Musik-evozierte Emotionen in fMRT-Paradigmen der sozialen Wahrnehmung: Eine neuartige Strategie zur Identifizierung von neuronaler Markern assoziiert mit veränderten Emotionsverarbeitung

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Art des Projektes: *Studie*

Music-evoked emotions in social cognition fMRI paradigms. A novel strategy for identifying neural markers associated with altered emotion processing

KEYWORDS

Music-evoked emotions, fMRI, Prosody, Autism Spectrum Disorders, social cognition

Dieses Projekt untersuchte die funktionelle Neuroanatomie, welche Musik-evozierten Emotionen in Paradigmen sozialer Kognition zugrunde liegt (d.h. Aufgaben in denen Probanden aufgefordert sind, Bewusstseinsvorgänge in anderen Personen einzuschätzen) mit dem Ziel, messbare neuronale Marker zu identifizieren, die mit Psychopathologie assoziiert sind. Die wichtigsten neurowissenschaftlichen Befunde ergaben: Erstens, dass musikalische Stimuli die Gehirnaktivität in rechtslateralisierten Bereichen (Nucleus caudatus und Gyrus temporalis superior) stark modulieren können. Diese Bereiche, welche an der Verarbeitung emotionaler Prosodie beteiligt sind, zeigen bei Personen mit Autismus-Spektrum-Störungen (ASD) eine abnormale Aktivierung. Zweitens, dass eine veränderte affektive Verarbeitung von Musikinformationen bei Menschen mit ASD unter Umständen mit funktionelle Veränderungen im somatosensorischen Kortex (S1) assoziiert ist. Insgesamt zeigen diese Erkenntnisse dass musikbasierte fMRI-Paradigmen für klinische Neurowissenschaft von großem Nutzen seien könnten. Insbesondere können sie als nicht-verbales Untersuchungsinstruments zur Bewertung der Emotionserkennung in Gruppen mit spezifischen Sprachbeeinträchtigungen eingesetzt werden.

This project investigated the functional neuroanatomy underlying music-evoked emotions in social cognition paradigms (i.e. tasks that require the attribution of mental states), with the aim to identify measurable neural markers associated with psychopathology. The main neuroscientific findings revealed that a) musical information can strongly modulate brain activity in right-lateralized areas involved in processing emotional prosody (caudate nucleus and superior temporal gyrus) that have shown abnormal activation in subjects suffering from autism spectrum disorders (ASD); and b) functional changes in the somatosensory cortex (S1) could underlie altered affective processing of musical information in subjects with ASD. Overall, the results show that music-based fMRI paradigms could have important implications for clinical neuroscience through the facilitation of non-verbal means of assessing emotion identification skills in groups with specific language impairments.

When I started planning this project (back in 2003), I was finishing my clinical training in psychology, reading Bradbury's Illustrated Man, fascinated by the Wright brothers' airplane design and learning about Carl Sagan's Voyager initiative.

I never designed any aircraft nor went into deep space.

I did, however, analyse most of Bach's, Beethoven's and Stravinsky's musical pieces that were included in the 12-inch gold-plated copper disk that went aboard the Voyager spacecraft. And, during my clinical residency at the Center for Mental Health (Pirovano Hospital), I did run far more than the 40 feet monorail track used by Wilbur and Orville's flying machine; carrying up in the air a six-year-old severely autistic child, who would be waiting for me every Wednesday at 8:30am, to fly. I would pick him up, and I would run through the endless hospital corridors resembling an airplane, with the boy's arms widely spread for lift, and my mouth uttering the propeller's sound, of course, for thrust. We would finally land in a room where ten other kids would wait for starting the music workshop, which I, so very happily, organised every Wednesday at the Center.

For almost twelve years, I worked in the field of clinical psychology, treating patients suffering from severe psychiatric disorders such as major depression, psychosis and autism spectrum disorders. Yet, in the year 2009, when I parallelly finished my music studies, I resolved to follow a scientific research path in the domains of music cognition and computational neuroscience, since I strongly believed that the utilisation of musical information in neuroscientific research could shed light on important aspects of our understanding of the neural basis of emotion.

Neuroscientific research on human emotion has predominantly used images as experimental stimuli. However, in the last decade, neuroscientists found music to be a potentially helpful tool. Listening to music can consistently modulate activity in brain areas linked to emotion. Furthermore, the fact that music unfolds over time makes it particularly suitable to investigate the time course of emotion processing and the underlying neural mechanisms.

Although research in music cognition has been growing steadily during the past years, relatively little progress has been made in exploring the higher levels of musical response, especially the emotional and aesthetic aspects. From a cognitive standpoint, music processing in audiovisual contexts such as film, provide a valuable framework within which the affective and connotative aspects of musical information can be analysed. My research work is aimed at understanding the brain underpinnings of emotion processing through the use of controlled audiovisual fMRI (functional Magnetic Resonance Imaging) paradigms. In particular, my research is focused on analysing how alterations of specific aspects within the musical structure may shape the emotional interpretation of visual information and impact on mental state inferences (i.e. social cognition processes).

The purpose of my proposed Andrea von Braun Foundation project was to develop advanced methods of applying musical information to the problem of characterising complex mental health disorders, with the aim of designing and testing new marker-tasks that could help to elucidate and detect the neural mechanisms that might contribute to the emergence of autism spectrum (ASD) symptoms.

Introduction

Current models of brain function view not only perception, but also higher order functions such as social cognition as a combination of two different sources of information: bottom-up sensory input and top-down influences from prior knowledge (Clark, 2013; Friston, 2009). The present project was set out to characterise the balance between top-down and bottom-up musical information processing in typically developing subjects and ASD diagnosed individuals. I employed systematically controlled non-verbal audiovisual fMRI paradigms and targeted the effects of musical information manipulation on mental state predictions [i.e. also known Theory of Mind or ToM processes (Bravo, Cross, Hawkins, et al., 2017)].

The research did not only evaluate clinically diagnosed ASD participants, but also clinically typical subjects who varied along a continuum of the autism spectrum. Individuals varying in autism spectrum traits may range from displaying normal psychosocial functioning to having severe problems in daily life. Since autism is a spectrum disorder expressed with vast heterogeneity, both between people diagnosed with autism and within the general population, an advantage of the present approach was that it enabled the assessment of how varying levels of symptoms would relate to task performance. The strategy, therefore, allowed the assessment of neural processing mechanisms that could be altered in association with the occurrence of early autism signs, which can be identifiable even before disorder specific symptoms arise. Moreover, as well as offering a more thorough assessment of the emergence of autistic experiences, this approach was grounded on strong evidence suggesting that autism exists on a continuum with normality (Baron-Cohen, 2002; Gaugler et al., 2014; Lee et al., 2013; Parihar & Ganesh, 2016; Robinson et al., 2016).

During the project's development a total of 146 participants were tested in behavioural and neuroscientific (fMRI) settings, through experiments that included three music-based tasks (referred here as Paradigms A, B and C). All three tasks were constructed with the purpose of assessing mental state inferences [i.e. inferring others' emotions, thoughts or feelings

(Happé, 2003; Schultz et al., 2004; Van Overwalle, 2009)] biased by musical information (Bravo et al., 2017b), and to enable the investigation of the underlying neural encoding.

Paradigm A was aimed at assessing whether musical information, and specifically the manipulation of musical mode, could trigger signal changes in areas involved in the processing and discrimination of emotional prosody [Internet link to Paradigm A - timepoint 12:18]. Deficits in the comprehension of affective prosody during mental state inferences have been consistently reported in individuals with ASD (Golan et al., 2007; McCann et al., 2007; Peppé et al., 2007; Rutherford et al., 2002).

Paradigms B and C entailed the replication of two already validated tasks: the SETi-Task (Bravo et al., 2017b) [Internet link to SETi-Task – timepoint 7:42; link to related-manuscript] and the Dissonance-Task (Bravo, 2013; Bravo et al., 2019) [Internet link to Dissonance-Task; link to related-manuscript-1 and manuscript-2) and manu in typically developing individuals, ASD-diagnosed and participants who varied along a continuum of the autism spectrum. The manipulated variable in Paradigms B and C were, respectively, sensory and tonal dissonance (Bigand et al., 1996; Bigand & Parncutt, 1999; Bravo, 2013).

A concise description of Paradigm A follows, in order to present the design of a prototypical task employed in the project. Paradigm A was built in the form of an audio-visual film clip, based on a point-of-view (POV) scene taken from Tarkovskly's film "The Mirror" (1975) (Explanatory Box 1, Figure 1). The musical stimuli comprised two novel soundtracks composed for the same POV scene. Musical mode (major-minor) was the manipulated variable (Green et al., 2008; Juslin & Laukka, 2004; Parncutt, 2014; Virtala & Tervaniemi, 2017). The assumption was that although participants would watch the same visual scene, their interpretative framework (Boltz, 2001) would be biased by the controlled musical structures, with the minor mode condition (compared to the major mode condition) inducing more negatively-valenced mental state inferences (i.e. more negative emotions).

Explanatory Box 1. Paradigm A - fMRI design and procedure. Prior to the start of the audio-visual film clip, and based on established methods (Gallagher et al., 2000; Saxe, 2010; Saxe & Kanwisher, 2003; Völlm et al., 2006), an instruction was given to participants designed to engage affective mental state inference processes. Subjects were instructed to "Please, think about the emotions of the person entering this place" (Figure 1). In the context of this POV scene, the paradigm required to ascribe temporary mental states (emotions) to an actor not seen but imagined (Van Overwalle, 2009; Van Overwalle et al., 2009). After the instruction, the film clip followed with either music condition 1 (major mode), music condition 2 (minor mode) or no music (control visual-alone) in randomized order (Figures

1 and 2). At the end of the respective clip, a valence inference question was presented ("What kind of emotions would the person entering this place have?"), which subjects could respond using a 4-point scale (ranging from 7 to 10) with extremes labelled "positive" or "negative" (order counterbalanced). Two control conditions were included; i) visual-only category (i.e. film clip with no soundtrack) with identical instructions as above to control for basic visual sensory processing, and; ii) the same audio-visual film clips with an instruction to describe the "physical" appearance of the objects that appear on-screen ("Please, focus on the physical appearance of the objects in the following film clip"). This additional control condition was aimed at controlling for multimodal sensory processing, working memory and attentional demands of the task, without cueing subjects to attend specifically to mental states (Happé, 1994; Saxe, 2010; Völlm et al., 2006).

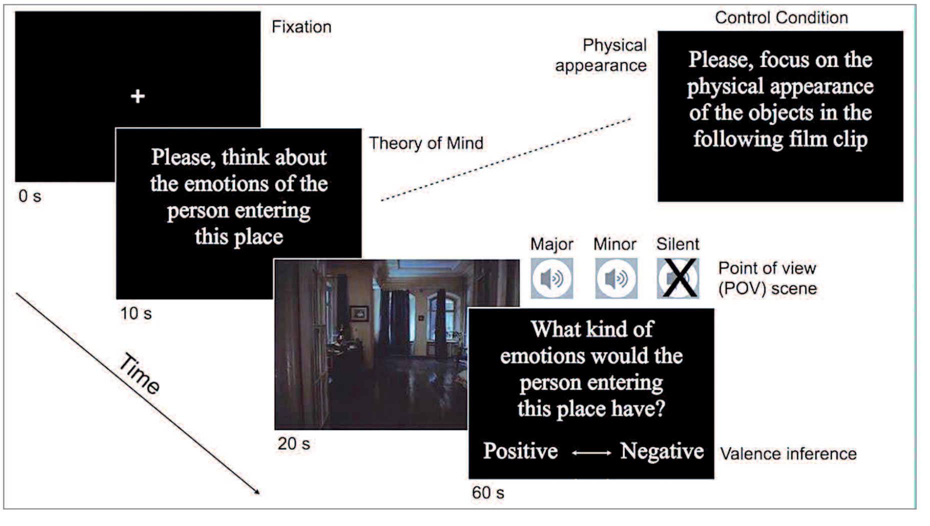

Fig. 1. Experimental stimuli and procedure: After 10 seconds of fixation, an instruction to attend specifically to mental states [or control condition: physical appearance] is given (10 seconds), the film clip [POV scene taken from Tarkovskly's film "The Mirror"(1975)] follows with either music condition 1 (major mode), condition 2 (minor mode) or no music (control visual-alone) in randomized order. At the end of each clip, a valence inference question is presented.

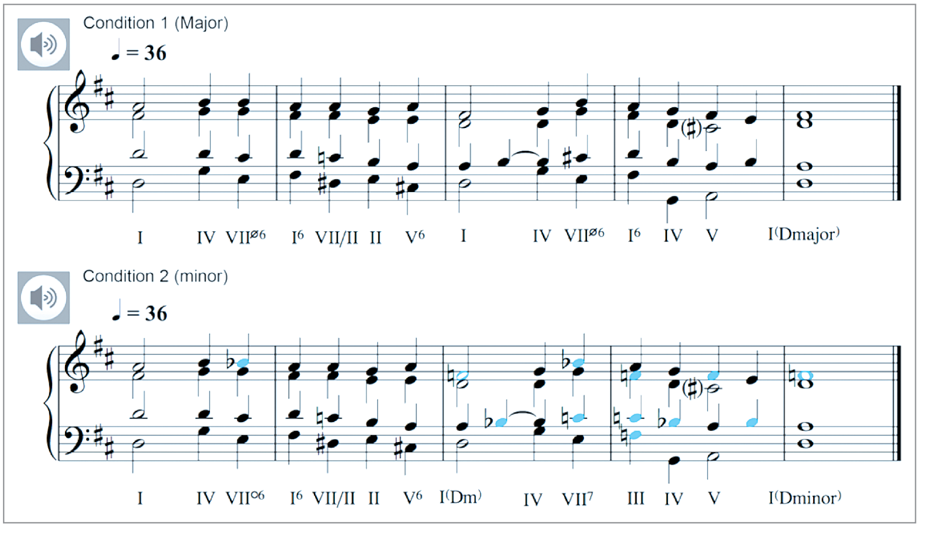

Fig. 2. Experimental music stimuli (scores). The minor category (Condition 2) incorporates harmonic transformations from the parallel minor key by modifying three pitches (F, C and B) from Condition 1 (i.e. major mode category). The musical scores were composed to follow a stochastic event-related design (Henson, 2007).

Findings

Several studies have demonstrated that individuals with autism process social affective cues differently. However, research directly assessing emotion recognition has, so far, reported contradictory results (Uljarevic and Hamilton, 2012). Most of these investigations have only examined emotions expressed by face and body, and, evidence suggests that these deficits might not generalize to the musical domain (Heaton et al., 1999; Allen et al., 2013). Some researchers, however, have proposed that more fine-grained and controlled music-based tasks would be required to reveal the failure of fundamental early emotion identification skills. (Humphreys et al., 2007; Heaton et al., 2012). Paradigm A, targeted typically developing individuals, and was aimed at assessing whether musical information processing could trigger signal changes in areas involved in the processing and discrimination of emotional prosody. The behavioral results indicated a significant effect of musical mode manipulation on mental state attribution (Gallagher et al., 2000; Saxe, 2010; Saxe & Kanwisher, 2003; Völlm et al., 2006). Consistent with previous findings, during the minor mode version participants inferred significantly more negative emotions (compared to the major mode condition) (Bravo, 2013; Costa et al., 2000; Green et al., 2008; Khalfa et al., 2005; Pallesen et al., 2005; Pehrs et al., 2014). The neuroscientific results (Figure 3) further showed that minor mode film-music modulated brain activity in right-lateralized auditory association areas sensitive to the spectral processing of acoustic parameters, and in regions implicated during 'explicit' affective prosody discrimination (right caudate nucleus and right superior temporal gyrus), providing empirical evidence for music and speech neural overlaps during the processing of non-verbal sound cues signaling negatively-valenced emotional states.

A broad range of studies have reported atypical higher-level social information processing in autism spectrum disorders (ASD), including deficits during mental state inferences based on cues expressed through the eyes and by voice (Baron Cohen et al., 1997; Baron-Cohen, 2000; Baron-Cohen et al., 2001b). Altered production and comprehension of affective prosody have been documented in individuals with ASD, who have difficulties in understanding and inferring the mental state of others when relying on non-verbal sound cues (Golan et al., 2007; McCann et al., 2007; Peppé et al., 2007; Rutherford et al., 2002). Particularly, abnormal activation of the right caudate and right superior temporal areas has been shown during processing of affective prosody in subjects suffering from ASD (Gebauer et al., 2014; Rosenblau et al., 2016). The findings from Paradigm A therefore indicate, that music-based paradigms could have potentially relevant implications for clinical neuroscience through the facilitation of non-verbal means for assessing emotion identification skills and prosody-linked neural mechanisms in groups with specific language impairments [Manuscript submitted, currently under review].

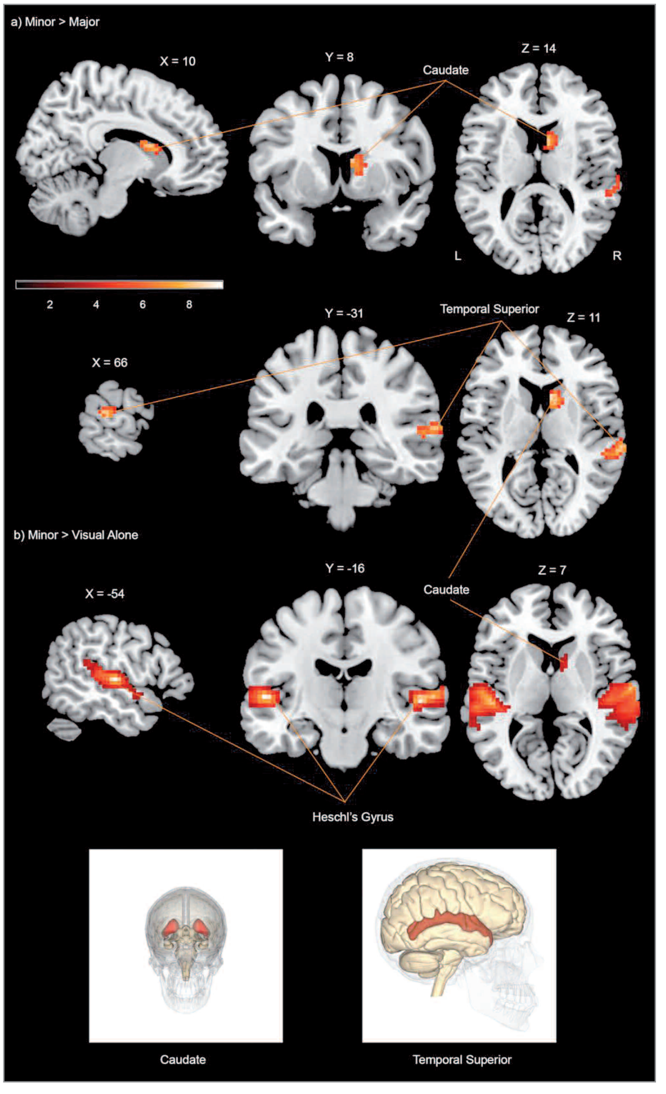

Fig. 3. fMRI results (FWE-corrected $p < 0.05$ for cluster-level inference) superimposed onto a standard brain in stereotactic MNI space. Coloured red areas reflect: (a) Statistical parametric maps showing voxels in in the superior temporal gyrus and in the right caudate nucleus in which the response was higher during the minor condition compared to major AV (sagittal, coronal and axial views). (b) Signal changes were observed bilaterally in primary and secondary auditory cortices including Heschl's gyri in the contrast between minor condition and visual alone (control) (sagittal, coronal and axial views).

In agreement with previous studies that targeted brain activity during social cognition tasks conducted in ASD participants [for a meta-analytic review see: (Di Martino et al., 2009)], the neuroimaging findings from Paradigm B indicated a reduced probability of activation throughout brain systems involved in processing social stimuli, contextual memory and negatively-valenced affect. Specifically, ASD-related patterns of hypoactivation were found in the medial prefrontal cortex, anterior cingulate cortex, parahippocampal cortex and in the temporo-parietal junction area. Consistent with previous neuroimaging literature, certain ASD participants evidenced increased engagement in neural regions that are not typically associated with task performance (e.g. inferior frontal and cerebellar regions), suggesting a potential triggering of compensatory brain mechanisms (Di Martino et al., 2009).

Although ASD individuals may be able to categorize certain types of stimuli during social cognition tasks (i.e. correctly identify whether mental states are involved, and even use mental state language for stimuli description), research has shown that they can manifest difficulties in accurately understanding the emotions represented by specific patterns of stimuli, to which they may attribute inappropriate mental states (Abell et al., 2000; Castelli et al., 2002). The behavioural findings from Paradigm C revealed a distinct manner of misinterpreting the audio-visual task that only affected the evaluation of consonant sound cues, supporting previous preliminary findings (Bravo et al., 2017a). Statistical analyses indicated that, during the consonant condition, participants with higher levels of autistic traits appraised the intentions of the film character as significantly more negative (Pearson $r_{37} = 0.293$, $P = 0.039$); revealing an abnormal appraisal of tonal consonance. This result is relevant since tonal consonance has been shown to consistently bias participants towards positive (and not negative) valence appraisals [both within this paradigm (Bravo, 2013) and throughout the general empirical literature (Blood et al., 1999; Koelsch et al., 2006; Plomp & Levelt, 1965; Schellenberg & Trehub, 1994; Zentner & Kagan, 1996)].

In order to estimate potential associations between brain encoding and autistic traits levels, a covariate analysis was implemented. The Autism Spectrum Quotient (AQ) scores (Baron-Cohen et al., 2001a) were used in voxelwise analyses to detect correlations between autistic traits and the neural signal changes during the performance of Paradigm C. Following the aforementioned biases in the appraisal of the consonant music condition, the correlational analysis was applied for this specific category (i.e. contrast dissonance > consonance). Results showed that AQ scores were correlated with activation in the left postcentral gyrus (cluster peak at -51 -22 47, Brodmann areas 1, 2 and 3), showing an association between presence of autistic traits and increased activation of somatosensory cortices modulated by dissonance (Figure 4). This finding could suggest a potential increased sensitivity towards tonal dissonance in ASD.

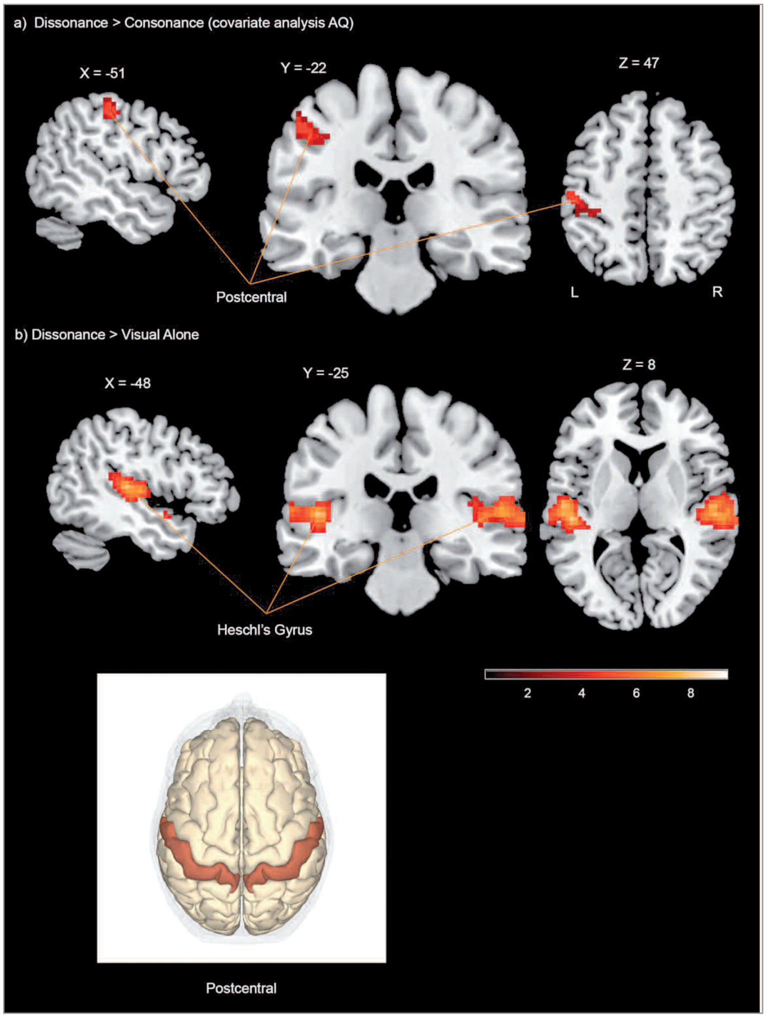

Fig. 4. fMRI results (FWE-corrected P < 0.05 for cluster-level inference) superimposed onto a standard brain in stereotactic MNI space. Coloured areas (red) reflect: (a) Results of covariate analysis (performed to detect correlations between autistic traits and neural response for the contrast dissonance > consonance). AQ scores were correlated with activation in the left postcentral gyrus (cluster peak at -51 -22 47). (b) Statistical parametric maps (SPM) of the direct contrast between dissonance and control (visual alone). Stronger BOLD signals during dissonance (compared to baseline) were yielded in temporal superior regions, including Heschl's gyri (HG) bilaterally. Bottom image shows the location of the postcentral gyrus projected onto a 3D rendering (red).

The postcentral gyrus is the location of the primary somatosensory cortex (S1). Although this area has been known for its central role in the processing of sensory information [i.e. sensory homunculus (Penfield & Boldrey, 1937)], a series of studies have recently suggested that inferring of other people's mental states (emotions and intentions) could proceed via a simulation process via the generation of a somatosensory image of the associated body state (Adolphs et al., 2000; Buckner & Carroll, 2007; Damasio et al., 2000).

The remarkable discovery of mirror neurons fifteen years ago (Gallese et al., 1996) showed that certain neurons within macaques brains were active, both when the monkeys moved, and when they would look at a person (the experimenter) moving in a comparable manner. Whilst originally found in the motor cortices, follow-up studies provided evidence for a wider distribution within somatosensory cortices (i.e. postcentral gyrus) (Buccino et al., 2001; Raos et al., 2007).

It has been argued that that mirror neurons may act as high-order hierarchy hubs, where signals from lower areas (e.g. sensory cortices) and other hubs would converge [convergence-divergence zones hypothesis (Damasio & Meyer, 2008)]. The ability of these hubs to collect and distribute signals is thought to support the generation "abstract records of coincident activations" [analogous to the "context frames" built by associative memory systems (Bar, 2004, 2007; Damasio, 1989)], which would in turn allow the simulation process. The notion that mental state attribution may rely on simulating another individual's perspective is consistent with several studies conducted in humans and monkeys (Iacoboni et al., 2005; Keysers et al., 2004; Rizzolatti & Luppino, 2001). Together with this evidence, the findings from Paradigm C suggest that a) high-order associative neural hubs, such as somatosensory cortices (S1), are recruited for conceiving and interpreting the viewpoint of others; and, b) that they can show abnormal functioning in ASD. Interestingly, a recent study investigating the effects of lacking a protein called Shank3, which has been previously linked with autism, showed that overactive excitatory neurons in the same area (somatosensory cortex) might underlie the atypical sensory responses that are established for the ASD diagnostic criteria (DSM-5) (Chen et al., 2020). Observations of functional changes in the somatosensory cortex have not only been documented in ASD (Di Martino et al., 2009), but have also been reported in studies conducted with individuals suffering from other severe mental disorders, such as major depression (Schmaal et al., 2017), bipolar disorder (Minuzzi et al., 2018), schizophrenia (Koutsouleris et al., 2015) and obsessive-compulsive disorder (Kropf et al., 2019). Current literature has further shown a role for the somatosensory cortex within each stage of emotion processing, including the recognition of emotional expression, the retrieval of socially relevant information from a stimulus (Adolphs et al., 2000) and the generation of an appropriate affective response (Satpute et al., 2015). Future research is envisioned, applying contemporary advances in data analytic methods, such as machine learning classification techniques, to social cognition fMRI paradigms that target somatosensory brain regions as potential neuroanatomical biomarkers associated with altered emotion processing.

Conclusions

The aim of this project was to develop (by experimental design, test and replication) advanced and systematically controlled methods of employing musical information to examine the neural mechanisms involved in complex emotional responses. It is my hope that the findings from the present work can contribute to support and further spread the use of music-based fMRI paradigms, for detecting relevant behavioral signatures and to identify measurable neural markers associated with severe psychopathology.

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Curriculum Vitae

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2018	Cyril and Elizabeth Challice Foundation for Musicians (Scholarship). Program “Concert in the 21st Century” at Banff Centre for Arts and Creativity.
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2017–Present	Visiting Research Associate Wolfson College Cambridge, University of Cambridge, UK.
2015–2017	Post-Doctoral Researcher in Music Technology and Neuroimaging. Institut für Kunst- und Musikwissenschaft, Technische Universität Dresden, Germany.
2014	CSAR Student Award in Music and Neuroscience Cambridge Society for the Application of Research.
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2012	SEMPRE Award "The Arnold Bentley New Initiatives Fund". Fund to support new, interdisciplinary initiatives concerned with the advancement of research in the psychology of music.
2011–2015	PhD in Computational Neuroscience and Music Cognition. Funding: Cambridge Overseas Trust - Queens' College Walker Cambridge Studentship Centre for Music and Science, University of Cambridge, UK.
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