevant neuronal processing and working memory function (Palva and Palva, 2011). Beta-band oscillations seem to be related to the integration and maintenance of sensorimotor information and top-down cognitive processes (Engel and Fries, 2010). Finally, gamma rhythms have been observed in cortical and subcortical structures involved in perceptual grouping (Tallon-Baudry and Bertrand, 1999) and attention (Jia and Kohn, 2011). Related to functional connectivity, there is "spectral fingerprints" framework which assumes that oscillatory changes in different frequency bands indicate different neural processes in different brain regions, each reflecting a specific cognitive function (Siegel et al., 2012).

### 2.4.4 Neural synchronization represents functional connectivity among brain areas

Thirty years ago, researchers were investigating the role of neural synchrony in the integration of sensory signals during perceptual organization (Siegel et al., 1996). The question was how information could be integrated and how coherent states could be established. This was called the "temporal binding problem". A solution was formulated entitled as the temporal binding model (Engel and Singer, 2001). This model states that neurons respond at approximately the same time with millisecond precision for object representation, attention, response selection and sensorimotor integration (Engel et al., 2001).

This model highlighted the functional significance of neuronal oscillations for the large-scale neuronal interactions underlying cognition (Fries, 2005). Neural communication (defined here as electrical communication through field effects) and interaction is achieved through neuronal coherence (Fries, 2005) which is defined as the quantitative measure of the consistency between two neuronal groups (Nunez et al., 1997). Coherence consists of phase synchronization within the group of neurons sending a message and phase-locking between the oscillations in the sending and the receiving group (Figure 2-5).

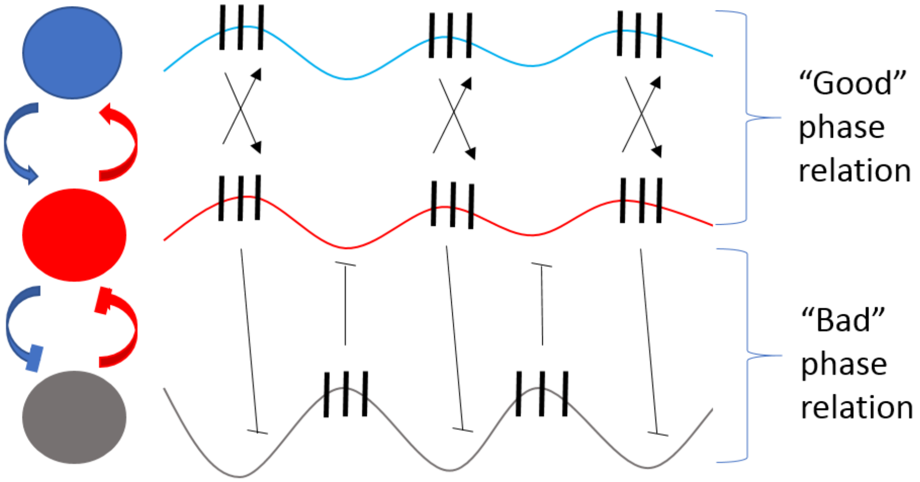

Figure 2-5: Neural coherence occurs in the temporal domain. Neural groups with differential timing of excitability such that communication can occur if spiking occurs at a period of peak excitability in coherence (shown as "Good" phase relation). Spikes that miss excitability peaks such as those between the red and gray neural groups have low communication or "bad" phase relation (Adapted from Fries, 2005).

As represented in Figure 2-5, the red and blue neural groups are undergoing high functional connectivity with one another. In contrast, the red and grey neural groups do not show synchronization and therefore do not communicate.

There are several methods to investigate phase synchrony as a mechanism of functional connectivity: phase lag index (PLI) (Stam et al., 2007), phase locking value (PLV) (Lachaux et al., 1999), and weighted phase lag index (wPLI) (Vinck et al., 2011). Other types of functional connectivity include amplitude-amplitude coherence and phase-amplitude coherence. All these concepts are discussed in more detail in Section 2.5.9.

In conclusion, there is considerable evidence that synchronized oscillatory activity is fundamental for coordination of normal brain function (Buzsáki and Draguhn, 2004).

### 2.4.5 Neural oscillations in typical and atypical development

Synchronized neural oscillations are crucial for normal brain functions, such as memory, perception and consciousness. Moreover, neural synchrony has been shown to play a key role in the development and self-organization of cortical networks (Uhlhaas et al., 2010). More specifically, it is crucial for stabilization and pruning of connections (Hebb, 1949) and an index of maturation and efficiency of cortical networks (Uhlhaas et al., 2010).

During childhood and adolescence the maturation of the neocortex involves increases in white-matter volume, due to axonal growth and myelination of cortico-cortical axons (Srinivasan, 1999). This fact implies brain changes in both structure and physiology. Srinivasan et al (1999) studied the spatial properties of dynamic processes in the neocortex using EEG and found that children showed a late maturation of long-range coupling between frontal and parietal regions (cortico-cortical connections). Uhlhaas et al. (2010) has reported that until early adolescence, developmental improvements in cognitive performance were followed by increases in neural synchrony, with a later reduction in neural synchrony during late adolescence and early adulthood. This reduction was due to decrease of gray matter volume in the frontal and parietal association cortices, as a result of “synaptic pruning”, the elimination of overproduced synapses and associated neuropil (dendrites, dendritic spines, and axon terminals) (Purves and Lichtman, 1980). Whitford et al. (2007) also suggested that during adolescence there is a reduction in the amplitude of the oscillations in the slow wave frequency bands (delta and theta bands). These findings highlight the importance of the relations between neural synchrony and brain development, and have implications for the understanding neurodevelopmental and neuropsychiatric disorders, such as autism and schizophrenia (Uhlhaas et al., 2010).

### 2.4.6 Functional brain connectivity in autism

ASD is a complex neurodevelopmental disorder and atypical brain development has been widely reported (Belmonte, 2004; Just, 2004; Maximo et al., 2014; Uhlhaas and Singer, 2007, 2010). Uhlhaas et al. (2010) hypothesized that atypical brain maturation in children with ASD during early prenatal and postnatal periods may result in altered cortical circuits that are impaired in supporting the expression of high-frequency oscillations (such as gamma) during the first years of life. Consequently, these impaired oscillations might impact the necessary temporal precision for synchronized firing patterns and as a result affect activity-dependent circuit selection during further development. Deficits in neural synchrony in ASD may involve alterations in synchronization between cortical regions (such as long-range synchronization in the beta and theta frequency ranges) and within cortical areas (local synchronization) which tend to occur at high frequencies (gamma band) (Uhlhaas and Singer, 2007).

Long before the study of functional brain connectivity in ASD at the neural synchrony level, it was studied using BOLD signals using fMRI methodology, which explored how different brain areas were communicating with each other. The first functional brain connectivity study in ASD was performed by Just and colleagues  (2004). The authors investigated performance on a sentence comprehension task and reported decreased functional connectivity among the cortical language system areas in adults with ASD which gave rise to the proposal of the "under-connectivity theory" for long range connections. This theory posits that under connected circuitry results in a deficit in information integration at neural and cognitive levels (Just et al., 2004). Subsequent fMRI studies in a variety of tasks (social-emotional, visual imagery, language, working memory, problem solving, response inhibition, theory of mind) had convergent results with the under-connectivity theory in ASD. Then, there was a boom of functional connectivity studies in ASD focusing in resting state, which also reported under-connectivity in long-range connections (Cherkassky et al., 2006; Kennedy and Courchesne, 2008). This theory of under-connectivity of Just et al. (2004) also provided a biological support for the Weak Central Cohesion (WCC) model, formulated by Frith (1989). In addition, some researchers suggested greater connectivity within local perceptual regions (short-range connectivity) in the ASD brain (Rubenstein and Merzenich, 2003) which supported the Enhanced Perceptual Functioning (EPF) model. These local connectivity networks could account for presence of  superior perceptual performance (Mottron et al., 2006).

More recently, there are reports of over-connectivity in ASD which conflict with the under-connectivity theory in ASD (Di Martino et al., 2011; Nomi and Uddin, 2015). Although methodological parameters may have contributed to these discrepancies, Uddin and colleagues proposed a developmental unifying framework to reconcile the discrepant findings in resting state studies (Uddin et al., 2013b). In this model it was suggested that hyper-connectivity was present in children less than 12 years old of age, and hypo-connectivity in adolescents and adults.

As previously mentioned functional connectivity in ASD has also been studied at the neural level, using magnetoencephalography (MEG) (for a review see O’Reilly et al., 2017). This method gives qualitatively different results from fMRI. It can provide measures of cortical and subcortical neural activity, expressed through the interaction (synchronization) of neural oscillations, importantly at different frequencies bands to which fMRI is blind. Neural synchrony is responsible for the coordination and communication among neurons underlying cognitive processes (Fries, 2005). Using MEG one can further elucidate the role of neural synchrony in the pathophysiology of autism, more specifically to demonstrate a correlation between impaired behaviour and dysfunctional neural synchrony. Atypical MEG connectivity patterns have been reported in the ASD population during a variety of different tasks and frequency bands; but no MEG study has ever used music to assess functional connectivity in children with ASD. This research could delineate frequency-specific functional networks underlying familiar and unfamiliar music processing in this population and further clarify the construct of familiarity in ASD and potentially novelty processing and repetitive behaviors.

## 2.5 Magnetoencephalography

Magnetoencephalography (MEG) is a functional neuroimaging technique developed by physicist David Cohen in 1968 at the University of Illinois (Cohen, 1968). Using a copper induction coil as the detector, Cohen recorded fluctuating magnetic fields around the head produced by the alpha-rhythms currents analogous to what was measured by conventional EEG. Aware that his first MEG recordings needed a more sensitive measurement technology, he pioneered the use of superconducting electronics for MEG measurement at the Massachusetts Institute of Technology and termed this detection system as MEG (Cohen, 1972). MEG demonstrated advantages to EEG, such as millisecond precision and better spatial resolution (Florin et al., 2017) and became important as a promising non-invasive clinical and research tool to measure brain activity.

### 2.5.1 MEG basics and instrumentation

It is technically very challenging to measure the tiny cerebral magnetic fields (10-12 femtotesla) which are orders of magnitude smaller than surrounding environmental electromagnetic noise. For this reason, MEG systems use a very sensitive magnetic field detector called a SQUID, or Superconducting Quantum Interference Device. These were developed by James Zimmerman (1970) in the late 1960s. Modern MEG systems contain 151-300 separate SQUIDs sensors which are coupled with pickup coils near the head and kept in a superconducting environment inside a dewar filled with liquid helium (4 K or -452° F).

Magnetic fields produced by the brain are 8 to 9 orders of magnitude smaller than the Earth's static magnetic field and also 2 to 4 orders smaller that the magnetic signals generated by the lungs, heart, skeletal muscles, eyes and background noise (Hämäläinen et al., 1993; Hansen et al., 2010; Lopes Da Silva, 2005).

In order to minimize electromagnetic noise from environmental and physiological sources, two strategies are implemented: (1) the MEG is built inside a multilayered magnetically shielded room and (2) each SQUID magnetometer is coupled to a flux transformer also known as gradiometer, which is close to the surface of the head and increases brain's signal-to-noise ratio (Cheyne and Papanicolaou, 2017).

There are three types of pick-up coils used in MEG systems (Figure 2-6); the basic type is a single loop pick-up coil called magnetometer, without compensation coil. This setup measures the magnetic field component perpendicular to the surface of the pick-up coil. It is very susceptible to noise but (in the absence of noise) has the highest sensitivity to sources far away, such as deep sources. The two other types are the gradiometers or flux transformers, which have a compensation coil. These two coils are arranged in an axial or planar configuration. The simplest is called a 1st order axial or radial gradiometer or 1st order planar gradiometer, depending on the MEG system. Both measure mostly the interfering signal, a spatial component of a magnetic field component rather than the field component itself. The difference between an axial and planar gradiometer is the direction of the gradient measured. The first-order axial gradiometer is sensitive to sources around the rim of the sensor and less sensitive to deep sources, while the first order planar gradiometer gives the maximum signal for sources right beneath them and is the least sensitive to deep sources.

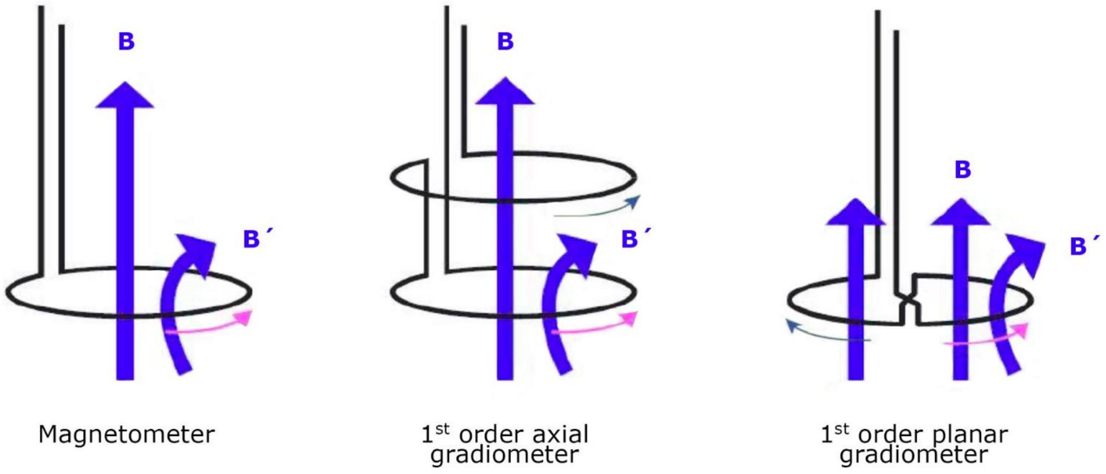

Figure 2-6: Three different pickup-coils designs for MEG systems. Magnetometer; First order axial gradiometer and first order planar gradiometer. B is uniform field (straight line); B' is uniform field (curved red line) (Adapted from Cheyne and Papanicolaou (2017).

### 2.5.2 Generation of MEG signals

The primary type of neuron that generates detectable magnetic fields is the pyramidal neuron. However, a single pyramidal cell is too weak to be detected by MEG or EEG. It needs the synchronous firing of millions of neurons (between 10,000 to 50,000), which is approximately 25 mm$^2$ of cortical sheet to produce a measurable signal (Hämäläinen et al., 1993; Hämäläinen and Hari, 2002). There are two types of neuroelectric activity: action potentials and post-synaptic potentials (PSPs). The first is unlikely to contribute to MEG signal, as the action potentials are brief spikes, difficult to sum in a synchrony. Moreover, the wave of depolarization is quickly followed by repolarization, which are two opposing current sources (Hämäläinen et al., 1993; Singh, 2006). For this reason, the magnetic induction is generated by the PSPs in the dendrites of the pyramidal neurons.

To generate a measurable signal, the apical dendrites need to be spatially aligned and synchronous. If a population of dendrites is randomly distributed, it will not generate a magnetic field as the current flow gets spread in all directions (Singh, 2006). Another fact to take into consideration is the organization of the brain. The cerebral cortex is folded forming gyri and sulci, which implies that the orientation of the neurons related to the skull influences the MEG signal acquisition. For maximum signal sensitivity sources should be in the fissures and sulcal walls which cause tangential fields that are detected by the MEG. On the other hand, sources at the top of the gyrus cause radially oriented sources which produces less detectable magnetic field (Singh, 2006) (Figure 2-7).

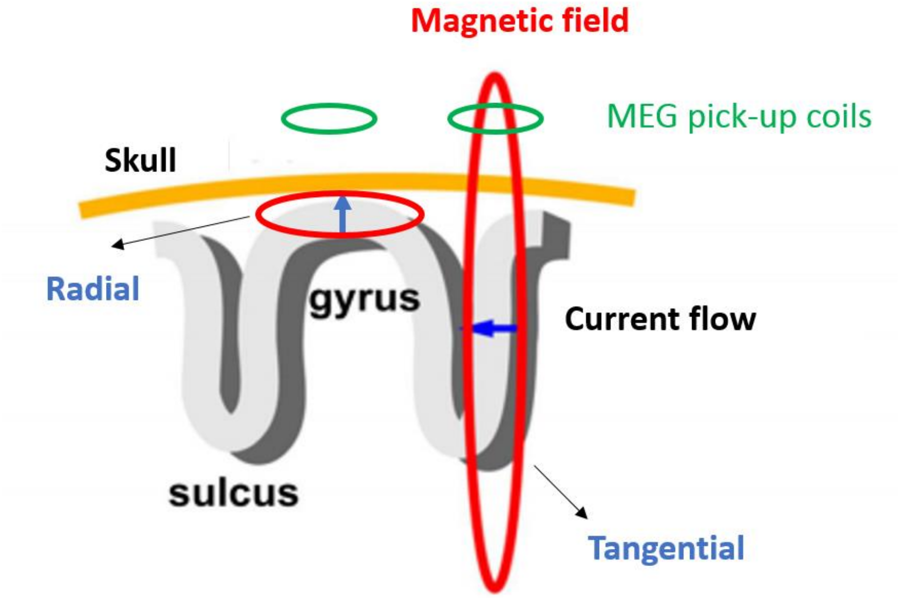

Figure 2-7: Schematic representation of a piece of cortex showing the crown of a gyrus and a sulcus. Intracellular electrical currents (blue arrows) generate magnetic fields (red rings) around apical dendrites. The magnetic field is picked up by the detection coils. Sources in the brain sulci or fissures cause tangential fields that can be readily detected by MEG and sources at the top of a gyrus cause radial fields that are less detectable by MEG coils immediately overlying the gyrus. Adapted from Tamilia et al. (2017).

### 2.5.3 Comparison between MEG and other electrophysiology and imaging methods

When we compare MEG and EEG, both are electrophysiological tools that measure direct brain activity non-invasively. While EEG is well established (with a history of over 80 years), MEG is more recent (since 1968) (Cohen, 1968). Another difference is that EEG records electric fields and can detect sources in all orientations, whilst MEG records magnetic fields (which are not influenced by tissues of different conductivities) and is most sensitive to tangentially oriented dipole sources (Hämäläinen et al., 1993). These two modalities complement each other, as MEG has a more accurate spatial localization of neural activities with the added advantage of excellent temporal resolution. In addition, MEG signals are reference free, whereas EEG relies on an electrode reference (Michel and Murray, 2012). MEG is more sensitive to superficial cortical activity due to the decay of magnetic fields as a function of distance (Singh, 2014), and MEG allows an independent assessment of the left and right hemispheric functions, even during binaural auditory stimuli. Previous EEG studies have been unable to separate the auditory-evoked responses in an accurate manner, while MEG can focus on the lateralization of the responses (Kikuchi et a., 2016).

When we compare MEG and fMRI, both are non-invasive neuroimaging modalities that measure brain activity inferred directly from magnetic fields (MEG) or indirectly through hemodynamics signals (fMRI) originated from post-synaptic currents (Hall, 2014). While MEG has a very high temporal resolution that follows the neuronal activity in the millisecond timescale, the hemodynamic blood oxygen level-dependent (BOLD) response has a timescale of a few seconds to tens of seconds. On the other hand, fMRI has a high spatial resolution while MEG is limited to a good one, on the order of a few millimetres.

### 2.5.4 Source localization, forward and inverse problems

The MEG signals produced by the magnetic fields in the head can be separated in two components: the primary current (neural currents) and the secondary or volume currents (result of macroscopic electric field) (Mosher et al., 1999; Tripp, 1983). The forward problem determines the potentials and magnetic fields that result from primary current sources, and the inverse problem estimates the location of these primary cortical current generators (Hansen et al., 2010; Tripp, 1983).

The magnetic source imaging (MSI) is the reconstruction of the current sources of the brain that arise from the recorded magnetic field. It uses mathematics and physics to determine the location, orientation and magnitude of these currents. One advantage of MSI is the absence of magnetic field distortion while propagating to the surface, as all body tissues are magnetically transparent (National Research Council; Division on Engineering and Physical Sciences; Commission on Physical Sciences, Mathematics, 1996). This makes the MEG forward problem solution straightforward, with a unique solution, as a given current configuration can only generate one possible magnetic field distribution. However, any magnetic field distribution measured at the surface of the head can be explained by an infinite number of current distributions inside the head. This fact is known as “solving the MEG inverse problem” (Singh, 2014) which does not have a unique solution (“non-uniqueness”: Singh, 2014), whereby multiple solutions of source analysis models are possible.

### 2.5.5 Forward solutions to the inverse problems

The solution for the forward problem uses models that combine realistic head geometry and conductivity distributions. There are two types of head conductor models: homogeneous spherical or multiple (overlapping, local) sphere model for each MEG detector (Huang et al., 1999). The first one, the spherical geometry has demonstrated that the radial component of the magnetic field is not affected by the volume currents, and only depends on the primary current source (Hansen et al., 2010). However, radially oriented currents do not produce magnetic field outside this head model. An alternative is the multi-sphere model, where spheres of different curvatures are fit at each individual sensor location (Hansen et al., 2010) The comparison of performance in source modeling between these two models has been variable, mostly due to different source locations. As such, there was no recommendation on the best fitting method (Lalancette et al., 2011).

To solve the inverse model, there are three common methods in MSI: discrete source modeling (Brenner et al., 1978), distributed source modeling (Hämäläinen and Ilmoniemi, 1994) and spatial filtering (Robinson, 1993).

In discrete source modeling, there are fewer number of sources (unknowns) responsible for the measurements (knowns, or sensors). A widely accepted model of this type is the equivalent current dipole (ECD) (Wheless et al., 2004) which assumes the underlying neuronal sources to be focal. ECD models can be of two types: single and multiple ECD. Both are used mostly in clinical MEG applications (e.g. localization of epileptiform activity) (Velmurugan et al., 2014).

Distributed source models divide the source space into a 3D grid containing many tiny dipoles. Each one of these dipoles represent one small brain segment. In this approach the number of unknown dipoles (sources) is greater than the number of MEG sensors causing a very underdetermined inverse solution (blurred or non-focal source images of the neuronal source distribution). This type of approach is mainly used in research studies: (a) Minimum-norm models, (b) low resolution electromagnetic tomography (LORETA) (Hämäläinen and Ilmoniemi, 1994; Hoechstetter et al., 2010; Velmurugan et al., 2014).

The last approach in MSI is the use of adaptive spatial filters, also called beamformers. These require a source and a forward model, as beamformers scan the entire source space and systematically test the prediction of the source and forward models on the observations (Hansen et al., 2010). Beamformers select weighted signals from a location of interest while attenuating signals from all other sites (Van Veen and Buckley, 1988) (Figure 2-8)

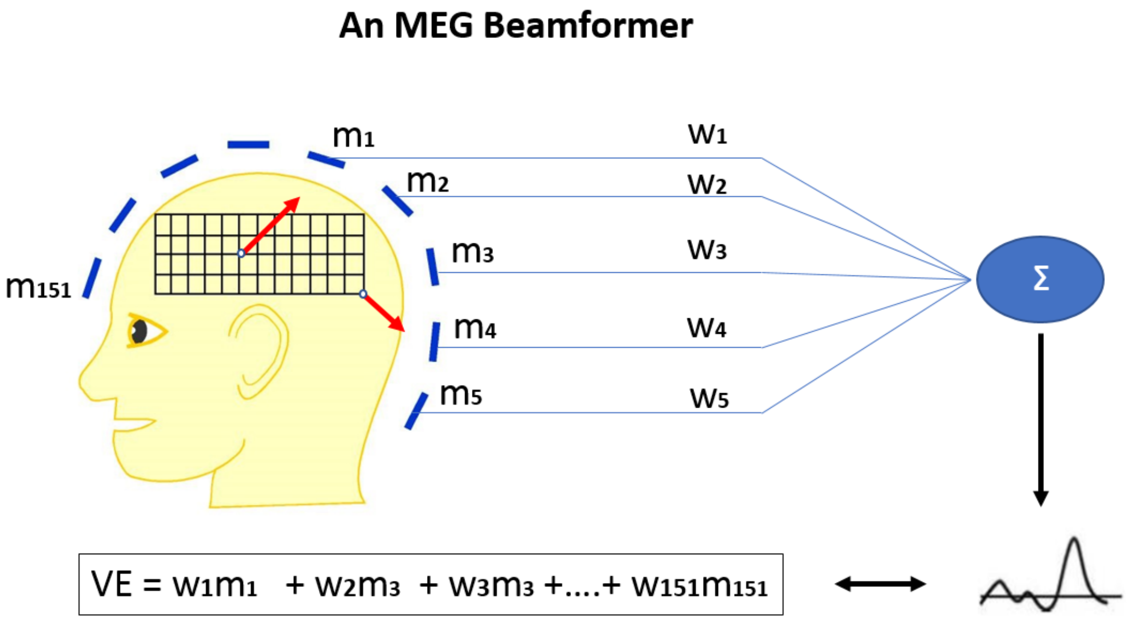

Figure 2-8: Representation of beamformer concepts in a 151 MEG system, adapted from Hillebrand and Barnes, (2005).

There are different variants of spatial filtering methods. The most popular ones are vector and scalar beamformers. The vector beamformer measures the orthogonal current sources at each voxel and the forward model and weights are multidimensional. An example of this type of beamformer is the Linearly Constrained Minimum-Variance (LCMV) beamformer (Van Veen et al., 1997). On the other hand, the scalar beamformers estimates a single optimal current direction at each voxel and the forward model and weights are one-dimensional. An example is the Synthetic Aperture Magnetometry (SAM) (Robinson and Vrba, 1999). There is also another approach called the dynamic imaging of coherent sources (DICS) which identifies the coherent brain sources at the pre-defined frequency bands (Gross et al., 2001). It should be noted that one disadvantage of spatial filters is that they cannot resolve sources with high coherence (e.g. bilateral auditory connectivity) (Van Veen et al., 1997).

### 2.5.6 Deep sources in MEG

The ability to detect and localize neuronal activity from deep gray matter structures using MEG used to be a controversial topic, with authors variously in favour of or against. There is now a large body of MEG studies from many labs demonstrating successful detection of signals from deep gray matter structures, such as thalamus, hippocampus, basal ganglia, amygdala (Attal et al., 2012; Attal and Schwartz, 2013; Cornwell et al., 2008; Garolera et al., 2007; Luo et al., 2007, 2014; Maratos et al., 2009). This procedure is possible due to optimized design parameters and methodologies still evolving. There are different factors influencing signal detection such as signal strength, the amount of brain noise background, the experimental design parameters (e.g. number of trials and subjects, use of control contrasts) and the methodology used to detect the activation (vector versus scalar beamformers) (Quraan et al., 2011). Moreover, the type of signal acquisition hardware (pick-up coils) has implications on detecting these deep sources. The MEG at the Hospital of Sick Children uses a radial (axial) gradiometer which has better noise subtraction but less sensitive to deep sources compared to magnetometers. Nevertheless, many experiments conducted at this site detected reliable activity in deep brain structures (Dunkley et al., 2014; Hung et al., 2012; Quraan et al., 2011) including studies completed in the ASD population (Bangel et al., 2014; Leung et al., 2014; Ye et al., 2014). Regarding this thesis, investigating deep structures (such as basal ganglia, thalami and hippocampi) brings the advantage of adding knowledge on altered brain connectivity in ASD children on processes mostly associated with memory, emotions and motor control in which these deep structures are implicated.

### 2.5.7 Time series techniques in MEG

A time series is a sequence of equally spaced data points in time which is used to analyze recorded brain activity. There are different time series methods which can be categorised into two classes: frequency-domain and time-domain (Mandal et al., 2018). The frequency domain, also called time frequency techniques can be divided into four groups: spectral analysis, signal complexity, signal regularity and signal predictability (Mandal et al., 2018). The most common technique for time-frequency analysis of MEG recordings is spectral analysis which decomposes the power of a signal into frequency components (Stam and van Straaten, 2012). This method is useful to determine the oscillatory components of a signal. Signal responses to sensory stimulation can be categorized as evoked (time and phase-locked to a stimulus) or induced (not locked to a stimulus) (Bullock and Achimowicz, 1994; Pantev, 1995). There is another category of oscillatory activity which does not require subjects to engage in any activity, called spontaneous or resting state activity.

There are many ways to obtain the power spectrum: the Fast Fourier Transform (FFT) converts a signal from time to frequency bands; wavelet transforms and Hilbert transforms, which are equivalent approaches, convert time-resolved power (phase) in a pre-defined frequency band to time-frequency domain (Stam and van Straaten, 2012).

### 2.5.8 Functional connectivity in MEG

The concept of functional connectivity has been introduced in section 2.4.4. Functional connectivity can be defined as the statistical dependence among measured time series from two brain regions. It can be characterized through coherence which is a measure that calculates the cross-correlation between two time series in the frequency domain (Wang et al., 2014).

MEG is the ideal modality to use for investigating the oscillatory coherence in distributed brain networks, in different frequency ranges, as it allows the measurement of electrophysiological signals on a millisecond timescale. In MEG studies, measures of coherence used to obtain an estimate of functional connectivity between two time series can be based on either phase difference or amplitude envelope of the two time series (Nunez et al., 1997). There are three possible combinations of interactions in oscillatory activity between distant brain regions: phase-phase coupling, amplitude-amplitude coupling and phase-amplitude coupling; Figure 2-9 shows examples of the first two.

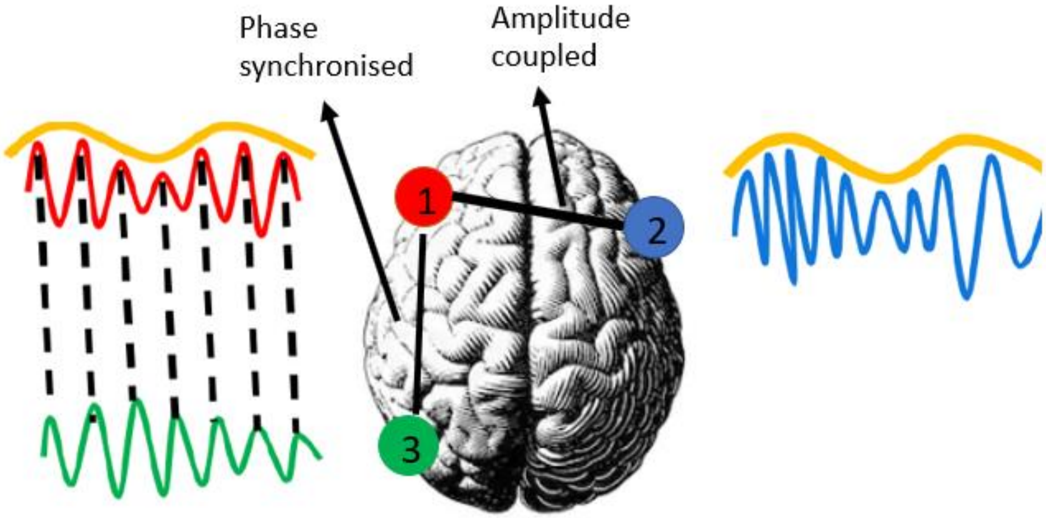

Figure 2-9: Representation of phase-phase coupling and amplitude coupling between neural sources. Sources 1 and 3 are phase synchronized (phase-phase coupling). Source 1 and 2 are synchronized in amplitude (yellow line: amplitude – amplitude coupling). Sources 2 and 3 are neither synchronized in phase nor amplitude.

### 2.5.9 Measurements of phase synchronization and amplitude

The two methods mentioned above differ in their coupling measures, frequency ranges, dynamics, functional role and cognitive significance (Engel et al., 2013). While phase synchronization occurs at fast frequencies (1-150 Hz), amplitude synchronization, also referred as amplitude envelope correlation (AEC), takes place over a slow timescale (< 0.1 Hz) ((Brookes et al., 2011b). Table 1 gives an overview of the main differences between phase-phase coupling and AEC.

Table 1: Overview of the differences between envelope and phase metrics, adapted from Engel et al. (2013)

| Feature | Amplitude Envelope | Phase |
|---|---|---|
| Coupling measures | Envelope correlation (amplitude or power correlation) | Phase coupling (coherence, imaginary coherence) |
| Typical frequency range | Below 0.1 Hz | 1 – 150 Hz |
| Dynamics | Scale-free (aperiodic) | Band-limited oscillations (slow-wave, delta, theta, alpha, beta, gamma oscillations) |
| Spatial range | From local (within regions) to large-scale (cross-regional) coupling | From local (within regions) to large-scale (cross-regional) coupling |
| Relation to structural connectivity | Close | Variable |
| State dependence | Low | High |

The third type of correlation technique is phase-amplitude coupling (PAC), also referred as cross-frequency coupling, which measures the correlation between the phase of one frequency and the amplitude of another frequency (Canolty and Knight, 2010). When the coupling occurs between the phase of slower rhythms and the amplitude of faster rhythms it has been referred as "nesting" (Siegel et al., 2012). Figure 2-10 shows a schematic of phase amplitude coupling.

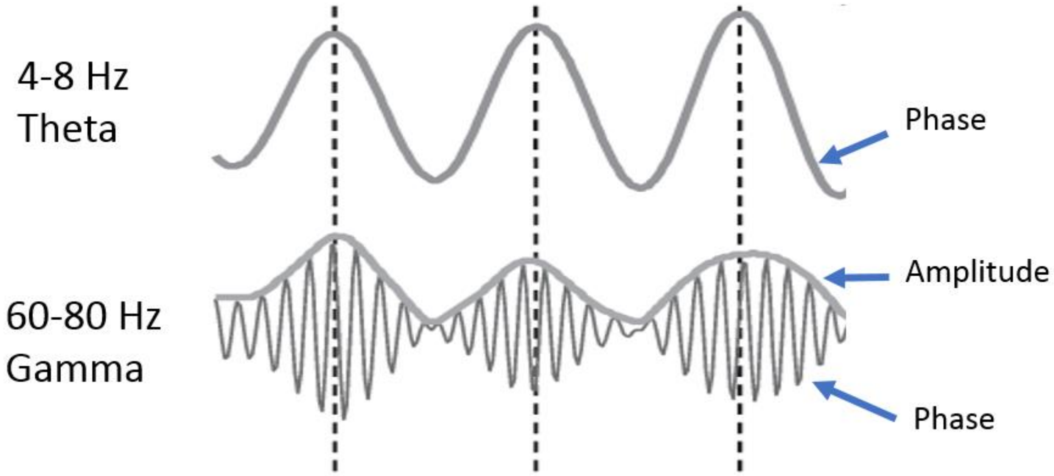

Figure 2-10: Representation of phase-amplitude coupling (PAC). In this case, the phase of a lower-frequency rhythm (the top signal) is aligned with the amplitude envelope (thick grey line) of a higher-frequency oscillation (the bottom signal). Adapted from Onslow et al., (2011).

For the purpose of this thesis, the focus will be on phase-phase and amplitude-amplitude relations.

There are several measures of phase synchrony such Phase Locking Value (PLV), Phase Lag Index (PLI), weight phase lag index (wPLI) and synchronization likelihood (SL) (Prendergast and Hymers, 2011). Although these metrics can be different in their underlying mathematics, their specific assumptions are similar, which reflect spatially separate brain areas communicating with each other.

The PLV was introduced by Lachaux et al. (1999). It calculates the absolute value of the mean phase difference between the two signals expressed as a complex unit-length vector. But this method had limitations such as overlapping lead field sensitivities, in which the same neural source could contribute to two channels. Stam et al. (2007) proposed an alternative technique, insensitive to volume conduction, but discarding true zero-phase synchrony. It was called Phase Lag Index which is a measure of the asymmetry of the distribution of instantaneous phase differences between two signals (two time series) and shows whether a consistent non-zero phase lag exists. The PLI ranges between 0 and 1. A PLI of zero indicates no coupling while a PLI of 1 reflects perfect phase synchrony. The stronger the nonzero phase locking, the larger PLI will be. Spurious connectivity results that are caused by two electrodes measuring activity from the same source will have phase lags of zero.

The wPLI is another related measure seen as an extension of the PLI. An advantage over the PLI measure, is that wPLI shows reduced sensitivity to uncorrelated noise sources. The wPLI estimates the degree of phase synchronization based on the magnitude of the imaginary component of the cross- spectrum (Lau et al., 2012; Vinck et al., 2011). By weighting each phase difference according to the magnitude of the lag, phase differences around zero only marginally contribute to the calculation of the wPLI. This method reduces the probability of detecting ‘‘false positive’’ connectivity in the case of volume conducted noise sources with near zero phase lag and increases the sensitivity in detecting phase synchronization. Weighting is achieved by using the imaginary component of the cross-spectra as a factor (Vinck et al., 2011).

Synchronization likelihood (SL) is an unbiased method of generalized phase synchronization which detects linear and non-linear relations between two signals (multivariate data sets) (Stam and Dijk, 2002).

Regarding the amplitude-amplitude coupling, the metric used is the amplitude envelope correlation (AEC) which reflects fluctuations in the envelope of spontaneous neural oscillations (Cohen, 2014) and is the correlation over time between regions.

Both measures, wPLI and AEC, offer complementary information about neural interactions and functional coupling across distinct areas of the brain (Engel et al., 2013).

### 2.5.10 Relevance of MEG research studies on children with ASD

Previous MEG studies in children with autism have focused primarily on school age-children, analyzing evoked (or induced) responses to different modalities of external stimuli (auditory, visual or somatosensory) (for review see (Kikuchi et al., 2016). Most of these studies focused on auditory-evoked responses, as with this stimulus, the participant does not need to pay attention. As such, brain responses to auditory stimuli were used as a physiological indicator group differences in brain processing in studies of language acquisition, cerebral laterality, connectivity and auditory hypersensitivity (Demopoulos et al., 2017; Oram Cardy et al., 2004, 2005, 2008; Roberts et al., 2010). These studies investigated components of the auditory-evoked field (AEF, which is an equivalent to the auditory-evoked potential (AEP) in EEG), mismatch field (MMF) or gamma oscillations. The relevance of these early MEG studies in children with ASD was adding reliable knowledge regarding bilateral brain responses and their lateralization.

More recently, investigating functional connectivity is crucial to understand underlying pathophysiology. MEG has the unique advantage of investigating the neuronal dynamics either during an explicit task or during spontaneous activity. Investigating spontaneous brain oscillations can provide information on network formation and synaptogenesis during brain development (Kikuchi et al., 2016). Also, brain connectivity studies during specific tasks can elucidate different aspects of brain dysfunction and explore if these are associated with clinical severity. For these reasons, MEG is ideal for the development of biomarkers in autism and advancement of neuroimaging methods in medicine (Uhlhaas et al., 2017).

# Chapter 3

# Aims and hypotheses

## 3.1 Thesis Aims

Familiarity in music listening and its neural correlates in typical adults have been investigated using a variety of neuroimaging techniques, yet the results are inconsistent. In addition, these correlates and respective functional connectivity related to music familiarity in typically developing children and children with ASD are unknown. The first objective of this thesis is to review and quantitatively synthesize relevant literature on the neural correlates of music familiarity and to estimate the brain areas most active when listening to familiar and unfamiliar musical excerpts using a coordinate-based meta-analyses technique of neuroimaging data. Results from this study guide our second aim, which is to investigate the effects of music familiarity in typical and atypical development in ASD, at the network level.

## 3.2 Study-specific objectives

### 3.2.1 Study 1: Neural correlates of familiarity in music listening: a systematic review and a neuroimaging meta-analysis

#### 3.2.1.1 Background and rationale

The concept of familiarity has been investigated across various scientific disciplines including, in music related fields, music psychology, musicology and music education (see **Section 2.2.2**). To date, several neuroimaging studies have attempted to investigate the brain regions involved in the processing of familiar and unfamiliar musical stimuli; however, the variety of modalities and experimental designs used have led to discrepant results and it is not clear which areas of the brain are most reliably engaged when listening to familiar and unfamiliar musical excerpts (see **Section 2.2.6**). It is known that familiarity and repetition in music listening increase the liking of a piece of music (see **Section 2.2.3**), which is a crucial factor modulating emotional and hedonic responses in the brain (see **Section 2.2.6**). Moreover, a recent study by Pereira et al. (2011) showed that familiarity with the music contributes more to the recruitment of the limbic and reward centres in the brain (see Section 2.2.6), raising the question of whether reward circuitry may be important in the processing of familiar music.

#### 3.2.1.2 Aim

The goal of this study was to systematically review the existing literature on the neural correlates of music familiarity, in healthy populations using different neuroimaging methods, and to conduct a neuroimaging meta-analysis using the activation likelihood estimation (ALE) method.

#### 3.2.1.3 Specific Hypothesis

Hypothesis: We expected to find brain areas related to emotion or reward as the most active regions when listening to familiar music, as familiarity is positively correlated with likeability and pleasure.

### 3.2.2 Study 2: Functional connectivity during a music familiarity task in children with autism

#### 3.2.2.1 Background and rationale

Atypical processing of unfamiliar but not familiar stimuli has been described in ASD (see **Section 2.3.3.1.**). Understanding processing of familiar/unfamiliar stimuli may be important in this disorder to better clarify novelty processing and potentially the domain of insistence on sameness, a diagnostic criterion of ASD. Yet, few experimental tasks have investigated the effect of familiarity across sensory modalities and at the network level.

#### 3.2.2.2 Aims

The goal of this study was to investigate the familiarity effect using familiar and unfamiliar music in children with ASD and typically developing children using MEG. This technique enabled us to study functional connectivity during familiar / unfamiliar listening and characterize the networks and frequency bands involved. The results of our study 1, guided the hypotheses for this study.

#### 3.2.2.3 Specific Hypotheses

Hypothesis 1: Listening to familiar music will enhance functional connectivity mostly in motor areas (SMA, Ventral Lateral nucleus of the thalamus) in typically developing children.

Please note, that although the original hypothesis for the thesis involved the engagement of reward circuitry during familiar music listening, the results of the systematic review suggested rather that the networks involved were motor and as such the hypothesis for study 2 was modified accordingly.

Hypothesis 2: Children with ASD will reveal atypical processing of familiar and unfamiliar songs compared to controls.

Hypothesis 3: Network connectivity in children with ASD will relate with the Repetitive Behaviours Scale Revised (RBS-R) - subscale IV (sameness) and Social Communication Questionnaire (SCQ).

4

# Chapter 4

## Neural correlates of familiarity in music listening: a systematic review and a neuroimaging meta-analysis

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Freitas, C., Manzato, E., Burini, A., Taylor, M. J., Lerch, J. P., and Anagnostou, E. (2018). Neural Correlates of Familiarity in Music Listening : A Systematic Review and a Neuroimaging. *Front. Hum. Neurosci.* 12, 1–14. doi:10.3389/fnins.2018.00686.

## 4.1 Abstract

Familiarity in music has been reported as an important factor modulating emotional and hedonic responses in the brain. Familiarity and repetition may increase the liking of a piece of music, thus inducing positive emotions. Neuroimaging studies have focused on identifying the brain regions involved in the processing of familiar and unfamiliar musical stimuli. However, the use of different modalities and experimental designs has led to discrepant results and it is not clear which areas of the brain are most reliably engaged when listening to familiar and unfamiliar musical excerpts.

In the present study, we conducted a systematic review from three databases (Medline, PsychoINFO and Embase) using the keywords (recognition OR familiar OR familiarity OR exposure effect OR repetition) AND (music OR song) AND (brain OR brains OR neuroimaging OR functional Magnetic Resonance Imaging OR Position Emission Tomography OR Electroencephalography OR Event Related Potential OR Magnetoencephalography). Of the 704 titles identified, 23 neuroimaging studies met our inclusion criteria for the systematic review. After removing studies providing insufficient information or contrasts, eleven studies (involving 212 participants) qualified for the meta-analysis using the activation likelihood estimation (ALE) approach.

Our results did not find significant peak activations consistently across included studies. Using a less conservative approach ($p < .001$, uncorrected for multiple comparisons) we found that the left superior frontal gyrus, the ventral lateral (VL) nucleus of the left thalamus, and the left medial surface of the superior frontal gyrus had the highest likelihood of being activated by familiar music. On the other hand, the left insula and the right anterior cingulate cortex had the highest likelihood of being activated by unfamiliar music. We had expected limbic structures as top clusters when listening to familiar music. But, instead, music familiarity had a motor pattern of activation. This could reflect an audio-motor synchronization to the rhythm which is more engaging for familiar tunes, and/or a sing-along response in one’s mind, anticipating melodic, harmonic progressions, rhythms, timbres and lyric events in the familiar songs. These data provide evidence for the need for larger neuroimaging studies to understand the neural correlates of music familiarity.

## 4.2 Introduction

Music is ubiquitous in human culture and has been present since prehistorical (Conard et al., 2009). Music does not appear to have a survival value, yet most of the current literature has pinpointed it as a fundamental aspect of human life, describing it as a "universal reward" (Trehub et al., 2015). People often value music for the emotions it generates (Brattico and Pearce, 2013; Juslin and Laukka, 2004) (Brattico and Pearce, 2013), and listening to music can help to regulate mood and increase well-being (Hills and Argyle, 1998; Kawakami et al., 2014). This might explain the use of music in people's everyday lives (Schäfer and Sedlmeier, 2010).

Familiarity or repeated exposure in music has been reported as an important factor modulating emotional and hedonic responses in the brain (Pereira et al., 2011). The familiarity principle, also known as the "mere exposure effect", was first described by Zajonc (1968). It is a psychological phenomenon which suggests that the more exposed we are to someone or something, the more we like it. Repetition in music can be of different types: within a piece, across pieces or across multiple hearings (Margulis, 2013). Both familiarity and repetition may increase the liking of a piece of music, thus inducing positive emotions (Omar Ali and Peynircioğlu, 2010; Witvliet and Vrana, 2007).

Long before its description in 1968, the phenomenon of familiarity had been known by social psychologists and applied to the music field (King and Prior, 2013). The first person who documented it was Meyer in 1903. He presented his subjects with a dozen repetitions of unfamiliar music that he had composed. After listening to the last repetition, most subjects asserted that "the aesthetic effect was improved by hearing the music repeatedly" (Meyer, 1903). Moreover, Meyer showed that melodies which ended on the frequency ratio symbol 2 (the Lipps-Meyer Law) was preferred to all other melodies. However, this law was later disputed by Paul Farnsworth, his student, who argued that interval ending preferences could be altered by training. Therefore, repetition and familiarity with a specific ratio ending could increase preference for that specific ending. This effect, explaining the perception of music closure, was called the "habit principle" (Farnsworth, 1926). Overall, it seems familiarity deepens the understanding of music and engagement with music listening (King and Prior, 2013).

However, according to numerous studies, the relationship between exposure and enjoyment is non-linear, following an inverted-U shape preference response. Repeated exposure to music can increase pleasure ("hedonic value") for a certain period, but ultimately gives rise to increasing displeasure (Berlyne, 1971; Jakobovits, 1966; Schellenberg, 2008; Szpunar et al., 2004).

There are different explanations for the inverted U-shape preference response. One is the perceptual fluency model (Bornstein and D'Agostino, 1994) which explains that people incorrectly assume that the facilitated processing of a familiar stimulus is associated to some positive attribute of the stimulus itself. However, as the conscious recognition of fluency processing increases, they stop misattributing this effect to the stimulus but to repeated exposure, and therefore pleasure decreases. Another explanation proposed by Berlyne (1971) states that the inverted U reflects the "interaction of two opposing impulses": the ascending part arises from an evolutionary conditioned preference for the familiar (positive learned safety effect), and the subsequent decline of the U favors for novelty seeking (aversion to boredom). Moreover, the complexity of the stimulus also influences the timescale of satiation effect. According to Szpunar et al. (2004), despite initial increases in liking, after the stimulus complexity has been absorbed, boredom intercedes, and satiation reduces likability.

Peretz et al. reported that familiarity is best conceptualized as an "implicit memory phenomenon", in which previous experience aids the performance of a task without conscious awareness of these previous episodes (Peretz et al., 1998b). The ability to recognize familiar melodies appeared to be dependent on the integrity of pitch and rhythm perception. Of these two factors, pitch is thought to play a more important role (Hébert and Peretz, 1997). The authors noted that "although the mere exposure effect is simple to define and to reproduce experimentally, it is more complicated to explain".

Familiarity is a complex subject and the neural mechanisms underlying this memory phenomenon toward music listening are still not very clear or consistent. Some authors define familiarity as a semantic memory process, which is a declarative knowledge (e.g. words, colors, faces or music) acquired over a lifetime. Musical semantic memory is defined as the long-term storage of songs or musical excerpts, which enables us to have a strong feeling of familiarity when we listen to music (Groussard et al., 2010a). Brain lesion studies showed that music semantic memory appears to involve both hemispheres; however, the integrity of the left hemisphere is critical, suggesting functional asymmetry favoring the left hemisphere for semantic memory (Platel et al., 2003). Neuroimaging studies featuring musical semantic memory have reported the involvement of the anterior part of the temporal lobes, either in the left hemisphere or bilaterally, and the activation of the left inferior frontal gyrus (Brodmann area (BA) 47) (Plailly et al., 2007). Groussard and her co-workers also found activation of the superior temporal gyri (BA 22). The right superior temporal gyrus is mostly involved in the retrieval of perceptual memory traces (information about rhythm and pitch), which are useful for deciding whether a melody is familiar or not. The left superior temporal gyrus seems to be involved in distinguishing between familiar and unfamiliar melodies (Groussard et al., 2010a). Plailly et al. (2007) also addressed the neural correlates of familiarity and its multimodal nature by studying odors and musical excerpts stimuli. These were used to investigate the feeling of familiarity and unfamiliarity. Results for the feeling of familiarity indicated a bimodal activation pattern in the left hemisphere, specifically the superior and inferior frontal gyri, the precuneus, the angular gyrus, the parahippocampal gyrus, and the hippocampus. On the other hand, the feeling of unfamiliarity (impression of novelty) of odors and music was related to the activation of the right anterior insula (Plailly et al., 2007). Janata (2009) studied the neural correlates of music-evoked autobiographical memories in healthy individuals and those with Alzheimer disease. His findings showed that familiar songs from our own past can trigger emotionally salient episodic memories and that this process is mediated by the medial prefrontal cortex (MPFC). In the same study, hearing familiar songs also activated the pre-supplementary motor area (SMA), left inferior frontal gyrus, bilateral thalamus, and the right cerebellar hemisphere (Janata, 2009).

Brain imaging studies in the neurobiology of reward during music listening demonstrated the involvement of mesolimbic striatal areas, especially the nucleus accumbens (NAcc) in the ventral striatum. This structure connects with subcortical limbic areas such as the amygdala and hippocampus, insula and anterior cingulate cortex, and is also integrated with cortical areas including the orbital cortex and ventromedial prefrontal cortex. These limbic and paralimbic structures are considered the core structures of emotional and reward processing (Koelsch, 2010;

Salimpoor et al., 2013; Zatorre and Salimpoor, 2013). Recently, Pereira et al. (2011) investigated familiarity and music preference effects in determining the emotional involvement of the listeners and showed that familiarity with the music contributed more to the recruitment of the limbic and reward centers of the brain.

Electroencephalography (EEG) is another neuroimaging technique that enabled us to address the brain's response to stimuli. It provides a real-time picture of neural activity, recording how it varies millisecond by millisecond. Time-locked EEG activity or event-related potential (ERP) are small voltages generated in the brain structures in response to specific sensory, cognitive or motor event (Luck, 2005). With regards to auditory stimuli – and, more specifically, to music listening and recognition – the N1, P200, P300, and N400 waves have been found to be particularly important. N1, a negative component found 80-110 ms after stimulus onset, is thought to represent the detection of a sound and its features, as well as detection of change of any kind (pitch, loudness, source location etc.) (Näätänen and Picton, 1987; Seppänen et al., 2012). It originates in the temporal lobe, predominantly in or near the primary auditory cortex, suggesting that it is involved in early phases of information processing (Hyde, 1997). Secondly, P2 is a positive component that arises 160-200 ms after the onset of the stimulus (Seppänen et al., 2012) and is localized in the parieto-occipital region (Rozynski and Chen, 2015). It is involved in evaluation and classification of the stimulus (Seppänen et al., 2012) as well as other related cognitive processes, such as working memory and semantic processing (Freunberger et al., 2007). P3, instead, is considered to be more related to selective attention and information processing, such as recognition and memory processes. It is traditionally divided into P3a, arising in the frontal region, and P3b, arising in the temporal and parietal regions; it appears 300-400 ms after the stimulus and lasts 300-600 ms (Patel and Azzam, 2005). However, its timing can vary widely, so it is often described as the late positive complex (LPC), a definition which also includes later deflections, such as P500 and P600 (Finnigan et al., 2002). Finally, N400 arises 200-600 ms after the stimulus, but its anatomical localization has not been well defined since it does not seem to be related to a specific mental operation only. Indeed, it seems to be connected to the processing of meaning at all levels, since it is influenced by factors acting both at lower and at higher levels of these cognitive processes (Kutas and Federmeier, 2011).

Advances in brain imaging techniques, have facilitated the examination of music familiarity processing in the human brain. Nevertheless, the use of different modalities and experimental designs has led to differing results. Over the years, studies have used varying music stimuli such as melodies, songs with and without lyrics, with diverse acoustic complexity. Due to this heterogeneity, it is not clear which areas are most reliably engaged when listening to familiar and unfamiliar songs and melodies.

To our knowledge, no systematic review or meta-analysis has been conducted to resolve the inconsistencies in the literature. The present study systematically reviews the existing literature to establish the neural correlates of music familiarity, in healthy population using different neuroimaging methods, including fMRI, PET, EEG, ERP, and MEG. Finally, we used the activation likelihood estimation (ALE) method (Eickhoff et al., 2009) to conduct a series of coordinate-based meta-analyses for fMRI and PET studies. We expected to find brain areas related to emotion or reward as the most active regions when listening to familiar music, as familiarity is positively correlated with likeability and pleasure, at least to a certain number of exposures.

## 4.3 Materials and Methods

### 4.3.1 Literature selection

Search Strategy: The search strategy was developed through consultation with the co-authors and a research librarian. The keywords used were (recognition OR familiar OR familiarity OR exposure effect OR repetition) AND (music OR song) AND (brain OR brains OR neuroimaging OR functional Magnetic Resonance Imaging OR Position Emission Tomography OR Electroencephalography OR Event Related Potential OR Magnetoencephalography). The following international electronic databases were searched on July 19th, 2016 and revised on July 11th, 2018: Medline, PsycINFO, Embase. The search was run simultaneously on these databases, using Ovid. For each study included in this review, manual searches of reference lists were conducted for additional articles. Research Ethics Board approval was not required as analysis in this study did not involve data collection.

### 4.3.2 Inclusion criteria

Articles selected for inclusion in the systematic review satisfied the following criteria: (a) published between 1996 and 2016; (b) published in English; (c) published in peer-reviewed journals; (d) study results reporting brain regions or coordinates; (e) familiar or unfamiliar music or tone listening as the primary stimulus, regardless of the genre of music and music instrument; (f) sample size to be equal or more than 10 subjects; (g) only experiments with non-clinical adult participants to eliminate potential differences in brain activation that may be associated with neurological or psychiatric illness.

For the meta-analysis the final inclusion criteria were (h) the activation foci where the contrast compared familiar music to unfamiliar music or vice versa; (i) the studies reported whole brain activity, rather than region-of-interest analysis, with complete coordinates of activation in standardized stereotaxic space (i.e., Montreal Neurological Institute [MNI] or Talairach) (Talairach and Tournoux, 1988).

Two reviewers (CF and EM) independently screened titles, abstracts and full text for relevance. Studies were included if they met the inclusion criteria. We followed the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement (Liberati et al., 2009; Moher, 2009). The flowchart of article selection is shown in Figure 4-1.

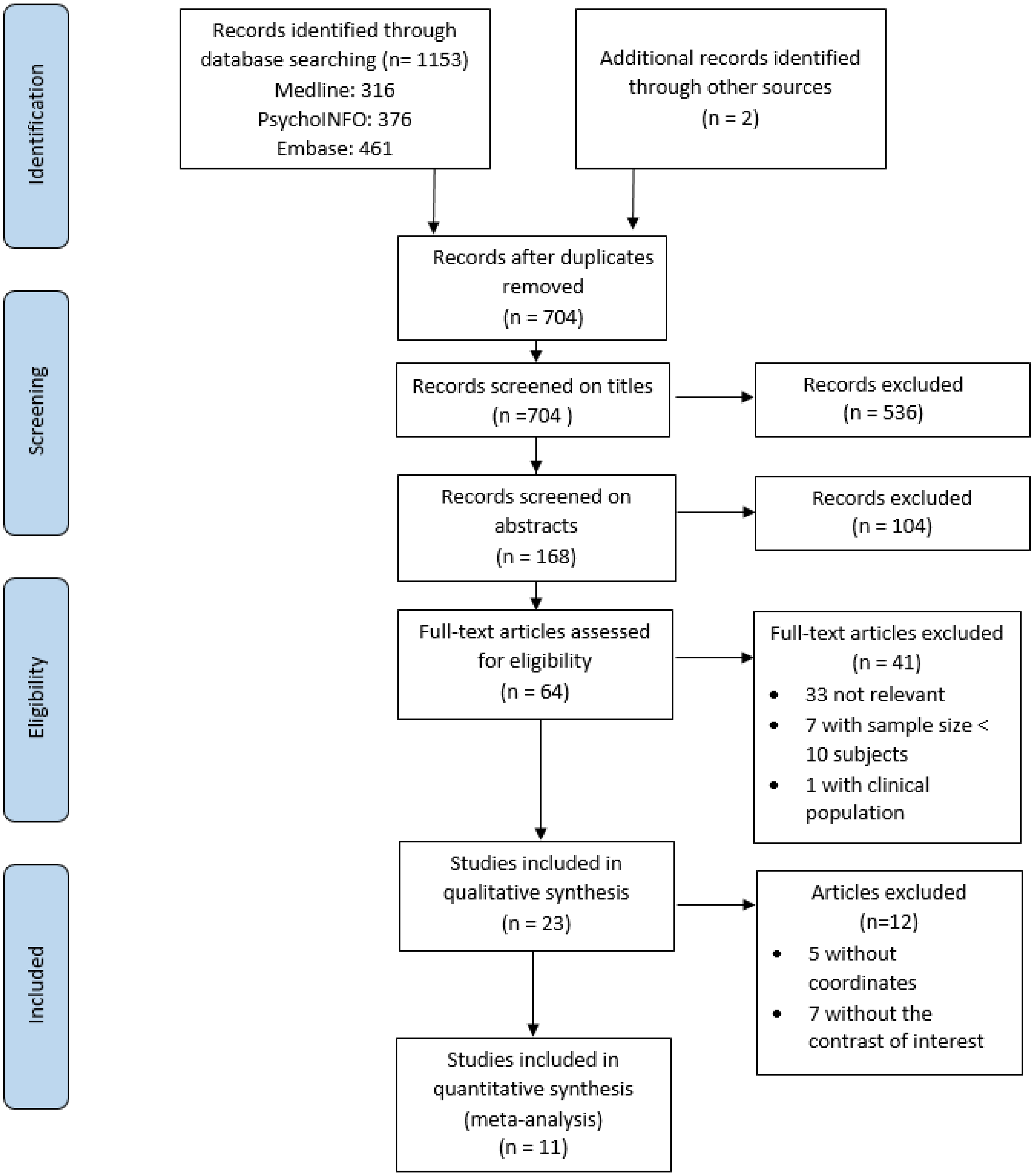

Figure 4-1: Flowchart of article selection, following PRISMA guidelines. Adapted from Moher et al. (2009)

### 4.3.3 Activation Likelihood Estimation

The meta-analysis was performed using the activation likelihood estimation (ALE) approach (Eickhoff et al., 2009; Turkeltaub et al., 2002, 2012) found in the GingerALE 2.3 software (http://brainmap.org/ale) (Lancaster et al., 2007). As most peak activations (70.0% of all foci) were specified in MNI space, we converted the remaining number of peak activations specified in Talairach space to MNI space using the Brain Map software (http://brainmap.org/icbm2tal/), which implements the Lancaster transformation prior to analysis (Laird et al., 2010). We followed the methodological guidelines described in the user manual for GingerALE 2.3.

We performed independent data-set analyses (one for each contrast), which was used to identify areas of consistent activation across all studies. In the ALE analysis, we first modelled an activation map (MA) for each experiment. These maps were created using the mask, the foci and three-dimensional Gaussian probabilities defined by the full-width at half-maximum (FWHM) values, derived from the subject size (Eickhoff et al., 2009). Subsequently, the union or summation of all MA maps from all experiments produced an ALE map that described the convergence of results at each voxel of the brain, estimating the likelihood of activation at each voxel. Then, the ALE map was compared with an empirically defined null distribution map resulting from a permutation procedure to assess statistical significance (Laird et al., 2009). Lastly, for each meta-analysis, the family-wise error (FWE) method was used to correct for multiple comparisons at a significant cluster level of threshold of $p < .05$ (cluster-forming threshold at voxel-level $p < .05$, 5000 permutations). However, no peaks survived the correction for multiple comparisons. We also performed an FDR correction which did not reach statistical significance as well. For this reason, we used $p < .001$ uncorrected for the threshold, with no minimum cluster size. The use of uncorrected p value threshold is also a valid method described in the user manual for GingerALE 2.3, along with a recommendation to choose a very conservative threshold, such as $p < .001$ or $p < .0001$. No foci were located outside the GingerALE 2.3 gray matter mask, so there were no foci excluded from analysis.

To visualize the meta-analysis results, ALE output images were overlaid onto an anatomical T1-weighted image, the Colin brain template in MNI space (Holmes et al., 1998). Mango software package version 3.2.3 (http://ric.uthscsa.edu/mango/) was used to create the region-of-interest (ROIs) identified from the ALE analyses. The final ALE scores indicated that the likelihood that any single peak of the total peaks occurred in a single voxel located in the template MRI. These ALE values ranged from .007 to a theoretical maximum of 1.0.

# 4.4 Results

## 4.4.1 Results of the literature search

### 4.4.1.1 Inclusion in the systematic review

Of the 704 titles identified, 23 neuroimaging studies met our inclusion criteria for the systematic review. These consisted of fifteen functional magnetic resonance imaging (fMRI), three positron emission tomography (PET), and five event-related potential (ERP) studies (Table 4-1). Twelve studies were not included in the meta-analysis for the following reasons: five fMRI (Groussard et al., 2010a; Herholz et al., 2012; Karmonik et al., 2016; Morrison et al., 2003; Sammler et al., 2010) and two PET (Saito et al., 2012; Satoh et al., 2006) did not include the contrast of interest; five ERP studies (Arikan et al., 1999; Chien and Chan, 2015; Daltrozzo et al., 2010; Partanen et al., 2013; Zhu et al., 2008) did not report the coordinates.

Table 4-1 - List of the 23 studies fulfilling the inclusion criteria in the systematic review

| Year | First author | No. of participants | Age (mean) | Control group | Method | Musical Training | Inclusion in the Meta-analysis or reason for exclusion |
|---|---|---|---|---|---|---|---|
| 1999 | Arikan | 10 | 31 | No | ERP | No | Excluded - without coordinates |
| 2003 | Morrison | 12 | 34.2 | Musicians vs non musicians | fMRI | Yes | Excluded - without the contrast of interest |
| 2005 | Satoh | 10 | 21.6 | No | PET | No | Excluded - without the contrast of interest |
| 2007 | Plailly | 13 | 27.2 | No | fMRI | Yes<1.5 y | Included |
| 2008 | Zhu | 15 | 23 | No | ERP | No | Excluded – without coordinates |
| 2008 | Nan | 20 | 27.3 | No | fMRI | Yes | Included |
| 2008 | Watanable | 18 | 22.4 | No | fMRI | No | Included |
| 2009 | Janata | 13 | 20.0 | No | fMRI | n.a | Included |
| 2010 | Daltrozzo | 21 | 25 | No | ERP | Yes<1.7 y | Excluded – without coordinates |
| 2009 | Klostermann | 16 | 22.4 | No | fMRI | No | Included |
| 2010 | Demorest | 16 | 28.6 | US vs Turkish | fMRI | Yes<1 y | Included |
| 2010 | Groussard | 20 | 24.5 | No | fMRI | No | Excluded - without the contrast of interest |
| 2010 | Groussard | 20 | 24.5 | No | PET | No | Included |
| 2010 | Sammler | 12 | 29 | No | fMRI | Yes <2y | Excluded – without the contrast of interest |
| 2011 | Pereira | 15 | 32 | No | fMRI | No | Included |
| 2012 | Herholz | 10 | 27 | No | fMRI | yes | Excluded – without the contrast of interest |
| 2012 | Saito | 11 | 20.8 | No | PET | No | Excluded - without the contrast of interest |
| 2013 | Partanen | 20 | 4 months | Yes | ERP | No | Excluded – without coordinates |
| 2014 | Altenmuller | 18 | 28.7 | No | fMRI | Yes | Included |
| 2015 | Sikka | 40 | 20; 71 | Young vs old | fMRI | Yes < 3y | Included |
| 2015 | Chien | 23 | 23.1 | No | ERP | No | Excluded – without coordinates |
| 2015 | Jacobsen | 32 | 28.0 | No | fMRI | Yes < 6y | Included |
| 2016 | Karmonik | 12 | n.a | No | fMRI | Yes | Excluded - without the contrast of interest |

n.a – not available; y – years.

### 4.4.1.2 Inclusion in the meta-analysis

Eleven studies (ten fMRI and one PET) involving 212 participants and 145 foci qualified for the meta-analysis using the activation likelihood estimation (ALE) approach. (Table 4-2). The imaging parameters and musical stimuli of included studies are shown in Table 4-2 and 4-3, respectively.

Table 4-2. List of the 11 studies fulfilling the inclusion criteria of the meta-analyses and its imaging parameters

| **Year** | **First author** | **Subjects (N)** | **Method** | **Field Strength** | **Imaging Sequence** | **Software** | **Blurring Kernel** | **Threshold** |
|---|---|---|---|---|---|---|---|---|
| 2007 | Plailly | 13 | fMRI | 3 T | T2* echoplanar | SPM2 | 7 mm | P < .01 uncorrected |
| 2008 | Nan | 20 | fMRI | 3 T | EPI | LIPSIA | 5.65 mm | P < .001 uncorrected |
| 2008 | Watanable | 18 | fMRI | 1.5 T | T2* echoplanar | SPM2 | 8 mm | P < .001 uncorrected |
| 2009 | Janata | 13 | fMRI | 3 T | EPI | SPM5 | 5 mm | P < .001 uncorrected |
| 2009 | Klostermann | 16 | fMRI | 4 T | EPI | SPM2 | n.a. | P < .0025 uncorrected |
| 2010 | Demorest | 16 | fMRI | 1.5 T | EPI | FSL version 4 | 5 mm | P = .05 corrected |
| 2010 | Groussard | 12 | PET | NA | 68Ga source | SPM5 | 12 mm | P < .001 uncorrected |
| 2011 | Pereira | 14 | fMRI | 1.5 T | EPI | FEAT version 5.98 | 5 mm | P = .05 corrected |
| 2014 | Altenmuller | 18 | fMRI | 3 T | T2* weighted | Brain Voyager QX | 8 mm | P < .001 uncorrected |
| 2015 | Sikka | 40 | fMRI | 3 T | EPI | SPM 10 | 8 mm | P(FWE)c of .05 |
| 2015 | Jacobsen | 32 | fMRI | 7 T | EPI | SPM 8 | n.a. | P= .001 corrected |

PET – Positron emission tomography; fMRI – functional magnetic resonance imaging: n.a. – not available; EPI – Echo planar imaging sequence.

Table 4-3. Music stimuli characterization (presence or absence of lyrics) of all 11 studies included in the ALE meta-analyses

| **Year** | **First author** | **Method** | **Sample (*N*)** | **Contrast** | **Music stimuli** | **Presence of Lyrics** |
|---|---|---|---|---|---|---|
| 2007 | Plailly | fMRI | 13 | Familiar music minus unfamiliar<br>Unfamiliar music minus familiar | Instrumental music | No |
| 2008 | Nan | fMRI | 20 | Western versus Chinese music | Melodies | No |
| 2008 | Watanable | fMRI | 18 | Hits minus CRs | Melodies | No |
| 2009 | Janata | fMRI | 13 | Familiar versus unfamiliar | Top Pop, R&B songs | Yes |
| 2009 | Klostermann | fMRI | 16 | Hits versus correct rejections | Musical clips with typical timbre and harmonies | N.A. |
| 2010 | Demorest | fMRI | 16 | Culturally unfamiliar vs culturally familiar<br>Memory for culturally unfamiliar vs memory for culturally familiar | Instrumental classic music | No |
| 2010 | Groussard | PET | 12 | Musical semantic > musical reference | Tonal melodies | No |
| 2011 | Pereira | fMRI | 14 | Familiar > unfamiliar<br>Unfamiliar > familiar | Pop-rock songs | Yes |
| 2014 | Altenmuller | fMRI | 18 | Old vs new pieces<br>New vs old pieces | Symphonic film music | No |
| 2015 | Sikka | fMRI | 40 | Familiar vs unfamiliar | Melodies from instrumental pieces | No |
| 2015 | Jacobsen | fMRI | 32 | Long-term known vs unknown | Top 10 songs from 1977-2007 | Yes |

N.A. – not available.

We identified two contrasts of interest (familiar music minus unfamiliar music and unfamiliar music minus familiar music) and we conducted separate activation likelihood estimation (ALE) meta-analyses for each contrast. Using the ALE approach, we expected to determine the core regions implicated in familiarity and unfamiliarity in music listening.

### 4.4.1.2.1 Contrast 1: familiar music minus unfamiliar music:

In total, 10 studies (Altenmüller et al., 2014; Groussard et al., 2010b; Jacobsen et al., 2015; Janata, 2009; Klostermann et al., 2009; Nan et al., 2008; Pereira et al., 2011; Plailly et al., 2007; Sikka et al., 2015; Watanabe et al., 2008a) were included. This meta-analysis was conducted on 128 activation foci involving 196 participants (Table 4-4).

Table 4-4. Types of contrasts of the 11 studies included in the meta-analyses

| **Year** | **First author** | **Method** | **Field Strength** | **Subjects (*N*)** | **Contrast** | **Number of foci** | **Type of contrast analysis** |
|---|---|---|---|---|---|---|---|
| 2007 | Plailly | fMRI | 3 T | 13 | Familiar music minus unfamiliar | 11 | 1 |
| | | | | | Unfamiliar music minus familiar | 5 | 2 |
| 2008 | Nan | fMRI | 3 T | 20 | Western versus Chinese music | 10 | 1 |
| 2008 | Watanable | fMRI | 1.5 T | 18 | Hits minus CRs | 7 | 1 |
| 2009 | Janata | fMRI | 3 T | 13 | Familiar versus unfamiliar | 28 | 1 |
| 2009 | Klostermann | fMRI | 4 T | 16 | Hits versus correct rejections | 17 | 1 |
| 2010 | Demorest | fMRI | 1.5 T | 16 | Culturally unfamiliar vs culturally familiar | 6 | 2 |
| | | | | | Memory for culturally unfamiliar vs memory for culturally familiar | 1 | 2 |
| 2010 | Groussard | PET | NA | 12 | Musical semantic > musical reference | 3 | 1 |
| 2011 | Pereira | fMRI | 1.5 T | 14 | Familiar > unfamiliar | 16 | 1 |
| | | | | | Unfamiliar > familiar | 4 | 2 |
| 2014 | Altenmuller | fMRI | 3 T | 18 | Old vs new pieces | 2 | 1 |
| | | | | | New vs old pieces | 1 | 2 |
| 2015 | Sikka | fMRI | 3 T | 40 | Familiar vs unfamiliar | 28 | 1 |
| 2015 | Jacobsen | fMRI | 7 T | 32 | Long-term known vs unknown | 6 | 1 |

PET – Positron emission tomography; fMRI – functional magnetic resonance imaging: n.a. – not available; CRs (correct rejections); 1 - contrast analysis (familiar music minus unfamiliar music); 2 - contrast analysis (unfamiliar music minus familiar music).

### 4.4.1.2.2 Contrast 2: unfamiliar music minus familiar music:

Four studies (Altenmüller et al., 2014; Demorest et al., 2010; Pereira et al., 2011; Plailly et al., 2007) with a total of 5 experiments, were included. This meta-analysis was conducted on 17 activation foci involving 61 participants (Table 4-4).

### 4.4.2 Results of the ALE Meta-Analysis

When adopting the threshold for statistical significance corrected for multiple comparisons (using FWE), we did not observe any significant activation for contrast 1 (familiar music minus unfamiliar music), or for contrast 2 (unfamiliar music minus familiar music). We then used uncorrected *P* value method, but choosing a conservative threshold, $p < .001$.

#### 4.4.2.1 Contrast 1: familiar music minus unfamiliar music:

Results of this ALE analysis yielded 37 regions with a significant likelihood (ranging from .009 to .017) of showing brain activation related to familiarity. The greatest likelihood that activation would be evoked in response to familiar music stimuli was in the left superior frontal gyrus (Brodmann area (BA) 6; ALE = .017), the ventral lateral nucleus of the left thalamus (ALE = .015), followed by the left medial frontal gyrus, commonly referred to as the medial surface of the superior frontal gyrus (BA 6; ALE = .015). A complete list of the ALE values for this study is reported in Table 4-5 and the top 3 ALE clusters are shown in Figure 4-2. The Table 4-7 in the supplementary materials displays all contributing studies to each cluster.

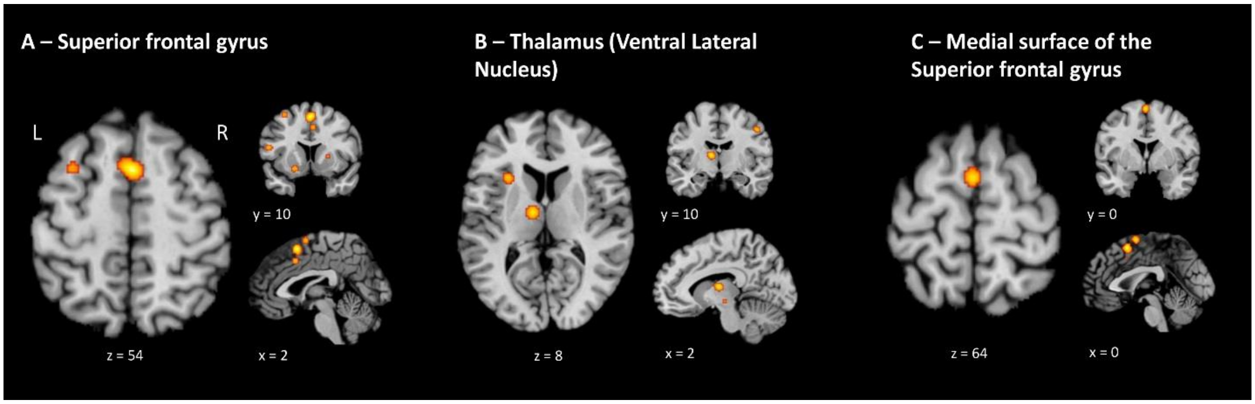

Figure 4-2: Brain areas showing greater likelihood of activation in familiar music compared to unfamiliar music. ALE maps for the familiar minus unfamiliar music contrast (p=0.001 uncorrected). The three biggest clusters were observed in the left superior frontal gyrus **(A)**, the ventral lateral nucleus of the left thalamus **(B)** and the left medial surface of the superior frontal gyrus **(C)**. Table 4-5 provides the full list of ALE peaks for this map.

Table 4-5. Spatial location and extent of ALE values for contrast 1 (familiar minus unfamiliar music)

| Cluster # | Volume (mm3) | ALE value | MNI |  |  | Side | Anatomical Region | BA | # of studies contributing to cluster |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  | *x* | *y* | *z* |  |  |  |  |
| **1** | 968 | .017 | 2 | 10 | 54 | Left | Superior Frontal Gyrus | 6 | 4/10 |
| **2** | 576 | .015 | -10 | -10 | 8 | Left | Thalamus (Ventral Lateral Nucleus) |  | 3/10 |
| **3** | 440 | .015 | 0 | 0 | 64 | Left | Medial surface of the Superior Frontal Gyrus | 6 | 2/10 |
| **4** | 424 | .012 | -52 | 10 | 14 | Left | Inferior Frontal Gyrus | 44 | 3/10 |
| **5** | 352 | .014 | -30 | 18 | 6 | Left | Claustrum |  | 2/10 |
| **6** | 336 | .012 | -52 | -42 | 24 | Left | Superior Temporal Lobe | 13 | 2/10 |
| **7** | 312 | .014 | 4 | 12 | 40 | Right | Cingulate Gyrus | 32 | 2/10 |
| **8** | 280 | .013 | -20 | 8 | -12 | Left | Lentiform Nucleus. Putamen |  | 2/10 |
| **9** | 280 | .013 | 50 | -8 | 42 | Right | Precentral Gyrus | 4 | 2/10 |
| **10** | 256 | .012 | -54 | -22 | -12 | Left | Middle Temporal Gyrus | 21 | 2/10 |
| **11** | 200 | .012 | -4 | 58 | 2 | Left | Medial Frontal Gyrus | 10 | 2/10 |
| **12** | 200 | .012 | 54 | 26 | 32 | Right | Middle Frontal Gyrus | 9 | 2/10 |
| **13** | 192 | .011 | 8 | -26 | -2 | Right | Thalamus |  | 2/10 |
| **14** | 176 | .011 | -32 | 10 | 56 | Left | Middle Frontal Gyrus | 6 | 2/10 |
| **15** | 128 | .011 | 30 | -18 | -2 | Right | Lentiform Nucleus. |  | 1/10 |
| **16** | 96 | .010 | -42 | 22 | 4 | Left | Insula | 13 | 1/10 |
| **17** | 64 | .009 | 22 | 8 | 4 | Right | Lentiform Nucleus |  | 1/10 |
| **18** | 64 | .010 | 36 | 42 | 24 | Right | Middle Frontal Gyrus | 9 | 1/10 |
| **19** | 64 | .009 | -26 | 48 | 22 | Left | Superior Frontal Gyrus | 10 | 1/10 |
| **20** | 48 | .009 | -10 | -18 | -10 | Left | Subthalamic Nucleus |  | 1/10 |
| **21** | 40 | .009 | -8 | 12 | 38 | Left | Cingulate Gyrus | 32 | 1/10 |
| **22** | 32 | .008 | 56 | -6 | -6 | Right | Superior Temporal Gyrus | 22 | 1/10 |
| **23** | 32 | .008 | -32 | -14 | -4 | Left | Lentiform Nucleus |  | 1/10 |
| **24** | 32 | .008 | 10 | -8 | 4 | Right | Thalamus |  | 1/10 |
| **25** | 32 | .009 | 46 | 20 | 24 | Right | Middle Frontal Gyrus | 9 | 1/10 |
| **26** | 32 | .008 | -50 | -6 | 46 | Left | Precentral Gyrus | 4 | 1/10 |
| **27** | 16 | .008 | 40 | 16 | -16 | Right | Extra-Nuclear | 13 | 1/10 |
| **28** | 16 | .009 | -24 | 26 | -8 | Left | Claustrum |  | 1/10 |
| **29** | 16 | .009 | -4 | -24 | 2 | Left | Thalamus |  | 1/10 |
| **30** | 16 | .009 | -46 | 6 | 4 | Left | Precentral Gyrus | 44 | 1/10 |
| **31** | 16 | .009 | -22 | 6 | 4 | Left | Lentiform Nucleus |  | 1/10 |
| **32** | 16 | .008 | -46 | 26 | 6 | Left | Inferior Frontal Gyrus | 13 | None |
| **33** | 16 | .009 | 65 | -34 | 14 | Right | Superior temporal Gyrus | 42 | 1/10 |
| **34** | 16 | .009 | -42 | 6 | 24 | Left | Precentral Gyrus | 6 | 1/10 |
| **35** | 16 | .009 | 52 | 2 | 50 | Right | Precentral Gyrus | 6 | 1/10 |
| **36** | 16 | .009 | -44 | -4 | 56 | Left | Precentral Gyrus | 6 | 1/10 |
| **37** | 8 | .009 | -22 | 52 | 22 | Left | Superior Frontal Gyrus | 10 | None |

ALE values for Study 1. ALE values refer to the likelihood of obtaining activation evoked by listening to familiar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior.

### 4.4.2.2 Contrast 2: unfamiliar music minus familiar music:

The areas with most significant likelihood of activation associated with listening to unfamiliar music were observed in the left insula (BA 13, ALE= .012); right cingulate (BA 32, ALE = .008 and BA 32, ALE = .008) and right middle frontal gyrus (BA 10, ALE = .008). All clusters are described in Table 4-6 and the top 3 ALE clusters are shown in Figure 3. Table 4-8 in the supplementary materials displays all contributing studies to each cluster.

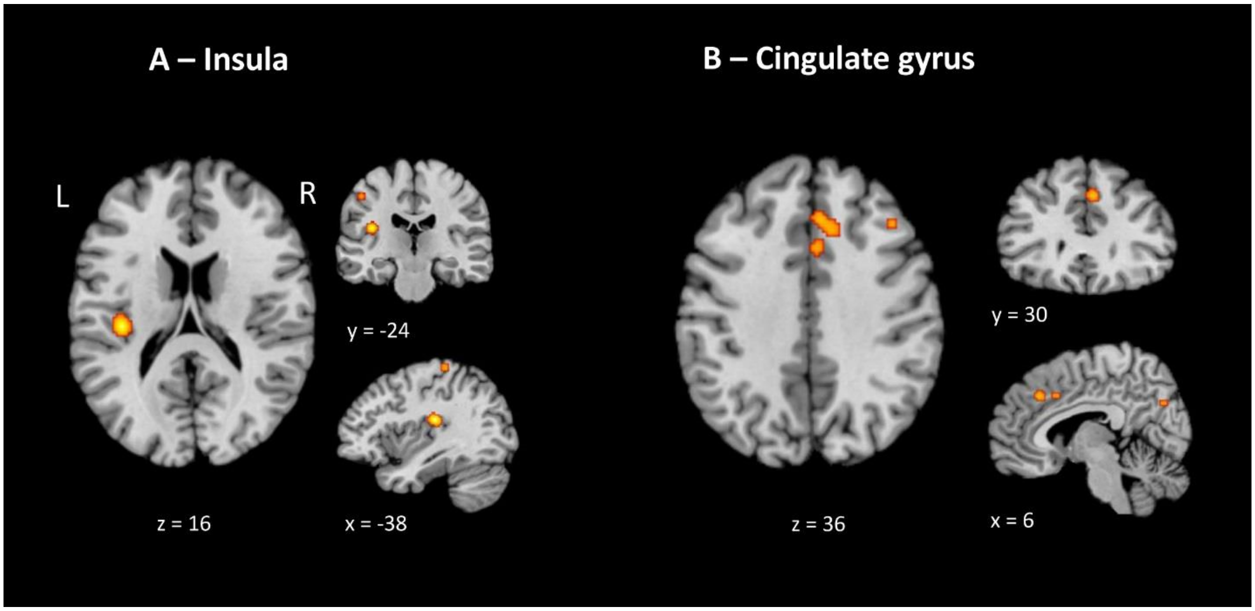

Figure 4-3: Brain areas showing greater likelihood of activation in unfamiliar music compared to familiar music. ALE maps for the unfamiliar minus familiar music contrast (p=0.001 uncorrected). The three biggest clusters were observed in the left insula **(A)** and on the right cingulate gyrus **(B).** Table 4-6 provides the full list of ALE peaks for this map.

Table 4-6. Spatial location and extent of ALE values for contrast 2 (unfamiliar minus familiar music)

| Cluster # | Volume (mm3) | ALE value | MNI | | | Side | Region | BA | # of studies contributing to cluster |
|---|---|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | | | |
| **1** | 664 | .012 | -38 | -24 | 16 | Left | Insula | 13 | 2/4 |
| **2** | 488 | .008 | 6 | 30 | 36 | Right | Cingulate Gyrus | 32 | 2/4 |
| **3** | 176 | .008 | 4 | 16 | 36 | Right | Cingulate Gyrus | 32 | ¼ |
| **4** | 160 | .008 | 38 | 58 | -10 | Right | Middle Frontal Gyrus | 10 | ¼ |
| **5** | 160 | .008 | 8 | -72 | 30 | Right | Precuneus | 31 | ¼ |
| **6** | 152 | .008 | -42 | -78 | -4 | Left | Inferior Occipital Gyrus | 19 | ¼ |
| **7** | 152 | .008 | 16 | -92 | 20 | Right | Middle Occipital Gyrus | 18 | ¼ |
| **8** | 152 | .007 | 42 | -48 | 40 | Right | Inferior Parietal Lobule | 40 | ¼ |
| **9** | 152 | .007 | -48 | -24 | 46 | Left | Postcentral Gyrus | 2 | ¼ |
| **10** | 152 | .008 | -38 | -32 | 62 | Left | Postcentral Gyrus | 40 | ¼ |
| **11** | 144 | .008 | 42 | 58 | 10 | Right | Superior Frontal Gyrus | 10 | ¼ |
| **12** | 96 | .007 | 40 | -40 | 32 | Right | Supramarginal Gyrus | 40 | ¼ |
| **13** | 80 | .007 | -28 | -18 | 56 | Left | Precentral Gyrus | 4 | ¼ |
| **14** | 64 | .007 | -21 | -75 | -47 | Left | Inferior Semi-Lunar Lobule | | ¼ |
| **15** | 64 | .007 | 41 | 27 | 35 | Right | Precentral Gyrus | 9 | ¼ |

ALE values for Study 2. ALE values refer to the likelihood of obtaining activation evoked by listening to unfamiliar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior.

### 4.4.3 Overview of ERP findings:

Our search found five ERP articles, which were published between 1999 and 2015. Regarding the first two studies, (Arikan et al., 1999) and Zhu et al.(2008), argued that hearing music of a familiar style increased the allocation of attentional resources during memory updating processes, demonstrated by an increase of P300 (P3) amplitude in frontal areas. Moreover, Zhu et al. (2008) showed a difference in N1 (negative component related to selective attention at an early stage of processing) and later positive complex (LPC; including P300 and P500) between culturally familiar and culturally unfamiliar music.

Daltrozzo et al. (2010) recorded ERPs while participants listened to highly familiar and less familiar melodies in a gating paradigm. The ERPs time-locked to a tone of the melody called the “familiarity emergence point” (defined by Dalla Bella et al. (2003) as the number of tones required for the participant to consider the stimulus as familiar) showed a larger fronto-central negativity for highly familiar compared to less familiar melodies between 200 and 500 ms, with a peak latency around 400 ms. This component was suggested to be N400, a marker of conceptual processing. Overall, this study suggested that the feeling of music familiarity could be accompanied by the processing of the concepts conveyed by emotions to, or semantic associations with, the melody.

Partanen et al. (2013) studied the neural correlates induced by prenatal music exposure using ERPs. After birth and at the age of 4 months, a modified melody was played while ERPs were recorded. Results showed that ERP amplitudes to the changed and unchanged notes of the melody were correlated with the amount of prenatal exposure, suggesting that prenatal exposure to a melody can have long-term plastic effects on the developing brain for at least four months.

Finally, Chien and Chan (2015) also concentrated on the N400 wave, but focusing on familiarity effects on the processing of the meaning of lyrics in familiar and unfamiliar songs. Surprisingly, this process is not influenced at all by familiarity, unlike what happens with normal speech. Indeed, repetition usually leads to a decreased processing of meaning (described as “semantic satiation”), but this phenomenon was not observed with song lyrics. Therefore, it would seem that normal speech and lyrics are processed differently, at least at higher levels; in other words, the presence of a melody seems to influence how words are processed.

In sum, ERP studies have suggested an increased attention in frontal brain areas, around 400ms, when listening to familiar music, and prenatal exposure to a melody can induce neural representations that last for four months. Table 4-9 in the supplementary materials summarizes the outcome measures and main findings of the ERP studies.

## 4.5 Discussion

To the best of our knowledge, this is the first systematic review and ALE meta-analysis investigating the neural correlates of familiar and unfamiliar music listening. In the following sections we will discuss our findings with respect to familiar and unfamiliar music processing proposals in the literature.

### 4.5.1 Overview of ALE meta-analysis findings (fMRI and PET studies):

#### 4.5.1.1 Meta-analysis of activation evoked by familiar music

Literature on “the mere exposure” effect has shown that prior familiarity tends to increase likeability for a stimulus. Moreover, familiarity in music has been reported as an important factor modulating emotional and hedonic responses in the brain (Pereira et al., 2011). For this reason, we expected emotion and reward brain structures to be the top clusters consistently active in the condition of listening to familiar music. To our surprise, the left superior frontal gyrus (BA 6) had the highest likelihood of being activated. This brain area has been previously implicated in the processing of musical semantic memory (Platel, 2005). It may underlie a top-down approach for intentional retrieval of prior episodes or items, selecting them from the semantic memory (Binder and Desai, 2011; Schott et al., 2005).

The ventral lateral (VL) nucleus of the left thalamus had the second highest likelihood of being active in listening to familiar music. This is a motor first-order relay nucleus, which receives input from the substantia nigra, from the internal globus pallidus, and from the contralateral cerebellum. It also has reciprocal connections with the motor and premotor cortex (Snell, 2010). Three articles (Altenmüller et al., 2014; Janata, 2009; Pereira et al., 2011) contributed to this result. It has been reported by Janata (2009) that the cerebellum is involved in music response planning. Possibly the brain prepares itself to react to music through dance and moves to the beat. Pereira et al. (2011) suggested that, like the putamen, the increased thalamic activity for familiar music could be associated with motor synchronization to the rhythms of the music excerpts, possibly reflecting top-down feedback due to anticipation of the familiar tune. Central thalamus activation seems to regulate attentional resources in task performance, even for very simple tasks, possible through continuing changes in motivation and arousal (Schiff et al., 2013).

As for cluster number 3, the left medial surface of the superior frontal gyrus, it has also been reported in two studies (Pereira et al., 2011; Sikka et al., 2015). This area (x=0: y=0; z=64) can also be labelled as supplementary motor area (SMA) and Brodmann area 6. Pereira et al. (2011) interpreted activations in the SMA by suggesting that the subjects might have mentally sung along with the familiar songs. Halpern and Zatorre (1999) and Halpern (2001) suggested that the SMA is activated during musical imagery, like a sing-along response in one's mind or by anticipating melodic, harmonic progressions, rhythms, timbres, and lyric events in the familiar songs. It is not surprising that passive listening of familiar songs can recruit motor areas of the brain. In fact, auditory and motor systems interact closely during both music perception and production. It has been previously demonstrated that the basal ganglia, cerebellum, dorsal premotor cortex, and SMA are often implicated during music listening (Chen et al., 2008b; Zatorre et al., 2007).

Nan et al. (2008) suggested that familiar music could be more appealing than unfamiliar songs and increased attention could be the reason for increased activation in motor areas. Rauschecker (2011) proposed an auditory processing model with an antero-ventral and a postero-dorsal stream. According to this hypothesis, the dorsal stream may play a role in auditory-motor transformations, and the premotor cortex and basal ganglia may be recruited when incoming sounds match expectations based on previous learned ones.

Literature on musical repetition has explored how increased motor activation can aid enjoyment. In her book, *On Repeat*, Margulis (2014) cites Bruno Nettl (1983), an ethnomusicologist who identifies musical repetition as a universal characteristic "shared across music," (p.19) and Fitch (2006), an evolutionary biologist who calls repetition a "design feature of music" (p.5). Margulis (2014) theorizes that repetition plays a special role in music. As passive music listening recruits motor areas of the brain, Margulis hypothesizes that repeated musical passages are procedurally encoded as chunked automatic sequences, activating motoric basal ganglia. This enhances a listener´s ability to automatically anticipate what notes are coming next, without attentional control. As music is repeated and encoded more and more as a fluid sequenced unit, it serves as a hook, compelling a person to execute the sequence imaginatively, without effort. The author suggests that listening to repeated music allows suppression of explicit thought and an increased sense of bodily involvement with the music. Ultimately, this gives a sense of pleasure and transcendence by participation or affiliation with the music (p.12, 67-69, 74).

The notion of musical expectation has been a central issue in music theory, cognition, and aesthetics (Huron, 2006; Huron and Margulis, 2010). Meyer (1956) postulated that expectations play an important role in emotional experiences during music listening. When listening to a musical piece, people can extract implicit, generalized knowledge of musical rules (Tillmann, 2005). This abstract knowledge, also called structural knowledge by Bharucha (1987), allows listeners to create temporal expectancies. The confirmation or violation of the expectancies influences cognitive and emotional experience. Furthermore, anticipation may also arise if one is familiar with the music, and this aspect has been labelled as veridical knowledge by Bharucha (1987).

Taking together, results from previous ERP studies and from this ALE analyses showed that frontal brain areas seemed to be important in the processing of familiar music.

Despite theories demonstrating familiarity increasing pleasure and liking, there was not much evidence that limbic engagement was modulated by familiarity in this ALE meta-analysis. One possible explanation for this is that ALE analysis is dependent on the coordinates from the original studies, the majority of them did not report limbic structures in their results. Either the music stimuli used were not highly familiar to subjects, or pleasure in music listening was not tied to explicit familiarity.

#### 4.5.1.2 Contrast 2: Meta-analysis of activation evoked by unfamiliar music

We explored common brain regions activated by unfamiliar music/tones and found a consistent pattern of activation in the left insula. The insular cortex is associated with cognitive, emotional and regulatory processing, self-awareness and evaluative judgements (Brattico and Pearce, 2013;

Menon and Uddin, 2010). The right anterior cingulate cortex (BA 32) had the second and third highest likelihood of being active to unfamiliar music stimuli. This brain area has been implicated in processing emotional salience and motivational aspects of movement (Snell, 2010). Pereira et al. (2011) states that the anterior cingulate cortex has been associated with the judgement of beauty in visual domain studies (Kawabata and Zeki, 2004; Kirk et al., 2009). Other authors, such as Copland et al. (2007) noted that the right anterior cingulate (ACC) is involved in the detection of a prime target relationship. The cingulate gyrus cortex, along with the prefrontal cortex and cuneus, has also been implicated in episodic memory processing for music (Platel, 2005; Platel et al., 2003). In the studies included in this meta-analysis the activation of the ACC might have been associated with successful detection of familiar or unfamiliar song or tones, as subjects had to decide on familiarity. According to Plailly et al. (2007) "the feeling of unfamiliarity refers to the absence of feeling of familiarity". In sum, the brain regions found to be more active when listening to unfamiliar songs may be related either with the "recognition of the songs or the detection of novelty" (Pereira et al., 2011).

### 4.5.2 Limitations and future work

Despite the novel findings of the current study, there are several shortcomings to be addressed. The first one is that our results lacked significance after correcting for multiple comparisons using FWE and FDR methods and, therefore, are based on conservative but uncorrected p values. As previously mentioned, this is still a valid method described in the GingerALE 2.3 user manual and used in (Turkeltaub et al., 2002) study. The second limitation is the small number of studies (n=11) included in this meta-analysis, limiting the statistical power and sensitivity to detect a common neural mechanism for the listening of familiar music/tones.

The third limitation is related to the statistical robustness of the original studies. Only four of the studies were corrected for multiple comparisons. All other studies reported uncorrected p values (Table 2). We are aware that lenient thresholds (such as $p < .01$; $p < .0025$ or $p < .001$ uncorrected) used in seven of the original studies would have resulted in a larger number of reported foci. In previous versions of GingerALE's methods the number of foci and their proximity of an experiment would determine a greater contribution of that experiment to an ALE map. Consequently, this would give stronger influence to less strict studies (Laird et al., 2005). In version 2.0 GingerALE switched and improved its methods. The modified ALE algorithm eliminated within-experiment effects (Turkeltaub et al., 2012) and incorporated variable uncertainty based on subject size (Eickhoff et al., 2009). As seen in table 4, the first three studies with greater number of foci included in this meta-analysis used uncorrected p values (please see table 2). These were Janata (2009), (Sikka et al., 2015), and Klostermann et al. (2009). These studies contributed with experiments only for the familiar music minus unfamiliar music contrast and did not have any influence in the meta-analysis of the unfamiliar music. The table 1 in Supplementary material displays the original studies contributing to each resulting cluster of the ALE method. Janata and Sikka et al. have undoubtedly contributed for the top results of activation evoked by familiar music, but as mentioned above, the sample size in those studies was the weighting factor in the ALE algorithm and not the number of foci.

Fourth, heterogeneity in the type of task and stimuli complexity used across studies may have played an important role in the present results as tasks both with and without lyrics were employed by the original studies. Due to the fact that there were few studies with lyrics within each contrast of interest and consequently lower statistical power, we did not perform separated ALE analyses for studies with and without lyrics. However, we explored whether the overall circuitry would be different if we removed the three studies with lyrics from the ALE analysis. The new ALE analysis eliminated the Superior Frontal Gyrus (a brain region associated with the processing of semantic memory), but the overall brain regions between the studies are highly overlapping, although the order is different. For completeness of reporting, we provide the results table in supplementary materials Table 4-10.

Finally, even though participants in the studies included in the meta-analysis were all non-musicians, half of the studies enrolled participants with musical training. It is known that musical training can change children’s brain structure (Hyde et al., 2009). Musicians, compared to non-musicians have better auditory skills, such a larger auditory working memory (Parbery-Clark et al., 2009) and enhanced auditory attention (Strait et al., 2010). Therefore, future studies need to account for stimuli complexity, presence or absence of lyrics, subject characteristics, and music expertise.

## 4.6 Conclusion

There is a large body of literature highlighting the importance of familiarity and repetition in aesthetics experiences of music. In this study, we have systematically reviewed the literature on the neural correlates of familiarity or repeated exposure of music listening in adult healthy participants. We did not find significant, consistent peak activations among included studies. We had expected limbic structures as top clusters when listening to familiar music. Using a less conservative approach we found, instead, that music familiarity and repetition had a motor pattern of activation.

The implications of this work highlight the need for further larger better-powered studies with more consideration for the nature of the music stimuli and prior music training. The understanding of the neural correlates of music familiarity has the potential to be useful for neurorehabilitation. Future studies involving clinical populations could be optimized and targeted to provide therapeutic support in patients with Alzheimer disease, Down syndrome, and those with severe verbal memory and motor deficits, and language impairments.

## 4.7 Supplementary materials

Table 4-7 – Spatial location and extent of ALE values for contrast 1 (familiar minus unfamiliar music)

| Cluster # | Volume (mm3) | ALE value | MNI *x* | *y* | *z* | Side | Region | BA | Studies contributing to cluster |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 968 | 0.017 | 2 | 10 | 54 | Left | Superior Frontal Gyrus | 6 | 1 focus from Janata<br>1 focus from Pereira et al.<br>1 focus from Sikka et al.<br>1 focus from Jacobsen et al. |
| **2** | 576 | 0.015 | -10 | -10 | 8 | Left | Thalamus (Ventral Lateral Nucleus) | | 1 focus from Janata<br>1 focus from Pereira et al.<br>1 focus from Altenmuller et al. |
| **3** | 440 | 0.015 | 0 | 0 | 64 | Left | Medial surface of Superior Frontal Gyrus | 6 | 1 focus from Pereira et al.<br>1 focus from Sikka et al. |
| **4** | 424 | 0.012 | -52 | 10 | 14 | Left | Inferior Frontal Gyrus | 44 | 1 focus from Janata<br>1 focus from Klostermann et al.<br>1 focus from Sikka et al. |
| **5** | 352 | 0.014 | -30 | 18 | 6 | Left | Claustrum | | 1 focus from Janata<br>1 focus from Jacobsen et al. |
| **6** | 336 | 0.012 | -52 | -42 | 24 | Left | Superior Temporal Lobe | 13 | 2 foci from Janata<br>1 focus from Sikka et al. |
| **7** | 312 | 0.014 | 4 | 12 | 40 | Right | Cingulate Gyrus | 32 | 1 focus from Pereira et al.<br>1 focus from Sikka et al. |
| **8** | 280 | 0.013 | -20 | 8 | -12 | Left | Lentiform Nucleus. | | 1 focus from Pereira et al.<br>1 focus from Sikka et al. |
| **9** | 280 | 0.013 | 50 | -8 | 42 | Right | Precentral Gyrus | 4 | 1 focus from Nan et al.<br>1 focus from Jacobsen et al. |
| **10** | 256 | 0.012 | -54 | -22 | -12 | Left | Middle Temporal Gyrus | 21 | 1 focus from Plailly et al.<br>1 focus from Janata |
| **11** | 200 | 0.012 | -4 | 58 | 2 | Left | Medial surface of the Superior Frontal Gyrus | 10 | 1 focus from Plailly et al.<br>1 focus from Janata |
| **12** | 200 | 0.012 | 54 | 26 | 32 | Right | Middle Frontal Gyrus | 9 | 2 foci from Janata<br>1 focus from Groussard et al. |
| **13** | 192 | 0.011 | 8 | -26 | -2 | Right | Thalamus | | 1 focus from Janata<br>1 focus from Sikka et al. |
| **14** | 176 | 0.011 | -32 | 10 | 56 | Left | Middle Frontal Gyrus | 6 | 1 focus from Plailly et al.<br>1 focus from Janata |
| **15** | 128 | 0.011 | 30 | -18 | -2 | Right | Lentiform Nucleus. | | 1 focus from Sikka et al. |
| **16** | 96 | 0.010 | -42 | 22 | 4 | Left | Insula | 13 | 1 focus from Sikka et al. |
| **17** | 64 | 0.009 | 22 | 8 | 4 | Right | Lentiform Nucleus | | 1 focus from Sikka et al. |
| **18** | 64 | 0.010 | 36 | 42 | 24 | Right | Middle Frontal Gyrus | 9 | 1 focus from Jacobsen et al. |
| **19** | 64 | 0.009 | -26 | 48 | 22 | Left | Superior Frontal Gyrus | 10 | 1 focus from Jacobsen et al. |
| **20** | 48 | 0.009 | -10 | -18 | -10 | Left | Subthalamic Nucleus | | 1 focus from Sikka et al. |
| **21** | 40 | 0.009 | -8 | 12 | 38 | Left | Cingulate Gyrus | 32 | 1 focus from Sikka et al. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **22** | 32 | 0.008 | 56 | -6 | -6 | Right | Superior Temporal Gyrus | 22 | 1 focus from Sikka et al. |
| **23** | 32 | 0.008 | -32 | -14 | -4 | Left | Lentiform Nucleus | | 1 focus from Sikka et al. |
| **24** | 32 | 0.008 | 10 | -8 | 4 | Right | Thalamus | | 1 focus from Sikka et al. |
| **25** | 32 | 0.009 | 46 | 20 | 24 | Right | Middle Frontal Gyrus | 9 | 1 focus from Sikka et al. |
| **26** | 32 | 0.008 | -50 | -6 | 46 | Left | Precentral Gyrus | 4 | 1 focus from Sikka et al. |
| **27** | 16 | 0.008 | 40 | 16 | -16 | Right | Extra-Nuclear | 13 | 1 focus from Jacobsen et al. |
| **28** | 16 | 0.009 | -24 | 26 | -8 | Left | Claustrum | | 1 focus from Sikka et al. |
| **29** | 16 | 0.009 | -4 | -24 | 2 | Left | Thalamus | | 1 focus from Sikka et al. |
| **30** | 16 | 0.009 | -46 | 6 | 4 | Left | Precentral Gyrus | 44 | 1 focus from Sikka et al. |
| **31** | 16 | 0.009 | -22 | 6 | 4 | Left | Lentiform Nucleus | | 1 focus from Sikka et al. |
| **32** | 16 | 0.008 | -46 | 26 | 6 | Left | Inferior Frontal Gyrus | 13 | None |
| **33** | 16 | 0.009 | 65 | -34 | 14 | Right | Superior temporal Gyrus | 42 | 1 focus from Sikka et al. |
| **34** | 16 | 0.009 | -42 | 6 | 24 | Left | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| **35** | 16 | 0.009 | 52 | 2 | 50 | Right | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| **36** | 16 | 0.009 | -44 | -4 | 56 | Left | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| **37** | 8 | 0.009 | -22 | 52 | 22 | Left | Superior Frontal Gyrus | 10 | None |

ALE values for Study 1. ALE values refer to the likelihood of obtaining activation evoked by listening to familiar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior.

Table 4-8 – Spatial location and extent of ALE values for contrast 2 (unfamiliar minus familiar music)

| Cluster # | Volume (mm3) | ALE value | MNI |  |  | Side | Region | BA | Studies contributing to cluster |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  | *x* | *y* | *z* |  |  |  |  |
| **1** | 664 | 0.012 | -38 | -24 | 16 | Left | Insula | 13 | 1 focus from Plailly et al.<br>1 focus from Pereira et al. |
| **2** | 488 | 0.008 | 6 | 30 | 36 | Right | Cingulate Gyrus | 32 | 1 focus from Plailly et al.<br>1 focus from Demorest et al. |
| **3** | 176 | 0.008 | 4 | 16 | 36 | Right | Cingulate Gyrus | 32 | 1 focus from Demorest et al. |
| **4** | 160 | 0.008 | 38 | 58 | -10 | Right | Middle Frontal Gyrus | 10 | 1 focus from Demorest et al. |
| **5** | 160 | 0.008 | 8 | -72 | 30 | Right | Precuneus | 31 | 1 focus from Demorest et al. |
| **6** | 152 | 0.008 | -42 | -78 | -4 | Left | Inferior Occipital Gyrus | 19 | 1 focus from Pereira et al. |
| **7** | 152 | 0.008 | 16 | -92 | 20 | Right | Middle Occipital Gyrus | 18 | 1 focus from Pereira et al. |
| **8** | 152 | 0.007 | 42 | -48 | 40 | Right | Inferior Parietal Lobule | 40 | 1 focus from Demorest et al. |
| **9** | 152 | 0.007 | -48 | -24 | 46 | Left | Postcentral Gyrus | 2 | 1 focus from Plailly et al. |
| **10** | 152 | 0.008 | -38 | -32 | 62 | Left | Postcentral Gyrus | 40 | 1 focus from Pereira et al. |
| **11** | 144 | 0.008 | 42 | 58 | 10 | Right | Superior Frontal Gyrus | 10 | 1 focus from Altenmuller et al. |
| **12** | 96 | 0.007 | 40 | -40 | 32 | Right | Supramarginal Gyrus | 40 | 1 focus from Plailly et al. |
| **13** | 80 | 0.007 | -28 | -18 | 56 | Left | Precentral Gyrus | 4 | 1 focus from Plailly et al. |
| **14** | 64 | 0.007 | -21 | -75 | -47 | Left | Inferior Semi-Lunar Lobule |  | 1 focus from Demorest et al. |
| **15** | 64 | 0.007 | 41 | 27 | 35 | Right | Precentral Gyrus | 9 | 1 focus from Demorest et al. |

ALE values for Study 2. ALE values refer to the likelihood of obtaining activation evoked by listening to unfamiliar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior.

Table 4-9 - List of the ERP studies included in the systematic review

| Year | First author | Sample size | Age (mean) | Type | Task Method | Outcome measures | Main Findings |
|---|---|---|---|---|---|---|---|
| 1999 | Arikan | 10 | 31 | Healthy | ERP | Increase of the P300 (P3) amplitude (reflection of a selective attention and memory updating process) | Hearing music of a familiar style increases allocation of attentional resources |
| 2008 | Zhu | 15 | 23 | Healthy | ERP | P300 amplitude and P500 | Greater P300 amplitude in frontal areas in a culture-familiar music environment |
| 2010 | Daltrozzo | 21 | 25 | Healthy | ERP | Familiarity emergence point | Larger fronto-central negativity N400 for highly familiar compared with less familiar melodies between 200 and 500 ms, with a peak latency around 400 msec. |
| 2013 | Partanen | 20 | 4 months | Healthy | ERP | Positive Mismatch Negativity (MMN) to changed sounds between 200 and 300 ms after stimulus onset | Prenatal exposure to a melody induces neural representations that last for four months |
| 2015 | Chien | 23 | 23.1 | Healthy | ERP | N400 did not vary with subjects' familiarity with the songs | Repetition in music did not diminish the processing of meaning in lyrics. The presence of melody seems to influence how words are processed. Normal speech and lyrics seem to be processed differently. |

Table 4-10 – Spatial location and extent of ALE values for contrast 1 (familiar minus unfamiliar music) using studies with instrumental music

| Cluster # | Volume (mm3) | ALE value | | MNI | | Side | Region | BA | Studies contributing to cluster |
|---|---|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | | | |
| 1 | 288 | .011 | -54 | 10 | 14 | Left | Inferior Frontal Gyrus | 44 | 1 focus from Klostermann et al.<br>1 focus from Sikka et al. |
| 2 | 200 | .010 | 30 | -18 | -2 | Right | Lentiform Nucleus (Lateral Globus Pallidus) | | 1 focus from Sikka et al. |
| 3 | 192 | .010 | -42 | 22 | 4 | Left | Insula | 13 | 1 focus from Watanabe et al.<br>1 focus from Sikka et al. |
| 4 | 80 | .009 | -48 | 6 | 4 | Left | Precentral Gyrus | 44 | 1 focus from Sikka et al. |
| 5 | 64 | .008 | -22 | 8 | -14 | Left | Lentiform Nucleus (Putamen) | | 1 focus from Sikka et al. |
| 6 | 64 | .008 | 56 | 12 | -14 | Left | Superior Temporal Gyrus | 22 | 1 focus from Sikka et al. |
| 7 | 64 | .009 | -10 | -18 | -10 | Left | Subthalamic nucleus | | 1 focus from Sikka et al. |
| 8 | 64 | .009 | -4 | -24 | 2 | Left | Thalamus | | 1 focus from Sikka et al. |
| 9 | 64 | .008 | 50 | 8 | 2 | Right | Precentral Gyrus | 44 | 1 focus from Sikka et al. |
| 10 | 64 | .008 | 40 | 28 | 2 | Right | Inferior Frontal Gyrus | 13 | 1 focus from Sikka et al. |
| 11 | 64 | .009 | -42 | 6 | 24 | Left | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| 12 | 64 | .009 | 46 | 20 | 24 | Right | Middle Frontal Gyrus | 9 | 1 focus from Sikka et al. |
| 13 | 64 | .009 | 52 | 2 | 50 | Right | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| 14 | 64 | .009 | -2 | 0 | 64 | Left | Medial surface of Superior Frontal Gyrus | 6 | 1 focus from Sikka et al. |
| 15 | 56 | .009 | -50 | -40 | 24 | Left | Insula | 13 | 1 focus from Sikka et al. |
| 16 | 32 | .008 | 56 | -6 | -6 | Right | Superior Temporal Gyrus | 22 | 1 focus from Sikka et al. |
| 17 | 32 | .008 | 8 | -24 | -4 | Right | Thalamus | | 1 focus from Sikka et al. |
| 18 | 32 | .008 | -32 | -14 | -4 | Left | Lentiform Nucleus (Putamen) | | 1 focus from Sikka et al. |
| 19 | 32 | .008 | 8 | -8 | 4 | Right | Thalamus (Medial Dorsal Nucleus) | | 1 focus from Sikka et al. |
| 20 | 32 | .008 | -8 | 12 | 38 | Left | Cingulate Gyrus | 32 | 1 focus from Sikka et al. |
| 21 | 32 | .008 | -50 | -6 | 46 | Left | Precentral Gyrus | 4 | 1 focus from Sikka et al. |
| 22 | 32 | .008 | -4 | 12 | 54 | Left | Medial surface of Superior Frontal Gyrus | 6 | 1 focus from Sikka et al. |
| 23 | 24 | .009 | -20 | 6 | 4 | Left | Lentiform Nucleus (Putamen) | | 1 focus from Sikka et al. |
| 24 | 16 | .009 | -24 | 26 | -8 | Left | Claustrum | | 1 focus from Sikka et al. |
| 25 | 16 | .009 | 22 | 9 | 4 | Right | Lentiform Nucleus (Putamen) | | 1 focus from Sikka et al. |
| 26 | 16 | .009 | 65 | -34 | 14 | Right | Superior Temporal Gyrus | 42 | 1 focus from Sikka et al. |
| 27 | 16 | .009 | 6 | 14 | 40 | Right | Cingulate Gyrus | 32 | 1 focus from Sikka et al. |
| 28 | 16 | .009 | -44 | -4 | 56 | Left | Precentral Gyrus | 6 | 1 focus from Sikka et al. |
| 29 | 8 | .008 | 36 | -12 | -30 | Right | Parahippocampal Gyrus (hippocampus) | | 1 focus from Watanabe et al. |

ALE values for contrast 1, using only studies with instrumental music. ALE values refer to the likelihood of obtaining activation evoked by listening to familiar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior.

# Chapter 5

# Functional connectivity during a music familiarity task in children with autism

This chapter is under review at Molecular Autism.

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## 5.1 Abstract

Background: Atypical processing of unfamiliar but less so familiar stimuli has been described in Autism Spectrum Disorder (ASD), in particular in relation to face processing. We further examined the construct of familiarity in ASD using familiar and unfamiliar songs, given that music is a stimulus that interests and motivates many children with ASD, and may have utility as a therapeutic modality.

Methods: Twenty-four children with ASD (21 males, mean age = 9.96 years ± 1.54) and 24 typically developing (TD) controls (21 males, mean age =10.17 ± 1.90) completed a music familiarity task using individually identified familiar compared to unfamiliar songs, while magnetoencephalography (MEG) was recorded. Each song was presented for 30 s. We used both amplitude envelope correlation (AEC) and the weighted phase lag index (wPLI) to assess functional connectivity between specific regions of interest (ROI) and non-ROI parcels, as well as at the whole brain level, in an effort to further understand what is preserved and what is impaired in familiar music listening in this population.

Results: Increased phase synchronization for familiar vs. unfamiliar music was noted for typically developing children in the gamma frequency. There were no significant differences within the ASD group for this comparison. During the processing of unfamiliar music, we demonstrated left lateralised increased theta and beta band connectivity in children with ASD compared to controls. An interaction effect found greater alpha band connectivity in the TD group compared to ASD to unfamiliar music only anchored in the left insula.

Conclusions: Our results revealed atypical processing of unfamiliar songs in children with ASD, consistent with previous studies in other modalities reporting that processing novelty is a challenge for ASD. Relatively typical processing of familiar stimuli may represent a strength and may be of interest to strength-based intervention planning.

Keywords: Functional connectivity, Autism spectrum disorders, Music, Familiarity processing, magnetoencephalography, neural oscillation, neural synchrony

## 5.2 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent difficulties in social interaction and social communication, and restricted, repetitive patterns of behaviours, interests and activities (American Psychiatric Association 2013).

In the first description of autism, Kanner described key features present in all of his 11 original cases of children; these were extreme aloneness, lack of interaction, inability to form close emotional ties with others and “an anxious desire for the maintenance of sameness” (Kanner, 1943). This need for sameness often presents as rigorous adherence to particular routines or rituals and resistance to change in the surroundings (such as placement of toys, bath towels). This subgroup of restricted and repetitive behaviours (RRBs) is currently referred as insistence on sameness (IS) behaviours (Bishop et al., 2013; Szatmari et al., 2006).

Both social communication and repetitive behaviour domains have been linked to novelty processing. In an interesting study, Munson et al. (2008) demonstrated that memory and preference for novelty are predictive of social and communication growth in pre-schoolers with ASD between the ages 4 and 6 ½. Furthermore, the desire for sameness and resistance to change may highlight a need for preservation and adherence to familiar environment and routines (Szatmari et al., 2006). It has been postulated that a heightened sensitivity to novel stimuli may underlie preference for sameness (Baron-Cohen and Belmonte, 2005).

The effect of familiarity has been investigated in the ASD population in only a few experimental tasks. The vast majority of these studies are on face processing, as understanding socio-emotional difficulties is relevant in this disorder. Faces are salient stimuli critical for social interaction and communication (Jack and Schyns, 2015). Atypical face recognition in the ASD population has been reported through different neuroimaging modalities, such as event-related potentials (ERPs) (Batty et al., 2011; Dawson et al., 2002; Webb et al., 2006, 2010) and fMRI (Grelotti et al., 2005; Pierce et al., 2004; Pierce and Redcay, 2008). Compared to controls, ASD individuals show face recognition impairments to the processing of unfamiliar, but not to familiar faces (Simmons et al., 2009), although some authors suggest delayed development of the processing of familiar faces (Batty et al., 2011; Webb et al., 2011). Nevertheless, unfamiliar faces have been preferred stimuli to investigate the altered emotional face processing in ASD individuals (Leung et al., 2014, 2018; Safar et al., 2018).

Music is a valuable tool to study human cognition, emotion and underlying brain networks, including familiarity (Koelsch, 2005a, 2005b). Unlike faces, music is an auditory stimulus that interests and motivates many children with ASD (Kanner, 1943). Despite a 50 year history of music therapy in autism (Reschke-Hernández, 2011) and many anecdotal reports of its importance to ASD children (Sacks, 2008), there has been only a handful of fMRI studies on songs or music processing in the ASD population. These early studies examined either emotional processing of music in adults with ASD (Caria et al., 2011; Gebauer et al., 2014) or compared music and language processing in autistic children (Lai et al., 2012; Sharda et al., 2015), given that both music and language share perceptual and neural mechanisms (Fedorenko et al., 2009; Rogalsky et al., 2011; Schön et al., 2010). These studies used different neuroimaging methods, such as fMRI, diffusion tensor imaging (DTI) or multimodal approaches, with a passive listening paradigm, but the familiarity effect was not investigated.

Even though familiar and unfamiliar songs were used separately in the above-mentioned studies, to our knowledge, there is no published neuroimaging (fMRI, magnetoencephalography; MEG) study that compared familiar and unfamiliar music listening in individuals with ASD. Understanding the neural mechanisms underlying music familiarity processing is important to understanding the neurobiological substrates of familiarity processing in ASD but also to inform therapeutics, especially given the potential impact of the construct of familiarity on both social communication and insistence on sameness.

Neuroimaging studies focusing on the processing of familiarity in music listening have been completed in healthy adults (Janata, 2009; Pereira et al., 2011; Plailly et al., 2007; Sikka et al., 2015; Watanabe et al., 2008b), in adults with Alzheimer’s disease (King et al., 2018; Yang et al., 2015) and Down syndrome (Virji-Babul et al., 2013). In our recent neuroimaging meta-analysis on familiarity in music listening in healthy adults (Freitas et al., 2018), we found that listening to familiar music demonstrated the highest likelihood of activation in left motor and premotor areas, suggesting an audio-motor synchronization to familiar tunes, anticipating music elements (melody, rhythm harmonic progression, lyrics) in one’s mind. On the other hand, unfamiliar music activated the left insula and the right anterior cingulate cortex, important structures for evaluative judgements (Brattico and Pearce, 2013), potentially deciding whether a song is familiar or novel. Surprisingly, the brain regions related to emotion and reward were not amongst the top clusters while listening to familiar songs, as we had previously expected.

In summary, familiarity and novelty processing relate to core ASD symptoms (social communication deficits and repetitive behaviours) and understanding deficits and strengths in this domain may provide insights into the nature of ASD. Understanding what is impaired and what is preserved in familiarity processing across different modalities will provide important insights for the development of therapeutic strategies in this population

With the present research we will fill the existing literature gap on music familiarity in ASD and address the following questions: i) What areas are important to familiarity music processing in typically developing children? We define familiarity as the “feeling of knowing a song”, as described in the literature. ii) Do children with autism differ from typically developing children when neurally processing the songs? If so, in which music condition and frequency bands? iii) Will atypical network connectivity relate with the insistence on sameness or social communication?

The MEG analyses of this study are guided by the results of the our previous systematic and neuroimaging meta-analysis (Freitas et al., 2018) which identified the most consistently active brain areas (nodes) when listening to familiar and unfamiliar songs. These areas include the left superior frontal gyrus, SMA, left ventral lateral nucleus of the thalamus, left insula, right cingulate, etc. We selected the top 8 nodes in each condition (familiar and unfamiliar) as our regions of interest (ROI) for connectivity analyses.

## 5.3 Methods

### 5.3.1 Participants

A total of 24 children and adolescents with ASD (21 males; range: 7 to 14 years, mean = 9.96 years ± 1.54, 20 right handed) sex-matched with 24 typically developing controls (21 males; range 7 to 14 years old, mean =10.17 ± 1.90, 20 right handed) were recruited from the Province of Ontario Neurodevelopmental Disorders (POND) Network dataset. Exclusion criteria included a history of brain injury and major psychiatric illness for children with ASD, and comorbid psychiatry disorder and first-degree family history of neurodevelopmental disorder for the control group. In addition, for both groups uncorrected vision, blindness, deafness, IQ <70 and ferromagnetic dental work or metallic implants were also exclusion factors. The study was approved by The Holland Bloorview Kids Rehabilitation Hospital and The Hospital for Sick Children Research Ethics Board in Toronto. All participants and their parents gave informed written assent and consent.

### 5.3.2 Clinical Evaluation

Participants with ASD had been diagnosed by a registered medical professional according to the DSM-5 criteria. Diagnoses were confirmed by the Autism Diagnostic Observation Schedule (ADOS-General or ADOS-2) and the Autism Diagnostic Interview- Revised (ADI-R) (Lord et al., 1994). All participants underwent cognitive testing using the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) (Wechsler, 2002). Parents were interviewed and completed the Social Communication Questionnaire (SCQ) (Rutter et al., 2003) and the Repetitive Behavior Scale Revised (RBS-R) (Lam and Aman, 2007). Participants were also asked about their musical training (if had formal musical education). Baseline demographic information and performance on cognitive/behavioural measures are presented in Table 5.1.

**Table 5.1** – Demographic, diagnostic and cognitive-behavioural assessment measures for ASD and control participants

| | **ASD**<br>**Mean ± SD (n)** | **Controls**<br>**Mean ± SD (n)** | **Test statistic** |
|---|---|---|---|
| Total N | 24 (3 female) | 24 (3 female) | |
| Male: female | 21:3 | 21:3 | |
| Age | 10..0 ± 1.5 (24) | 10.17 ± 1.90 (24) | N.S |
| ADOS2 | 6.8 ± 2.1 (20) | NA | |
| WASI-II | 98.0 ± 15. (24) | 109.0 ± 11.1 (24) | t = -2.72, df = 46, p = 0.016 |
| SCQ-L | 19.3 ± 6.3 (21) | 4.2 ± 2.9 (21) | t = 9.84, df = 40, p = 0.003 |
| RBS-R | 14.2 ± 11.6 (24) | 1.9 ± 3.7 (24) | t = 4.92, df = 46, p < 0.001 |
| Music training Yes (total N) | 8 (24) | 6 (24) | N. S |
| Pitch Discrimination | See suppl. Fig 1 | | |

ADOS-2, Autism Diagnostic Observation Schedule- Second Edition; WASI, Wechsler Abbreviated Scale if Intelligence; SCQ, Social Communication Questionnaire- Lifetime; RBS-R, Repetitive Behavior Scale Revised – subscale (Ritualistic/Sameness Behavior)

### 5.3.3 Study Design

There were two visits. In the first visit, participants were asked to bring a set of 10 familiar liked and 10 disliked songs, rating their likability using a Likert scale – ranging from 1 (least liked or most disliked) to 5 (most liked). They also completed a music questionnaire (Bhatara et al., 2013) and a pitch discrimination test (Stanutz et al.,2014) (See supplementary Figure 1). The complete list of all familiar songs used in this study is in Supplementary table 1. During the second visit they completed a hearing screening and the MEG task.

### 5.3.4 Music stimuli

Our music task paradigm was adapted from an fMRI study on music familiarity in healthy adults described by Pereira et al. (2011). Using songs that are listened to and known by the participants instead of tones increases ecological value of the experiment. After the first study visit, we selected 8 familiar most-liked songs and 8 familiar most-disliked songs for each participant from their self-selected music list. This selection was based on participants´ likability ratings: songs rated in the extreme positions of the rating scale. Then, we selected the first 30 s of each song, using Audacity 2.1.0 music software program for editing these music excerpts, due to its relevance of effectiveness on listeners' attention (Brandon Miler; Crane, 2017; Léveillé Gauvin, 2018). Subsequently, we extracted three musical features (tempo, mode and dissonance) from the 30 s excerpts, using the Matlab Toolbox for Music Information Retrieval (MIR Toolbox) (Lartillot et al., 2008) version 1.6, running on Matlab 2017b (The MathWorks Inc, Natick, MA). This program provided us with an objective measure of the musical features. Two other musical features, genre and presence or absence of lyrics, were classified by auditory inspection. We matched the familiar songs with unfamiliar ones on the following musical characteristics: tempo (slow, moderate and fast); mode (minor or major); loudness (intensity); genre (i.e. classic, pop, rock) and presence or absence of lyrics (vocal or instrumental). The unfamiliar songs were selected from a database of European music, mostly from the Eurovision Song Contest. European music was chosen as, like most North American popular music, it shares the rules and regularities of Western tonal music, but is less likely to be familiar to North-American participants. In total, for each participant 16 extracts (30 s each) of familiar songs (liked and disliked) were matched with 24 unfamiliar songs. The list of all unfamiliar songs is available in the supplementary table 2.

### 5.3.5 Choice of MEG Paradigm

The stimuli duration was 30 s consistent with other studies (Demorest et al., 2010; Janata, 2009; Pereira et al., 2011); this choice was related to the uniqueness of our question. Listening to music excerpts and recognizing if that excerpt is familiar or not is a cognitive task that requires time, especially in children. Recognition is a process that develops gradually while the melody unfolds over time (Dalla Bella et al., 2003).

### 5.3.5.1 MEG task

During the MEG task, stimuli were delivered using Presentation software (Version 18.1, Neurobehavioural Systems, Berkeley, CA). A unique set of 40 song extracts of 30 s each was prepared for each participant. Before entering the MEG scanner, each participant was trained to complete the task with familiar and unfamiliar songs not used in the task experiment. Inside the magnetically shield room, participants were positioned supine and instructed to maintain visual fixation on an X within a circle projected on the screen, situated ~70 cm from the participant's eyes. The whole task consisted of 6 runs: 2 resting state scans of 3 minutes each (before and after the music task) and 4 runs of the music task which included 10 music excerpts in each run (Fig 5-1). The songs presented were of three different conditions: familiar liked (FL), familiar disliked (FD), and unfamiliar (UF). After hearing each song extract for 30 s through MEG compatible earphones, participants responded to two questions, by pressing left (Yes) or right (No) buttons. The questions were "Do you know this song?" and "Do you like this music?" Participants were instructed to wait until the end of the 30 s before answering, to avoid MEG contamination by finger movement. Ratings took approximately 10 s each. The familiarity rating done during the scanning session was used in the analysis.  This task produced a total of 40 trials for each participant.

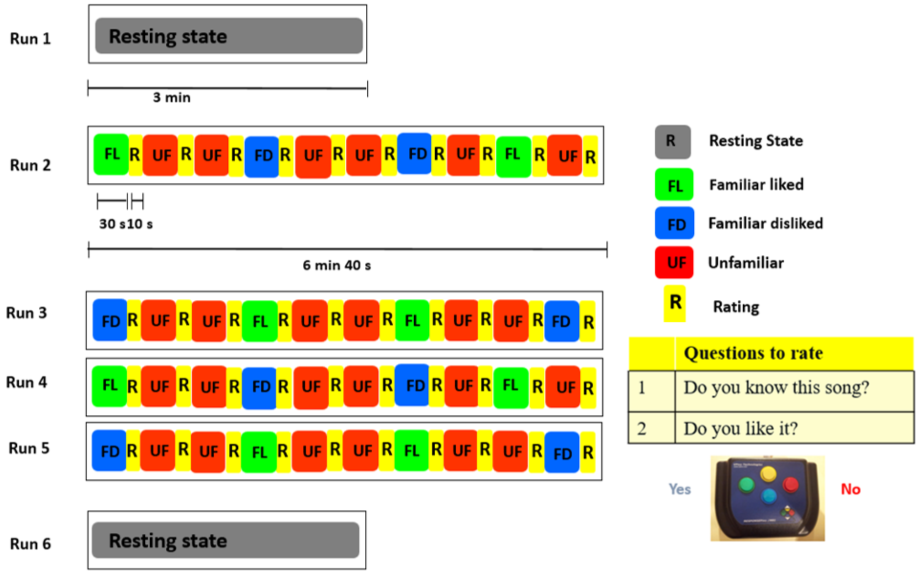

Figure 5-1: The MEG experimental paradigm.

### 5.3.6 Neuroimaging data acquisition

The MEG data were obtained using a 151-channel whole-head system with axial gradiometers (CTF MEG International Services LP Coquitlam, Canada). Data were recorded at a 600 Hz sampling rate with a band-pass filter of 1-150 Hz. Localization coils (fiducial markers) positioned at the nasion and left and right pre-auricular points were used to monitor the head position continuously during the task. Trials with greater than 10 mm of head motion were not included (Pang, 2011). The mean head displacement during the task, for the 45 minutes recording, did not differ between groups (ASD mean = 5.9 mm ± 2.6; TD mean = 4.32 mm ±1.98; $p = 0.54$). There were also no group differences in motion during the two resting state recordings (ASD mean = 2.6 mm ± 1.3; TD mean = 1.7 mm ± 1.2; $p = 0.964$ and ASD mean = 3.0 mm ± 1.4; TD mean = 2.6 mm ± 1.7; $p = 0.164$). It should be noted that while motion tolerance is typically less than 5 mm in adults and older children, 10 mm is acceptable for younger children (Bangel et al., 2014; Taylor et al., 2011; Ye et al., 2014). After the MEG session, for co-registration purposes, fiducial coils were replaced by MRI radio-opaque markers. Structural brain MRIs were obtained in all children. In five children a whole brain T1-weighted MRI sequence in a 3.0 T MR scanner (MAGNETOM Tim Trio, Siemens AG, Erlanger, Germany) with a 12-channel head coil was completed. Their brain images were obtained using a high-resolution 3D SAG MPRAGE sequence (PAT, GRAPPA =2, TR/TE/FA = 2300/2.96ms/90, FOV = 28.8 x 19.2 cm, 256x 256 matrix, 192 slices, slice thickness = 1.0 mm isotropic voxels). The remaining 43 participants were scanned using a 3.0 T MR (PrismaFIT, Siemens Healthineers, Germany) with a head and neck 20-channel coil. Images were obtained using a similar protocol but with 0.8 mm isotropic voxels.

### 5.3.7 Neuroimaging data preprocessing

Music trials were 30 s in duration and were epoched in chunks of 10 s (10+10+10) to avoid rejection of the whole trial due to head movement. This epoching convention was preserved for the all analysis. The data epochs for familiar (FL and FD) and unfamiliar (UL and UD) music conditions were selected according to participant’s responses during the MEG task. As a result of variability in each participant’s likeability ratings and the higher number of unfamiliar stimuli in the MEG paradigm, the final number of trials in each music condition differed. To be considered for data analysis, participants had to have a minimum of 3 trials in each condition (>90s of data per participant and condition). As the numbers were highly variable between liked and disliked trials, these two categories were collapsed into familiar and unfamiliar conditions. Independent Component Analysis (ICA) was used to identify the components that reflected ocular artefacts, generated by eye movement and non-ocular artefacts such as cardiac and muscle activity on a trial-by-trial basis for each participant and condition. A maximum of 60 components per participant were visually inspected and artefacts were removed (Muthukumaraswamy, 2013).

### 5.3.8 Atlas-guided source reconstruction

For MEG data processing we used the FieldTrip software toolbox (Oostenveld et al., 2011) implemented in MATLAB R2017b (The MathWorks Inc, Natick, MA). A single shell head model based on initial fiducial positions using each individual's MRI scan was constructed and normalized into standard MNI space (ICBM 152; (Fonov et al., 2009, 2011). A total of 92 source (seed) locations were then selected for time-series to be extracted and analyzed. We used the coordinates of 90 sources representing the centre of mass of all cortical and subcortical parcels in the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as well as 2 additional coordinates for the accumbens nuclei defined in the Yale BioImage Suite Package (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). All 92 seeds were projected from standard space into subject space. A linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997) was used to reconstruct broadband time series ("virtual sensors") for each source location and trial for each subject representing the activity of each of the 92 sources. Beamformers are a type of spatial filter used to estimate activity at a given brain location while suppressing activity from other locations (Van Veen et al., 1997). These broadband time series were filtered using a two-pass FIR filter into five frequency bands for further analysis: theta (4-7 Hz), alpha (8-14 Hz), beta (15-29 Hz), and gamma (30-80 Hz). The gamma frequency was split into gamma 1 (30-55 Hz) and gamma 2 (65-80Hz). A notch filter was applied at 60 Hz to remove power-line interference (Chimeno and Pallàs-Areny, 2000).

### 5.3.9 Assessing functional connectivity

To investigate functional connectivity during the music familiarity task, we used both amplitude envelope correlation (AEC; Cohen, 2014) and the weighted phase lag index (wPLI; Vinck et al., 2011) to assess connectivity amongst *a priori* defined 13 regions of interest (ROI) (from (Freitas et al., 2018) and at the whole brain level (AAL – 92 regions). The wPLI estimates the degree of phase synchronization based on the magnitude of the imaginary component of the cross-spectrum (Lau et al., 2012; Vinck et al., 2011). The amplitude envelope reflects fluctuations in the envelope of spontaneous neural oscillations (Cohen, 2014), and AEC is the correlation over time between seed regions. These two measures offer complementary information about neural interactions and functional coupling across distinct areas of the brain (Engel et al., 2013). The seed selection was based on our previous meta-analysis on the neural correlates of familiarity in music listening (Freitas et al., 2018; see Supplementary tables 3 and 4). For both ROI and whole-brain analyses, the Hilbert transform was used to obtain time series of the instantaneous phase and amplitude envelope for each source, frequency band and condition. Both AEC and wPLI were calculated within trials.

For the specified ROI analysis, both amplitude and phase-based metrics were used to assess connectivity between thirteen AAL nodes and each of the other 92 AAL nodes, representing the rest of the brain. A 92x13 adjacency matrix was created for each trial, frequency band, condition and participant. Following seed analysis, we performed a whole brain analysis, which generated a 92 x 92 adjacency matrix. In both cases, after calculating adjacency matrices, similar subsequent analyses were performed to produce baselined estimates of functional connectivity revealing task-dependent connectomic effects.

For each frequency, condition and subject, functional connectivity matrices were averaged over ‘music’ trials. This trial-average was baselined by subtracting the average of 30-second epochs of resting state recording; generating a single functional connectivity matrix per condition, frequency and subject for wPLI and AEC.

### 5.3.10 Statistical analysis of networks dynamics

The non-parametric Network-Based Statistics (NBS) method (Zalesky et al., 2010) was used for statistical comparison of amplitude and phase connectivity differences within and between-groups while controlling for family wise error rate (FWER) (Zalesky et al., 2010, 2012). This method performs multiple univariate tests (t-tests) on all 92 edges (each element of the adjacency matrix) or 92 x 13 for the ROI seed analysis. This yields a t-value for each connection in the matrix, the t-values are then thresholded by a primary component-forming threshold and those that exceeded this cut-off were identified and subject to permutation test at the network level (5000 permutation in the present study). We set the primary component forming threshold for between and within group comparisons to $t = 2.75, 3.0, 3.5$ for AEC metric and $t = 3.0$ for wPLI measures. Using this method, statistical significance was assigned at the level of the connectivity component as a whole, defining clusters of functionally integrated nodes that significantly differed between groups or conditions. Statistical correction controlling for false positives due to multiple comparisons was performed within each frequency band using Bonferroni correction ($p < 0.0125$ and $p < 0.025$ for between and within groups' differences, respectively). The results obtained using the NBS were plotted using the Brain Net Viewer toolbox (Xia et al., 2013).

### 5.3.11 Brain-behavioural analyses

We performed a correlation analysis across ASD and TD groups between mean network strength (edge weights summed for each individual subject) of significant group difference networks and the scores of the Social Communication Questionnaire (SCQ) Scores (Rutter et al., 2003), as well as the ritualistic/sameness subscale of the Repetitive Behavior Scale Revised (RBS-R) (Lam and Aman, 2007) using SPSS 25.0 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) to explore whether atypicalities seen on connectivity during familiar /unfamiliar music listening were related to core symptom domains of ASD.

## 5.4 Results

### 5.4.1 Behavioural results (table 5.1, suppl Fig 1)

### 5.4.2 MEG results

#### 5.4.2.1 Connectivity within groups: familiar vs. unfamiliar

ROI analysis: for the within-group analysis, we compared familiar to unfamiliar music for both ASD and control groups, separately, in both amplitude and phase measures. Increased phase synchronization was noted for control children in the gamma 1 frequency band for familiar music > unfamiliar music. The network comprised a total of seven edges and eight nodes ($p_{corr}$ = 0.007), involving connections in the left hemisphere among the superior and inferior opercular frontal gyri, the putamen, the middle orbital gyrus, the insula and the precuneus, and also the right middle temporal pole and the right putamen (**Figure 5-2**). There were no significant differences within the ASD group. For the opposite contrast (unfamiliar > familiar music) there were no significant differences in connectivity in either group.

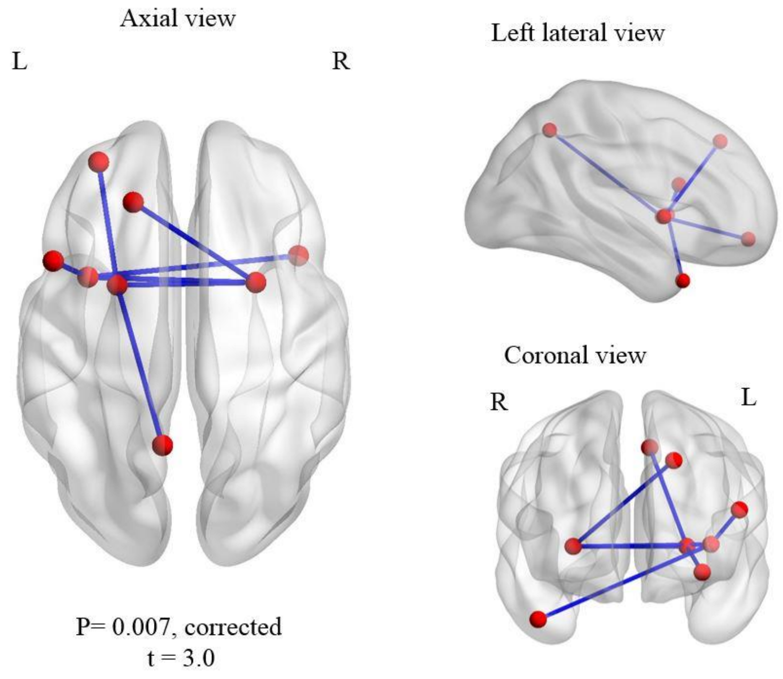

Figure 5-2: Within TD group contrast: familiar > unfamiliar music. Increased gamma 1 band (30-55 Hz) phase synchronization during processing of familiar music in TD children.

Whole-brain analysis: there were no significant differences at the whole brain level in either amplitude or wPLI metrics for all 5 frequencies bands tested for either ASD or control group, for the same contrasts.

ROI and whole brain connectivity within groups comparing the active window with the baseline for ASD and control groups, separately, for familiar and unfamiliar music conditions is reported in **Supplementary Tables 5-8**.

### 5.4.2.2 Connectivity between groups:

ROI analyses: we also conducted between-group contrasts for each frequency band and music condition (i.e., familiar and unfamiliar). A difference emerged for the processing of unfamiliar music. Specifically, children with ASD showed increased amplitude connectivity in the theta and beta frequency bands compared to controls ($p_{corr} = 0.018$ and $p_{corr} = 0.0064$, respectively). Increased theta connectivity involved four edges and six connected nodes: the right middle frontal and right post-central gyri, the left superior occipital gyrus, the left mid-cingulum and the left superior and inferior temporal gyri (**Figure 5-3 A1**). Increased beta connectivity involved six edges and seven connected nodes, all left lateralized: the superior frontal gyrus, the opercular frontal, the insula, the fusiform gyrus, the inferior parietal gyrus, the angular gyrus and the middle occipital gyrus (**Figure 5-3 A2**). No significant differences emerged for the between-group contrasts in the familiar music condition. There were no significant differences in other frequencies bands.

Whole brain analysis: We also performed between-group contrasts for each frequency band and music condition (i.e., familiar and unfamiliar) using a whole-brain analysis. Again, a difference emerged only for the processing of unfamiliar music. ASD children showed increased amplitude connectivity in the beta frequency band compared to controls ($p_{corr} = 0.010$). Increased beta connectivity involved three edges and four connected nodes, all in the left hemisphere: the opercular part of the inferior frontal gyrus, the postcentral gyrus, the fusiform gyrus and the precuneus (**Figure 5-3 B2**). No other significant differences emerged for the between-group contrasts in other frequencies bands.

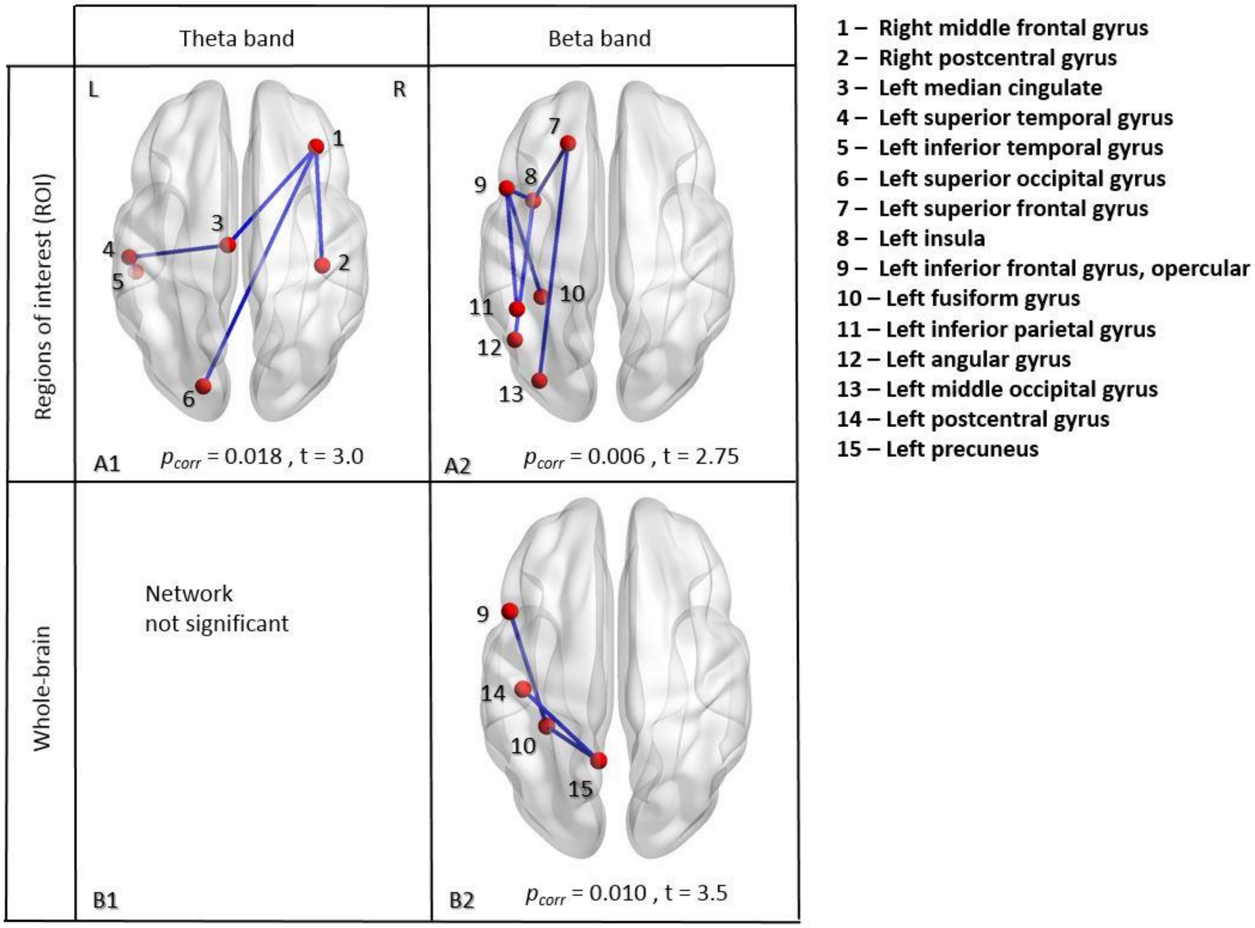

Figure 5-3: Between-group analyses. All significant results indicated increased connectivity in the ASD group compared to TD during the presentation of familiar greater than unfamiliar music, measured using amplitude envelope connectivity.

### 5.4.2.3 Interaction effects in ROI analysis:

We also explored interaction effects using a 2 (group: ASD, TD) x 2 (music condition: familiar, unfamiliar) mixed design ANOVA using NBS, in all 5 frequencies bands, using both amplitude and wPLI metrics. The primary threshold was set to F = 7. Significant results were found using the wPLI metric in the alpha frequency band. The mean network connectivity was different for ASD and TD groups depending on music familiarity (p = 0.023). The TD group had greater connectivity in the unfamiliar condition. No effect was seen in the ASD group (**Figure 5-4a**). A significant interaction for TD children is represented by a network consisting of 15 edges and 12 nodes (**Figure 5-4b**). This network was anchored in the left insula and putamen, but with nodes in both hemispheres. No significant results were found using the amplitude metric.

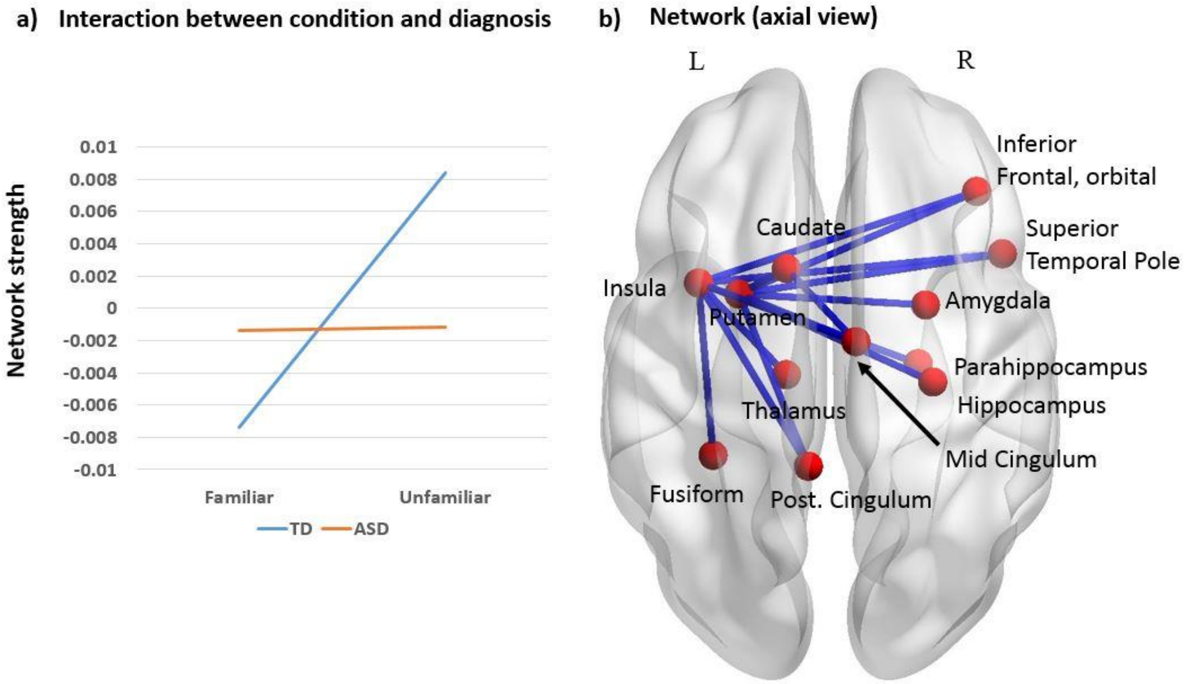

Figure 5-4: Interaction effects between music condition and group 4a); 4b – Network representing the significant interaction (p = 0.023).

### 5.4.2.4 Brain-behaviour relations:

We had 3 networks emerge from statistically significant between group differences, all in the unfamiliar music condition (network 1 = ROI _theta, network 2 = ROI_ beta, and network 3 = WB _theta). We selected global strength (average of the strengths of all nodes) of these networks as one of the simplest and most fundamental measures of brain topology assessed by graph theory. First, we correlated these network connectivity strengths with the ADOS calibrated severity score within the ASD group, but did not find any significant correlations (network 1: r = 0.008, p = 0.975; network 2: r = 0.334, p = 0.191; and network 3: r = 0.147, p = 0.574; uncorrected). We also explored if RBS-R-subscale IV (sameness) scores in ASD participants were correlated with network connectivity strength, but no significant results were found in any of the three networks (network 1: r = -0.037, p=0.889; network 2: r = 0.031, p=0.906 and network 3: r = -0.307, p=0.230). Lastly, no significant correlations were noted between SCQ and RBS and network connectivity strength within either group (Supplementary Table 9).

## 5.5 Discussion

In this study, we examined the neural correlates of the processing of familiarity in music listening in typically developing and autistic children using MEG, at the macro-scale level to fill an existing literature gap. For this, we performed a connectivity analyses within and between groups using wPLI and AEC measures, at both ROI and whole-brain level. In the following sections we will discuss our findings with respect to these two groups.

### Typically developing children

We demonstrated increased gamma phase synchronization in typically developing children for familiar music > unfamiliar music. Listening to familiar music increased phase connectivity in a network that consisted of frontal, parietal, temporal and subcortical areas. The function of these regions has been associated with expressive language (the left inferior opercular frontal gyrus), memory (left superior frontal gyrus), emotional processing (right temporal pole and left insula) (Olson et al., 2007), mental imagery, memory recollection, information integration, and visuo-spatial imagery (precuneus) (Cavanna and Trimble, 2006). The motor areas activated here (i.e., the left and right putamen and left caudate) can reflect auditory-motor synchronization to music elements (Chen et al., 2008b; Freitas et al., 2018). More specifically, Grahn (2009) has demonstrated that basal ganglia are crucial for rhythm processing, as their role seem to be linked to internal generation of the beat. It is not surprising that auditory areas were not included in our network, as the sound was delivered bilaterally, and was equated for familiar and unfamiliar stimuli, so in the contrasts no auditory cortex effects would be expected.  Our resulting network for control children was very similar to the results of music familiarity processing in the typical adult neuroimaging meta-analysis (Freitas et al., 2018). This was consistent with our strategy of selecting ROIs based on top clusters of the meta-analysis.

Our connectivity findings in the TD group were found in gamma band frequency only. The gamma band oscillations (30-100Hz) have been shown to be correlated with various cognitive processes (Engel et al., 2001), the most prominent of which is memory (encoding and performance) (Sederberg et al., 2003) and perceptual binding (Rodriguez et al., 1999). As recognizing a familiar song involves linking and integrating memory processes with auditory percepts, our results align with this explanation that gamma synchrony mediates the coupling of functionally specialised regions involved in music listening.

### Children with ASD

In the children with ASD there were no differences in the MEG metrics between the processing of familiar and unfamiliar music. However, between ASD and TD groups our results demonstrated consistent, significant differences in the unfamiliar music condition at both ROI and whole-brain analyses, assessed by amplitude envelopes (AEC). ASD children showed increased connectivity compared to controls, while the processing of familiar music was similar in the two groups.

This is the first neuroimaging study focusing on understanding familiarity in music in the ASD population; thus, there is no comparative study available. Nevertheless, neuroimaging literature on the processing of familiarity in faces in ASD individuals has shown atypicalities. It has been suggested  that there may be impaired processing of unfamiliar faces, with no deficit or delayed development of familiar faces (Simmons et al., 2009).  Pierce and Redcay (2008) reported a selective deficit in fusiform function in response to adult stranger faces, but no atypicalities in the fusiform in response to familiar faces. One possible explanation for this finding was either reduced or enhanced attention or motivation to attend unfamiliar and familiar faces, respectively. Our findings of atypical processing of unfamiliar music in ASD children could be consistent with this interpretation. Our task (listening to songs for 30 s and deciding if familiar or not) required sustained attention. In addition, repetition increases perceptual fluency (Alter and Oppenheimer, 2009; Joye et al., 2016), or the ease of processing stimuli. As such, we could interpret that unfamiliar songs would require more effort to process. As an example, Pernet et al. (2003) demonstrated in the visual recognition domain using ERPs that the more familiar an object is, fewer cognitive resources are required. Another interpretation is that ASD children showed reduced neural adaptation-like effects (also referred as habituation or repetition suppression) to unfamiliar music. Neural adaptation is defined by decreasing sensitivity to a consistently presented stimulus, whereby the sensory system codes for the derivative or change in the stimulus, priming the individual for changes in the environment: for example, no longer being consciously aware of clothes on the skin over time. In ASD neural adaptation is attenuated in sensory domains, at multiple levels in time and space, from short time scales to long, and multiple sensory pathways, from the level of neurons, through to the macroscopic BOLD signal, with reduced cortical adaptation effects to sensory stimuli (Noel et al., 2017; Turi et al., 2015), including the auditory domain (Millin et al., 2018). In other words, the ASD brain processes novelty differently compared with the typical brain, driven by maladaptive neural adaptation and deficits in the dynamic range of neural responsiveness.

Another consideration is whether music training would have affected familiarity processing. Dalla Bella et al. (2003) reported that music training affects familiarity judgements, and musicians recognize familiar songs in fewer notes than non-musicians. However, our participants did not show group differences in music training (Table 1) or pitch discrimination abilities (an ability correlated with music training) (Supplementary Figure 1), meaning that this was not a selection bias that could be a potential confounding factor.

In this study the differences in the unfamiliar condition in ASD compared to controls were in theta and beta frequencies. Theta oscillations are associated with long-range communication between brain areas implicated in various cognitive processes, such as imitation, language acquisition, working memory, attention, cognitive control, emotional arousal and fear conditioning (Engel and Fries, 2010; Kikuchi et al., 2015). Consistent with the existing literature, these theta-band dependent alterations were identified across nodes involving long distance connections that comprise large-scale networks, integrating and coordinating information between frontal, parietal and occipital brain regions. Synchrony in beta oscillations has also been found in long-range cortical interactions related to sensorimotor function, primary-motor integration and switching from the ‘status quo’ (Engel and Fries, 2010; Siegel et al., 2012). We found increased beta band synchrony in frontal-temporal, fronto-occipital and parieto-temporal connections with a left lateralization. More specifically, both networks (see Figure 2A and 2B) included part of the Broca´s area, the pars opercularis of the inferior frontal gyrus (IFG; Brodmann area 44). This area is a component of the motor articulatory network involved in speech production, phonological (Snell, 2010) and semantic processing (Roskies et al., 2001). Moreover, the pars opercularis has been found to be one of the human mirror neurons regions. It is active in motor imagery, imitation and action observation of distal hand and mouth actions (Rajmohan and Mohandas, 2007). Listening to songs requires processing verbal (lyrics) and musical (tunes) components, as well as motor preparation to sing along, dance or tap to the beat. One interpretation could be that children with ASD compared to controls showed impaired processing of these left-brain functions when listening to unknown songs. Many fMRI studies have reported that ASD individuals lack left lateralization in structure and function of brain areas involved in language (Boddaert et al., 2003; Knaus et al., 2010; Nielsen et al., 2014) which can support this interpretation.

Our findings of differences in theta and beta frequencies are of particular interest in the context of music processing.  Previous MEG studies in the auditory domain have implicated theta as well as beta-band activity in the detection of pitch changes (Florin et al., 2017). Also, theta oscillations are important for temporal integration and for the detection of sounds (Florin et al., 2017; Ng et al., 2012). One potential explanation could be that children with ASD would have atypical processing of pitch compared to TD children, even though we did not find behavioural differences between groups in pitch discrimination ability. In addition, beta band is implicated in motor functions, and motor atypicalities have been previously reported in individuals with ASD (Buard et al., 2018; Fournier et al., 2010; Williams et al., 2004), implicating the mµ and beta rhythms during a fine motor imitation task in ASD adolescents. Listening to music is a sensorimotor experience in which we recognize a pulse of a rhythm pattern and naturally synchronize to that beat (through foot tapping or clapping). One could hypothesize that ASD children lack typical motor synchronization and entrainment to unfamiliar songs, but this requires further investigation.

Between group differences results in theta and beta bands were seen in amplitude envelope connectivity. This measure which correlates fluctuations in regional neuronal activity is much slower than wPLI, and networks defined by AEC closely align with resting state networks seen with the blood oxygenation-dependent (BOLD) signal in fMRI (Biswal et al., 1995; Brookes et al., 2011a). The slow timescale (< 0.1 Hz) of AEC can provide new insights of local signal power that regulates the activation of neural populations underlying large scale cortical interactions (Siegel et al., 2012).

When we explored the interaction between familiarity and groups, comparing the effects of connectivity (network strength) in familiar versus unfamiliar music in ASD versus TD children (using phase synchronization), we saw a pattern of increased connectivity strength in the unfamiliar condition compared to familiar stimuli in TD in the alpha frequency, but no effects in the ASD group. The resulting network is important for processing music familiarity in TD and comprises nodes of the limbic system, anchored in the left insula and putamen, and including the right amygdala, parahippocampus, hippocampus, mid and post cingulum, motor areas (caudate and putamen) and fusiform gyrus, often linked with face processing. The insulae are important in processing stimuli which are salient, related to the salience network, and atypical insular function has been reported in ASD (Uddin et al., 2013a). The fact that the main hub of this network was the left insula suggests that for the TD children, the familiar songs had far more salience for them, capturing their attention, but that this was not the case for the children with ASD. This is also consistent with the work by Odriozola et al. (2016), who showed that for faces the right insula activity was atypical in ASD.

It was also not surprising to find brain areas related to face processing in this interaction network when processing music familiarity, as recognizing a song also implies recognizing the singer´s voice. There is emerging evidence showing that when we hear a familiar voice, even without seeing the face, our visual face processing brain areas become active (Blank et al., 2011; Kriegstein et al., 2005; Von Kriegstein and Giraud, 2006). This cross-modal activation is fast, automatic and well supported by neural circuits, which have been shaped by multisensory stimuli. For example, in an MEG study with typically adults, Schall et al. (2013) investigated early auditory processing of familiar voices and showed that it is facilitated by visual mechanisms.

Alpha phase synchronization, as reported in our interaction effect, has been implicated in visual perception in TD individuals (Freunberger et al., 2008; Palva and Palva, 2011) and also plays a key role in cognitive functions, coordinating neuronal processing (Palva and Palva, 2007, 2011). The effect we see here in TD but not in ASD children suggests that individuals in this group process novel songs differently due to deficits in neural adaptation-like effects.

Lastly the lack of association between differences in connectivity and measures of core symptom domains is somewhat disappointing. This may be partially explained by the fact that processing of familiar stimuli was relatively preserved and as such unlikely to be associated with down-stream behavioral effects. The choice of measures may not be best suited to capture potential associations or there may exist domain specific effects (e.g. auditory vs visual).

## Limitations

There are some potential limitations of the present study. The first one relates to the sample size. Forty eight participants (24 per group) is a relatively small sample, although aligned with previous MEG studies in autistic children (Gandal et al., 2010; Roberts et al., 2011; Safar et al., 2018; Yuk et al., 2018). The second limitation is that our clinical and control groups were not matched on IQ (Table1), which was significantly lower in our clinical group yet still in the average range.

Another limitation is the exclusion of the cerebellum from our analysis plan due to technical and methodological reasons. The cerebellum is important for sensorimotor, cognitive and emotional processing (Buckner, 2013) and plays a key role in rhythm and timing processes (Nozaradan et al., 2017; Schmahmann, 2004), but MEG signals from the cerebellum are difficult to record and subject to considerable artefact and distortion (Ioannides, 2005; Muthukumaraswamy, 2013). It would also be important for future studies to assess the rhythm abilities of participants since successful recognition of familiar songs builds on melody (pitch) and rhythm identification (Peretz and Coltheart, 2003; Volkova et al., 2014), and differences in these skills may impact the findings.

Our results on relatively preserved processing of familiar songs in ASD cannot address whether this is specific to music networks, as it could be domain-general to all familiar auditory stimuli. Future research could compare the processing of familiar music to the processing of familiar speech or familiar environmental sounds to shed light on this matter.

## 5.6 Conclusion

This study provides the first evidence of brain connectivity patterns involved in familiarity in music listening in both typically developing and autistic children. Our results revealed atypical processing of unfamiliar songs in children with ASD. During the processing of unfamiliar music, we demonstrated increased theta and beta band task-dependent connectivity in children with ASD compared to controls. The effects of connectivity (network strength) between familiarity and groups showed increased alpha connectivity strength in unfamiliar condition compared to familiar stimuli in TD but no effect was seen in the ASD group. These results, in addition to adding valuable information to the growing literature on atypical brain connectivity in the ASD population, inform future research on the neurobiological correlates of music familiarity in autism that may guide the development of music-based interventions. Future work is needed to replicate and expand our findings throughout development, both in typically developing and children with ASD.

## 5.7 Supplementary materials

Supplementary Table 1 (5-SI): List of familiar songs used to set up MEG paradigm.

| | **Name of the song** | **Artist** | **Nationality** | **Language lyrics** | **Genre** | **Tempo (group)** | **Tempo (bpm)** | **Mode (V)** | **Mode** |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (You're) having my baby | Paul Anka, Odia Coates | Canadian | English | Rock | Fast | 152 | 0.20 | Major |
| 2 | 679 | Fetty Way | American | English | Rap | Fast | 129 | -0.13 | Minor |
| 3 | #thatPOWER | will.i.am, Justin Bieber | American | English | EDM | Fast | 128 | 0.15 | Major |
| 4 | 0 to 100 | Drake | Canadian | English | Rap/hip hop | Fast | 180 | -0.11 | Minor |
| 5 | 1-800-273-8255 | Logic, Alessia Cara, Khalid | American | English | Rap/hip hop | Moderate | 105 | 0.06 | Major |
| 6 | 24K magic | Bruno Mars | American | English | Pop/disco/funk | Moderate | 107 | 0.19 | Minor |
| 7 | 50 ways to say goodbye | Train | American | English | Alternative rock | Fast | 140 | 0.03 | Minor |
| 8 | 500 miles | The Proclaimers | Scottish | English | Pop/voice/bass | Fast | 132 | 0.01 | Major |
| 9 | 5th symphony | Beethoven | German | not applicable | Classical | Moderate | 92 | 0.01 | Minor |
| 10 | 7 years | Lukas Graham | Danish | English | Pop | Slow | 65 | 0.05 | Minor |
| 11 | A bicyclette | Bourvil | French | French | Pop | Fast | 139 | 0.16 | Major |
| 12 | A dream is a wish your heart makes (Cinderella movie) | Disney | American | English | Classical | Moderate | 116 | -0.02 | Minor |
| 13 | A sky full of stars | Coldplay | British | English | Pop | Fast | 125 | 0.30 | Major |
| 14 | A whole new world (Aladdin movie) | Disney | American | English | Musical | Slow | 62 | 0.36 | Minor |
| 15 | ABC song | Nursery Rhymes &Kids Songs | American | English | Cartoons | Moderate | 110 | 0.09 | Major |
| 16 | Above all | Michael W. Smith | American | English | Church/pop | Slow | 66 | 0.16 | Major |
| 17 | Achy breaky heart | Billy Ray Cyrus | American | English | Pop country | Fast | 121 | -0.21 | Minor |
| 18 | Act naturally | Beatles | British | English | Rock | Fast | 187 | 0.24 | Major |
| 19 | Afraid | The Neighbourhood | French | English | Hip hop | Fast | 170 | -0.12 | Minor |
| 20 | Africa | Karl Wolf | Canadian | English | Pop | Fast | 126 | 0.36 | Major |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 21 | Ain't no mountain high enough | Marvin Gaye, Tammi Terrel | American | English | Soul | Fast | 125 | 0.10 | Major |
| 22 | Ain't nobody | Felix Jaehn | German | English | House | Moderate | 119 | 0.14 | Major |
| 23 | All about that bass | Meghan Trainor | American | English | Pop/doo-wop | Moderate | 90 | 0.01 | Major |
| 24 | All I do is win | DJ Kahled | American | English | Hip hop | Moderate | 100 | -0.05 | Minor |
| 25 | All the way | Jacksepticeye | Irish | English | Rap | Fast | 128 | -0.16 | Minor |
| 26 | All time low | Jon Bellion | American | English | Pop rock | Moderate | 93 | 0.08 | Major |
| 27 | All together now | Beatles | British | English | Pop | Moderate | 96 | 0.04 | Major |
| 28 | All you need is love | Beatles | British | English | Pop | Moderate | 97 | 0.34 | Major |
| 29 | Alone | Marshmello | American | English | Electro dance | Moderate | 95 | 0.22 | Major |
| 30 | Alphabet medley | Nursery Rhyme | American | English | Cartoons | Fast | 126 | 0.09 | Major |
| 31 | Amazed | Lonestar | American | English | Pop | Slow | 71 | 0.13 | Major |
| 32 | American beauty | Drew Holcomb | American | English | Pop | Moderate | 112 | 0.03 | Minor |
| 33 | Angel dance | Robert Plant | British | English | Rock | Fast | 167 | -0.11 | Major |
| 34 | Animals | Maroon 5 | American | English | Pop | Moderate | 96 | -0.20 | Minor |
| 35 | Animals | Martin Garrix | Dutch | English | Dance | Fast | 128 | -0.29 | Minor |
| 36 | Anything | Hedley | Canadian | English | Pop rock | Moderate | 103 | 0.16 | Major |
| 37 | As long as you love me | Justin Bieber | Canadian | English | Pop | Slow | 70 | 0.00 | Minor |
| 38 | Ave Maria | Charlotte Church | British | English | Classic | Fast | 136 | 0.02 | Minor |
| 39 | Ba ba ba banana | Splash'N Boots | Canadian | English | Children | Fast | 139 | -0.15 | Minor |
| 40 | Baa baa black sheep have you any wool | Nursery Rhyme | American | English | Cartoons | Moderate | 111 | 0.15 | Major |
| 41 | Baby | Justin Bieber, Ludacris | Canadian | English | Pop | Fast | 130 | 0.30 | Major |
| 42 | Baby mine | Disney | American | N.A. | Soundtrack | Slow | 53 | -0.19 | Minor |
| 43 | Baby one more time | Britney Spears | American | English | Pop | Fast | 185 | -0.10 | Minor |
| 44 | Back in black | AC/DC | Australian | English | Hard rock | Moderate | 91 | 0.04 | Major |
| 45 | Backflip | Casey Veggies | American | English | Hip hop | Fast | 195 | -0.01 | Minor |
| 46 | Bad blood | Taylor Swift, Kendrick Lamar | American | English | Pop rap | Fast | 170 | -0.08 | Major |
| 47 | Bad romance | Lady Gaga | American | English | Pop | Moderate | 119 | 0.08 | Major |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 48 | Bang bang | Jessie J, Ariana Grande, Nicki Minaj | British | English | Funk | Fast | 150 | 0.15 | Major |
| 49 | Batman soundtrack | Prince | American | English | Soundtrack | Fast | 168 | -0.01 | Minor |
| 50 | Bear band serenade | Disney | American | English | Soundtrack | Fast | 132 | 0.24 | Major |
| 51 | Beds are burning | Midnight Oil | Australian | English | Rock | Moderate | 119 | -0.18 | Minor |
| 52 | Between the raindrops | Lifehouse | American | English | Pop | Moderate | 107 | 0.02 | Major |
| 53 | Bingo | Super Simple Songs | Canadian | English | Cartoons | Fast | 161 | 0.31 | Major |
| 54 | Black magic | Little Mix | English | English | Pop | Moderate | 112 | 0.17 | Major |
| 55 | Black SpiderMan | Logic, Damian Lemar Hudson | American | English | Rap/hip hop | Moderate | 93 | 0.02 | Minor |
| 56 | Blackbird | Beatles | British | English | Rock | Moderate | 94 | 0.00 | Minor |
| 57 | Blank | Disfigure | British | N.A. | Electro house | Fast | 140 | 0.02 | Major |
| 58 | Blue (da ba dee) | Eiffel 65 | Italian | English | Electronic | Fast | 126 | 0.04 | Minor |
| 59 | Body language | Queen | British | English | Pop rock | Fast | 129 | 0.23 | Major |
| 60 | Body like a back road | Sam Hunt | American | English | Pop | Slow | 66 | 0.12 | Major |
| 61 | Bones | Ginny Blackmore | New Zealandese | English | Pop | Moderate | 77 | 0.26 | Major |
| 62 | Books are fun | Barney & Friends | American | English | Cartoons | Fast | 137 | 0.29 | Major |
| 63 | Boom boom pow | The Black Eyed Peas | American | English | Electro | Fast | 123 | -0.11 | Minor |
| 64 | Boomerang | Jojo Siwa | American | English | Pop | Moderate | 115 | 0.09 | Major |
| 65 | Booty | Jennifer Lopez | American | English | Pop | Fast | 129 | -0.01 | Minor |
| 66 | Break my mind | DAGames | American | English | Rock | Fast | 130 | 0.11 | Major |
| 67 | Broken wings | Mr Mister | American | English | Pop 80s | Moderate | 103 | -0.08 | Minor |
| 68 | Cache-cache | Maxime Landry | Canadian | English | Pop | Moderate | 116 | 0.20 | Major |
| 69 | Cake | Flo Rida, 99 Percent | American | English | Rap, hip hop | Moderate | 105 | 0.31 | Major |
| 70 | Cake by the ocean | DNCE | American | English | R & B | Moderate | 119 | -0.26 | Minor |
| 71 | California girls | Katy Perry, Snoop Dogg | American | English | Pop | Fast | 125 | -0.16 | Minor |
| 72 | Call me maybe | Carly Rae Jepsen | Canadian | English | Pop | Moderate | 107 | 0.20 | Major |
| 73 | Can it fix it | Bob the builder | British | English | Cartoons | Fast | 140 | 0.22 | Major |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 74 | Can you feel my heart | Bring Me The Horizon | British | English | Punk Rock | Fast | 170 | -0.23 | Minor |
| 75 | Candyland | Tobu | Latvian | N.A. | Electro house | Moderate | 102 | 0.31 | Major |
| 76 | Can't feel my face | The Weeknd | Canadian | English | Pop | Moderate | 110 | -0.22 | Minor |
| 77 | Can't stop the feeling | Justin Timberlake | American | English | Pop | Moderate | 119 | -0.17 | Minor |
| 78 | Capture of Triiliam | Disney | American | N.A. | Soundtrack | Moderate | 98 | -0.02 | Minor |
| 79 | Carpe diem | Green Day | American | English | Rock | Fast | 140 | -0.16 | Minor |
| 80 | Castle on the hill | Ed Sheeran | British | English | Pop | Fast | 135 | 0.09 | Major |
| 81 | Centuries | Fall Out Boy | American | English | Pop funk | Moderate | 117 | -0.16 | Minor |
| 82 | Chandelier | Sia | Australian | English | Pop | Moderate | 116 | -0.25 | Minor |
| 83 | Cheap thrills | Sia, Sean Paul | Australian | English | Pop | Moderate | 90 | 0.03 | Major |
| 84 | Cheerleader | OMI | Jamaican | English | Pop | Moderate | 78 | -0.02 | Minor |
| 85 | Cherry bomb | The Runaways | American | N.A. | Rock | Fast | 134 | 0.04 | Major |
| 86 | Chop suey! | System of a Down | American | English | Metal alternative | Fast | 130 | -0.05 | Minor |
| 87 | Christ arose (low in the grave he lay) | Robert Lowry | American | English | Church/pop/choir | Moderate | 81 | 0.18 | Major |
| 88 | Chum 2 | Earl Sweatshirt | American | English | Alternative rock | Moderate | 116 | 0.00 | Minor |
| 89 | Cinquante fois | Bruno Pelletier | Canadian | English | Pop | Moderate | 88 | -0.01 | Major |
| 90 | Circle of life (Lion King movie) | Carmen Twillie | American | Zulu | Ethnic | Moderate | 82 | -0.05 | Minor |
| 91 | Closer | The Chainsmokers | American | English | Pop | Moderate | 95 | 0.05 | Major |
| 92 | Cloud 9 | Itro & Tobu | Latvian | N.A. | Electro House | Fast | 128 | 0.20 | Major |
| 93 | Cold | Maroon 5, Future | American | English | Pop | Moderate | 119 | -0.01 | Minor |
| 94 | Cold water | Major Lazer | American | English | Pop | Moderate | 73 | -0.07 | Minor |
| 95 | Come and get your love | Redbone | American | English | Pop | Moderate | 107 | 0.12 | Major |
| 96 | Come on Eileen | The Clash | British | English | New wave | Moderate | 106 | -0.06 | Major |
| 97 | Come with me now | Longos | South African | English | Alternative rock | Moderate | 104 | 0.03 | Major |
| 98 | Company | Justin Bieber | Canadian | English | Pop | Moderate | 82 | 0.00 | Major |
| 99 | Congratulations | Post Malone, Quavo | American | English | Rap/hip hop | Slow | 122 | 0.02 | Minor |
| 100 | Controlla | Alex Aiono | American | English | Pop | Slow | 65 | -0.28 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 101 | Cotton eye Joe | Rednex | Swedish | English | Pop country | Fast | 132 | 0.22 | Major |
| 102 | Counting stars | OneRepublic | American | English | Folk pop | Fast | 122 | 0.19 | Minor |
| 103 | Crown of love | Arcade Fire | Canadian | English | Rock | Slow | 70 | 0.09 | Major |
| 104 | Cruisin' for a bruisin' | from Teen Beach Movie | American | English | Pop | Moderate | 82 | -0.18 | Major |
| 105 | Cucumber | N. A. | Russian | N.A. | Instrumental | Fast | 141 | 0.04 | Major |
| 106 | Dazed and confused | Led Zeppelin | British | English | Pop | Moderate | 114 | -0.14 | Minor |
| 107 | Deep thoughts | Disney | American | English | Soundtrack | Fast | 121 | 0.09 | Minor |
| 108 | Delirous | Jason Derulo | American | English | Pop funk | Fast | 128 | 0.10 | Minor |
| 109 | Demons | Imagine Dragons | American | English | Pop rock | Moderate | 89 | 0.19 | Major |
| 110 | Den of thieves | The Trews | Canadian | English | Pop rock | Moderate | 116 | -0.01 | Major |
| 111 | Despacito | Luis Fonsi, Daddy Yankee | Portorican | English | Latin pop | Moderate | 111 | -0.10 | Minor |
| 112 | Despacito | Luis Fonsi, Daddy Yankee, Justin Bieber | Portorican | Spanish | Latin pop | Moderate | 85 | -0.10 | Minor |
| 113 | Did u ever think | R Kelly | American | English | Hip hop | Moderate | 89 | -0.04 | Minor |
| 114 | Do it like me | iAmDLOW | American | English | Rap/hip hop | Moderate | 76 | -0.17 | Minor |
| 115 | Dollhouse | Melanie Martinez | American | English | Pop | Fast | 131 | 0.10 | Minor |
| 116 | Don't let me down | The Chainsmokers | American | English | Pop | Moderate | 109 | -0.08 | Minor |
| 117 | Don't let me down | The Chainsmokers | American | English | Electrohouse | Moderate | 109 | -0.10 | Minor |
| 118 | Don't mind onscreen | Kent Jones | American | English | Rap | Moderate | 106 | 0.18 | Major |
| 119 | Don't stop believing | Journey | American | English | Rock | Moderate | 118 | 0.20 | Major |
| 120 | Dora the explorer theme song | Joshua Sitron, Billy Straus | American | English | Cartoons | Moderate | 119 | 0.10 | Major |
| 121 | Dream on | Aerosmith | American | English | Rock | Moderate | 79 | -0.05 | Minor |
| 122 | Duel of the fate (Star Wars) | John Williams | American | N. A. | Instrumental | Fast | 155 | 0.02 | Major |
| 123 | Dynamite | Taio Cruz | British | English | Pop | Moderate | 83 | 0.03 | Major |
| 124 | Easy lover | Philip Bailey | American | English | Pop | Fast | 129 | -0.04 | Major |
| 125 | Electric | Shawn Desman | Canadian | English | Pop | Moderate | 114 | -0.05 | Minor |
| 126 | Empire | Rococode | Canadina | English | Alternative | Moderate | 104 | 0.08 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 127 | Enter in these gates of old | Concordia Publishing House | American | English | Church/pop | Moderate | 73 | 0.07 | Major |
| 128 | Esquece o mundo | Yasmine Carvalho | Portuguese | Portuguese | Pop | Fast | 186 | 0.21 | Major |
| 129 | Every little step | Bobby Brown | American | English | Hip hop/dance pop | Moderate | 100 | -0.18 | Minor |
| 130 | Everybody talks | Neon Trees | American | English | Rock | Moderate | 104 | 0.11 | Major |
| 131 | Everyday | Rod Stewart | British | English | Pop | Moderate | 100 | -0.06 | Minor |
| 132 | Everything is awesome (The Lego movie) | Tegan and Sara | Canadian | English | Pop dance | Fast | 148 | 0.22 | Major |
| 133 | Eye of the tiger | Survivor | American | English | Rock | Fast | 145 | -0.10 | Minor |
| 134 | Faded | Alan Walke | English | English | Pop | Moderate | 105 | -0.13 | Minor |
| 135 | Fairly OddParents theme song | Ron Jones, Butch Hartman | American | English | Cartoons | Moderate | 104 | -0.22 | Minor |
| 136 | Fall out boy | Uma Thurman | American | English | Pop | Fast | 150 | 0.12 | Major |
| 137 | Fallen angel | Robbie Roberston | Canadian | English | Rock | Fast | 129 | -0.13 | Minor |
| 138 | Fancy | Iggy Azalean | Australian | English | Rap | Fast | 190 | -0.26 | Minor |
| 139 | Fight song | Rachel Platten | American | English | Pop | Moderate | 91 | 0.11 | Minor |
| 140 | Fireball | Pitbull | American | English | Pop | Fast | 123 | 0.01 | Minor |
| 141 | Fixing a hole | Beatles | British | English | Rock | Moderate | 106 | -0.29 | Minor |
| 142 | Flaws | Bastille | British | English | Pop | Fast | 144 | 0.06 | Major |
| 143 | Footloose | Kenny Loggins | American | English | Pop | Fast | 174 | -0.03 | Major |
| 144 | Freaks | Timmy Trumpet, Savage | Australian | English | Pop | Fast | 128 | 0.01 | Minor |
| 145 | French kiss | Black M | French | French | Rap/hip hop | Fast | 122 | 0.05 | Minor |
| 146 | Frérot | Black M, Soprano | French | French | Rap/hip hop | Fast | 135 | 0.19 | Major |
| 147 | Friends are family | Oh, Hush! | American | English | Pop rock | Moderate | 106 | 0.05 | Major |
| 148 | Friendship is magic theme song from My Little Pony | Daniel Ingram | American | English | Cartoons | Moderate | 129 | -0.22 | Minor |
| 149 | Full extreme | Ultimate Rejects | Caraibic | English | Pop | Fast | 170 | 0.02 | Minor |
| 150 | Game shaker theme song | Michael Corcoran | American | English | Pop | Fast | 141 | -0.15 | Minor |
| 151 | Gangnam style | PSY | South Corean | English | K-pop | Fast | 132 | -0.22 | Minor |
| 152 | GDFR | Flo Rida | American | English | Rap | Moderate | 97 | 0.04 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 153 | Ginza | J Balvin | Colombian | Spanish | Pop | Moderate | 102 | -0.14 | Minor |
| 154 | Girl talking bout | Mindless Behavior | American | English | Hip hop | Fast | 123 | -0.10 | Minor |
| 155 | Girls just wanna have fun | Cyndi Lauper | American | English | Pop | Slow | 60 | -0.24 | Major |
| 156 | Girls on fire | Alicia Keys | American | English | R&B/soul | Fast | 186 | -0.28 | Minor |
| 157 | Give me love | Kyle Braun, Broderick Jones | | English | Pop | Moderate | 100 | 0.28 | Major |
| 158 | Glad you came | The Wanted | British, Irish | English | Folk country | Moderate | 114 | -0.04 | Minor |
| 159 | Go off | Lil Uzi Vert, Quavo, Travis Scott | American | English | Rap | Moderate | 118 | -0.12 | Minor |
| 160 | Go your own way | Fleetwood Mac | British, American | English | Rock | Fast | 135 | -0.03 | Major |
| 161 | Good drank | 2 Chainz, Gucci Mane, Quavo | American | English | Rap | Fast | 130 | 0.19 | Minor |
| 162 | Good feeling | Flo Rida | American | English | Pop rap | Fast | 129 | 0.01 | Minor |
| 163 | Good to be alive | Andy Grammer | American | English | Pop | Moderate | 120 | 0.04 | Major |
| 164 | Goosebumps | Travis Scott, Kendrick Lamar | American | English | Rap | Moderate | 88 | -0.14 | Minor |
| 165 | Half way there | Bon Jovi | American | English | Rock | Fast | 121 | -0.23 | Minor |
| 166 | Hallelujah chorus from Handel's Messiah | Handel | German | English | Classic | Fast | 188 | 0.37 | Major |
| 167 | Hands to myself | Selena Gomez | American | English | Pop | Moderate | 73 | 0.18 | Major |
| 168 | Happy | Pharrell Williams | American | English | Pop | Moderate | 107 | -0.05 | Minor |
| 169 | Haunted | Bejoncè | American | English | R&B | Fast | 125 | -0.01 | Minor |
| 170 | Havana young thug | Camila Cabello | Cuban | English | Latin pop | Moderate | 105 | -0.03 | Minor |
| 171 | Head over heels | Tears for Fears | British | N. A. | New wave/pop | Moderate | 95 | 0.26 | Major |
| 172 | Heavy dirty soul | 21 Pilots | American | English | Rap | Fast | 130 | -0.23 | Minor |
| 173 | Hedwig's theme (Harry Potter and the Sorcerer's Stone) | John Williams | American | N. A. | Soundtrack | Slow | 52 | -0.32 | Minor |
| 174 | Hello | Adele | British | English | Pop | Moderate | 106 | 0.08 | Minor |
| 175 | Here comes the Sun | Beatles | British | English | Folk pop | Moderate | 88 | 0.10 | Major |
| 176 | Here I am (come and take me) | Al Green | American | N. A. | Pop/R&B | Moderate | 91 | -0.10 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 177 | Here I am to worship | Michael W. Smith | American | English | Church/pop | Moderate | 77 | 0.17 | Major |
| 178 | Hero | Mariah Carey, Luciano Pavarotti | American, Italian | English | Pop | Moderate | 116 | 0.05 | Minor |
| 179 | Hey there Delilah | Plain White Ts | American | English | Pop/country | Moderate | 105 | 0.24 | Major |
| 180 | Hide away | Daya | American | English | Pop | Moderate | 94 | 0.15 | Major |
| 181 | Hideaway | Kiesza | Canadian | English | Pop | Moderate | 79 | 0.13 | Major |
| 182 | Hold on (the break) | Walk Off The Earth | Canadian | English | Rock | Fast | 88 | 0.31 | Major |
| 183 | Hollaback girl | Gwen Stefani | American | English | Pop | Moderate | 110 | -0.16 | Minor |
| 184 | Honey bear | Bryant Oden | American | English | Pop | Fast | 161 | 0.16 | Major |
| 185 | Hooked on a feeling | Blue Swede | Swedish | English | Pop | Moderate | 114 | -0.03 | Minor |
| 186 | Hope | Tobu | Latvian | N. A. | Electro House | Fast | 128 | 0.19 | Major |
| 187 | Hot hot hot | Vengaboys | German | English | Pop | Moderate | 65 | 0.29 | Major |
| 188 | Hotline bling | Drake | Canadian | English | Hip hop | Moderate | 90 | -0.13 | Minor |
| 189 | How are you (greeting song) | Busy Beavers | American | English | Cartoons | Moderate | 116 | 0.07 | Major |
| 190 | How far I'll go | Alessia Cara | Canadian | English | Pop | Fast | 117 | 0.28 | Major |
| 191 | How I am supposed to live without you | Michael Bolton | American | English | Pop | Fast | 139 | 0.00 | Minor |
| 192 | How soon is now | The Smiths | British | English | Pop dance | Fast | 127 | -0.03 | Major |
| 193 | Hungry like a wolf | Duran Duran | English | English | Rock, new wave | Fast | 130 | 0.14 | Major |
| 194 | I believe I can fly | R. Kelly | American | English | Pop | Moderate | 117 | -0.01 | Major |
| 195 | I bet my life | Imagine Dragons | American | English | Pop, guitar, voice | Fast | 147 | 0.15 | Major |
| 196 | I don't wanna know | Maroon 5 | American | English | Pop | Fast | 131 | 0.11 | Major |
| 197 | I feel it coming | Canadian | Canadian | English | Pop | Moderate | 93 | -0.04 | Minor |
| 198 | I found you | The wanted | Irish | English | Dance | Fast | 129 | -0.31 | Minor |
| 199 | I gotta feeling | The Black Eyed Peas | American | English | Pop | Fast | 128 | 0.14 | Major |
| 200 | I knew you were trouble | Taylor Swift | American | English | Pop | Moderate | 103 | 0.08 | Major |
| 201 | I love it (I don't care) | Icona Pop | Swedish | English | Dance | Fast | 126 | 0.07 | Major |
| 202 | I love you song | Barney Songs | American | English | Cartoons | Fast | 173 | 0.14 | Major |
| 203 | I want it that way | Backstreet boys | American | English | Pop, dance | Moderate | 104 | 0.12 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 204 | I want you (she's so heavy) | Beatles | British | English | Pop | Fast | 161 | -0.23 | Minor |
| 205 | I worship You, almighty God I give you my heart | Teo Poh Heng | Singaporean | English | Church/pop | Moderate | 71 | 0.15 | Major |
| 206 | I'll make some cake | ItsAllMinecraft | American | English | Pop | Fast | 124 | -0.03 | Minor |
| 207 | I'm a bun (from "The amazing world of Gumball") | Dan Russell | American | English | Cartoons | Fast | 213 | -0.05 | Major |
| 208 | I'm a teenager | N. A. | Russian | Hebrew | Pop ethnic | Fast | 142 | -0.09 | Minor |
| 209 | I'm an albatraoz | AronChupa | Swedish | English | House | Fast | 128 | -0.16 | Minor |
| 210 | I'm bringing home a baby bumblebee | Evokids | German | English | Cartoons | Fast | 166 | 0.19 | Major |
| 211 | I'm happy song | Busy Beavers | American | English | Cartoons | Fast | 122 | 0.18 | Major |
| 212 | I'm not the only one | Sam Smith | English | English | Pop | Moderate | 82 | -0.02 | Minor |
| 213 | I'm not the only one | Sam Smith | British | English | Pop | Moderate | 82 | -0.09 | Minor |
| 214 | I'm singing in the rain | Gene Kelly | American | English | Pop | Fast | 123 | 0.15 | Major |
| 215 | I'm still standing | Elton John | British | English | Pop | Fast | 175 | 0.13 | Major |
| 216 | I'm the one | DJ Khaled | American | English | Hip Hop | Slow | 65 | 0.21 | Major |
| 217 | Immortals | Fall Out Boy | American | English | Pop | Moderate | 107 | -0.15 | Minor |
| 218 | Indian summer | Jai Wolf | American | English | Pop/disco | Fast | 174 | 0.12 | Major |
| 219 | Infectious | Tobu | Latvian | N. A. | Electro House | Fast | 128 | 0.10 | Major |
| 220 | Inner ninja | Classified | Canadian | English | Hip hop | Moderate | 113 | 0.02 | Major |
| 221 | Inside the vogon ship | Disney | American | English | Soundtrack | Moderate | 116 | -0.12 | Minor |
| 222 | Invincible | Deaf Kev | German | N. A. | Instrumental | Fast | 136 | 0.21 | Major |
| 223 | Invisible (RED) | U2 | Irish | English | Rock | Fast | 137 | 0.16 | Major |
| 224 | Iron man | Black Sabbath | British | English | Punk Rock | Slow | 64 | -0.04 | Minor |
| 225 | iSpy | KYLE, Lil Yachty | American | English | Rap/hip hop | Moderate | 75 | 0.01 | Major |
| 226 | It ain't me | Kygo, Selena Gomez | Norse | English | Pop | Moderate | 98 | -0.01 | Minor |
| 227 | IT trailer music (2017 movie) | Benjamin Wallfisch | British | N. A. | Soundtrack | Fast | 128 | 0.16 | Major |
| 228 | It's all on u | Illenium, Liam O'Donnell | American | English | Pop | Moderate | 109 | -0.15 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 229 | I've got you under my skin | Frank Sinatra | American | English | Jazz | Fast | 124 | 0.07 | Major |
| 230 | Jesus loves me | Listener Kids | American | English | Church/pop/folk | Moderate | 119 | 0.11 | Major |
| 231 | Johny Johny (Yes papa cartoon) | Nursery Rhyme | American | English | Cartoons | Moderate | 79 | 0.19 | Major |
| 232 | Jordan Belfort | Wes Walker, Dyl | American | English | Rap | Moderate | 80 | -0.08 | Minor |
| 233 | Juju on that beat | Zay Hilfigerrr & Zayion McCall | American | English | Rap/hip hop | Moderate | 107 | -0.06 | Minor |
| 234 | Jump in the line | Harry Belafonte | American | English | Reggae | Moderate | 116 | 0.16 | Major |
| 235 | Just like fire | P!nk | American | English | Soundtrack | Moderate | 83 | 0.24 | Major |
| 236 | Just the way you are | Bruno Mars | American | English | Pop | Moderate | 109 | 0.15 | Major |
| 237 | Kids | MGMT | American | English | Rock | Fast | 123 | -0.03 | Major |
| 238 | King of wishful thinking | Go West | British | English | Alternative rock | Moderate | 108 | 0.11 | Major |
| 239 | Knock me off my feet | Dan Talevski | Canadian | English | Pop | Fast | 120 | 0.00 | Major |
| 240 | Kylo Ren (Star Wars) | John Williams | American | N. A. | Instrumental | Moderate | 114 | -0.17 | Minor |
| 241 | La Maza en vivo | Mercedes Sosa | Argentinian | Spanish | Pop | Moderate | 111 | -0.12 | Minor |
| 242 | Last day | N. A. | Russian | Hebrew | Pop ethnic | Fast | 126 | -0.07 | Minor |
| 243 | Leave me alone | Michael Jackson | American | English | Funk pop | Fast | 123 | 0.18 | Minor |
| 244 | Lego house | Ed Sheeran | British | English | Pop, voice | Fast | 158 | 0.07 | Major |
| 245 | Let it go | Idina Menzel | American | English | Pop | Moderate | 89 | 0.03 | Major |
| 246 | Let mee love you | DJ Snake ft Justin Bieber | French | English | Techno | Fast | 133 | 0.27 | Major |
| 247 | Life | Tobu | Latvian | N. A. | Electro house | Fast | 128 | 0.09 | Major |
| 248 | Life is a highway (Cars 2006 movie) | Rascal Flatts | American | English | Rock | Moderate | 103 | 0.16 | Major |
| 249 | Like a Rolling Stone | The Rolling Stones | British | English | Pop | Fast | 184 | 0.09 | Major |
| 250 | Like an enderman | ThnxCya | British | English | Pop | Fast | 132 | -0.30 | Minor |
| 251 | Like me like I am | Traditional | Hebrew | Hebrew | Voice, guitar | Moderate | 103 | -0.13 | Minor |
| 252 | Lithium | Nirvana | American | English | Rock | Moderate | 83 | -0.13 | Major |
| 253 | Little black rain cloud (Winnie the Pooh movie) | Disney | American | English | Waltz, cartoons | Moderate | 110 | 0.11 | Major |
| 254 | Living well is best revenge | REM | American | English | Rock | Fast | 181 | -0.10 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 255 | Lollipop | Lil Wayne, Static | American | English | Rap | Moderate | 99 | -0.02 | Minor |
| 256 | Look what you made me do | Taylor Swift | American | English | Pop | Fast | 128 | -0.22 | Minor |
| 257 | Lose yourself (8 mile movie) | Eminem | American | English | Hip hop | Slow | 64 | -0.01 | Minor |
| 258 | Lost Boy | Ruth B | Canadian | English | Pop | Slow | 59 | 0.12 | Minor |
| 259 | Love 3X | ZZ Ward | American | English | Pop | Fast | 160 | -0.02 | Minor |
| 260 | Love is an open door from Frozen movie repeat | Kristen Bell, Santino Fontana | American | English | Musical | Moderate | 107 | 0.24 | Major |
| 261 | Love me harder | Ariana Grande, The Weeknd | American | English | Pop | Moderate | 99 | 0.30 | Major |
| 262 | Love me now | John Legend | American | English | Pop | Slow | 63 | 0.17 | Major |
| 263 | Love you like a love song baby | Selena | Mexican | English | Dance pop | Moderate | 117 | -0.16 | Minor |
| 264 | Love yourself | Justin Bieber | Canadian | English | Pop | Slow | 64 | -0.04 | Minor |
| 265 | Mad hatter | Melanie Martinez | American | English | Pop | Slow | 60 | -0.28 | Minor |
| 266 | Mah-nà mah-nà Muppet Show | Piero Umiliani | Italian | N. A. | Cartoons | Moderate | 106 | -0.09 | Minor |
| 267 | Main theme (Star Wars) | John Williams | American | N. A. | Instrumental | Moderate | 109 | 0.08 | Major |
| 268 | Make me move (remix) | Culture Code, Karra | British | English | Pop | Fast | 138 | 0.17 | Major |
| 269 | Make you feel my love | Adele | English | English | Pop | Moderate | 78 | 0.04 | Minor |
| 270 | Mamma Mia | Abba | Swedish | English | Pop | Fast | 136 | -0.09 | Minor |
| 271 | Mari-Mac | Great Big Sea | Canadian | English | Folk | Fast | 128 | 0.02 | Major |
| 272 | Max and Ruby theme song | Treehouse Direct | American | English | Cartoons | Fast | 156 | 0.08 | Major |
| 273 | Me too | Meghan Trainor | American | English | Pop | Fast | 124 | -0.02 | Minor |
| 274 | Me, myself & I | G-Eazy and Bebe Rexha | American | English | Rap | Moderate | 112 | 0.18 | Minor |
| 275 | Mercy | Shawn Mendes | Canadian | English | Pop | Moderate | 139 | -0.03 | Minor |
| 276 | Mermaid | Train | American | English | Alternative rock | Moderate | 104 | -0.09 | Minor |
| 277 | Mesmerize | Tobu | Latvian | N. A. | Electro house | Fast | 128 | 0.26 | Major |
| 278 | Michael Myers theme song | John Carpenter | American | N. A. | Soundtrack | Fast | 137 | -0.04 | Minor |
| 279 | Mickey mouse march | Disney | American | English | Soundtrack | Fast | 133 | 0.03 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 280 | Mighty fortress music thanks be to God | Concordia Publishing House | American | English | Pop/children | Fast | 130 | -0.09 | Major |
| 281 | Mighty machines theme song | Ian Graham | American | English | Cartoons | Moderate | 106 | 0.21 | Major |
| 282 | Milord | Edith Piaf | French | French | Pop | Moderate | 104 | 0.27 | Major |
| 283 | Miniature fugue 1 | Alec Rowley | British | N. A. | Instrumental | Moderate | 119 | -0.10 | Minor |
| 284 | Miniature fugue 2 | Alec Rowley | British | N. A. | Instrumental | Moderate | 96 | -0.09 | Minor |
| 285 | Miniature fugue 3 | Alec Rowley | British | N. A. | Instrumental | Fast | 124 | 0.05 | Minor |
| 286 | Minions banana song | Minions official | American | N. A. | Cartoons | Fast | 171 | -0.03 | Minor |
| 287 | Miss you | 54-40 | Canadian | English | Rock | Moderate | 97 | -0.04 | Minor |
| 288 | Mmm yeah | Austin Mahone, Pitbull | American | English | Rap | Fast | 126 | 0.13 | Major |
| 289 | Moonlight sonata (first movement) | Beethoven | German | N. A. | Classic | Moderate | 82 | -0.26 | Minor |
| 290 | Mortals | Warriyo, Laura Brehm | German | English | Pop | Moderate | 120 | -0.18 | Minor |
| 291 | Mot de passe | Damien Robitaille | Canadian | French | Rock | Fast | 174 | -0.18 | Major |
| 292 | Mourir d'aimer | Isabelle Boulay | Canadian | French | Pop | Moderate | 78 | 0.12 | Minor |
| 293 | Move like a soldier | Kristina Maria | Canadian | English | Dance pop | Fast | 130 | 0.01 | Minor |
| 294 | My house | Flo Rida | American | English | Pop | Fast | 188 | 0.06 | Major |
| 295 | My lovely name* | N. A. | Russian | Russian | Dance pop | Fast | 161 | -0.13 | Minor |
| 296 | My songs know what you did | Fall out boy | American | English | Pop funk | Fast | 152 | -0.17 | Minor |
| 297 | My type | Saint Motel | American | English | Pop | Moderate | 118 | -0.24 | Minor |
| 298 | My way | Frank Sinatra | American | English | Pop | Moderate | 106 | 0.10 | Minor |
| 299 | Narwhals | Weebl | British | English | Electro dance | Fast | 151 | 0.02 | Major |
| 300 | Neighborhood #1 | Arcade Fire | Canadian | English | Rock | Moderate | 111 | 0.06 | Major |
| 301 | Never close your eyes | Adam lambert | American | English | Pop | Fast | 134 | -0.12 | Minor |
| 302 | Never gonna give you up | Rick Astley | English | English | Pop | Moderate | 113 | 0.27 | Major |
| 303 | Never has the winter | Valentina Tolkunova | Russian | Russian | Pop ethnic | Fast | 179 | -0.23 | Minor |
| 304 | New theme song | Thomas and Fr | English | English | Cartoons | Fast | 181 | 0.14 | Major |
| 305 | Night like this | Shawn Desman | Canadian | English | Pop | Moderate | 120 | -0.13 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 306 | No | Meghan Trainor | American | English | Pop | Fast | 188 | -0.11 | Minor |
| 307 | No soy de aquí, ni soy de allá | Facundo Cabral | Argentinian | Spanish | Folk pop | Moderate | 96 | 0.02 | Minor |
| 308 | No strings | Groundbreaking | American | English | Rock | Slow | 68 | 0.27 | Major |
| 309 | No weapon | Fred Hammond | American | English | Gospel | Slow | 57 | 0.14 | Major |
| 310 | Not going home | DVBBS & CMC$, Gia Koka | Canadian | English | Electro dance | Fast | 145 | 0.02 | Major |
| 311 | Nothing without love | Nate Ruess | American | English | Pop voice | Moderate | 88 | 0.24 | Major |
| 312 | Nuclear family | Green Day | American | English | Rock | Fast | 176 | 0.05 | Major |
| 313 | Numb chucks theme song | Graeme Cornies | Canadian | English | Cartoons | Fast | 190 | -0.01 | Minor |
| 314 | Numba 1 (tide is high) | Kardinal Offishall, Keri Hilson | Canadian | English | Pop | Moderate | 107 | 0.06 | Major |
| 315 | Numbers 1, 2, 3 | The Kids Club | American | N. A. | Cartoons | Moderate | 80 | -0.03 | Minor |
| 316 | Octopus's garden | Beatles | British | English | Pop | Moderate | 89 | 0.09 | Major |
| 317 | Oh be careful little eyes what you see | Cedarmont Kids | American | English | Children | Fast | 126 | 0.00 | Major |
| 318 | Oh Hanukkah | Traditional | Hebrew | English | Pop | Fast | 176 | 0.16 | Major |
| 319 | Old MacDonald had a farm | Nursery Rhyme | American | English | Pop | Moderate | 115 | 0.10 | Major |
| 320 | On the run | Pink Floyd | British | N. A. | Rock | Moderate | 82 | -0.01 | Major |
| 321 | One dance | Drake | Canadian | English | Rap | Moderate | 104 | 0.02 | Major |
| 322 | One less lonely girl | Justin Bieber | Canadian | English | Pop | Moderate | 116 | 0.31 | Major |
| 323 | One more time | Daft Punk | French | English | House | Fast | 123 | 0.15 | Major |
| 324 | Open the eyes of my heart lord | Paul Baloche | American | English | Pop | Moderate | 95 | -0.01 | Major |
| 325 | Ophelia | The Lumineers | American | English | Folk | Moderate | 75 | -0.16 | Minor |
| 326 | Packt like sardines in a crushed tiny box | Radiohead | British | N. A. | Alternative | Slow | 62 | -0.01 | Minor |
| 327 | Panda | Desiigner | American | English | Rap | Moderate | 97 | 0.02 | Major |
| 328 | Paris | The Chainsmokers | American | English | Pop | Moderate | 100 | 0.15 | Minor |
| 329 | Part of me | Katy Perry | American | English | Pop | Fast | 130 | -0.07 | Minor |
| 330 | Party in the USA | Miley Cyrus | American | English | Electropop | Fast | 191 | 0.14 | Minor |
| 331 | Party monster | The Weeknd | Canadian | English | Pop | Moderate | 79 | 0.17 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 332 | Party rock anthem | LMFAO | American | English | Rock | Moderate | 110 | 0.25 | Major |
| 333 | Peanut butter jelly time | The Buckwheat Boys | American | English | Cartoons | Fast | 154 | -0.01 | Minor |
| 334 | People are people | Depeche Mode | British | English | Pop | Fast | 121 | -0.10 | Minor |
| 335 | Phonics song 2 | Kids TV 123 | American | English | Children | Fast | 130 | -0.09 | Minor |
| 336 | Piano man | Billy Joel | American | N. A. | Piano rock | Fast | 171 | 0.25 | Major |
| 337 | PIKOTARO - PPAP (Pen Pineapple Apple Pen) | Daimaō Kosaka | Japanese | English | Pop electro | Fast | 136 | -0.19 | Minor |
| 338 | Pillowtalk | Zayn Malik | English | English | R&B | Slow | 62 | -0.06 | Minor |
| 339 | Planes - nothing can stop me now | Mark Holman | American | English | Pop | Moderate | 113 | 0.13 | Major |
| 340 | Pokemon GO | Junichi Masuda | Japanese | N. A. | Soundtrack | Fast | 128 | 0.02 | Major |
| 341 | Poker face | Lady Gaga | American | English | Pop | Moderate | 119 | -0.21 | Minor |
| 342 | Political rap | Jeremy Shada | American | English | Rap | Fast | 160 | -0.18 | Minor |
| 343 | Pompei | Bastille | British | English | Indie rock | Fast | 130 | 0.28 | Major |
| 344 | Praise Him, praise Him all ye little children | Integrity Kids | British | English | Church/pop | Moderate | 72 | 0.15 | Major |
| 345 | Pre | Earl Sweatshirt | American | English | Hip hop | Fast | 198 | -0.10 | Minor |
| 346 | Qian qian | Chinese Music | Chinede | N. A. | Ethnic | Moderate | 89 | -0.01 | Minor |
| 347 | Quando m'en vo'soletta la bohème | Anna Netrebko | Russian | Italian | Classic | Moderate | 120 | 0.17 | Minor |
| 348 | Radioactive | Imagine Dragons | American | English | Alternative rock | Slow | 67 | -0.01 | Minor |
| 349 | Rainbow connection from the Muppet movie | Steve Whitmire | American | English | Soundtrack | Moderate | 116 | 0.08 | Major |
| 350 | Rainbow road theme from Mario Kart | Kenta Nagata | Japanese | N. A. | Soundtrack | Fast | 136 | 0.28 | Major |
| 351 | Ready for it | Taylor Swift | American | English | Pop - grunge | Moderate | 107 | -0.11 | Minor |
| 352 | Real gone (Cars 2006 movie) | Sheryl Crow | American | English | Rock | Moderate | 118 | -0.14 | Major |
| 353 | Red solo cup | Toby Keith | American | English | Country | Moderate | 82 | -0.05 | Minor |
| 354 | Renegades | X Ambassadors | American | English | Pop | Fast | 180 | 0.19 | Major |
| 355 | Respect each other * | N. A. | Russian | Hebrew | Pop ethnic | Fast | 130 | -0.14 | Minor |
| 356 | Revolution | Diplo | American | English | Pop | Fast | 148 | -0.16 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 357 | Rey's theme (Star Wars) | John Williams | American | N. A. | Instrumental | Moderate | 103 | -0.28 | Minor |
| 358 | Ride | 21 Pilots | American | English | Pop | Moderate | 75 | 0.20 | Major |
| 359 | Ring around the rosy | The Countdown Kids | Canadian | English | Cartoons | Fast | 121 | 0.27 | Major |
| 360 | Ring of Fire | Johnny Cash | American | English | Rock | Moderate | 80 | -0.08 | Minor |
| 361 | Riptide | Vance Joy | Australian | English | Folk country | Moderate | 99 | -0.02 | Minor |
| 362 | Ritual | Marshmello ft Wrabel | American | English | Electro dance | Moderate | 111 | -0.07 | Major |
| 363 | Roar | Katy Perry | American | English | Pop | Fast | 179 | 0.17 | Major |
| 364 | Rockit | Herbie Hancock | American | N. A. | Funk | Moderate | 119 | -0.27 | Minor |
| 365 | Rolex | Ayo &Teo | American | English | Rap hip hop | Moderate | 72 | -0.14 | Minor |
| 366 | Route 66 (Cars 2006 movie) | John Mayer | American | English | Rock | Fast | 167 | -0.07 | Major |
| 367 | Ruby, don't take your love to town | Kenny Rogers | American | English | Country | Moderate | 107 | 0.05 | Major |
| 368 | Rude | Magic! | Canadian | English | Reggae | Fast | 144 | 0.12 | Major |
| 369 | Runnin' (lose it all) | Naughty Boy | English | English | Pop | Slow | 71 | 0.06 | Minor |
| 370 | Same Old Love | Selena Gomez | American | English | Pop | Moderate | 99 | -0.06 | Minor |
| 371 | Sandstorm | DJ Darude | Finnish | English | Trance | Fast | 136 | -0.19 | Minor |
| 372 | Santa Claus is coming to town (Children version) | Mary Liguori | Italian | English | Pop/folk/choir | Fast | 132 | 0.07 | Major |
| 373 | Saturday - Schabat | Traditional | Hebrew | Hebrew | Ethnic | Fast | 138 | 0.20 | Minor |
| 374 | Savage mode | Metro Boomin, 21 Savage | American | English | Rap | Moderate | 93 | -0.18 | Minor |
| 375 | Sax | Fleur East | British | English | Pop | Moderate | 118 | 0.09 | Major |
| 376 | Scars to your beautiful | Alessia Cara | Canadian | English | Pop | Moderate | 91 | -0.20 | Minor |
| 377 | Science is real | They Might Be Giants | American | English | Alternative rock | Fast | 180 | -0.01 | Minor |
| 378 | Seagulls! (Stop it now) | Bad Lip Reading | American | English | Cartoons | Moderate | 120 | -0.20 | Major |
| 379 | See you again | Wiz Khalifa | American | English | Pop | Moderate | 102 | 0.20 | Minor |
| 380 | Send my love (to your new lover) | Adele | English | English | Pop | Moderate | 109 | 0.03 | Major |
| 381 | Seven eleven | Beyonce | American | English | Rap | Fast | 136 | -0.25 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 382 | Sever the ties | Arman Cekin, Esther Sparkes | Dutch | English | Pop | Moderate | 100 | 0.10 | Minor |
| 383 | Shake it off | Taylor Swift | American | English | Pop | Fast | 107 | -0.03 | Major |
| 384 | Shape of you | Ed Sheeran | British | English | Pop | Fast | 130 | -0.22 | Minor |
| 385 | She-Ra opening theme | Melendy Britt | American | English | Cartoons | Fast | 138 | 0.03 | Major |
| 386 | Shine | Pillar | American | English | Post Grunge | Moderate | 111 | -0.08 | Major |
| 387 | Shoo-rah | Betty Wright | American | English | R&B | Fast | 121 | 0.02 | Major |
| 388 | Shooting stars | Aero Chord, DDARK | Greek | English | Rap | Fast | 140 | -0.15 | Minor |
| 389 | Shut up and dance | Walk the Moon | American | English | Pop | Fast | 128 | 0.04 | Major |
| 390 | Side to side | Ariana Grande, Nicki Minaj | American | English | Pop | Moderate | 106 | 0.24 | Major |
| 391 | Sign of the times | Harry Styles | British | English | Pop | Slow | 60 | 0.26 | Major |
| 392 | Single ladies | Beyonce | American | English | R&B pop | Moderate | 98 | -0.10 | Minor |
| 393 | Sisters and brothers | Sidewalks prophets | American | English | Pop rock | Moderate | 103 | -0.02 | Minor |
| 394 | Sitting on the toilet | Eloina Nonnie | American | English | Voice | Fast | 155 | 0.05 | Major |
| 395 | Sleep like a baby | U2 | Irish | English | Rock | Fast | 172 | -0.02 | Minor |
| 396 | Smells like teen spirit | Nirvana | American | English | Rock | Moderate | 117 | 0.16 | Major |
| 397 | Smile | Avril Lavigne | Canadian | English | Pop punk | Fast | 140 | 0.13 | Major |
| 398 | Smoke on the water | Deep Purple | British | English | Hard Rock/metal | Moderate | 113 | -0.07 | Minor |
| 399 | So long and thanks for all the fish | Disney | American | English | Instrumental | Moderate | 110 | 0.02 | Major |
| 400 | So this is love (Cinderella movie) | Ilene Woods | American | English | classic movie | Slow | 62 | -0.01 | Minor |
| 401 | Somebody is watching me | Rockwell | American | English | Pop | Fast | 123 | 0.00 | Minor |
| 402 | Somebody like you - Golden Road | Keith Urban | Australian | English | Country pop | Moderate | 111 | 0.09 | Major |
| 403 | Somebody that I used to know | Gotye | Belgian | English | Pop rock | Slow | 64 | -0.14 | Minor |
| 404 | Someday my prince will come | Adriana Caselotti | American | English | classic movie | Slow | 65 | -0.19 | Minor |
| 405 | Something big | Shawn Mendes | Canadian | English | Pop | Moderate | 112 | -0.01 | Minor |
| 406 | Something 'bout a truck | Kip Moore | American | English | Pop country | Fast | 174 | 0.08 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 407 | Something just like this | The Chainsmokers, Coldplay | American | English | Pop | Moderate | 107 | 0.25 | Major |
| 408 | Somewhere Over the Rainbow Scene (The Wizard of Oz 1939 movie) | Judy Garland | American | English | Pop | Slow | 68 | 0.20 | Major |
| 409 | Sonatine, Op 30 - I Allegrement- Harp | Marcel Tournier | French | N. A. | Classical | Moderate | 103 | -0.08 | Minor |
| 410 | Song 2 | Blur | British | English | Rock | Fast | 130 | 0.05 | Major |
| 411 | Sorry | Beyonce | American | English | Pop | Moderate | 87 | 0.09 | Minor |
| 412 | Sorry | Justin Bieber | Canadian | English | Pop | Fast | 134 | 0.18 | Minor |
| 413 | Sorry for party rocking | LMFAQ | American | English | Electro hop | Fast | 134 | 0.05 | Major |
| 414 | South park theme | PRIMUS | American | English | Rock | Fast | 144 | 0.13 | Major |
| 415 | Space | Disney | American | English | Soundtrack | Fast | 141 | -0.13 | Minor |
| 416 | Space Is Cool | Markiplier, The Gregory Brothers | American | English | Pop | Moderate | 105 | 0.14 | Major |
| 417 | Space oddity | David Bowie | British | English | Progressive rock | Moderate | 90 | 0.04 | Minor |
| 418 | Spirits | The Strumbellas | Canadian | English | Rock | Moderate | 81 | 0.02 | Major |
| 419 | SpongeBob SquarePants | Nickelodeon | American | English | Cartoons | Moderate | 118 | 0.15 | Major |
| 420 | Starboy | The Weeknd, Daft Punk | Canadian | English | Pop | Moderate | 108 | 0.06 | Major |
| 421 | Stitches | Shawn Mendes | Canadian | English | Pop | Fast | 149 | 0.11 | Minor |
| 422 | Stole my heart | One Direction | British | English | Dance pop | Fast | 127 | 0.15 | Major |
| 423 | Stressed out | 21 Pilots | American | English | Rap | Fast | 171 | -0.09 | Minor |
| 424 | Stronger than you | Estelle | British | English | Rap | Fast | 133 | -0.13 | Minor |
| 425 | Stuck in the middle with you | Stealers Wheel | Scottish | English | Rock | Fast | 124 | 0.10 | Major |
| 426 | Stupid hoe | Nicki Minaj | Trinidadian | English | Rap | Fast | 125 | 0.16 | Major |
| 427 | Style | Taylor Swift | American | English | Pop | Slow | 48 | -0.08 | Minor |
| 428 | Suck my kiss | Red Hot Chili Peppers | American | English | Rock | Fast | 135 | 0.00 | Major |
| 429 | Sugar | Maroon 5 | American | English | Pop | Moderate | 81 | 0.07 | Minor |
| 430 | Summer of 69 | Bryan Adams | Canadian | English | Rock | Fast | 139 | 0.02 | Major |
| 431 | Sun goes down | Fabian Mazur | Danish | English | disco | Fast | 151 | -0.11 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 432 | Sunburst | Itro & Tobu | Latvian | | Electro House | Fast | 128 | 0.37 | Major |
| 433 | Super Mario soundtrack - videogame | Koji Kondo | Japanese | English | Cartoons | Fast | 133 | 0.30 | Major |
| 434 | Superbass | Nicki Minaj | American | English | R&B/Soul | Moderate | 85 | 0.03 | Major |
| 435 | Superman theme | John Williams | American | | Contemporary classical | Fast | 121 | -0.07 | Major |
| 436 | Sweatshirt | Jacob Sartorius | American | English | Pop | Fast | 128 | 0.17 | Major |
| 437 | Sweet child of mine | Guns 'n' Roses | American | English | Rock | Fast | 127 | 0.08 | Major |
| 438 | Sweet dreams (Goodnight Song) | Super Simple Songs | Canadian | English | Cartoons | Moderate | 118 | 0.17 | Minor |
| 439 | Sweet home Alabama | Lynyrd Skynyrd | American | English | Pop | Fast | 129 | 0.25 | Major |
| 440 | Sweet victory | Van Halen | American | English | Pop | Slow | 62 | 0.05 | Major |
| 441 | Symbolism | Electro-Light | Scottish | N. A. | Electro House | Moderate | 114 | 0.10 | Major |
| 442 | Symphony no. 9 (Scherzo) | Beethoven | German | N. A. | Classical | Fast | 181 | -0.28 | Minor |
| 443 | Take a step back | Every Avenue | American | English | Alternative Rock | Moderate | 116 | -0.08 | Minor |
| 444 | Take five | The Dave Brubeck quartet | American | N. A. | Jazz | Moderate | 83 | -0.15 | Minor |
| 445 | Take me home | Cayman Cline | American | English | Rap | Moderate | 119 | 0.01 | Major |
| 446 | Take me to church | Hozier | Irish | English | Indie Rock | Fast | 129 | -0.25 | Minor |
| 447 | Tale as old as time (Beauty and the beast movie) | Disney | American | English | Pop | Fast | 157 | 0.29 | Major |
| 448 | Ten thousand ways to die | Obituary | American | English | Funk | Fast | 186 | -0.04 | Minor |
| 449 | Thank you | MKTO | American | English | Pop- rock | Fast | 126 | -0.20 | Major |
| 450 | Thank you for saving me | Martin Smith | English | English | Alternative rock | Slow | 90 | -0.15 | Minor |
| 451 | That should be me | Justin Bieber | Canadian | English | Pop, dance pop | Slow | 68 | 0.12 | Minor |
| 452 | That’s what I like | Bruno Mars | British | English | Pop | Fast | 134 | 0.19 | Minor |
| 453 | The alphabet song | ESL Kids Games | Spain | English | Cartoons | Moderate | 116 | 0.11 | Major |
| 454 | The backyardigans theme song remix | Attic Stein | American | English | Streetpunk | Fast | 192 | -0.05 | Minor |
| 455 | The boys are back | Dropkick Murphys | American | English | Streetpunk | Fast | 140 | 0.09 | Major |
| 456 | The Christmas song | Vince Guaraldi | American | English | Jazz - piano | Fast | 186 | 0.25 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 457 | The cold | Exitmusic | American | English | Pop | Slow | 67 | -0.26 | Minor |
| 458 | The cure | Lady Gaga | American | English | Pop | Moderate | 112 | 0.33 | Major |
| 459 | The duck song | Bryant Oden | American | English | Cartoons | Fast | 187 | -0.03 | Major |
| 460 | The duck song 3 | Bryant Oden | American | English | Cartoons | Moderate | 105 | 0.05 | Major |
| 461 | The final countdown | Europe | Swedish | N. A. | Rock | Fast | 145 | -0.14 | Minor |
| 462 | The force theme (Star Wars Episode IV) | Meco Monardo | American | N. A. | Instrumental | Moderate | 98 | -0.07 | Minor |
| 463 | The fox (what does the fox say) | Ylvis | Norwegian | English | Pop | Fast | 128 | 0.19 | Major |
| 464 | The greatest | Sia, Kendrick Lamar | Australian | English | Pop | Fast | 128 | -0.07 | Major |
| 465 | The heart wants what it wants | Selena Gomez | American | English | Pop | Moderate | 111 | -0.09 | Minor |
| 466 | The house hunting song | Pendleton Ward | American | English | Soundtrack | Fast | 126 | -0.10 | Minor |
| 467 | The imperial march (Darth Vader's theme) | John Williams | American | N. A. | Instrumental | Moderate | 105 | -0.17 | Minor |
| 468 | The Jedi steps and finale | John Williams | American | N. A. | Instrumental | Moderate | 103 | -0.25 | Minor |
| 469 | The loud house intro | Nickelodeon | American | English | Cartoons | Fast | 185 | -0.06 | Minor |
| 470 | The miracle of Joey Ramone | U2 | Irish | English | Rock | Fast | 134 | -0.15 | Major |
| 471 | The oaf | Big Wreck | American | English | Pop- rock | Fast | 135 | -0.16 | Minor |
| 472 | The piano | EY - Bass Nation | American | English | Dance | Moderate | 107 | 0.06 | Major |
| 473 | The snake | Renée Christopher | Canadian | N.A. | Classical | Moderate | 118 | -0.11 | Minor |
| 474 | The time is now (You Can't See Me) | John Cena, Tha Trademarc | American | English | rap- reggae | Moderate | 111 | -0.13 | Minor |
| 475 | The weekend whip (LEGO Ninjago theme) | The Fold | American | English | Indie rock | Fast | 163 | 0.19 | Major |
| 476 | The Wheels On The Bus - Fun Songs for Children | LooLoo Kids | American | English | Cartoons | Fast | 136 | 0.27 | Major |
| 477 | Them bones | Alice in Chains | American | English | Metal | Fast | 164 | -0.15 | Minor |
| 478 | Thinking out loud | Ed Sheeran | British | English | Pop | Moderate | 78 | 0.13 | Major |
| 479 | This house is not for sale | Bon Jovi | American | English | Hard rock | Fast | 122 | -0.04 | Major |
| 480 | This is what you came for | Calvin Harris | British | English | Electronic dance music | Fast | 166 | 0.17 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 481 | This life | Curtis Stigers, The Forest Rangers | American | English | Pop | Fast | 161 | -0.23 | Minor |
| 482 | Thomas the tank engine theme song | Nick Jr. | British | English | Cartoons | Moderate | 106 | 0.14 | Major |
| 483 | Three pistols | The Tragically Hip | Canadian | English | Pop | Fast | 133 | -0.04 | Minor |
| 484 | Through it all | Hillsong Worship | Australian | English | Pop | Moderate | 75 | 0.15 | Major |
| 485 | Thundershuk | AC/DC | American | English | Pop, dance | Fast | 134 | 0.04 | Major |
| 486 | Tik tok | Ke$ha | American | English | Rap - Funk | Moderate | 113 | 0.03 | Major |
| 487 | Timber | Pitbull | American | English | Pop | Fast | 130 | 0.21 | Major |
| 489 | TNT | AC/DC | Australian | English | Hard rock | Fast | 125 | -0.13 | Minor |
| 490 | TNT | CaptainSparklez | American | English | Pop | Moderate | 120 | -0.05 | Major |
| 491 | Tokyo drift | Teriyaki boyz | Japanese | English | Hip hop | Fast | 129 | -0.23 | Minor |
| 492 | Tonigh you belong to me | Eddie Vedder | American | English | Pop | Moderate | 109 | 0.05 | Major |
| 493 | TOOPY and BINOO theme song 2013 | TV Channel | Canadian | English | Cartoons | Fast | 132 | -0.09 | Major |
| 494 | Trap queen | Fetty Wap | American | English | Rap | Moderate | 99 | 0.24 | Major |
| 495 | Treat you better | Shawn Mendes | Canadian | English | Pop | Moderate | 111 | -0.07 | Minor |
| 496 | Trillian and Arthus reinvented | Disney | American | English | Soundtrack | Fast | 135 | 0.13 | Major |
| 497 | Trophies | Young Money | American | English | Hip hop | Moderate | 114 | 0.06 | Major |
| 498 | Truly madly deeply | Savage Garden | Australian | English | Pop | Fast | 167 | -0.15 | Minor |
| 499 | Trumpets | Jason Derulo | American | English | R&B | Fast | 159 | 0.14 | Major |
| 500 | Tu peux partir | Daniel Bélanger | Canadian | English | Pop | Fast | 179 | 0.13 | Major |
| 501 | Tunnel vision | Kodak Black | American | French | RAP | Moderate | 114 | -0.04 | Minor |
| 502 | Turn down for what | DJ snake | French | English | Electronic | Fast | 133 | 0.19 | Major |
| 503 | Twinkle twinkle little star | Rhymes for the Nursery | English | English | Cartoons | Moderate | 88 | 0.18 | Major |
| 504 | Uma Thurman | Fall Out Boy | American | English | Pop | Fast | 150 | 0.12 | Major |
| 505 | Under pressure | Queen | British | English | Pop | Moderate | 114 | -0.07 | Major |
| 506 | Undergound girl | Blondie | American | English | New wave | Fast | 169 | 0.01 | Major |
| 507 | Undo it | Carrie Underwood | American | English | Pop | Fast | 155 | 0.04 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 508 | Unsteady | X Ambassadors | American | English | Rock | Moderate | 116 | 0.08 | Minor |
| 509 | Uptown funk | Mark Ronson, Bruno Mars | British | English | Pop funk | Moderate | 115 | -0.08 | Minor |
| 510 | Veltvodle street music | Disney | American | English | Jazz | Fast | 176 | 0.08 | Major |
| 511 | Vertigo | U2 | Irish | English | Rock | Fast | 140 | -0.15 | Minor |
| 512 | Via dolorosa | Lea Salonga | Philippines | English | Church | Slow | 67 | -0.13 | Minor |
| 513 | Victorious | Panic! At the Disco | American | English | Pop, dance | Moderate | 110 | -0.14 | Minor |
| 514 | Victory's won85 | Concordia Publishing House | American | English | Children pop rock | Moderate | 100 | -0.08 | Major |
| 515 | Viva la vida | Coldplay | British | English | Rock | Fast | 138 | 0.34 | Major |
| 516 | Vivir mi vida | Marc Anthony | American | Spanish | Pop | Moderate | 95 | 0.34 | Major |
| 517 | Wanna be startin' somethin' | Michael Jackson | American | English | Funk pop | Fast | 163 | -0.07 | Minor |
| 518 | Wasn't expecting that | Jamie Lawson | British | English | Pop guitar | Fast | 175 | 0.16 | Major |
| 519 | Watch me (whip/nae nae) | Silentò | American | English | Rap | Fast | 140 | -0.27 | Minor |
| 520 | Waving flag | Young artists for Haiti | Canadian | English | Pop | Moderate | 68 | -0.02 | Major |
| 521 | We can't stop the beat | Miley Cirus | American | English | Pop , rock | Moderate | 80 | -0.03 | Minor |
| 522 | We don’t believe what's on TV | 21 Pilots | American | English | pop | Moderate | 120 | 0.17 | Major |
| 523 | We don't talk anymore | Charlie Puth, Selena Gomez | American | English | Pop | Moderate | 105 | 0.00 | Major |
| 524 | We exist | Arcade Fire | Canadian | English | Rock | Moderate | 116 | 0.00 | Minor |
| 525 | We will rock you | Queen | American | English | Rock | Moderate | 80 | -0.18 | Major |
| 526 | Welcome to the jungle | Guns 'n' Roses | American | N.A | Hard rock | Moderate | 111 | -0.09 | Minor |
| 527 | What a wonderful world | Louis Armstrong | American | English | Jazz | Moderate | 111 | 0.19 | Major |
| 528 | What about us | P!nk | American | English | Pop | Moderate | 114 | 0.10 | Minor |
| 529 | What do you mean | Justin Bieber | Canadian | English | Pop | Fast | 125 | 0.14 | Major |
| 530 | What is a shooting star | Louis Singer | American | English | Children pop rock | Moderate | 96 | -0.27 | Minor |
| 531 | What's up | 4 Non Blondes | American | English | Rock | Fast | 136 | 0.10 | Major |
| 532 | Where are u now | Skrillex, Diplo, Justin Bieber | American | English | Pop | Fast | 140 | 0.11 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 533 | Where is the love | The Black Eyed Peas | American | English | Pop | Moderate | 91 | 0.23 | Major |
| 534 | Wherever I go | OneRepublic | American | English | Pop | Moderate | 97 | -0.16 | Minor |
| 535 | White iverson | Post Malone | American | English | Rap/hip hop | Moderate | 85 | 0.10 | Major |
| 536 | Who let the dogs out | Baha Men | Bahamian | English | Pop | Fast | 131 | 0.09 | Major |
| 537 | Wildest dreams | Taylor Swift | American | English | Pop | Moderate | 140 | 0.00 | Minor |
| 538 | Wings | Little mix | American | English | Pop | Moderate | 115 | 0.10 | Major |
| 539 | Winnie the Pooh theme song | Disney | American | English | Cartoons | Fast | 157 | 0.10 | Major |
| 540 | Work | Rihanna, Drake | American | English | Pop | Moderate | 92 | -0.11 | Minor |
| 541 | Work from home | Fifth Harmony | Canadian | English | pop | Moderate | 110 | 0.09 | Minor |
| 542 | Worth it | Fifth Harmony | Canadian | English | Pop/R&B | Moderate | 112 | 0.03 | Minor |
| 543 | Wrecking ball | Miley Cyrus | American | English | Pop | Fast | 121 | -0.06 | Minor |
| 544 | XO tour llif3 | Lil Uzi Vert | American | English | Rap/hip hop | Moderate | 78 | -0.34 | Minor |
| 545 | Yellow submarine | Beatles | British | English | Pop | Moderate | 110 | 0.09 | Major |
| 546 | Yesterday | Beatles | British | English | Rock | Moderate | 91 | 0.04 | Minor |
| 547 | Yo ho (a pirate's life for me) | Disney | American | N.A | Soundtrack | Fast | 121 | -0.17 | Minor |
| 548 | Yonce | Beyonce | American | English | Rap | Fast | 176 | -0.05 | Minor |
| 549 | You can't touch this | MC Hammer | American | English | Rap | Moderate | 90 | 0.09 | Major |
| 550 | You shook me all night long | AC/DC | Australian | English | Hard rock | Moderate | 118 | -0.13 | Major |
| 551 | You was right | Lil Uzi Vert | American | English | Rap/hip hop | Moderate | 82 | -0.02 | Minor |

Tempo groups: slow (40 to 72 bpm), moderate (72 to 120 bpm) and fast (120 to 208 bpm); bpm – beats per minute; Mode (v) – value given for the mode by the MIR toolbox software; N.A. - not available; EDM – Electronic Dance Music; R&B – rhythms and blues; K-pop - Korean pop; * - name of the song translated to English

*Note: Not all songs identified as familiar in visit 1 were identified as familiar in the MEG (6.7/8 in TD and 5.8/8 in ASD). As such we used the in-scanner familiarity assessment in analyses*

Supplementary table 2 (5-S2): List of unfamiliar songs used in this study

| N | Name of the song | Artist | Nationality | Language lyrics | Genre | Tempo (group) | Tempo | Mode (V) | Mode |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1985 | Haken | English | English | Rock/metal | Moderate | 95 | 0.13 | Major |
| 2 | Dreaming Wild | Klahr & Kev | Swedish | English | Electronic | Moderate | 105 | 0.08 | Major |
| 3 | Jumbo [NCS Release] | Alex Skrindo | Danish | Instrumental | Electronic | Fast | 130 | -0.08 | Minor |
| 4 | Kick Out The Jams - | The Portugal Japan | Japanese | English | Punk Rock | Moderate | 116 | -0.17 | Minor |
| 5 | Star Citizen Main Theme | Pedro Macedo | Portuguese | Instrumental | Orchestral | Fast | 131 | -0.08 | Minor |
| 6 | Walk on Water | Ira Losco | Maltese | English | Rap | Fast | 174 | -0.09 | Minor |
| 7 | Rock lobster | The B-52's. | American | English | New wave | Fast | 182 | -0.06 | Minor |
| 8 | 100Ms | Dave | British | English | Rap/hip hop | Moderate | 71 | -0.08 | Minor |
| 9 | 3 Wheel-ups | Kano | British | English | Rap/hip hop | Moderate | 76 | -0.12 | Minor |
| 10 | A little respect | Silence 4 | Portuguese | English | Pop | Moderate | 110 | 0.27 | Major |
| 11 | A million voices | Polina Gagarina | Russian | English | Pop | Fast | 139 | -0.05 | Minor |
| 12 | Agnus Dei | Pedro Macedo | Portuguese | Instrumental | Orchestral | Moderate | 100 | -0.27 | Minor |
| 13 | All I Have Is My Soul | Natascha St. Pier | French | English | Pop | Moderate | 95 | 0.16 | Major |
| 14 | Alphabet, Phonics Songs Beavers | Busy Beavers | American | English | Cartoons | Moderate | 111 | 0.08 | Major |
| 15 | Alquimia, segredo guardado | Carina Freitas | Portuguese | Instrumental | Classic | Fast | 153 | -0.02 | Minor |
| 16 | Amanecer | Edurne | Spanish | Spanish | Pop | Moderate | 85 | -0.19 | Minor |
| 17 | Another Life E | Afrojack, David Guetta | Dutch | English | Electronic | Fast | 145 | -0.01 | Minor |
| 18 | Atmosphere | Joy Division | English | English | Rock | Moderate | 115 | -0.07 | Major |
| 19 | Au printemps | Jacques Brel | Belgian | French | Pop | Moderate | 85 | 0.04 | Major |
| 20 | Automatic | Inverted Mountain Beats | Dutch | Instrumental | Electrohouse | Moderate | 118 | 0.25 | Major |
| 21 | Back to life | Mikkel Solnado | Portuguese | English | Pop rock | Fast | 128 | 0.14 | Major |
| 22 | Beautiful | Chip | English | English | Rap/hip hop | Moderate | 88 | -0.03 | Minor |
| 23 | Beauty Never Lies | Bojana Stamenov | Serbian | English | Pop | Moderate | 85 | -0.16 | Minor |
| 24 | Big Man +BB2:B136 | Hyperaptive | British | English | Rap | Moderate | 95 | -0.02 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 25 | Black Tears | Hands on approach | Portuguese | English | Pop | Fast | 135 | 0.26 | Major |
| 26 | Blink | Cascada | German | English | Dance/Techno | Fast | 128 | 0.09 | Major |
| 27 | Blood Red Sandman | Lordi | Finnish | English | Hard rock | Fast | 124 | -0.01 | Major |
| 28 | Break of Day | Edurne | Spanish | English | Pop | Fast | 123 | -0.28 | Minor |
| 29 | Breathing Deeper | Shapov & MEG/NERAK | Russian | English | Electronic | Fast | 166 | 0.12 | Major |
| 30 | Bring it back | Catherine Russell | American | English | Jazz | Moderate | 74 | -0.03 | Major |
| 31 | Built To Last | HammerFall | Swedish | English | Hard rock | Moderate | 105 | 0.00 | Minor |
| 32 | Busy for me | Aurea | Portuguese | English | Jazz | Fast | 182 | 0.03 | Minor |
| 33 | Cancao de ninar | Se acalme | Brazilian | Instrumental | Cartoons | Moderate | 90 | 0.11 | Major |
| 34 | Carcassonne | George Brassens | French | French | Pop | Fast | 136 | -0.01 | Major |
| 35 | Champions | Mikkel Solnado | Portuguese | English | Pop | Moderate | 86 | -0.09 | Minor |
| 36 | Cosmic Energy - Progressive House Mix | Fluidified | Finnish | Instrumental | Electrohouse | Fast | 170 | 0.16 | Major |
| 37 | Cosmic Energy 2 - Progressive House Mix | Fluidified | Finnish | Instrumental | Electrohouse | Fast | 128 | 0.06 | Major |
| 38 | Daisy | EZ Special | Portuguese | English | pop/rock | Fast | 147 | 0.12 | Major |
| 39 | Da-ma abraco | Miguel Gameiro | Portuguese | Instrumental | Piano | Moderate | 95 | 0.22 | Major |
| 40 | Danca dos Passaros | Antonio Pinho | Portuguese | Classical music | classical | Fast | 182 | 0.24 | Major |
| 41 | Dangerous | Cascada | German | English | Dance/Techno | Fast | 145 | 0.03 | Major |
| 42 | Days of your own | Hands on approach | Portuguese | English | Pop | Fast | 122 | -0.10 | Minor |
| 43 | Do it | Fingertips | Portuguese | Instrumental | pop | Fast | 129 | 0.10 | Major |
| 44 | Dollar bill | Screaming Trees | American | English | Grunge | Moderate | 82 | 0.13 | Major |
| 45 | Driving all night | EZ Special | Portuguese | Instrumental | Pop/rock | Moderate | 114 | -0.04 | Major |
| 46 | Duerme Negrito | Mercedes Sosa | Spanish | Spanish | Pop/Folk | Moderate | 78 | -0.08 | Major |
| 47 | Earthrise | Haken | English | English | Rock/metal | Moderate | 89 | 0.08 | Major |
| 48 | Easy to See | Feminnem | Croatian | English | Pop | slow | 64 | 0.09 | Minor |
| 49 | El arriero | Atahualpa Yupanqui | Argentine | Spanish | Pop/Folk | Fast | 125 | -0.19 | Minor |
| 50 | El Run Run | Estopa | Spanish | Spanish | Pop | Moderate | 86 | 0.22 | Major |

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|---|---|---|---|---|---|---|---|---|---|---|
| 51 | Euphoria | Loreen | Swedish | English | Pop | Fast | 176 | -0.17 | Minor |
| 52 | Evacuate the Dancefloor | Cascada | German | English | Dance/Techno | slow | 64 | -0.07 | Minor |
| 53 | Fairytale | Alexander Rybak | Norwegian | English | Ethnic | Moderate | 108 | -0.23 | Minor |
| 54 | Family | Chip feat Loick Essien | English | English | Rap/hip hop | Moderate | 80 | 0.23 | Major |
| 55 | Feeling myself | Chip | English | English | Rap/hip hop | Moderate | 95 | 0.06 | Major |
| 56 | Figurative Language | Pr2A | N.A. | English | Rap | Fast | 124 | -0.02 | Minor |
| 57 | First kiss | Alexander Rybak | Norwegian | English | Pop | slow | 71 | -0.26 | Minor |
| 58 | Flashbacks | Franco | Portuguese | English | Pop | Moderate | 120 | 0.24 | Major |
| 59 | Fly on the wings of love | Olsen Brothers | Dennish | English | Pop | Moderate | 104 | 0.13 | Major |
| 60 | Give Me The Night | George Benson | American | English | Funk | Moderate | 111 | 0.06 | Minor |
| 61 | Give Your Life For Rock And Roll | Lordi | Finland | English | Rock/metal | Moderate | 107 | 0.04 | Major |
| 62 | Glorious | Cascada | German | English | Dance/Techno | Fast | 128 | 0.09 | Minor |
| 63 | Golden Boy | Nadav Guedj | Israelis | English | voice | Moderate | 83 | -0.17 | Minor |
| 64 | Goodbye to Yesterday | Elina Born & Stig Rasta | Estonian | English | Pop | Moderate | 94 | 0.03 | Minor |
| 65 | Gravity | Zlata Ognevich | Ukraine | English | Pop | Fast | 170 | -0.10 | Minor |
| 66 | Gulliver Little Man of the Year | Hanna-Barbera Productions | American | Instrumental | Cartoons | Moderate | 80 | -0.21 | Minor |
| 67 | Hard Rock Hallelujah | Lordi | Finnish | English | Hard rock | Fast | 123 | -0.09 | Major |
| 68 | Head In The Clouds | Gazoon  Cartoons | American | English | Cartoons | Fast | 121 | 0.13 | Major |
| 69 | Hear them calling | Greta Salome | Icelander | English | Voice, guitar | Moderate | 117 | -0.35 | Minor |
| 70 | Here For You | Maraaya | Slovenian | English | Pop | Moderate | 105 | 0.01 | Minor |
| 71 | Hero March | Pedro Macedo | Portuguese | Instrumental | Orchestral | Moderate | 106 | -0.11 | Minor |
| 72 | Heroes | Mans Zelmerlow | Swedish | English | Pop | Moderate | 83 | -0.22 | Minor |
| 73 | Hour of the Wolf | Elnur Huseynov | Azerbaijani | English | Pop | Moderate | 108 | 0.22 | Major |
| 74 | I Don't Remember Your Name | Friðrik Dór | Icelandic | English | Dance/Techno | Moderate | 113 | 0.11 | Major |
| 75 | I feel like John Travolta | EZ Special | Portuguese | English | pop/rock | Moderate | 92 | 0.03 | Major |
| 76 | I miss you | Franco | Portuguese | English | Pop | Moderate | 104 | 0.25 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 77 | I really am such a fool | EZ Special | Portuguese | English | pop | Fast | 169 | -0.09 | Major |
| 78 | I Wanna | Maria N | Latvia | English | Pop/rock | Fast | 144 | -0.14 | Minor |
| 79 | Icebraker | Agnete | Norwegian | English | House music | Fast | 163 | 0.01 | Minor |
| 80 | I'd like to walk around in your mind | Vashti Bunyan | English | English | Folk | Fast | 127 | 0.22 | Major |
| 81 | Igneous | Moon Tooth | American | Instrumental | Metal | Fast | 125 | -0.09 | Major |
| 82 | I'll remember to forget | Rita Redshoes | Portuguese | English | pop | Moderate | 104 | 0.05 | Amb. |
| 83 | I'm alive | Ethaide | Albanian | English | Ethnic | Moderate | 103 | -0.04 | Minor |
| 84 | I'm fine | Chip feat. Stormzy & Shalo | English | English | Rap/hip hop | Fast | 169 | -0.02 | Minor |
| 85 | I'm on the road to happiness | Rita Redshoes | Portuguese | English | Pop | slow | 69 | -0.01 | Major |
| 86 | In Front Of Your Eyes | Garmiani | Swedish | English | Electronic | Fast | 125 | 0.00 | Minor |
| 87 | In love with U | EZ Special | Portuguese | English | pop/rock | Fast | 135 | 0.05 | Major |
| 88 | In My Place | Ana Free | Portuguese | Instrumental | Pop | Moderate | 97 | -0.20 | Minor |
| 89 | In n'Out | EZ Special | Portuguese | English | pop/rock | slow | 121 | -0.03 | Major |
| 90 | In the Air | Chipmunk feat Keri Hilson | English | English | Rap/hip hop | Moderate | 85 | -0.10 | Minor |
| 91 | In your eyes | Niamh Kavan | Irish | English | Pop | Fast | 129 | -0.09 | Minor |
| 92 | Integration I for two pianos | Pedro Macedo | Portuguese | Instrumental | Classic | Fast | 138 | 0.10 | Major |
| 93 | Jungle 81 | Rita Redshoes | Portuguese | English | Pop | slow | 63 | -0.09 | Minor |
| 94 | Kiss me, oh kiss me | David Fonseca | Portuguese | English | Pop | Moderate | 103 | -0.24 | major |
| 95 | Le Gorille | Georges Brassens | French | French | Pop | Fast | 124 | 0.00 | Major |
| 96 | Le Petit Cheval Blanc | Georges Brassens | French | French | Pop | Fast | 125 | 0.05 | Major |
| 97 | Les bonbons | Jacques Brel | Belgian | French | Pop | Moderate | 77 | -0.02 | Major |
| 98 | Les vieux | Jacques Brel | Belgian | French | Pop | Moderate | 72 | 0.26 | Major |
| 99 | Let's be in love | Hands on approach | Portuguese | English | Pop | slow | 76 | -0.03 | Major |
| 100 | Lighthouse | Nina Kraljić | Croatian | English | Rock | Moderate | 77 | 0.14 | Major |
| 101 | Live in Peace | One Love Family | Portuguese | English | Reggae | Fast | 133 | 0.01 | Major |
| 102 | Lolek und Bolek - Die Armbrust | N. A. | Polish | Instrumental | Cartoons | Fast | 133 | 0.21 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 103 | Lordi Devil Is A Loser | Lordi | Finnish | English | Heavy Rock | Moderate | 73 | -0.02 | Minor |
| 104 | Los ejes de mi carreta | Atahualpa Yupanqui | Argentine | Spanish | Pop/Folk | Moderate | 119 | -0.29 | Minor |
| 105 | Love injected | Aminata | Latvian | English | House music | Fast | 144 | 0.07 | Major |
| 106 | Love is | Katrina Elam | American | English | Country | Slow | 72 | 0.12 | Major |
| 107 | Magical | Nina | Serbian | English | Pop | Moderate | 92 | 0.18 | Major |
| 108 | Malabares | Estopa | Spanish | Spanish | Pop | Moderate | 111 | -0.19 | Minor |
| 109 | Marble Machine | Wintergatan | Swedish | Instrumental | New Age | Moderate | 98 | 0.24 | Major |
| 110 | Maya the Bee | Karel Svoboda | German | English | Cartoons | Fast | 124 | 0.30 | Major |
| 111 | Megadeth - Tornado of Souls (HD).wav' | Megadeth | American | English | Heavy Metal | Moderate | 79 | -0.25 | Major |
| 112 | Message to my girl | Split Enz | New Zealander | English | Rock | Moderate | 104 | -0.06 | Major |
| 113 | Moskau | Dschinghis Khan | German | German | Disco | Fast | 131 | 0.17 | Major |
| 114 | Move Faster | Fingertips | Portuguese | Instrumental | Pop | Fast | 127 | -0.16 | Minor |
| 115 | Music For Monetize | Joseespirit | N.A. | English | Progressive House | Fast | 128 | -0.06 | Minor |
| 116 | Musica Para Bebe Dormir | Cassio Toledo | N.A. | Instrumental | Cartoons | Moderate | 87 | 0.02 | Major |
| 117 | My number one | Helena Paparizou | Greek | English | Pop | Fast | 151 | -0.22 | Minor |
| 118 | My Own Beat | Leonar Andrade | Portuguese | English | Pop/rock | Moderate | 112 | -0.16 | Minor |
| 119 | My wonder moon | Hands on approach | Portuguese | English | Pop rock | Fast | 137 | 0.21 | Major |
| 120 | New Way to Go | Birgit | Estonian | English | Pop | Moderate | 72 | 0.15 | Major |
| 121 | No limits | Franco | Portuguese | English | Reggae | Fast | 175 | 0.20 | Major |
| 122 | No, No, Never | Texas Lightning | German | English | Pop | Moderate | 121 | 0.14 | Minor |
| 123 | Northern lights | Kate Boy | Swedish | English | Electropop | Moderate | 97 | 0.04 | Major |
| 124 | Numbers Counting Baby Songs, Nursery Rhymes | Busy Beavers | American | English | Cartoons | Moderate | 95 | 0.12 | Major |
| 125 | Oblivion | Tavram | N.A. | Instrumental | Electrohouse | Moderate | 99 | 0.09 | Major |
| 126 | Once Again | Friðrik Dór | Icelandic | English | Pop | slow | 65 | 0.16 | Minor |
| 127 | One For Me | ByeAlex | Hungarian | English | Pop | Fast | 161 | 0.07 | Major |
| 128 | Only teardrops | Emmelie de Forest | Danish | English | Pop/Ethnic | Moderate | 111 | -0.14 | Minor |

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|---|---|---|---|---|---|---|---|---|---|
| 129 | OPA! | Giorgos Alkaios & Friends | Greek | English | Ehtnic | Fast | 121 | -0.10 | Minor |
| 130 | Paisley | The Holydrug Couple | Chilean | English | Pop | Fast | 180 | 0.06 | Major |
| 131 | Para Llenarme De Ti | Ramón | Spanish | Spanish | Latin pop | Moderate | 102 | -0.22 | Minor |
| 132 | Pass Out | Tinie Tempah | British | English | Rap/hip hop | Moderate | 99 | -0.05 | Minor |
| 133 | Pat a mat | Lubomír Beneš | Czechoslovak | Instrumental | Cartoons | Moderate | 90 | 0.17 | Major |
| 134 | Picture of my own | Fingertips | Portuguese | Instrumental | Pop | Moderate | 123 | -0.04 | Minor |
| 135 | Planquez-vous | Keny Arkana | Argentine-French | French | Rap | Fast | 132 | -0.15 | Minor |
| 136 | Prendimi | Giovanni Allevi | Italian | Instrumental | Classical | Fast | 127 | 0.33 | Major |
| 137 | Professor Balthazar - Opening | Zlatko Grgić | Croatian | Instrumental | Cartoons | Fast | 144 | 0.13 | Major |
| 138 | Psych Out! | Garage Psyché | N.A. | English | Punk Rock | Fast | 128 | 0.31 | Major |
| 139 | Real | Of Mice and Men | American | English | Rock | Moderate | 113 | 0.05 | Major |
| 140 | Reksio - dog from Poland | Zenon Kowalowski | Polish | Instrumental | Cartoons | Fast | 137 | 0.02 | Major |
| 141 | Remember Afro House Music | DJ Manja | Portuguese | English | House music | Fast | 171 | 0.20 | Major |
| 142 | Rhythm inside | Lic Nottet | Belgium | English | Pop | Fast | 178 | -0.10 | Minor |
| 143 | Rise like a Phoenix | Conchita Wurst | Austrian | English | Pop Opera | Fast | 147 | -0.04 | Minor |
| 144 | Rumba Portuguesa | Intensa Music | Portuguese | English | Dance/Electronic | Fast | 171 | 0.07 | Major |
| 145 | Run Away | Sunstroke Project & Olia Tira | Moldovan | English | Rap | Fast | 130 | -0.03 | Minor |
| 146 | Russian Electro House 2013 Mix 70 | DJ Team Steve Strife & JayJay | Russian | Instrumental | Electrohouse | Fast | 135 | -0.05 | Minor |
| 147 | Safety dance | Men Without Hats | Canadian | English | New wave | Moderate | 106 | -0.03 | Major |
| 148 | Satellite | Lena Mayer-Landrut | German | English | Pop | Fast | 167 | -0.02 | Major |
| 149 | Scenario | A Tribe Called Quest | American | English | Rap | Fast | 169 | -0.09 | Minor |
| 150 | Sky | Alan Walker  Alex Skrindo | Norwegian | Instrumental | Electronic | Fast | 130 | -0.16 | Minor |
| 151 | Snow On the Sahara | Anggun | French | English | Pop | Moderate | 112 | -0.15 | Minor |
| 152 | Some People | Shapov & Beverly Pills | Russian | English | Electronic | Fast | 122 | 0.03 | Major |

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|---|---|---|---|---|---|---|---|---|---|---|
| 153 | Someone that cannot love | David Fonseca | Portuguese | English | Pop | Moderate | 103 | 0.32 | minor |
| 154 | Song from a secret garden | Cascada | German | English | Dance/Techno | Fast | 128 | 0.09 | Minor |
| 155 | Song from a secret garden | Alexander Rybak | Norwegian | English | Classic | Moderate | 118 | -0.23 | Minor |
| 156 | Starfarer (Youre the one for me | Pedro Macedo | Portuguese | Instrumental | Orchestral | Moderate | 90 | -0.14 | Minor |
| 157 | Start It Over | Club Dogo ft Cris Cab | Italian | English /Italian | Rap | Slow | 79 | -0.06 | Minor |
| 158 | Still in Love With You | Electro Velvet | British | English | Dance/Techno | Moderate | 117 | -0.14 | Minor |
| 159 | Storm pill | Moon Tooth | American | English | Metal | Fast | 185 | 0.00 | Minor |
| 160 | Sunlight | Nicky Byrne | Irish | English | Pop dance | Fast | 125 | 0.10 | Major |
| 161 | Sunshine | Vaquero | Spanish | English | Pop | Fast | 125 | 0.24 | Major |
| 162 | Suus | Rona Nishliu | Albanian | English | Jazz | Fast | 174 | -0.38 | Minor |
| 163 | Swallow my pride | Green River | American | English | Grunge | Moderate | 87 | 0.09 | Minor |
| 164 | Swing, brother, swing! | Catherine Russell | American | English | Jazz | Moderate | 110 | -0.19 | Minor |
| 165 | Tainted love | Soft Cell | British | English | Electronic | Fast | 145 | -0.02 | Major |
| 166 | Take me to your heaven | Charlotte Nilsson | Swiss | English | Pop/rock | Fast | 145 | 0.11 | Major |
| 167 | Talkin 'bout money | Fred the Godson | American | English | Rap | Moderate | 85 | -0.25 | Minor |
| 168 | Teenage Life | Daz Sampson | British | English | Rap | Fast | 180 | 0.16 | Major |
| 169 | Tennessee Tuxedo Theme song | W. Watts Biggers | American | Instrumental | Cartoons | Fast | 140 | -0.02 | Major |
| 170 | The beginning song | Rita Redshoes | Portuguese | English | Pop | Fast | 140 | -0.09 | Minor |
| 171 | The Endless Knot | Haken | English | English | Rock/metal | Moderate | 80 | -0.18 | Minor |
| 172 | The Great Grape Ape Show | Hanna-Barbera Productions | American | Instrumental | Cartoons | Fast | 121 | -0.05 | Minor |
| 173 | The Inspector Main Theme | Henry Mancini | American | Instrumental | Cartoons | Fast | 126 | 0.22 | Major |
| 174 | The Mind's Eye | Haken | English | English | Rock | Fast | 131 | 0.22 | Major |
| 175 | The Terrorist | Dj Vadim | Russian | English | Rap/hip hop | Moderate | 105 | -0.03 | Minor |
| 176 | The Voice | Eimear Quinn | Irish | English | Ethnic/ folk | Moderate | 94 | -0.11 | Minor |
| 177 | The World Is Yours | Arch Enemy | Swedish | English | Hard rock | Fast | 185 | -0.06 | Minor |
| 178 | This Child | Kings Of Spade | American | English | Rock | Moderate | 104 | 0.00 | Major |

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|---|---|---|---|---|---|---|---|---|---|
| 179 | Tiger Boo - English Version | Jamstar Records | American | English | Cartoons | Fast | 182 | -0.18 | Minor |
| 180 | Time | Work Drugs | American | English | Electropop | Moderate | 89 | 0.07 | Major |
| 181 | Time to Shine | Melanie Reneu | Swiss | English | Pop | Fast | 144 | -0.05 | Minor |
| 182 | Tonight again | Guy Sebastian | Australian | English | Pop | Moderate | 73 | -0.15 | Minor |
| 183 | T-shirt Weather In The Manor | Kano | British | English | Rap/hip hop | Moderate | 99 | -0.02 | Minor |
| 184 | Unbroken | Maria Olafsdottir | Icelandic | English | Pop | Fast | 188 | 0.06 | Major |
| 185 | Vilas Morenas | Antonio Pinho | Portuguese | Instrumental | classical | Moderate | 109 | -0.04 | Minor |
| 186 | Wars for Nothing | Magyar Felirat | Hungarian | English | Pop | Moderate | 88 | 0.10 | Minor |
| 187 | We Are One | One Love Family | Portuguese | English | Reggae | Fast | 164 | 0.00 | Major |
| 188 | We Are Slavic | Donatan Cleo | Polish | English | Rap | Fast | 156 | -0.11 | Minor |
| 189 | We can do anything | Gabriel | Portuguese | English | Pop | Moderate | 82 | -0.25 | Minor |
| 190 | We Could Be The Same | maNga | Turkish | English | Rock | Fast | 133 | -0.13 | Minor |
| 191 | White Lies | Rita Redshoes | Portuguese | English | Pop | Moderate | 115 | 0.11 | Major |
| 192 | Witcher 3 Main Theme | Pedro Macedo | Portuguese | Instrumental | Orchestral | Moderate | 111 | -0.12 | Minor |
| 193 | Woman, snake | Rita Redshoes | Portuguese | English | pop/progressive | Moderate | 88 | -0.03 | Minor |
| 194 | Won't let you go | Franco | Portuguese | English | Pop | Moderate | 106 | 0.15 | Major |
| 195 | Yodel It | Ilinca ft Alex Florea | Romania | English | Rap | Moderate | 87 | 0.29 | Major |
| 196 | You're gone | Fingertips | Portuguese | English | Pop | slow | 62 | 0.21 | Major |

Tempo groups: slow (40 to 72 bpm), moderate (72 to 120 bpm) and fast (120 to 208 bpm); bpm – beats per minute; Mode (v) – value given for the mode by the MIR toolbox software; N.A. - not available.

Table 5-S3 – Top 8 spatial location and extent of ALE values for contrast 1 (familiar minus unfamiliar music) and AAL labels correspondence

| Cluster # | Volume (mm3) | ALE value | MNI | | | Side | Region | BA | AAL number | AAL Labels |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | | | | |
| **1** | 968 | 0.017 | 2 | 10 | 54 | Left | Superior Frontal Gyrus | 6 | 3 | Frontal Superior Left |
| **2** | 576 | 0.015 | -10 | -10 | 8 | Left | Thalamus (Ventral Lateral Nucleus) | | 77 | Thalamus Left |
| **3** | 440 | 0.015 | 0 | 0 | 64 | Left | Medial surface of Superior Frontal Gyrus | 6 | 23 | Frontal Superior Medial Left |
| **4** | 424 | 0.012 | -52 | 10 | 14 | Left | Inferior Frontal Gyrus | 44 | 11 | Frontal Inferior Opercular Left |
| **5** | 352 | 0.014 | -30 | 18 | 6 | Left | Claustrum | | 29 | Insula Left |
| **6** | 336 | 0.012 | -52 | -42 | 24 | Left | Superior Temporal Lobe | 13 | 81 | Temporal Superior Left. |
| **7** | 312 | 0.014 | 4 | 12 | 40 | Right | Cingulate Gyrus | 32 | 34 | Cingulum Mid Right. |
| **8** | 280 | 0.013 | -20 | 8 | -12 | Left | Lentiform Nucleus. | | 73 | Putamen Left |

Modified version of Freitas et al (2018) ALE values for Study 1. ALE values refer to the likelihood of obtaining activation evoked by listening to familiar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior; AAL: Automated Atlas.

Table 5-S4 – Top 8 spatial location and extent of ALE values for contrast 2 (unfamiliar minus familiar music) and AAL labels correspondence

| Cluster # | Volume (mm3) | ALE value | MNI | | | Side | Region | BA | AAL number | AAL Labels |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | | | | |
| **1** | 664 | 0.012 | -38 | -24 | 16 | Left | Insula | 13 | 29 | Insula Left |
| **2** | 488 | 0.008 | 6 | 30 | 36 | Right | Cingulate Gyrus | 32 | 34 | Cingulum Mid Right |
| **3** | 176 | 0.008 | 4 | 16 | 36 | Right | Cingulate Gyrus | 32 | 34 | Cingulum Mid Right |
| **4** | 160 | 0.008 | 38 | 58 | -10 | Right | Middle Frontal Gyrus | 10 | 8 | Frontal Mid Right |
| **5** | 160 | 0.008 | 8 | -72 | 30 | Right | Precuneus | 31 | 68 | Precuneus Right |
| **6** | 152 | 0.008 | -42 | -78 | -4 | Left | Inferior Occipital Gyrus | 19 | 53 | Occipital Inferior Left. |
| **7** | 152 | 0.008 | 16 | -92 | 20 | Right | Middle Occipital Gyrus | 18 | 52 | Occipital Mid Right. |
| **8** | 152 | 0.007 | 42 | -48 | 40 | Right | Inferior Parietal Lobule | 40 | 62 | Parietal Inferior Right |

Modified version of Freitas et al (2018) ALE values for Study 2. ALE values refer to the likelihood of obtaining activation evoked by listening to unfamiliar music stimuli in a given voxel of the standard template MRI. Coordinates are in the MNI space. Cluster #: The clusters are ranked according to their size in millimeters cubed (mm3). Abbreviations: BA, Brodmann area; x, medial-lateral; y, anterior posterior; z, superior-inferior. AAL: Automated Atlas.

Table 5-S5. Summary of all within-group network contrasts, regions of interest (ROI) analysis, task >rest, threshold = 3.0.

| Frequency-band | Measure | Condition | ASD ($p_{corr}$) | Controls ($p_{corr}$) |
|---|---|---|---|---|
| Theta | aec | Fam > Rest | 1 | 1 |
| | | Unfam > Rest | 1 | 1 |
| Alpha | aec | Fam > Rest | 0.924 | 0.894 |
| | | Unfam > Rest | 0.912 | 1 |
| Beta | aec | Fam > Rest | 0.966 | 0.954 |
| | | Unfam > Rest | 0.962 | 0.946 |
| Low Gamma 1 | aec | Fam > Rest | 0.404 | 0.966 |
| | | Unfam > Rest | 0.343 | 0.007* - significant |
| Low Gamma 2 | aec | Fam > Rest | 0.395 | 0.124 |
| | | Unfam > Rest | 0.041 | 0.418 |

*p < 0.025

Table 5-S6. Summary of all within-group network contrasts, regions of interest analysis (ROI), task >rest, threshold = 3.0.

| Frequency-band | Measure | Condition | ASD ($p_{corr}$) | Controls ($p_{corr}$) |
|---|---|---|---|---|
| Theta | wPLI | Fam > Rest | 0.217 | 1 |
| | | Unfam > Rest | 0.185 | 0.919 |
| Alpha | wPLI | Fam > Rest | 0.242 | 0.444 |
| | | Unfam > Rest | 0.865 | 1 |
| Beta | wPLI | Fam > Rest | 0.936 | 0.890 |
| | | Unfam > Rest | 1 | 0.108 |
| Low Gamma 1 | wPLI | Fam > Rest | 0.205 | 0.531 |
| | | Unfam > Rest | 0.197 | 0.220 |
| Low Gamma 2 | wPLI | Fam > Rest | 0.105 | 0.083 |
| | | Unfam > Rest | 0.376 | 0.008* - significant |

*p < 0.025

Table 5-S7. Summary of all within-group network contrasts, whole brain analysis, task >rest, threshold = 3.0.

| Frequency-band | Measure | Condition | ASD ($p_{corr}$) | Controls ($p_{corr}$) |
|---|---|---|---|---|
| Theta | aec | Fam > Rest | 1 | 1 |
| | | Unfam > Rest | 1 | 1 |
| Alpha | aec | Fam > Rest | 0.814 | 0.997 |
| | | Unfam > Rest | 0.997 | 0.995 |
| Beta | aec | Fam > Rest | 0.573 | 0.907 |
| | | Unfam > Rest | 0.246 | 0.568 |
| Low Gamma 1 | aec | Fam > Rest | 0.005* - significant | 0.004* - significant |
| | | Unfam > Rest | 0.007* - significant | 0* - significant |
| Low Gamma 2 | aec | Fam > Rest | 0.062 | 0.021 |
| | | Unfam > Rest | 0.014* - significant | 0.003* - significant |

*p < 0.025

Table 5-S8. Summary of all within-group network contrasts, whole brain analysis, task >rest, threshold = 3.0.

| Frequency-band | Measure | Condition | ASD ($p_{corr}$) | Controls ($p_{corr}$) |
|---|---|---|---|---|
| Theta | wPLI | Fam > Rest | 0.104 | 0.908 |
| | | Unfam > Rest | 0.267 | 0.903 |
| Alpha | wPLI | Fam > Rest | 0.53 | 0.802 |
| | | Unfam > Rest | 0.522 | 0.983 |
| Beta | wPLI | Fam > Rest | 0.954 | 0.864 |
| | | Unfam > Rest | 0.999 | 0.244 |
| Low Gamma 1 | wPLI | Fam > Rest | 0.703 | 0.144 |
| | | Unfam > Rest | 0.191 | 0.003* - significant |
| Low Gamma 2 | wPLI | Fam > Rest | 0.152 | 0.129 |
| | | Unfam > Rest | 0.036 | 0.006* - significant |

*p < 0.025

Table 5-S9. Correlation analysis within group (ASD and TD) between networks (1, 2 or 3) connectivity strength and 3SCQ and RBS measures

| Correlations | ASD Group | TD Group |
|---|---|---|
| SCQ-total and Network 1 connectivity strength | r = 0.210; p=0.419 | r = - 0.163; p=0.491 |
| SCQ-total and Network 2 connectivity strength | r = 0.394; p=0.118 | r = 0.034; p=0.888 |
| SCQ-total and Network 3 connectivity strength | r = -0.059; p=0.821 | r = 0.077; p=0.748 |
| RBS-R (IV) and Network 1 connectivity strength | r = -0.017; p=0.950 | r = -0.016; p=0.945 |
| RBS-R (IV) and Network 2 connectivity strength | r = 0.092; p=0.725 | r = -0.061; p=0.793 |
| RBS-R (IV) and Network 3 connectivity strength | r = -0.280; p=0.277 | r = 0.180; p=0.435 |

Network 1: ROI _theta; Network 2: ROI_ beta; Network 3 = WB _theta; SCQ: Social Communication Questionnaire; RBS-R (IV): Repetitive Behaviors Scale-Revised- subscale IV (Sameness).

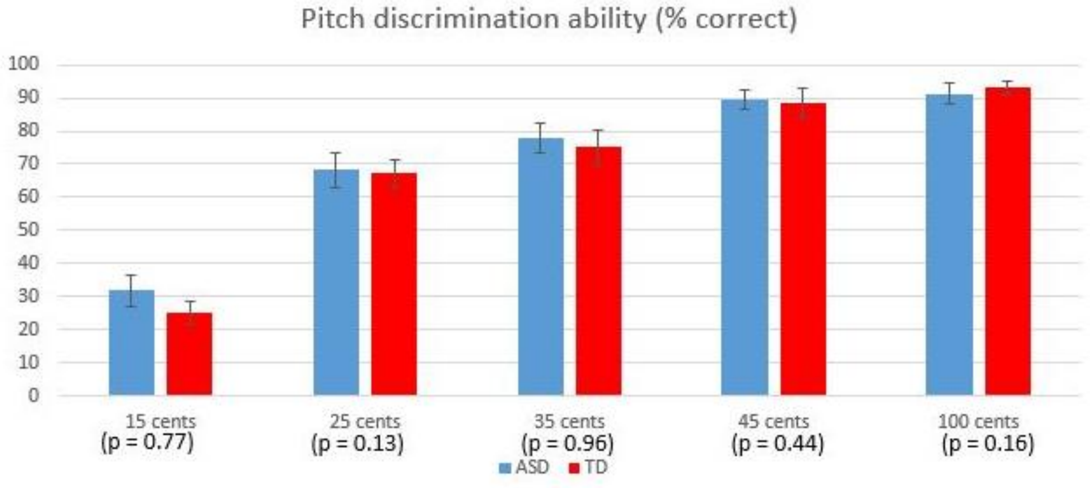

Figure 5-S1: Pitch discrimination ability of tone pairs tested in 5 conditions (15, 25, 35, 45 and 100 cents) in ASD and TD groups. There were no significant group differences within each condition.

# Chapter 6

# General Discussion

## 6.1 Summary of key findings

This thesis investigated the neural correlates of familiarity in music listening. The first aim of the thesis (study 1) was to ascertain which brain areas were most active when listening to familiar and unfamiliar songs by systematically reviewing existing studies in adults and performing a neuroimaging meta-analysis using the ALE method. We hypothesized that emotion and reward areas of the brain would be the most active regions during familiar music listening. The second aim was to determine if the processing of familiarity in music listening was shared or distinct in TD and ASD children (study 2). We used MEG as it enabled us to characterize functional connectivity during familiar and unfamiliar music conditions across multiple frequencies bands. The key findings of this thesis were:

The brain areas most frequently active when listening to familiar music in healthy adults were memory and motor related areas, namely, the left superior frontal gyrus, the ventral lateral nucleus of the left thalamus and the left supplementary motor area. These results were surprising as we had expected limbic structures as top clusters, as familiarity with music recruits emotion and reward areas of the brain. These active motor regions could reflect auditory-motor synchronization to music elements. In contrast, for unfamiliar music listening, the left insula and the right anterior cingulate were the brain regions with the most consistent activation, which may be associated either with the attempts to recognize the songs  or detection of novelty (Copland et al., 2007; Platel, 2005; Platel et al., 2003).

Typically developing children demonstrated increased gamma phase synchronization (known to be related to attention and perception mechanisms) when listening to familiar songs compared to unfamiliar songs. The resulting connectivity network was very similar to the results obtained in our neuroimaging meta-analysis. This network consisted of widespread areas (frontal, parietal, temporal and subcortical) which were associated with various functions (expressive language, emotional processing, memory recollection, mental imagery and auditory-motor synchronization).

Compared to controls, ASD children showed increased amplitude connectivity during the processing of unfamiliar songs, in the theta and beta-bands. Atypical processing of unfamiliar stimuli has been previous reported, which suggests that ASD children process novel stimuli differently. The processing of familiar music was similar in children with autism and controls.

## 6.2 Discussion

### 6.2.1 Neural correlates of familiarity in music listening

Several neuroimaging studies using different modalities have previously reported the neural correlates of familiarity in music listening in typically developing adults, but results were not consistent (see **Section 2.2.4**). Chapter 4 of this thesis (study1) described the systematic review and meta-analysis which extends our understanding of the brain structures most consistently active in the processing of familiar and unfamiliar music.

We found that motor brain structures (ventral lateral nucleus of the thalamus, SMA) were consistently active during familiar music listening. The activation of these motor related areas could reflect auditory-motor synchronization to elements of the music, such as rhythm, melody, so that a one can tap, dance and inner sing along with a known song.

Activation of motor circuitry during music listening is not a novel finding (Chen et al., 2008a, 2008b; Zatorre et al., 2007), but the knowledge that it is consistently active during familiar rather than unfamiliar music is. This finding related to music familiarity processing has already contributed meaningfully to the field of neuroscience of music, as evident by recent citations by three different research groups. Their work investigated amusia (Sihvonen et al., 2019), using electroencephalography (EEG) and pupillometry to explore the temporal signatures of the brain processes  between a familiar and unfamiliar piece of music (Jagiello et al., 2019) and preservation of musical memory in Alzheimer´s disease (Groussard et al., 2019).

This interdisciplinary field of music neuroscience also aims to understand how music can mitigate impairments from disorders by promoting neuroplastic brain changes. The new information provided by study 1 can guide and reinforce neurorehabilitation interventions, for example, the music supported therapy (MST) developed to restore motor deficits (Schneider et al., 2010). In patients with stroke, music activates multiple neural regions (including auditory and premotor cortex), and may modulate neuroplasticity in the motor cortex (Chen, 2018; Grau-Sánchez et al., 2013; Ripollés et al., 2016). As such, the audio–motor coupling during familiar music listening could directly facilitate the execution of movements and motor recovery, especially in those patients with auditory and motor regions intact. Although the Cochrane review (Magee et al., 2017) concluded that the quality of evidence for MST in stroke recovery was low, this weakness was mostly due to methodological bias and small sample sizes; thus better research is needed in the future to determine the role of familiar music in therapeutic interventions.

### 6.2.2 Functional connectivity using a music familiarity task

This was the first study to investigate brain connectivity patterns involved in familiarity in music listening in both typically developing and children with ASD using MEG.

#### 6.2.2.1 Typical developing children

One of the hypotheses of study 2 was that TD children would process familiar music in a similar way as typical adults. This was confirmed, as a connectivity network in these participants in the gamma band for familiar songs included brain areas very similar to the results obtained in our neuroimaging meta-analysis. This knowledge contributes to the advancement of the field of music neuroscience, as this information is new and, at the neural synchrony level, revealed the frequency band associated with this task, using MEG.

The most comparable music-related MEG study was completed by Fujioka et al. (2012) in a clinical population of 3 patients with stroke. The authors demonstrated that listening and tapping to a beat were both associated with the periodic modulation of beta oscillations in the brain. Oscillations in the beta-band are typically linked to motor functions. This research provided insight into how rhythmic auditory stimulation (RAS) using music or metronome sounds may successfully enhance rehabilitation exercises through activating the sensorimotor beta-band network.

#### 6.2.2.2 Children with ASD

There was no difference between children with ASD and TD in processing familiar songs. This highlights a relatively preserved function and a relative strength in children with ASD that may have implications for design of strength-based interventions in clinical and educations settings. However, these results cannot address whether this is specific to music, as it could be domain-nonspecific to all familiar auditory stimuli. As such, future research is needed to compare the processing of familiar music to the processing of other familiar auditory stimuli (i.e. speech or environmental sounds).

The processing of unfamiliar songs revealed increased functional connectivity in children with ASD, in theta and beta frequencies bands using amplitude envelope correlations (AEC). Theta and beta band are frequencies associated with long-range communications (long distance connections) that comprise large-scale networks. While theta oscillations are important for temporal integration and for the detection of sounds (Florin et al., 2017), beta oscillations are implicated in motor functions (Engel and Fries, 2010). Both atypicalities observed using the AEC measure provide information of local signal power that underlies large scale cortical interactions. Our findings of atypical patterns of connectivity in children with ASD are in line with the “connectivity theory” of autism (Belmonte, 2004; Just, 2004) and consistent with MEG literature in children with ASD using different task-specific frequencies bands (Doesburg et al., 2013; Safar et al., 2018), resting state (O’Reilly et al., 2017) and across modalities (Belmonte, 2004; Hong et al., 2019).

The processing of other unfamiliar stimuli, such as faces, has also been reported to be atypical (Leung et al., 2014; Safar et al., 2018; Simmons et al., 2009) (section 2.3.3.1). One potential explanation was either enhanced or reduced attention or motivation to attend familiar and unfamiliar faces respectively. Taken together, our finding of atypical processing of unfamiliar music and previous research on unfamiliar faces reinforce that processing novelty is a challenge for the ASD population.

## 6.3 Limitations, strengths and future directions

This thesis consisted of two studies that are methodologically distinct. For this reason, strengths and limitations are specific to each of them.

With regards to the meta-analysis on the neural correlates of familiarity in music listening (study 1), the small number of studies (n=11) limited its statistical power. In addition, only four of these studies provided statistically robust results (corrected *p* values). The novel findings were nevertheless interesting, as they suggested motor circuitry involvement in music familiarity rather than reward circuitry. Future studies need to be better-powered and account for heterogeneity in the type of music task, stimuli complexity, presence or absence of lyrics, subject characteristics, clinical population and music expertise.

The advantage of conducting systematic reviews and meta-analyses is that available evidence is quantitatively synthesized, in order to establish what is known and to identify gaps and refine future studies. The consistent finding that listening to familiar music activates motor brain areas contributes to what is known and may have therapeutic applications that need to be tested in a clinical context. For example, familiar music could facilitate motor adaptation learning, in similar ways as it has been reported with pleasurable music (Bock, 2010; Chen et al., 2008a; Fujii et al., 2017). In the ASD population, familiar music could benefit those children with motor impairments such as clumsy gait, poor balance, posture instability and delayed motor development (Janzen and Thaut, 2018) but may also be of benefit for functions that require motor planning such as speech.

In study 2, there are shortcomings to be addressed related to our sample size and sample characteristics. The sample size of our cross-sectional cohort is 48 participants, 24 typically developing children and 24 children with ASD. Although comparable to other studies, the sample size presents some challenges in terms of power especially given that ASD is a heterogeneous disorder. One barrier to recruitment that may require technical solution is the high rate ferromagnetic dental work, such as dental fillings and braces in this age group, which interfere with the MEG recordings. The second potential limitation is that our clinical and control groups were not matched on IQ, although both groups had IQs in the average range. There is controversy in the field about whether it is appropriate to adjust for IQ in cognitive studies of neurodevelopmental disorders. Specifically, one theoretical argument states that the IQ construct is a volatile index of global functioning, dependent on multiple correlated abilities, and that it measures aptitude and potential, rather than achievement and performance (Dennis et al. 2009). Still, listening to familiar and unfamiliar songs and rating them is a low cognitive demand task and as such small IQ differences within the average range are unlikely to be a confounding factor.

Another limitation is that we did not assess the rhythm abilities of our participants. Given the fact that the successful recognition of familiar songs builds on melody and rhythm identification (see **Section 2.1**.), differences in these skills could be a confounding factor for music memory recognition. Future music studies could use tests like the child version of the Rhythm Synchronization Task (c-RST) (Ireland et al., 2018) to assess rhythmic skills.

For a full understanding of atypical brain connectivity in children with ASD it would have been ideal to include the cerebellum in our analyses. Not only has this structure has been described as one of the most frequent disrupted brain regions in ASD individuals, but it also plays a key role in rhythm and timing processing which is relevant for music recognition. However, due to technical and methodological reasons, its activity is not reliably measured with MEG. First, the deep and posterior location of the cerebellum in the skull implies relatively low signal-to-noise ratio (Marek et al., 2018). Second, the cerebellar cortex is organized in a densely folded form, consisting of inhibitory Purkinje cells causes opposing current sources and a weak signal (Lin et al., 2018). In fact, less than 1% of MEG literature has investigated the cerebellum (Dalal et al., 2013), due to these difficulties and the unreliability of the MEG signals from the cerebellum

One of study 2’s strengths is its ecological validity, as we used each participant´s self-selected familiar songs as our research materials. As such our results can be generalized and applied to real-world settings, either educational and/or clinical. Furthermore, we are aware that variability in analytic approaches can significantly influence research outcomes. Methodological differences can be related to the type of analysis (sensor-space versus source-space), type of head model (sphere versus multi-sphere), connectivity measure (PLI, wPLI, AEC), frequency-band selection and method used for multiple comparison correction. We developed a robust experimental paradigm and analytic pipeline, which we share in detail to facilitate replication in the future.

Several future considerations are worth contemplating given what we have learnt. Firstly, longitudinal MEG studies will be relevant to investigate the developmental trajectory of the familiarity effect in music listening in the ASD population. It would be important to examine whether differences identified in unfamiliar music processing persist in similar frequency bands and the networks involved across the lifespan. Secondly, given the variability of unfamiliar music each participant was exposed to in study 2, it would be interesting to select participants (TD and ASD children) that listened to the same set of unfamiliar songs and re-analyze their processing. This approach would reduce noise, as it would reduce variability in music characteristics such as genre, tempo, mode, dissonance, language, orchestration among others that may influence the results, but would require a much larger N to have sufficient numbers of participants with the same unfamiliar songs. Thirdly, building on knowledge of atypical processing of unfamiliar songs by children with ASD compared to TD children, in the theta and beta band, future studies could investigate the potential role of entrainment (synchronization of independent rhythmical processes) between brain rhythms and the tempo (beats per minute) of a song to facilitate therapeutic advancements, such as rhythmic training to improve sensorimotor functioning in ASD, which is gaining increasing attention (Bharathi et al., 2019). Overall, research in the field of neuroscience of music can lead to the development of music therapy techniques that propel cortical plasticity for rehabilitation programs for a range of medical conditions.

## 6.4 Concluding remarks

Clarifying the neural correlates of familiarity in music listening in typically developed adults allowed us to learn that motor brain structures are the most consistently active regions during familiar music listening. Characterizing functional connectivity using a music familiarity task in TD and ASD children confirmed that: i) TD children recruit a similar brain network as those in typical adults; ii) children with ASD show intact processing of familiar songs but atypical processing of unfamiliar songs in theta and beta-bands. The atypical functional connectivity of unfamiliar stimuli reinforced that processing novelty is a challenge for children with ASD and future studies are needed to further uncover the underlying neural mechanisms.

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# Appendices

## 7.1 Supplementary Methods for Study 2: Atypical brain connectivity during a music familiarity task in children with autism

For the first study session, participants were asked to bring their familiar music (10 liked and 10 disliked musical pieces), in mp3 or wave file format. Each participant was also asked to rate the self-selected songs that they brought for likeability, fill a questionnaire about music background and interests and completed a pitch discrimination test. We will explain in more detail these assessments.

### 7.1.1 Rating songs for likeability

All participants brought their familiar liked and disliked songs. In order to quantify the likeability we used a visual face displays rating scale previously used by Dennis et al. (2000) in a study on emotion recognition in ASD children (Figure 7-1). Number 1 refers to the most liked and number 5 to the least liked or most disliked. We collected the data to a form.

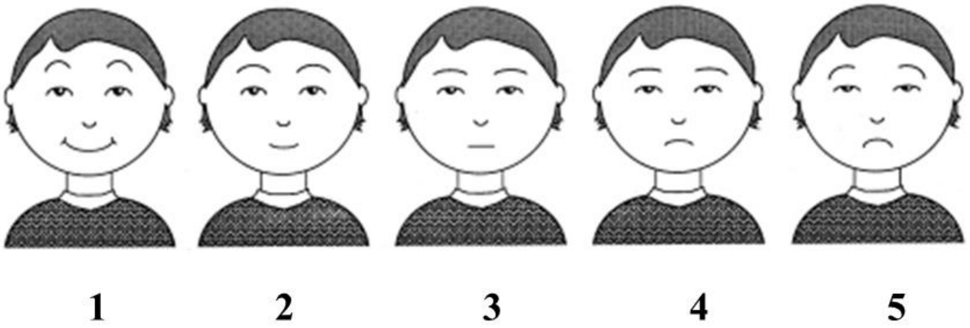


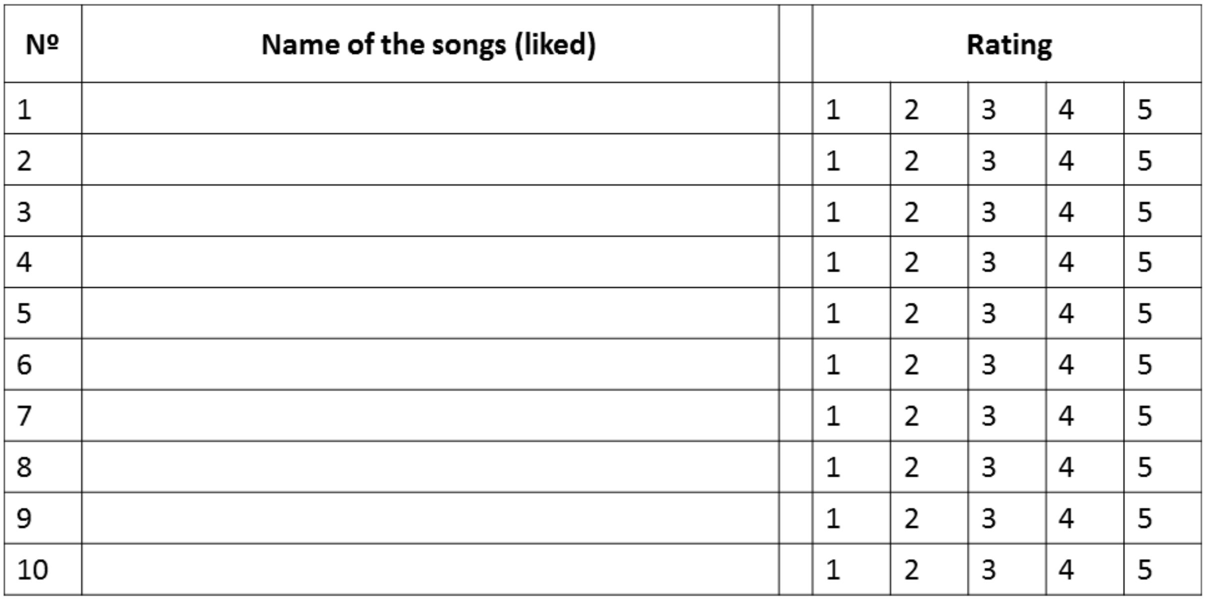
Figure 7-1 shows the visual face display rating scale.

All participants heard the first 30 seconds of their familiar liked and disliked songs and rated them. The songs' names and ratings were logged in a data collection form.

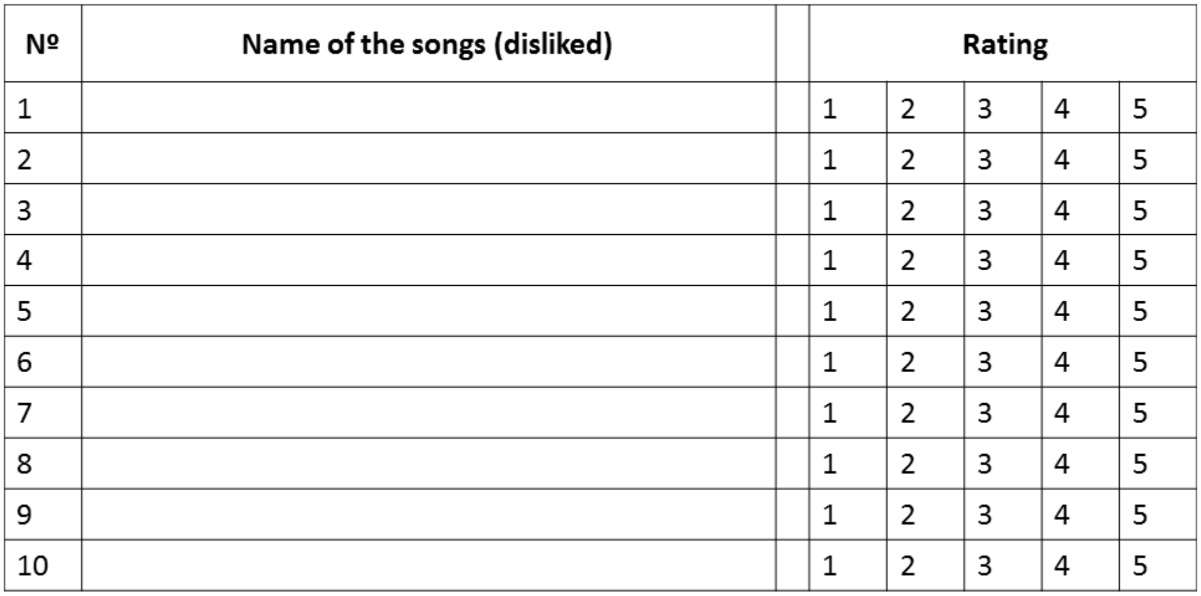
Data collection form for self-selected familiar songs

POND ID number: ___________________ Date of study__________________

**List of familiar songs (liked and disliked) and respective ratings**



| **№** | **Name of the songs (liked)** | | **Rating** | | | | |
|---|---|---|---|---|---|---|---|
| 1 | | | 1 | 2 | 3 | 4 | 5 |
| 2 | | | 1 | 2 | 3 | 4 | 5 |
| 3 | | | 1 | 2 | 3 | 4 | 5 |
| 4 | | | 1 | 2 | 3 | 4 | 5 |
| 5 | | | 1 | 2 | 3 | 4 | 5 |
| 6 | | | 1 | 2 | 3 | 4 | 5 |
| 7 | | | 1 | 2 | 3 | 4 | 5 |
| 8 | | | 1 | 2 | 3 | 4 | 5 |
| 9 | | | 1 | 2 | 3 | 4 | 5 |
| 10 | | | 1 | 2 | 3 | 4 | 5 |



| **№** | **Name of the songs (disliked)** | | **Rating** | | | | |
|---|---|---|---|---|---|---|---|
| 1 | | | 1 | 2 | 3 | 4 | 5 |
| 2 | | | 1 | 2 | 3 | 4 | 5 |
| 3 | | | 1 | 2 | 3 | 4 | 5 |
| 4 | | | 1 | 2 | 3 | 4 | 5 |
| 5 | | | 1 | 2 | 3 | 4 | 5 |
| 6 | | | 1 | 2 | 3 | 4 | 5 |
| 7 | | | 1 | 2 | 3 | 4 | 5 |
| 8 | | | 1 | 2 | 3 | 4 | 5 |
| 9 | | | 1 | 2 | 3 | 4 | 5 |
| 10 | | | 1 | 2 | 3 | 4 | 5 |

### 7.1.2 Musical background assessment

All participants completed a musical background assessment using the Queen's University Musical Questionnaire (Bhatara et al., 2013). It consists of 22 questions about music training, favorite music styles and family involvement in musical activities. This questionnaire, as well a guide for asking questions are included here:

**Queen's University Music Questionnaire- Revised**

Study ID number: _______________ Date of study__________________

Coded study number for files: __________

**Child Interview**

1. Gender M/F Age:
2. Grade in school:
3. Are you left/right-handed?
4. Is English your first language? Yes/No

**Music Training**

5. Have you ever taken any music lessons?

(NOTE: ANY kind of lessons count, including high school band class)

**If YES, complete #6-11; if NO, proceed to # 12

6. At what age did you start music lessons?
7. Private or group/classroom lessons?

8. What instrument(s)? How many years of training for each instrument?

9. Years of training in total:

10. Royal Conservaotory Grade Level:

11. If not Royal Conservatory, what method of training?

12. If you have brothers and/or sisters, have they had music lessons?

13. Are your parents involved in music any way (sing, play an instrument, avid listeners, etc.)

14. Do you consider yourself musical?

15. Are you currently involved in musical activities (i.e. do you currently play an instrument or sing)?

16. How often do you listen to music? (e.g. everyday for about 3 hours)

17. What type of music do you usually listen to (e.g., classical, rock)

18. What is your favorite type of music?

19. Do your parents often listen to/play music in your home?

20. If so, what type of music?

21. To the best of your knowledge, are you tone deaf?Yes/No/Somewhat/Don’t know

22. To the best of your knowledge, are you an aboslute pitch (perfect pitch) possessor? Yes/No/Don’t know

## Guide for asking interview questions

When answering to this questionnaire, you can:

- refuse to answer
- say “Don’t know or Don’t Remember”

Question #8 – What instrument? Is it individual or group as in choir lessons?

Piano, guitar, voice, ukulele, violin, flute, clarinet, saxophone are examples of common musical instruments as well as voice (vocal lessons)

Question #9 – In which grade level are you?

Question #12 – If you have brothers and/or sisters, have they had music lessons?

If you do not have siblings, the answer is - “not applicable’ or “I have no siblings”.

Question #13 – Are your parents involved in music anyway? Yes or no.

If yes, please tell how (example: sing, play an instrument, avid listeners)

Question #15: Types of musical activities: play an instrument or sing

Question #16: Include: do you listen to music? Yes or no. If yes, how often? Every day (less than 3 hours), Everyday (more than 3 hours), 3 types a week, once a week.

Question #17: If you listen to music, what type of music do you usually listen to? If you do not, please answer “not applicable’ or “I don’t listen to music”.

Question #19: Do your parents often listen to or play music in your home?

☐ Listen to music
☐ Play music
☐ Neither
☐ Listen to and play music

Question #20: If so, what type of music? Some examples are classical, pop, rock, jazz, opera, electronic

Question #21: Some people have tone deafness, meaning that they are unable to distinguish between musical notes. To your best knowledge are you tone deaf? Yes, No, don’t know, refuse to answer.

Question #22: Absolute pitch possessors are persons who have the ability to identify and create a given musical note without a reference tone.

### 7.1.3 Pitch Discrimination Task

For the pitch discrimination task, we performed a pitch discrimination of tone pairs, using an adapted version of the Stanutz et al. (2014) paradigm. This model has been validated in children with ASD. In this procedure, participants listened to two consecutive tones and then choose to say whether the tones were the same or different. Once a decision had been made, we would proceed to the next trial. Four middle range piano tone were presented randomly throughout the 44-pitch discrimination trials: G3 (196.00 Hz), C4 (261.63 Hz), F4 (349.23 Hz), and A4 (440 Hz). Each tone and its pair were presented in 11times, in five different conditions: one was the same or 100 cents (the pairs of notes were identical in frequency), and 15, 25, 35, or 45 cents sharp or flat (the second note of the pair was different). Cent is a logarithmic unit of measure used for musical intervals. One octave consists of twelve semitones of 100 cents each, being the semitone the smallest tonal unit in the Western music (Mary Zarate et al., 2012). Therefore, all pitch alterations were smaller than half of a semitone. The tones were one second in duration, and they were separated by one second of silence. Tones were created using a Yamaha YPP-35 as a midi controller and Cubase 8 software to edit and export those files. The experiment was conducted using a Toshiba Satellite P750 laptop computer, with a UA-4FX Edirol ® sound card, running Microsoft PowerPoint 2016, which presented sound stimuli. The participants listened to sounds through a set of headphones (HD 250-II Sennheiser) at 70-75 decibels (dB) average of intensity, in a very quiet room. Prior to the task, each participant underwent a series of practice trials for familiarization purposes.

### 7.1.4 Preparing music stimuli for the MEG Task

After the first visit, we selected 8 familiar songs liked and 8 familiar songs disliked for each participant from their self-selected familiar music list. This selection was based on participants´ likeability ratings and we chose songs rated in the most extreme positions of the rating scale. Then, we selected the “first 30 seconds” of each song, using Audacity® 2.1.0 music software program for editing these music excerpts.

The reasons why selecting the first 30 seconds of each song and not the chorus are related to the current relevance of the effectiveness of the first 30 seconds of any recorded track, caused by technological changes in music consumption and music composition. Nowadays, the popularity of digital streaming services and the listener's short attention contribute to shorter intros in songs. Intros are the time before the voice enters in a song. In the mid-80s it averaged more than 20 seconds and now they are about 5 seconds long (Léveillé Gauvin, 2018). If the first 30 seconds of a recording are not catchy and grab the listening audience, the track would be skipped (Brandon Miler; Crane, 2017).

Subsequently, we extracted three musical features (tempo, mode and dissonance) from the 30 seconds excerpts, using a Matlab Toolbox for Music Information Retrieval, called MIR Toolbox 1.6, using Matlab 8.0 software  (Lartillot et al., 2008). This software was developed within the context of a European Project called "Tuning the Brain for Music", which is dedicated to the study of music and emotion. This program provided us with an objective measure of the musical features, with numeric values. Two other musical features, as genre and presence or absence if lyrics in songs were classified by auditory inspection. We matched the familiar songs with unfamiliar ones to the following musical characteristics: tempo (slow, moderate and fast); mode (minor or major); loudness (intensity); genre (i.e. classic, pop, rock) and presence or absence of lyrics (vocal or instrumental). For example, in musical terminology, tempo is the speed or pace of a given piece and is usually indicated in beats per minute (BPM). According to Med (1996), tempo can be classified in three groups: slow (40 to 72 BPM), moderate (72 to 120 BPM) and fast (120 to 208 BPM). The unfamiliar songs were selected from a database of European music, mostly from Eurovision Song Contest. The choice for European music is due to its similarities to the rules and regularities of Western tonal music, and less probability of previous contact and exposure by the North American participants. In total, for each participant 16 extracts (30 seconds each) of familiar songs (liked and disliked) was matched with 24 unfamiliar songs. In sum, a unique set of 40 auditory stimuli was prepared for each participant for the second visit. Figure 7-2 schematically shows the procedures performed between the first and second study visit.

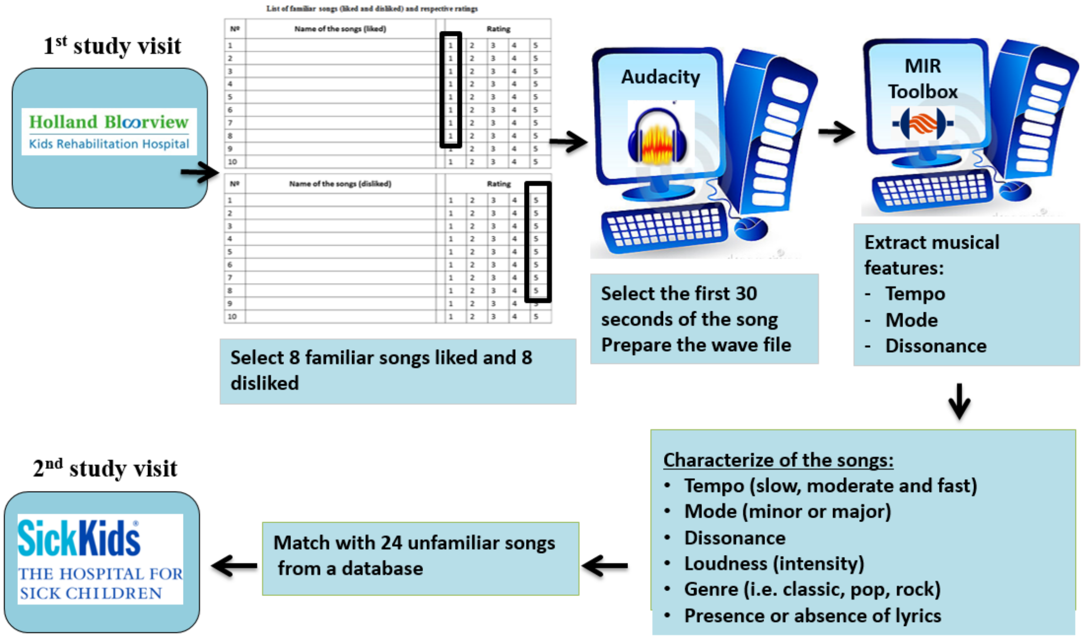


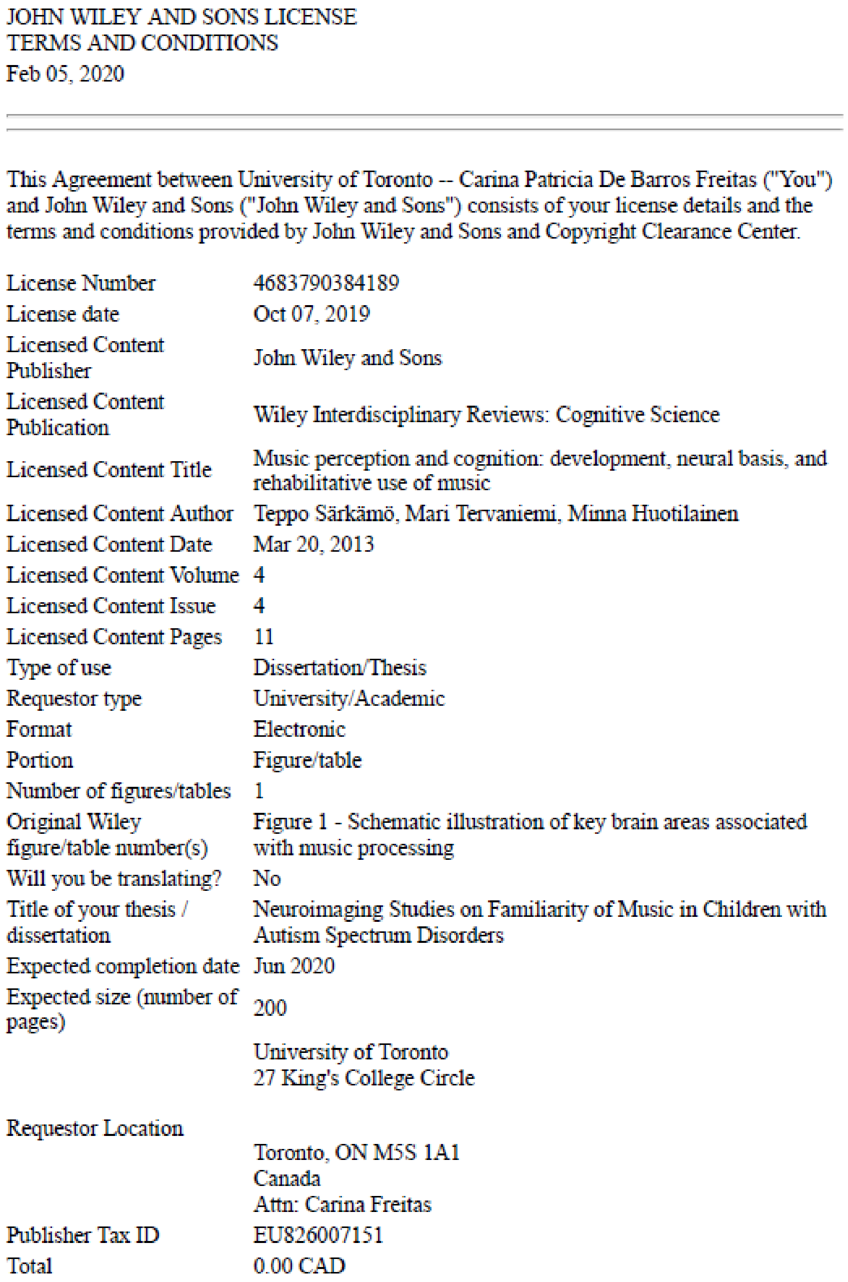
Figure 7-2: Schematic of the preparation of the MEG music task for each participant.

### 7.1.5 The hearing test

During the second study visit that took place at the Hospital for Sick Children, all participants completed a hearing screening. The hearing test was carried out using the Grason-Stadler GSI 17 Audiometer model in a very quiet room. Children were tested at six frequencies (250, 500, 1000, 2000, 4000 and 8000 Hz) at 20 and 30 db. Figure 7-3 displays the portable audiometer used in this study.

Figure 7-3: Portable Audiometer (GSI 17 Model).

# Copyright Acknowledgments



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