Neurophysiology and neurobiology of the musical experience

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Summary

Music, a universal art form that exists in every culture around the world, is integral to a number of social and courtship activities, and is closely associated with other creative behaviours such as dancing. Recently, neuroimaging studies have allowed researchers to investigate the neural correlates of music processing and perception in the brain. Notably, musical stimuli have been shown to activate specific pathways in several brain areas associated with emotional behaviours, such as the insular and cingulate cortex, hypothalamus, hippocampus, amygdala, and prefrontal cortex. In addition, neurochemical studies have suggested that several biochemical mediators, such as endorphins, endocannabinoids, dopamine and nitric oxide, may play a role in the musical experience. A growing body of evidence also indicates that music therapy could be useful in the clinical management of numerous neurological and psychiatric disorders. Indeed, music therapy could be effective in patients with neurodegenerative disorders, such as Alzheimer’s dementia and Parkinson’s disease, as well as in psychiatric illnesses, such as schizophrenia, depression, anxiety and autism spectrum disorders.

Unfortunately, there is still a shortage of rigorous scientific data supporting the clinical application of music therapy, and there is thus a need to confirm and expand the preliminary findings regarding the potential and actual effectiveness of music therapy. This need should be addressed through prospective, randomized, controlled, single-blinded investigations of the short- and long-term effects of music therapy in diverse clinical conditions.

KEY WORDS: electrophysiology, music, music therapy, neuroimaging, neurology, psychiatry.

Introduction

Music is a creative art form that exists in all the cultures of the world. As well as being integral to numerous social and courtship activities, music may also be a means through which people are able to cope with emotional conflicts, increase their self-awareness, and express their unspoken and often unconscious concerns (1). Notably, music possesses an intrinsic expressive power that can be manifested in different ways, not only on a mental but also on a physical level: listening is not only a spiritually and intellectually enriching and pleasurable experience, it also induces changes in heart and respiratory rates (2). Similarly, music can be the source of a variety of pleasant bodily sensations, such as chills, thrills and tingles running down the spine (3).

Given this universal social importance of music, the neural pathways by which musical stimuli might exert their emotional and physical effects have recently become a focus of intense research activity (4-10). Understanding the neurobiological, neurophysiological and neuropsychological bases of the musical experience is important not only from the perspective of promoting basic research and knowledge, but also in view of the potential application of music in clinical practice. In fact, preliminary evidence seems to indicate a possible role for music therapy in the clinical management of a variety of neurological (11-13) and psychiatric conditions (14,15).

Starting from these premises, this review will examine the complex interplay of diverse neurobiological factors involved in musical processing in the brain, including the neural correlates and the neurochemical modifications evoked by musical stimuli. We will also discuss the potential clinical applications of music in the light of recent literature findings.

Neuroanatomy of the perceptual processing of music

The primary acoustic circuit in humans consists of the auditory nerve, brainstem, thalamus (i.e., medial geniculate body) and auditory cortex (4,10).

Sound waves are collected mainly by the outer ear, although it is widely accepted that musical vibrations can also activate some skin receptors stimulated by changes in local pressure. The transduction of sound into a neural signal occurs in the cochlea, a snail shell-like structure located within the inner ear. The auditory nerve thus carries the signal to the brainstem and synapses in the cochlear nucleus. From the cochlear nucleus, the pathway continues through the medial geniculate body – or auditory thalamus – ultimately continuing up the neuronal projections to the auditory cortex. Interestingly, functional auditory projections can also be routed from
the auditory thalamus to the amygdala and medial orbitofrontal cortex (4), a set of regions associated with the processing of emotional behaviours (16).

There are many auditory areas within the neocortex (4). The primary auditory cortex is located on the transverse gyri of Heschl in the lateral fissure, although a small part of it extends onto the lateral surface of the temporal lobe. The primary auditory cortex is tonotopically organized: different parts of this brain area can be activated by sounds of different pitches. Besides the primary auditory cortex, other cortical areas involved in sound processing include the secondary auditory cortex, the posterior auditory field, and the anterior auditory field. The whole auditory cortex carries out the perceptual analysis of music, extracting more specific information about its acoustic features, such as pitch, timbre, intensity and roughness (4,10).

**Neuroanatomy of the emotional processing of music**

Given that music is evaluated not only on a perceptual, but also on an emotional level, it is important to understand the anatomical correlates of the emotional processing of music in the brain. There is evidence to suggest that music activates several areas of the limbic system, such as the amygdala and cingulate gyrus (5,6). It is important to emphasize, however, that the emotional processing of musical stimuli is not confined to subcortical areas, but is also cortically mediated (17). This phenomenon has been shown to involve primarily the right hemispheric structures, although the left frontal regions may also contribute to it (18).

Interestingly, in recent years, a growing body of research has also begun to entangle the different neuronal responses to pleasant and unpleasant music. To address this issue, Blood et al. (19) analyzed the cerebral blood flow of subjects listening to music of varying levels of pleasantness (consonance or harmony) as opposed to unpleasantness (dissonance or disharmony). The results showed that brain activity was present predominantly in the frontal lobes while the subjects listened to pleasant music, and in the temporal lobes while they listened to unpleasant music (19).

To analyze further how pleasant and unpleasant music can be used to evoke emotions, Koelsch (6) investigated, by means of functional magnetic resonance imaging, the neural correlates of emotion processing in response to music with emotional valence. They found that the unpleasant (i.e., permanently dissonant) music activated the amygdala, hippocampus, parahippocampal gyrus and temporal lobes, a common set of structures playing an important role in the processing of stimuli with various degrees of negative emotional valence. On the other hand, pleasant music was shown to activate the inferior frontal gyrus, inferior Brodmann’s area of the neocortex, anterior superior insula, ventral striatum, Heschl’s gyrus, as well as the Rolandic operculum. In all of the aforementioned structures, except the hippocampus, the level of activation increased over time during the presentation of the musical stimuli, indicating that the effects of emotion processing may display a precise temporal pattern (6).

Interestingly, Peretz et al. (18) have shown that the emotions generated by music may differ crucially from those associated with other inputs, the most important difference being the absence of a relationship between the intrinsic happy-sad character of music and the subjective perception of it as pleasant-unpleasant. Accordingly, sadness can sometimes be a source of pleasure in music, whereas in most other forms of creative art it is negatively perceived (18). In view of this complex emotional processing, future studies are warranted, in order to shed more light on the functional aspects of emotional perception of music, as well as to entangle further the anatomical substrates underlying the complex emotional response to musical stimuli.

It should probably be borne in mind that a rigid distinction between perceptual and emotional processing of music is probably unjustified and may in fact represent an oversimplification, given that these two dimensions are strongly correlated. Hence, musical stimuli are simultaneously evaluated by different cerebral systems working in an intermodal manner. In this regard, an important aspect that merits consideration is the old idea that music, unlike language, is mainly processed in the right hemisphere (20). This view was challenged some decades ago when it was demonstrated that music education can have an important effect on brain organization (20). As a result, the traditional dichotomous view of music processing was replaced by the so-called modular theory of music perception (20). According to this theoretical framework, different aspects of music are processed in distinct, although partly overlapping, neural networks in both cerebral hemispheres. It is interesting that these regions appear to show a considerable interindividual variability, which seems to depend to a great extent, on different personal experiences (20).

**Electrophysiological aspects of music processing**

As means of obtaining precise accounts of the covert activity of the brain, electrophysiological techniques are still unequalled, and they have also been used to record electrical brain responses to musical stimuli. In this regard, electroencephalography (EEG) could be a useful tool for investigating how musical emotions are processed in the brain. Reflecting what is generally observed in emotional processing, left frontal asymmetry, documented on EEG, has been associated with positive affect or decreased negative affect in response to musical stimuli, whereas right frontal asymmetry has been associated with negative affect or decreased positive affect (21). In addition, the event-related potential (ERP) technique in cognitive neuroscience has allowed scientists to observe the stereotyped electrophysiological response to music listening (22). ERPs have proved to be particularly useful for comparing language and music processing in the brain (22). Typically, ERPs are illustrated by plotting changes in amplitude, measured in microvolts, along the ordinate axis, against changes in latency, measured in milliseconds (msec), along the abscissa axis. ERP components are usually named according to their polarity (P for positive, N for negative), and their peak latency. For example, a positive component that typically reaches its peak amplitude at 400 msec is called the P400, whereas a positive component reaching its peak amplitude at 600 msec is called the...
P600. There is growing evidence that unexpected words within a sentence produce a P400 component, whereas unexpected notes in a melody produce a P600 component (23).

This finding indicates that the processes that govern semantic expectancy (as reflected in the P400) are qualitatively different from those involved in musical expectancy (as reflected in the P600) (23). Interestingly, a doubly incongruous condition – namely an incongruous word delivered out of tune in an excerpt from an opera – has been shown to elicit both a P400 and a P600 component (23).

Emotional effects of music in pathology: seizures and music

The emotional effects that music can produce in pathological conditions, as well as its electrophysiological correlates, are clearly demonstrated by so-called musico- genetic epilepsy. This is a rare condition characterized by epileptic seizures that are generally provoked by listening to music (24,25). It is interesting to note that a degree of cognitive or emotional appreciation of the auditory stimulus may usually be involved in musicogenic seizures, thereby emphasizing the important role that the emotional state evoked by music may play in triggering seizures (24). The occurrence of this phenomenon is likely to depend on the activation not only of temporal acoustic regions, but also of the frontal cortex and the limbic structure, which are involved in the emotional processing of the musical stimuli (25). Accordingly, it has been reported that musical stimuli usually induce emotional responses, such as agitation and autonomic activation (as manifested by tachycardia and hyperventilation), immediately before the onset of these seizures (26).

Another form of epileptic seizure involving the musical experience is the musical hallucination, which is probably due to abnormal electrical activation of the mesolimbic temporal lobe structures (26,27). This well-known, but rare, phenomenon was originally reported by Wieser (26), who described the case of a Portuguese woman who, during a seizure, had hallucinations for a song that was very familiar to her. Although numerous case reports of musical hallucinations have been published (27), it is important to emphasize that consensus, and even theories, regarding the classification and pathophysiology of this phenomenon are currently lacking. It is nonetheless feasible that musical hallucinations may represent a phenomenon with heterogeneous clinical and pathophysiological backgrounds (27).

Complex musical automatisms, such as singing events, have also been described in epilepsy, both ictally and postictally (28).

Biochemical correlates of the musical experience

Several neurotransmitters, neuropeptides and other biochemical mediators are likely to play a role in the perceptual and emotional processing of music in the brain (3). In this regard, the neurotransmitter dopamine, which is thought to play a crucial role in the response to naturally rewarding stimuli (29), may be involved in the enjoyment of music as well. Indeed, dopamine has been demonstrated to be released from the ventral striatum and in the ventral tegmental area in subjects listening to pleasant music (5).

In addition, musical stimuli have also been shown to promote the release of endorphins and endocannabinoids into the bloodstream (3). Accordingly, the administration of naloxone, a well-known antagonist of the opioid receptors, may decrease the pleasant sensations and/or shivers evoked by listening to music (3). Music could also produce some physical effects by inducing the peripheral production and release of nitric oxide (NO) (30). This molecule may act on peripheral vasomotor tone by inducing vasodilatation, local warming of the skin, and a reduction in blood pressure values (31). Since NO is well known to possess an antibacterial, antiviral and immunomodulatory function, it is also possible to speculate that listening to pleasant music could help to protect the organism against bacterial and viral infections, excessive immune and endothelial activation, as well as the detrimental effects of arterial hypertension (30).

Implications of music therapy in the clinical setting

The use of music therapy in a number of different medical specialties is probably based on a widespread belief in the beneficial effects of music. Music has been shown to decrease pain and stress in surgical patients (32), and it has been successfully used in the different fields of oncology (33), neurology (11-13), and psychiatry (14, 15).

In the neurological setting, there is some evidence that music therapy may be useful for dementia patients, in whom it could have beneficial effects on behavioural alterations, as well as on social, emotional and cognitive deficits (11). Unfortunately, available studies on the efficacy of music in patients with dementia raise important methodological issues, highlighting the pressing need for more rigorous investigations. It has also been suggested that music could be very useful in patients with Parkinson’s disease (PD). In this regard, Pacchetti et al. (12) conducted a prospective, randomized, controlled, single-blinded study on the potential effects of music in this patient group. Their results indicated that music therapy could contribute to the improvement of several clinical parameters in PD patients, such as motor, affective, and behavioural functions. In the light of their findings, these authors proposed the inclusion of active music therapy as a novel potential tool in rehabilitation programmes involving PD subjects (12). Third, there is also strong evidence that music may be beneficial in some forms of epilepsy (13). Indeed, the so-called "Mozart effect" (i.e., an improvement of spatial temporal reasoning and intellectual performances while listening to Mozart) may have therapeutic value in some generalized or focal epileptiform patterns (13). Additional data have also demonstrated that music composed by other classical composers, such as Haydn and Liszt, can decrease seizure activity (34). Nevertheless, the beneficial effects associated with listening to Mozart’s music seem to be greater than those associated with listening to the music of other composers. Jausovec and Habe (13) investigated event-related potentials and EEG coherence in 18 individuals as they listened to music by three different
composers (Mozart, Brahms, and Haydn). These authors showed that, during the Mozart clip, the subjects displayed increased coherence in the lower alpha bands, whereas a less pronounced increase was observed in the gamma band (13). This finding is in keeping with a possible influence of Mozart’s music on the level of arousal. In this regard, it has been hypothesized that this possible influence on arousal may be a mechanism through which Mozart’s music is able to enhance cognitive performances, and also exert some positive effects on epileptiform patterns (13).

In the psychiatric setting, music – as a creative means of expression and communication – could help to improve the symptoms and social relations of people with serious mental illnesses. The potential usefulness of music therapy in psychiatry has been extensively investigated in schizophrenia subjects (14). There are at least four studies (reviewed in ref. 14) that suggest that music therapy, in addition to standard care, may help schizophrenic patients to improve their global and mental states, as well as their social functioning. Nonetheless, current literature in this field presents major shortcomings (especially, a lack of long-term evaluations and variability in the number of music therapy sessions between different studies) that warrant consideration and should urge caution against over-interpretation of its findings. In the light of these limitations, we believe that further research is needed to shed more light on the dose-effect relationship as well as the long-term effects of music therapy in schizophrenia. Applying more rigorous scientific standards, Gold et al. (15) are currently investigating whether music therapy may help psychiatric patients with low therapy motivation to improve clinical symptoms and other health-related outcomes. They are studying a cohort of 144 adults with a non-organic mental disorder who show low therapy motivation and a willingness to work with music (15). In their study, patients are randomly assigned to an experimental (standard care plus biweekly sessions of music therapy over a period of three months) or a standard therapeutic protocol. Outcomes will be measured by a blinded assessor before and 1, 3, and 9 months after randomization. The findings this study is expected to produce will fill an important gap in the knowledge on how music therapy could exert its effects in psychiatric patients (15). Moreover, given its methodologically rigorous protocol (prospective, randomized, controlled and single-blinded study), this study could have important implications as regards the effectiveness and generalizability of music therapy in clinical practice, and may also offer a long-term evaluation of the effects of music.

Similar, well-designed investigations could serve in the near future to shed light on the potential effects of music therapy in other psychiatric illnesses, such as depression, anxiety, and autism spectrum disorders.

Concluding remarks

Music is not just an aspect of human culture; it also has a number of neurophysiological and neurochemical facets. Music is present in every society around the world and seems to have emerged spontaneously and quite early on in man’s evolution. The adaptive function of music may thus explain its widespread, cross-cultural presence. Music is an integral part of complex behaviours such as dancing, religious rituals, and ceremonies. It can also play an important social role by favouring cohesion and the sense of belonging to a group. These social aspects of music may also be involved in the development of mother-infant communication, as well as in other forms of human bonding (35).

In summary, the musical experience – by reducing stress, and improving social relationships and wellbeing – is not only an important part of our own life, but could also play a role in the rehabilitation of a number of different neurological and psychiatric diseases. Unfortunately, there is still a shortage of rigorous scientific data supporting the efficacy of music therapy in clinical practice. Future research programmes, including prospective, randomized, controlled, single-blinded studies, are needed to address this issue and to evaluate the possible long-term effects of music therapy. In addition, electrophysiological or neuroradiological studies setting out to investigate the neuronal correlates of the musical experience in psychiatric patients are to be welcomed. Such investigations would also help to clarify whether there exist differences in music perception between patients with and without mental illness.

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