MUSIC AND DISORDERS OF CONSCIOUSNESS: EMERGING RESEARCH, PRACTICE AND THEORY

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MUSIC AND DISORDERS OF CONSCIOUSNESS: EMERGING RESEARCH, PRACTICE AND THEORY

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Music processing in severely brain-injured patients with disorders of consciousness has been an emergent field of interest for over 30 years, spanning the disciplines of neuroscience, medicine, the arts and humanities. Disorders of consciousness (DOC) is an umbrella term that encompasses patients who present with disorders across a continuum of consciousness including people who are in a coma, in vegetative state (VS)/have unresponsive wakefulness syndrome (UWS), and in minimally conscious state (MCS). Technological developments in recent years, resulting in improvements in medical care and technologies, have increased DOC population numbers, the means for investigating DOC, and the range of clinical and therapeutic interventions under validation. In neuroimaging and behavioural studies, the auditory modality has been shown to be the most sensitive in diagnosing awareness in this complex population. As misdiagnosis remains a major problem in DOC, exploring auditory responsiveness and processing in DOC is, therefore, of central importance to improve therapeutic interventions and medical technologies in DOC.

In recent years, there has been a growing interest in the role of music as a potential treatment and medium for diagnosis with patients with DOC, from the perspectives of research, clinical practice and theory. As there are almost no treatment options, such a non-invasive method could constitute a promising strategy to stimulate brain plasticity and to improve consciousness recovery. It is therefore an ideal time to draw together specialists from diverse disciplines and interests to share the latest methods, opinions, and research on this topic in order to identify research priorities and progress inquiry in a coordinated way.

This Research Topic aimed to bring together specialists from diverse disciplines involved in using and researching music with DOC populations or who have an interest in theoretical development on this topic. Specialists from the following disciplines participated in this special issue: neuroscience; medicine; music therapy; clinical psychology; neuromusicology; and cognitive neuroscience.

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Editorial: Music and disorders of consciousness: emerging research, practice and theory

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The Editorial on the Research Topic

Music and disorders of consciousness: emerging research, practice and theory

> *"No other diagnosis within the field of neurological rehabilitation carries with it such a vast range of clinical, medico-legal, ethical, philosophical, moral and religious implications"*
>
> (Wilson et al., 2005, p. 432)

Despite the body of research on disorders of consciousness (DOC) that has emerged since the "persistent vegetative state" was first named (Jennet and Plum, 1972), the provision of optimal care for this complex population continues to challenge health, medical and science professionals. This is in notwithstanding continual developments in definitions to enhance diagnostic criteria, for example the definition of the minimally conscious state by Giacino et al. (2002) and the term "Unresponsive Wakefulness Syndrome" to replace "vegetative state" proposed by Laureys et al. (2010). Of central concern is the recovery of consciousness (Whyte, 2014), an ambiguous concept that encompasses both wakefulness and awareness (Royal College of Physicians, 2013). Consciousness cannot be directly assessed using verbal reports in this non-communicative population (Seel et al., 2010). The ability to demonstrate consciousness is further compromised in these patients who show minimal motor responses (often due to spasticity), are poorly aroused, and may have significant cognitive and sensory impairments.

The prescient issue has been accurate diagnosis in order to plan appropriate treatment and identify potential in people with DOC. The incidence of misdiagnosis remains unacceptably high (Schnakers et al., 2009; van Erp et al., 2015). For some time, the auditory modality has emerged as potentially sensitive for indicating awareness in people diagnosed as being in vegetative state (Gill-Thwaites and Munday, 2004; Owen et al., 2005, 2006). This insight has prompted greater exploration of auditory stimulation within research and practice, particularly given the suspected incidence of visual impairment in DOC contributing to misdiagnosis (Andrews et al., 1996). More particularly, auditory stimulation with an emotional valence, such as a familiar voice or the patient's own name, has been shown as helpful when trying to understand residual brain processing and when uncovering consciousness in patients with severe brain injury (Bekinschtein et al., 2004; Laureys et al., 2004; Schiff et al., 2005; Perrin et al., 2006; Di et al., 2007). As music has a well-known relationship with emotional processing (Frühholz et al., 2014; Omigie, 2016), such stimulation might be crucial when assessing the recovery of consciousness in this challenging population.

MUSIC AND DOC

Based in early studies from the 1990's, an interest in using music as a medium for diagnosis, exploration and treatment in DOC has rapidly expanded in recent years, and in particular with the

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growing research community of music and neurosciences interested in the use of music as a tool for promoting sensory, cognitive and motor stimulation of the normal and pathological brain (see Bigand et al., 2015, for recent reviews). Current behavioral explorations with DOC populations have used music to train behaviors (Charland-Verville et al., 2014) and have demonstrated that music can elicit behavioral responses indicative of arousal (O'Kelly et al., 2013). Music listening has a beneficial effect on cognitive processes in people with DOC (Castro et al., 2015) including increased EEG amplitude in alpha and theta bands suggestive of attentional processes (O'Kelly et al., 2013). Case studies suggest music may have diagnostic value to distinguish between vegetative and minimally conscious states, as well as prognostic potential (Okumura et al., 2014). Clinical music protocols for therapeutic intervention have been developed and music-based diagnostic measures have been standardized (Magee and O'Kelly, 2015).

Interest in this topic is growing at an exponential rate, on the understanding that language impairment is likely following profound brain injury and that music is both an alerting and an emotional stimulus (Castro et al., 2015). It is apparent that energies need to be harnessed, coordinating the efforts of diverse disciplines spanning research, science, and clinical practice. This special issue grew from a desire to strengthen the body of evidence for using music in the assessment, diagnosis, and treatment of people with DOC in order to improve research and practice. We aimed to provide a platform for cross disciplinary discussion to encourage multiple perspectives. This international collection helps to consolidate the foundations of this field of study for future work on the topic.

Our call for papers was responded to by scientists, researchers and clinical practitioners, resulting in nine articles. Three papers are Original Research Articles, three are Opinion Papers, two are Reviews, and one is a Perspective paper. The research groups span seven countries (Austria, France, Germany, Italy, Russia, UK, USA) and include 28 authors.

THE NEUROMUSICOLOGY OF DISORDERS OF CONSCIOUSNESS

Different methodologies have been used to investigate the effect of music on the brain functioning of DOC patients. The present issue reports four articles in which the interest of autonomic recordings, EEG and functional MRI connectivity are evaluated. First, Kotchoubey et al. reviewed empirical data on different functions (perception, cognition, emotions, and motor functions) that musical stimulation can address in DOC patients. This is supported by an original study in which Riganello et al. investigated the link between music listening and heart rate variability, and in which they found differences between DOC and healthy subjects, characterized by lower values in VS/UWS patients. Lord and Opacka-Juffry, in an opinion paper, claim that EEG studies of coherence can be used to assess the effects of auditory stimuli in DOCs, for example during the course of music therapy. According to them, these studies could help to understand whether changes in connectivity across the mesocircuit pathways are an indicator of the conscious state and neuroplasticity. Cerebral connectivity is also investigated in an original contribution, with functional MRI methodology, in which Heine et al. showed that the auditory network is more connected with the left precentral gyrus and the left dorsolateral prefrontal cortex, and the external network with the temporo-parietal junction, during preferred music listening (as compared to a noise control condition). Thus, this is a first demonstration that music listening might have effects, in DOC patients, on networks implied in rhythm and music perception, as well as in autobiographical memory.

CLINICAL APPLICATIONS OF MUSIC WITH DOC: THEORY AND PRACTICE

Perspectives on potential clinical applications were discussed in five papers. The theoretical principles for the efficacy of sensory stimulation vs. music stimulation is discussed by Schnakers et al. Further, investigation is warranted as methodological issues, including small sample sizes, agreement on core outcomes, and sensitivity of measures, have all contributed to limiting adequate investigations to draw conclusive results. Nevertheless, the preliminary findings obtained until now encourage further investigations to confirm the benefit of music, not only in the detection of consciousness, but also in the treatment of patients with severe brain injury.

The theoretical position for using music is developed by Perrin et al. who highlight that the selection of stimuli with emotional, autobiographical or self-related characteristics is critical in people with DOC. In their review, they position music as a potential tool for engaging both internal and external networks, facilitating awareness of self in addition to awareness of environment and contributing to long-term cognitive improvement.

Research into pediatric DOC is a neglected topic with no measures currently standardized for use with children and adolescents and no guidelines for clinical practice. Pool and Magee continue the discussion comparing sensory stimulation and music with pediatric DOC, presenting an overview of the theoretical literature. Music is a primary modality for learning and development in normal pediatric populations, due to its utility for cross-modal application, cognitive priming, and emotional stimulation. As the incidence of visual impairment in children and youth with DOC is notably high, the authors argue that music provides a developmentally appropriate medium that is also accessible. Following from this, Magee et al. explore the clinical utility of a music-based measure with a pediatric DOC population. Data from four cases examine outcomes from the music therapy assessment tool for awareness in disorders of consciousness (MATADOC), a protocol and measure that have been standardized for adults. The results suggest higher functioning in the visual and auditory domains when compared to several external reference standards whose protocols do not optimize non-verbal auditory stimuli. This is promising for clinical practice and supports further investigation into using music as a diagnostic and treatment tool for pediatric DOC.

Lastly, Vogl et al. present the case for a neuroanthropological approach in research with DOC patients for obtaining knowledge and influencing practice. This approach positions music as representing meaning from the individual patient's perspective. Two case descriptions illustrate how quantitative PET data can be augmented by qualitative behavioral observations. The cases illustrate how clinical music protocols can be adapted to individual needs, and that these investigations can contribute to the multidisciplinary team's understanding of how to manage the patient's daily life and environment.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Music in Research and Rehabilitation of Disorders of Consciousness: Psychological and Neurophysiological Foundations

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According to a prevailing view, the visual system works by dissecting stimuli into primitives, whereas the auditory system processes simple and complex stimuli with their corresponding features in parallel. This makes musical stimulation particularly suitable for patients with disorders of consciousness (DoC), because the processing pathways related to complex stimulus features can be preserved even when those related to simple features are no longer available. An additional factor speaking in favor of musical stimulation in DoC is the low efficiency of visual stimulation due to prevalent maladies of vision or gaze fixation in DoC patients. Hearing disorders, in contrast, are much less frequent in DoC, which allows us to use auditory stimulation at various levels of complexity. The current paper overviews empirical data concerning the four main domains of brain functioning in DoC patients that musical stimulation can address: perception (e.g., pitch, timbre, and harmony), cognition (e.g., musical syntax and meaning), emotions, and motor functions. Music can approach basic levels of patients' self-consciousness, which may even exist when all higher-level cognitions are lost, whereas music induced emotions and rhythmic stimulation can affect the dopaminergic reward-system and activity in the motor system respectively, thus serving as a starting point for rehabilitation.

Keywords: consciousness, DoC, music, rehabilitation, psychology, neurophysiology

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INTRODUCTION

The aim of the present paper is to show that music is a particular kind of auditory stimulation that may be most beneficial for use in patients with disorders of consciousness (DoC) in both research and therapy. With respect to therapy, the enormous complexity of such studies partly accounts for the currently low number of well-controlled trials and hence the limited demonstration of evidence-based effects of music therapy in DoC (see Giacino et al., 2012). However, one-time experimental interventions using musical stimuli yielded promising results in a few studies with middle-sized DoC samples (e.g., Formisano et al., 2001; O'Kelly and Magee, 2013; Magee and O'Kelly, 2015). Less clear-cut are the data of music therapy interventions, which are summarized in **Table 1**. As can be seen in the table, only three studies (Formisano et al., 2001; Raglio et al., 2014; Sun and Chen, 2015) tested the effects of musical therapy using 10 or more DoC patients. Only the last one employed a sufficient level of control and showed some promising results. However, these data are in need of replication.

TABLE 1 | Music therapeutic interventions and outcomes in DoC.

Source	Participants	Design	Outcome
Formisano et al. (2001)	Thirty-four MCS patients, 13–70 years, $M = 35.94$; 18 TBI, 16 non-TBI	Music therapy program included singing or playing different musical instruments. Three 20–40 min sessions per week during 2 months.	Decreasing in inertia or psychomotor agitation in 21 patients. No significant change of CRS scores.
Magee (2005)	One VS patient, >50 years old anoxic brain injury	Music therapy program with singing and playing musical pieces. Music selection based on the participant's life history. No information about the duration of the program.	The patient demonstrated some behavioral responses in response to music and song exposition. No information about changes in objective measures.
Raglio et al. (2014)	Four MCS and six VS patients (five with anoxic brain injury, four hemorrhage, one TBI)	Music therapy included two cycles of 15 sessions (three sessions/week, 30 min each). The cycles spaced out by 2 weeks.	Improvements of some observed behaviors in MCS patients: eye contacts, smiles, communicative use of instruments/voice, reduction of annoyance, and suffering expressions. VS patients only increased eye contacts.
Seibert et al. (2000)	One MCS patient, 20 years old after severe hypothermia, cardiac arrest, and brain anoxia; GCS score – 12 Rancho Los Amigos Scale – 4	Music therapy program involved exposure to oboe music, physical contact with the instrument, and the presentation of favorite music during 2.5 years.	At the end of the program: GCS score – 15, Rancho Los Amigos Scale – 6; Persisting moderate deficits in orientation/attention, visual-spatial skills, memory, and language. Reading comprehension and ability to follow commands were at a moderate level.
Lee et al. (2011)	One VS patient, age 45 years Intracerebral hemorrhage GCS score – 4	ECG data collected during 7 weeks. First week: six baseline sessions with no music, each lasting for 180 min. Next 6 weeks: six music sessions when the patient listened to Mahler's symphony no. 2, each session lasted for 210 min.	Changes in the standard deviation of time sequences showed positive changes in the cardiovascular system.
Steinhoff et al. (2015)	Four VS patients after cardiopulmonary resuscitation	Music therapy group ($n = 2$): standard care plus live and individual music therapy sessions for 5 weeks (three sessions/week, about 27 min each). Control group ($n = 2$): only standard care. PET in the baseline in rest state; PET at the end of the second and sixth weeks in response to musical stimulation (both in the music and control groups).	Patients in the music therapy group appeared to show higher brain activity than control group patients in the last PET scan.
Sun and Chen (2015)	Forty TBI coma patients, 18–55 years old GCS score between 3 and 8 6.55 ± 2.82 days after injury	Music therapy group ($n = 20$): listening to their favorite and familiar music for 15–30 min three times every day during 4 weeks. Control group ($n = 20$): waiting control.	GCS scores increased significantly in both groups, yet significantly more in the music therapy group. Relative power of slow EEG rhythms decreased in both groups, yet these changes were significantly stronger in the music therapy group.

CRS, Coma Recovery Scale; ECG, electrocardiography; EEG, electroencephalography; GCS, Glasgow Coma Scale; MCS, minimally conscious state, PET, positron emission tomography; TBI, traumatic brain injury; VS, vegetative state.

In contrast to therapeutic effects in DoC, we can draw on a large number of studies that examined the highly specific effects of music on basic perceptual, higher-cognitive, and emotional processes in the brain of healthy subjects, and derive suggestions for their use in DoC. In this review, we will concentrate on features of music that play, or can play, a significant role in the examination and/or rehabilitation of chronic DoC. We do not present a comprehensive review on music perception and cognition but rather intend to analyze the potential and applicability of music stimulation in DoC.

This review starts with some fundamental reasons why auditory stimulation might be particularly useful in DoC. We then first provide essential information about the neural specializations of auditory processing (e.g., basic sensory and sensorimotor mechanisms) before describing higher-level perceptual organization of sound, including the neural differences associated with the processing of musical syntax and semantics. After we moved on to discuss the potential benefits of multisensory stimulation in DoC, we finally provide evidence and suggestions for the use of musical stimulation as a therapeutic tool with respected to effects on cognition, emotion, and stress in DoC. The scheme we adopted throughout all sections is to first describe how healthy subjects respond to music before reviewing the evidence-based practice or potential application of music stimulation in chronic DoC.

WHY AUDITORY STIMULATION IN DOC?

Many DoC patients cannot see. Andrews et al. (1996) indicated in their frequently cited article that blindness is a major issue contributing to the exceptionally high rate of misdiagnosis in DoC: "The very high prevalence of severe visual impairment… is an additional complicating factor since clinicians making the diagnosis of the vegetative state place great emphasis on the inability of the patient to visually track or blink to threat" (p. 15). Moreover, even if both sensory pathways from the retina to the visual cortex and the cortical centers themselves are intact, this does not indicate that a DoC patient can see, as the role of motor control in visual perception is vital. To perceive anything more than just light, not only must the eyelids be open but also the ocular muscles and their controlling brain areas must be able to perform following and searching saccadic movements, a skill that is drastically reduced in vegetative state (VS) and also severely impaired in minimally conscious state. Conversely, the ability to consistently perform following gaze movements is considered a criterion to rule out a DoC diagnosis, whereas inconsistent followings may be compatible with the diagnosis the minimally conscious state (MSC+; Bruno et al., 2011). In an unpublished pilot study, we examined electroencephalography (EEG) responses to visual stimuli as simple as checkerboard patterns in five patients who fulfilled the diagnostic criteria of MCS+ according to Bruno et al. (2011). We failed to record a consistent evoked potential (EP) in any of them, although EPs to simple flash as well as the primary EP complex (P1–N1–P2) to auditory stimuli were virtually normal.

The situation seems indeed to be completely different in the auditory modality, not only because ears cannot be physically closed like eyes but also because active voluntary control of peripheral muscles is not vital for immediate sound sensation, although motor and corresponding somatosensory factors are of great importance in the perception of complex auditory stimulation (see below). We could not find data about the prevalence of lacking brain stem auditory EPs (BSAEP) in DoC, perhaps because the presence of this response is an inclusion criterion in most studies and therefore patients without BSAEP would be excluded from the very beginning. It follows that studies in DoC should not only provide detailed exclusion criteria with respect to auditory EPs but also how many patients were effectively excluded from the sample based on these rules. In fact, auditory EPs are frequently used in ENT clinics to distinguish between normal or hearing-impaired states in otherwise healthy infants (Paulraj et al., 2015). Among 83 VS patients with at least partially preserved BSAEP, 71 patients (i.e., 86%) also showed cortical EP components (as a rule, N1). If we introduce a further criterion and eliminate 10 VS patients with large-amplitude diffuse delta waves dominating the EEG all the time, only two patients (2.7%) with BSAEP would not show cortical EPs. All 49 examined MCS patients exhibited cortical auditory EPs. A subsample of this patient group (i.e., 50 VS and 39 MCS patients) has been reported in detail elsewhere (Kotchoubey, 2005; Kotchoubey et al., 2005). Notably, we observed a highly significant N1 component to complex tonal stimuli and even highly differentiated responses to speech (Kotchoubey et al., 2014) in patients with anoxic brain injury up to 11 years in the VS with Level 4 brain atrophy according to the classification of Galton et al. (2001) and Bekinschtein et al. (2009). Moreover, about half of the DoC patients without a specific lesion of the right temporal lobe exhibited significant responses to affective prosody (exclamations like "wow," "ooh," etc.: Kotchoubey et al., 2009). Taken together, deafness does not seem to be a major problem in most DoC patients. If deafness should be present, however, it is usually detected at very early stages of the disease because BSAEP are routinely recorded from the very beginning in most German hospitals for neurological rehabilitation. The cases of cortical deafness in DoC seem to be rare. If, as suggested in a stepwise procedure (Kübler and Kotchoubey, 2007; Kotchoubey et al., 2013), we first exclude patients without brain stem EP and patients with diffuse delta activity (the two groups usually overlap strongly), cortical auditory EPs can be obtained in nearly every DoC patient. Therefore, we suggest to use complex tonal stimuli for auditory EPs as a rule and the use of music therapy only in DoC patients with preserved neurophysiological findings [e.g., brainstem and middle-latency auditory EPs and event-related potential (ERP)].

NEURAL SPECIALIZATIONS FOR AUDITORY PROCESSING

Basic Considerations

The oscillatory structure of acoustic events can be conceptualized as two perceptually quite distinct components: one that consists of *higher frequencies*, which provide the basis of *pitch* and *timbre* perception, and one that consists of *lower frequencies*, which provide the basis of musical rhythm and meter perception (i.e., the temporal organization of sounds). According to a well justified (although not yet in all respects empirically tested) hypothesis, this distinction has been related to two discrete anatomical and physiological components of the auditory system that have been classically described in the neurophysiology of afferent systems as specific versus non-specific, or lemniscal versus extralemniscal subsystems (e.g., Abrams et al., 2011).

Anatomically, the auditory cortex is subdivided into the primary cortex, or A1 [Brodmann area (BA) 41], the belt, or A2 (BA 42), and the parabelt, or A3 (BA22). The belt extends from inside the lateral sulcus or the supratemporal plane out onto the open surface of the superior temporal gyrus (STG) and receives independent input from the superior colliculus separately from A1 (Pandya, 1995). Neurons in the ventral part of the medial geniculate body (MGB) terminate in deeper layers (mainly, Layer 4 and the deep portion of Layer 3) of A1 and their impulsion immediately elicits action potentials in pyramidal neurons located there. The narrow frequency tuning of these neurons results in a relatively tonotopic organization of A1 (Formisano et al., 2003), providing specific frequency information and thus contributing to the perception of pitch and timbre (the "content" of a melody). In contrast, neurons located in various parts of the MGB (mostly in its dorsal division) that target at superficial Layers 1 and 2 of A1 and the belt, are more broadly tuned and deliver non-specific information. Activating apical dendrites of the pyramidal cells, they do not directly result in their firing, but rather regulate the firing threshold by "warming up" pyramidal neurons according to the basic rhythm (or the metrical "context") of a musical phrase. The high-frequency content is therefore synchronized with the low-frequency context in such a way that responses "driven" by events associated with contextual accents are amplified, while the responses that occur out of beat are weakened. The context is therefore created by a modulatory input, and the content by a "driving" input of the auditory cortex (Musacchia et al., 2014).

As regards pitch perception, Rauschecker (1997, 1999) and Rauschecker et al. (1997) was probably the first who demonstrated, in macaque monkey experiments, the independence of the processing of pure tones and chords. Since the primary auditory cortex (BA 41) and the belt (A42) receive largely independent input, the tonotopic structure that is typical for the superior colliculus and A1 is basically lost in the belt and even more so in the parabelt. Pure tones are therefore the least effective auditory stimulation to elicit neuronal responses in these areas (Rauschecker, 1997), which may have implications for their use in DoC. In contrast, the cells of the belt strongly respond to complex sounds and frequency-modulated sweeps, indicating the non-reductive processing of complex sounds that builds the basis for the perception of pitch modulation independently of intensity (Rauschecker, 1999). The same research team further hypothesized that the auditory system, like its visual counterpart, entails two different pathways to higher-order cortical areas, designed for processing spatial and temporal information, the "where" and "when" subsystems (Romanski et al., 1999). This hypothesis, however, remains under debate (e.g., Griffiths, 2001). Instead, another model proposed that auditory pathways could be segregated by their modes of auditory processing, such that a dorsal pathway extracts the message or melody from sound, whereas the ventral pathway identifies the speaker or instrument by its timbre (Zatorre et al., 2002b).

The independence of single frequency and harmonic processing is also critically important for the separation of auditory objects (e.g., Yost, 2007), because objects can be conceived as particular correlations of several frequency bands (Nelken et al., 2014). Moreover, the non-linear analysis of physical stimuli in the cochlea can result in internally generated new harmonics produced by the auditory system itself (Pickles, 1988). These facts demonstrate the inadequacy of the idea that the primary auditory processes sound in a Fourier-like manner.

Notably, the relation between the three auditory cortex regions (i.e., A1, A2, and A3) changed very much in the course of human evolution. While the primary auditory cortex in humans is slightly smaller than in macaques, the human belt and parabelt areas are almost 10 times larger (Angulo-Perkins and Concha, 2014). Another interesting fact is that the origin of auditory cortical input is mostly top-down. This is true even for A1, as only 23% of neurons projecting to A1 are of purely acoustic subcortical (i.e., thalamic) origin, while 66% are cortical neurons, most of them being localized at higher levels of the auditory system. Therefore, one cannot speak about feature analysis at the A1 level. Rather, stimulus representation in the auditory cortex is task-specific, i.e., "spatio-temporal activation patterns of neuronal ensembles in AC, passively generated by a given stimulus and basically reflecting all features of a stimulus, can be modified according to the context and the procedural and cognitive demands of a listening task, i.e., also reflect semantic aspects of a stimulus" (Scheich et al., 2007, p. 214).

As receptive fields of cortical neurons can flexibly adjust to the auditory task, the tonotopy of A1 should not be overvalued. Many A1 neurons in most investigated mammalian species respond to several frequencies (for primates, see, e.g., Sadagopan and Wang, 2009), and even those with a single-frequency peak do not respond to individual components of harmonic tones that are outside of its tone-derived frequency response area (Wang and Walker, 2012). This suggests that frequency-driven responses can be harmonically modulated. While the relatively few axons from the geniculate nucleus of the thalamus frequently end at cell bodies or basal dendrites, the big portion of the top-down cortical input comes to apical dendrites, thus creating a "context" modulating responsivity to specific factors. The relation between top-down and bottom-up input in higher-order areas is even more shifted toward the former. Together, these data support the view that the purpose of the auditory cortex in higher animals (mainly investigated in monkeys) is not only sensory analysis but also the adjustment to the auditory environment and identification of auditory objects (Yost, 2007; Reybrouck and Brattico, 2015).

Human Studies

As cellular mechanisms of music perception at subcortical and cortical levels cannot be studied directly in humans, the neural characteristics of music processing have mostly been investigated using event-related brain responses measured with the EEG and the magnetoencephalogram (MEG), or by assessing the blood oxygenation (BOLD) response to auditory stimulation with functional magnetic resonance imaging (fMRI). The latter, for example, revealed that optimized auditory processing of rhythm and frequency is associated with a relative hemispheric advantage, with the left auditory cortex being more sensitive to temporal characteristics of auditory cues (i.e., more prevalent in speech production) and the right auditory cortex being better for decoding pitch and harmony content of acoustic stimuli, which is emphasized in music (Zatorre et al., 2002a). Given the huge difference in the methodological precision (each EEG, MEG, or fMRI recording encompasses the activity of many thousands of neurons, compared with single cell recordings in animals), however, one may even be surprised how similar are the conclusions of human and animal experiments.

The arrival of auditory input at the cortex in humans is manifested in ERPs by the obligatory (exogenous) primary complex P1–N1 with the latencies of about 50 ms and 100–120 ms for P1 and N1, respectively. Processing of stimulus deviation is reflected in an endogenous ERP component mismatch negativity (MMN: Näätänen, 1995) that attains its peak around 200 ms post stimulus. MEG data show that at least a large portion of the MMN is generated in the auditory cortex. An important property of the MMN is that its generators do not require active attention. Even though attention to stimuli can increase MMN amplitude (e.g., Erlbeck et al., 2014), other ERP components (which can mask the MMN) are increased to a much larger extent; therefore, it is practically better to record the MMN in a condition in which the subject's attention is caught by some other activity such as reading a book or looking at a movie. Higher-order music processing can be manifested in an early right anterior negativity (ERAN), an ERP component of frontal origin (for review, see Koelsch, 2014), or in two late components, N400 and P600, with the latencies of about 400 and 600 ms, respectively. These components, however, are much more attention-dependent than the MMN.

For a long time, the MMN was studied in response to rather simple stimulus deviations such as deviations in pitch (e.g., 800 Hz–800 Hz–800 Hz–800 Hz–600 Hz), intensity (e.g., 80 dB–80 dB–80 dB–80 dB–65 dB), or tone duration (e.g., 50 ms–50 ms–50 ms–50 ms–30 ms). Later studies showed, however, that the MMN also responds to much more complex pattern changes in the auditory stream (e.g., Tervaniemi et al., 1994). Thus, the repetition of a short sequence like AAB results in an MMN after omission of the last tone (AA_), reversal (ABA), or even repetition of the same tone (AAA). Moreover, MMN mechanisms are also sensitive to some level of abstraction. This is shown in an experiment in which standard (repeated) stimuli were ascendant pairs combining five different chords (AB, CD, AC, BE, etc.). Two kinds of rare deviants were either descendent pairs (DA, CB, etc.), or repetitions (AA, DD, etc.). Both kinds of deviants elicited a strong MMN (Tervaniemi et al., 2001).

Dipole localization using MEG indicates that the generator of the MMN to chords in the STG is located more medial than the MMN generator for sine tones. However, stimulus complexity is not the only factor affecting the generator structures, as demonstrated by experiments in which the magnetic counterpart of the electric MMN was compared between phoneme change and chord change of the same acoustic complexity. The source of the "musical" MMN was located superior to the source of the "phonetic" MMN. Moreover, the former was lateralized to the right side, while the latter was symmetrical. Importantly, the generator of the component P1 was identical for all stimuli of comparable complexity regardless of their origin. Apparently the mechanism of the MMN is the first processing stage at which music-specific analysis of auditory stimuli begins (Angulo-Perkins and Concha, 2014).

In support of animal data presented above, indicating a strong independence of processing of harmonic tones compared to that of single sine frequencies, MMN data indicate that also in humans pitch deviations of chords result in a larger MMN than comparable deviations of pure tones (Tervaniemi et al., 2000). By successfully replicating this MMN paradigm in a large sample of DoC patients, our group demonstrated that the MMN to harmonic tones not only led to a larger amplitude as shown before but also to a higher frequency of occurrence than the MMN to sine tones (Kotchoubey et al., 2003). About a half of the patients who did not have an MMN to simple sine tones exhibited, however, an MMN to harmonic tones. The MMN seems to be present in about 30–60% of all patients with acute or chronic DoC (Kotchoubey, 2015). In acute coma it belongs to the most reliable predictors of further awakening (meta-analytic review of Daltrozzo et al., 2007), and there is also evidence of its predictive meaning in chronic DoC (Kotchoubey et al., 2005). In order to evaluate the effectiveness of music therapy in chronic DoC, the habitual assessment of MMN to complex tones could help developing a potential outcome predictor.

Other ERP components, later than the MMN, occur with a lower frequency in DoC, but confirm that the auditory system of many DoC patients remains flexible enough to process stimuli of very high complexity (Kotchoubey, 2015). Thus the attention-dependent component P3 in these patients responds, like the MMN, much better to harmonic stimuli than to sine tones (Kotchoubey et al., 2001). ERP responses to complex violations in rhythmic sound sequences have recently been demonstrated in 10 of 24 patients in deep post-anoxic coma who were additionally sedated (Tzovara et al., 2015).

Key messages:

- Auditory processing is related to one of the most basic processes underlying all higher forms of life, i.e., the processing of environmental events in their temporal sequence.
- The auditory cortex entails specialized regions for the processing of complex sounds and their components. Auditory scene analysis and the identification of auditory objects is an important task of the auditory cortex, which can result in clinically important dissociations between disorders that entail the processing of simpler versus more complex sounds.
- Consistent responses to chords and to changes in harmonic patterns have also been observed in DoC cases where cortical responses to sine tones could not be recorded. We therefore suggest complex sounds for auditory stimulation in DoC as a rule.
- Non-responsiveness to simple sounds is no reason to withdraw from musical therapy!

HIGHER-LEVEL AUDITORY PROCESSING

Segregation and Integration

Beyond basic aspects of sound processing, music perception represent a highly complex process that involves the segregation and integration of various different acoustic elements such as melody, harmony, pitch, rhythm, and timbre, which engage networks that are not only implicated in auditory but also in syntactic and visual processing (Schmithorst, 2005). In fact, both music and language engage partly overlapping (Liegeois-Chauvel et al., 1998; Buchsbaum et al., 2001; Koelsch and Siebel, 2005; Koelsch, 2006; Chang et al., 2010; Schön et al., 2010; Patel, 2011) as well as domain-specific subcortical and cortical structures (Belin et al., 2000; Tervaniemi et al., 2001; Zatorre et al., 2002a; Zatorre and Gandour, 2008).

Sound perception first requires the extraction of auditory features in the brain stem, the thalamus, and the auditory cortex (Koelsch and Siebel, 2005), leading to auditory percepts of *pitch-height and pitch-chroma, rhythm, and intensity*. However, the lower-level frequencies related to the temporal organization of music may also be processed independently from melodic intervals (Peretz and Zatorre, 2005), engaging additionally pre- and supplementary motor areas, the basal ganglia, and the cerebellum (Grahn and Brett, 2007; Thaut et al., 2009). This integration of sequentially ordered acoustic elements on longer time-scales is a highly demanding task that requires the structuring (e.g., separation or grouping) of musical elements, leading to a cognitive representation of acoustic objects based on Gestalt principles (Darwin, 2008; Ono et al., 2015). The cognitive involvement of musical pattern processing is evident from the joint activation of auditory association cortices with pre-frontal regions in the brain (Griffiths, 2001).

All basic forms of learning, some of which presented even in the simplest animals like worms, necessarily involve the ability to perceive events in their temporal order. Thus habituation results from perceiving one and the same stimulus as repeating; classical (Pavlovian) conditioning is based on the perception that one stimulus (CS) consistently precedes another one (UCS); and so on. The perception of sequential events is essential to all higher forms of life, because it allows for the timely preparation of appropriate responses. The steady anticipation of consecutively presented information units therefore relates music to one of the most fundamental necessities of life, the predictability of events in their temporal succession (e.g., Francois and Schön, 2014; Wang, 2015). Events that are out of rhythm are unpredictable.

The sequential ordering of individual pitches also leads to the perception of melody, whereas their vertical ordering leads to the perception of harmony. To achieve perceptual coherence, a rule-based hierarchical organization of acoustic inputs is therefore elemental for determining how tones may be combined to form chords, how chords may be combined to form harmonic progressions, and how they are all united within a metric framework. This process of hierarchical structuring and temporal ordering of acoustic objects is indeed a shared feature in the syntactic organization of both music and speech.

Musical Syntax and Semantics

Syntax in music (just as in language), "refers to the principles governing the combination of discrete structural elements into sequences" (Patel, 2008, p. 241), with independent (yet interrelated) principles for melody, harmony, and rhythm. Musical syntax has been most thoroughly investigated with respect to harmony (e.g., Koelsch, 2012), as syntactic perception of harmonic dissonance and consonance depends crucially on the functional relationships of preceding and subsequent chords (or tones). As outlined above, these percepts build on expectancies based on previously acquired long-term knowledge and thus trigger distinct responses in the brain when they are violated.

An early study with musicians by Janata (1995) demonstrated that the violation of expectancy in the final chord of a chord sequence elicits larger P3 peaks as a function of the degree of violation, thus reflecting both attentional (P3a; 310 ms latency) and decisional (P3b; 450 ms latency) processes. Another study (Patel et al., 1998), reported that incongruences in both language and music syntactic would elicit a parieto-temporal P600, which had been associated with language processing, suggesting that this ERP component reflects more general processes of structural acoustic integration across domains. Likewise, some kinds of syntactic violations in language may elicit a specific negative component in the ERP with a latency about 200–300 ms and a maximum over the left frontal cortex, the so-called early left anterior negativity (ELAN). Beginning with a first study by Koelsch et al. (2000), a comparable syntactic violation in music was found to result in a quite similar ERP component over the right frontal cortex: the ERAN (Koelsch et al., 2001; Koelsch and Jentschke, 2010; Koelsch, 2012). Accordingly, the ERAN reflected "a disruption of musical structure building, the violation of a local prediction based on musical expectancy formation, and acoustic deviance" (Koelsch, 2012, p. 111). A later negative component around 500–550 ms (N5) was also observed over frontal regions following the ERAN, but was rather associated with musical meaning (Poulin-Charronnat et al., 2006, see below). Other, simpler kinds of syntactic violations resulted mainly in a late positive parietal complex rather than an early frontal negativity for both language (e.g., Osterhout, 1995) and music (e.g., Besson and Faïta, 1995), although studies on melodic syntactic violations also reported a frontal ERP response with a slope emerging around 100 ms and peaking around 120–180 ms that resembled the ERAN in harmonic violation paradigms (Brattico et al., 2006; Koelsch and Jentschke, 2010).

A conceptual similarity between music and speech perception is also reflected in the dynamics of the N400 ERP component (e.g., Patel, 2003; Kotchoubey, 2006; Daltrozzo and Schön, 2009a,b). Like the N5, the N400 has been attributed to musical meaning rather than syntax, contributing to the subjective interpretation of musical information, which involves affective processing. Koelsch (2012) used the term musical semantics to account for the different dimensions of extra-musical, intra-musical, and musicogenic meaning. Extra-musical meaning can be derived from musical sign qualities by making reference to the extra-musical world, such as the imitation of naturally occurring sounds (e.g., the river Rhine in Wagner's "Rheingold" prelude), the psychological state of a protagonist (e.g., in the pranks of Richard Strauss's "Till Eulenspiegel"), or arbitrary symbolic associations (e.g., national anthems). Intra-musical meaning in turn refers to the interpretation of structural relations between musical elements, whereas musicogenic meaning describes the experience of emotional, physical, or personal effects of music, which are evoked within the listener.

Several studies have demonstrated that the representation of extra-musical meaning can be related to the N400, which is thought to reflect to the processing of meaning, for example when the content of target words in a semantic priming paradigm is meaningfully unrelated to the content of preceding musical excerpts (Koelsch et al., 2004). The N400 seems to be generated in the posterior temporal lobe, in close vicinity to regions that also process speech related semantics (Lau et al., 2008) and non-verbal vocalization (Belin et al., 2000; Kriegstein and Giraud, 2004). The notion that the N400 processes meaning from musical information has been confirmed in recent studies (Goerlich et al., 2011), where the N400 was triggered when the affective valence of word primes did not match the valence of musical or prosodic stimuli. Intra-musical meaning, in contrast, seems to be reflected by the N500 (or N5). As indicated above, the N5 follows the ERAN elicited by the perception of harmonic incongruence. However, the N5 does not just represent a function of incongruity in harmonic progressions but is rather modulated by the harmonic integration and contextual information in music that is not related to an extra-musical reference (Steinbeis and Koelsch, 2008). Lastly, musicogenic meaning may emerge from emotions evoked by the musical stimulus, which can also be associated with corresponding personal memories (see music evoked emotions below).

Although we do not know about any direct effects of music listening on language comprehension or other verbal functions in DoC patients, such effects have been demonstrated in other clinical populations. Music training has been used in language disorders (Daltrozzo et al., 2013) and the rehabilitation of aphasia patients, which led to increased structural integrity of white-matter tracts between fronto-temporal regions involved in language processing (Schlaug et al., 2010; Marchina et al., 2011). Also perceptual treatments have shown strong effects, including increased gray-matter volume after passive musical and verbal stimulation in stroke patients (Särkämö et al., 2014a). In this study, long-term changes (6-month follow up) were found in the orbitofrontal cortex, anterior cingulate cortex, ventral striatum, fusiform gyrus, insula, and superior frontal gyrus (SFG) areas after patients listened regularly to their preferred music. Changes in frontolimbic cortex moreover correlated with the improvement of verbal memory, speech and focused attention. Thus the SFG and the anterior cingulated cortex (ACC) appear to be important structures that mediate between music processing and cognition.

Key messages:

- Music and language both work with temporal features of stimulation. The two domains are implemented in partially overlapping, partially analogous morphological and functional mechanisms. Successful therapeutic interventions in one of these domains can result in significant improvement in the other one as well.
- We propose that the distinct ERP components associated with the neural difference in the processing of musical syntax and musical semantics (i.e., extra-musical, intra-musical, and musicogenic meaning) may prove useful for the detection of disparate cognitive processes during music perception in DoC.

IMPLICATIONS FOR MULTISENSORY STIMULATION

Although both music and speech perception are based on auditory scene analysis (Janata, 2014), perceptual modalities should not be treated as independent entities but rather considered in the context of simultaneous multisensory integration, which explains why somatosensory and visual feedback can significantly modulate auditory perception (Wu et al., 2014). In the same vein, the close connection between production and perception in music and speech tightly links auditory and somatosensory modalities. During production, we compare acoustic feedback with the intended sound to adjust motor commands, yet we simultaneously develop corresponding somatosensory representations related to inputs from cutaneous and muscle receptors (Ito and Ostry, 2010; Simonyan and Horwitz, 2011). Based on Hebbian learning mechanisms (Hebb, 1949), this simultaneous co-activation of perceptual and motor systems leads to the phenomenon of cross-modal plasticity, which manifests as mutual facilitation of neural activity and explains altered perception in one modality when the expected sensory feedback of another modality is not in register (Gick and Derrick, 2009). For example, stretching the facial skin during listening to words alters the subjective perception of auditory feedback (Ito et al., 2009). Conversely, the manipulation of auditory feedback during speech can also alter somatosensory orofacial perception (Ito and Ostry, 2012). Champoux et al. (2011) demonstrated that amplitude modulation of auditory feedback during speech production can even induce distinct laryngeal and labial sensations that are not a mechanic consequence of the motor task, whereas Schürmann et al. (2006) showed that vibrotactile stimulation helps auditory perception in both healthy and hearing impaired subjects.

As a rule, mutual perceptually facilitating effects are stronger when co-activation has been learned over a longer period, as shown in the example of trained musicians. In a study from Christo Pantev's lab (Schulz et al., 2003), professional trumpet players and non-musicians received auditory (i.e., trumpet sound) and somatosensory (i.e., lip) stimulation, presented either alone or in combination. Results showed that the combined stimulation yielded significantly larger responses in MEG source waveforms in musicians than in non-musicians, suggesting that the stronger experience in task-dependent co-stimulation of somatosensory and auditory feedback facilitates their cross-modal functional processing in musicians (Pantev et al., 2003). Similar effects have been described for audio-visual processing of music, corresponding to an increased N400 response when the two modalities were incongruent. Studies in the speech domain furthermore suggest that accurate corrective vocal-motor responses to somatosensory and auditory perturbation exist in both modalities (Lametti et al., 2012), although somatosensory feedback seems to gain importance as experience increases in trained singers (Kleber et al., 2010, 2013).

The logic behind cross-modal plasticity in the context of DoC is related to the idea that simultaneously stimulating functionally corresponding auditory and somatosensory modalities could potentially boost (i.e., facilitate) the neural responses in both systems. Although there is no large-size statistical data about the frequency of somatosensory disorders in DoC, somatosensory EP (SSEP) are standardly recorded in most hospitals for neurological rehabilitation. In fact, the functionality of somatosensory pathways has been successfully used to predict the long-term outcome of these disorders (de Tommaso et al., 2015; Li et al., 2015). Therefore, we suggest that the somatosensory system can be explored by means of neurophysiological techniques.

The idea of using more than one sensory modality for interacting or stimulating DoC patients is not new. In fact, "basal" multisensory (i.e., visual, auditory, tactile, gustatory, and olfactory) stimulation has been used as a therapeutic intervention and represents a standard procedure in many German intensive care and early rehabilitation facilities (Menke, 2006). However, multisensory stimulation in DoC patients is not standardized and the therapeutic use of multisensory stimulation has not been well documented (Rollnik and Altenmüller, 2014). Moreover, the concurrent stimulation of individual sensory modalities may be functionally unrelated and thus not trigger a facilitating effect, which could account for the lack of reliable evidence to support the effectiveness of multisensory stimulation programs in patients in coma or the VS (Lombardi et al., 2002). We therefore propose to apply multisensory stimulation only in a functionally related way, for example with concurrent orofacial-tactile and corresponding auditory stimulation associated with song or speech production. This might increase chances to enhance the potential of multisensory stimulation for the detection of diagnostic ERP components in DoC and/or to facilitate therapeutic processes.

A similar line of thought follows the tight coupling between perception and action when we synchronize our body movements to an external rhythm even without being aware of it. Timing is extremely important for movement, which can be facilitated by music perception via activation of distinct cerebellar-cortical networks involved with movements control (Thaut et al., 2009). Indeed rhythm production and perception engages similar brain regions including the supplementary motor area (i.e., involved in motor sequencing), the cerebellum (i.e., involved in timing), and the pre-motor cortex (Chen et al., 2008a). In musicians, activity in pre-motor cortex has been linked to the rhythm difficulty, suggesting that also working memory contributes to the organization and decomposition of acoustic temporal structures (Chen et al., 2008b). The involvement of pre-frontal and temporal regions during auditory rhythm stimulation has been confirmed with both electrophysiological (direct current; Kuck et al., 2003) and PET data (Janata, 2014). The latter study found furthermore common activation patterns for rhythm, meter, and tempo within frontal, pre-frontal, temporal, cingulate, parietal, and cerebellar regions. Not surprisingly, auditory rhythmic stimulation has been successfully used to facilitate motor acts in both healthy subjects and in neural rehabilitation (Molinari et al., 2003; Chen et al., 2006), since musical rhythms activate a network that is otherwise engaged by motor production and that can be distinguished from melodic processing (Bengtsson and Ullen, 2005).

Key messages:

- Multisensory stimulation in DoC is suggested to take into account the potentially facilitating effects of cross-modal plasticity as a result of functionally corresponding processes during production and perception in well-trained motor tasks (e.g., speech or song).
- The strong link between musical rhythm and motor behavior might be useful for testing motor related responses to rhythmic auditory stimulation as a complementary approach to the testing of syntactic (melodic/harmonic) processing in the brain of DoC patients.

THERAPEUTIC EFFECTS OF MUSICAL STIMULATION

Cognitive Effects

Music production is a uniquely rich multisensory experience. The development of musical skills enhances not only the cognitive, sensorimotor, and perceptual abilities but also changes corresponding motor, sensory, and multimodal representations in the brain (Herholz and Zatorre, 2012). Although these changes are particularly apparent in trained musicians, available clinical studies indicate that musical stimulation and musical training can also have beneficial effects for the rehabilitation of higher-order cognitive functions, e.g., on autobiographical memory in Alzheimer's patients (Irish et al., 2006; El Haj et al., 2012; García et al., 2012) and other kinds of dementia (Foster and Valentine, 2001). Irish et al. (2006) found that participants with mild Alzheimer's disease were recalling significantly more life events when listening to Vivaldi's "The Spring" compared to a silence condition, whereas the same effect was even higher with patients' self-chosen music (El Haj et al., 2012).

Possible mechanisms underlying the effect of musical stimulation on cognitive functions in patients with severe neurological disorders may be associated with neuroplasticity and neurogenesis in brain regions that are activated by music. Neuroplasticity may result in healthy brain areas compensating the disordered functions of injured areas and/or may increase the rate of neurogenesis and gray matter volume. The effect of music on neuroplasticity has been demonstrated in several studies (Stewart et al., 2003; Rickard et al., 2005; Pantev and Herholz, 2011; Herholz and Zatorre, 2012; Särkämö and Soto, 2012) and appears to be, at least partly, mediated by the production of the neurotrophin BDNF (brain-derived neurotrophic factor) in the hippocampus, which is increased in music-rich environments (Angelucci et al., 2007; Marzban et al., 2011) and involved in processes of memory formation and learning.

Another explanation for the effects of music on cognition involves the ACC and its product, the frontal midline theta rhythm, which is crucially important for emotional and cognitive processes (Bush et al., 2000). The frontal midline theta (fm-theta) is involved in working memory (Klimesch, 1997, 1999; Doppelmayr et al., 2000), episodic memory (Klimesch, 1997; von Stein and Sarnthein, 2000), emotional processing (Aftanas and Golocheikine, 2001), cognitive control (Gruendler et al., 2011; Cavanagh and Frank, 2014), and executive functioning (Miyake et al., 2000; Fisk and Sharp, 2004). In healthy subjects, ACC activation was found to correlate with pleasure responses to music (Blood and Zatorre, 2001; Baumgartner et al., 2006). Accordingly, the spectral power of the fm-theta is increased during listening preferred pleasant music in contrast to unpleasant one (Sammler et al., 2007). Interestingly, the only study that investigated the cognitive correlates of music perception in DoC patients replicated this effect (O'Kelly et al., 2013). In this study, the information about personal music preferences in patients was obtained from their close relatives, while for control participants this information was obtained directly. Listening to preferred songs has increased the power of the fm-theta in both groups.

To avoid superficial optimism, it should be said that the effects of music on cognition could critically depend on the amount of training. Probably in this case the rule of "the more the better" works. Särkämö et al. (2014b) attained significant effects of musical stimulation after 10 weeks of intensive training in 29 patients with dementia, which included not only passive listening to music but also conversations in small groups about the music-evoked emotions, thoughts and memories. Moreover, participants also performed homework assignments dedicated to listening their favorite music, while their caregivers organized the music intervention sessions. Beneficial effects at the 9-month follow-up involved a positive correlation between participants' mood, working memory performance and the frequency of music sessions. Together, these findings indicate that music therapy and stimulation can have significant effects on cognitive and emotional aspects, whereas the intensity of music intervention can play a key role for producing long-lasting and stable structural and functional changes in the brain.

Key messages:

- Passive listening to preferred music over longer time-periods might particularly enhance processes related to memory and cognition in DoC.

- Changes in fm-theta amplitudes during listening pleasant music could indicate emotional and cognitive responses.
- More intensive music therapy interventions might provide better therapeutic results.

Emotional Effects

The putative association between music stimulation and cognitive improvement in DoC patients might also be mediated by positive music-evoked emotions. These positive emotions can be associated with activation of the reward system of the brain and related dopamine release. At the same time, dopamine levels can be directly related to working memory, cognitive control, and attention (Nieoullon, 2002; Cools and D'Esposito, 2011). Pharmacological studies have shown that the increase of dopamine level improves performance in working memory and executive functions in both healthy subjects (Mehta and Riedel, 2006) and patients with traumatic brain injuries (Bales et al., 2009).

Music is a potent stimulator for a wide range of basic and complex emotions associated with changes in physiological arousal, subjective feeling, and motor expression (Koelsch et al., 2006, 2008; Grewe et al., 2007a,b). The reward value of music is moreover reflected in the classic reward circuitry of the brain (Zatorre, 2015), which entails dopaminergic mesolimbic pathways including the ventral tegmental area, the striatum (dorsal: nucleus accumbens; ventral: the head of the caudate nucleus), the ventromedial and orbitofrontal cortices, the amygdala, and the insula (Berridge and Kringelbach, 2013). These regions are traditionally associated with primary and secondary rewards, yet pleasurable music is also able to activate this system (Koelsch, 2014). For example, dopamine release in response to music stimulation accompanied by pleasurable emotional reactions has been reported in a study by Salimpoor et al. (2011).

The positive effects of music on emotional states (and correspondingly cognitive processing) may be related to acoustic features of music but have also been attributed to familiarity, as the subjective liking of music can be directly correlated with the familiarity of the piece (Peretz et al., 1998; Schellenberg et al., 2008). Listening to familiar versus unfamiliar music yields higher activity in the limbic system and the orbitofrontal cortex (Pereira et al., 2011), which is in accord with data demonstrating a correlation between music-elicited positive emotions and orbitofrontal activation (Menon and Levitin, 2005).

Familiarity implies the anticipation of a pleasurable musical passage, in line with the difference between anticipation and actual experience that has been found by Salimpoor et al. (2011). That is, activation in dopaminergic areas peaked in the dorsal striatum seconds before the maximum pleasure was experienced, related to the number of chill experiences, whereas activation in the ventral striatum was associated with the emotional intensity at the moment of the peak pleasure experience. Yet also novel (i.e., unfamiliar) pieces of music can trigger responses in the dorsal striatum when their reward values are high (Salimpoor et al., 2013), which was taken as further evidence that temporal (i.e., musical structural) predictions may also be involved in the emotional experience of music. On the other hand, striatal connectivity with auditory cortex that increased as a function of reward value suggests that previous memory formation could affect expectations related to emotional experience in music. Individual differences in memory formation could therefore modulate both the anticipation of intra-musical meaning (i.e., based on statistical leaning of functional relationships between consecutive musical elements) and the allocation of personal "musicogenic" meaning to a musical sequence (i.e., based on personal relevance). In addition, episodic memory and musical valence are closely interrelated, such that musical pieces with a positive association are also better remembered (Eschrich et al., 2008).

Särkämö and Soto (2012) suggested that the effects of music on working memory and attention performance, which they observed in stroke patients, were partly mediated by dopamine increase related to positive emotion. This idea is supported by the fact that depression and confusion were inversely correlated with verbal memory performance after music therapy. In another study including patients with visual neglect, the same research team (Soto et al., 2009) showed that listening to pleasant music enhanced awareness to contralesional targets.

Interestingly, brain injuries leading to DoC are often related to widespread damage of dopaminergic system axons and a reduced level of dopamine in the cerebrospinal fluid (Meythaler et al., 2002). There is even a hypothesis that DoC are mainly caused by destruction in the dopamine system (Hayashi et al., 2004), whereas restoration of the normal regulation of dopamine level has a positive effect on cognitive recovery in DoC patients. In several studies, levodopa (a precursor of dopamine) not only improved motor functions of DoC patients but also resulted in positive changes of their consciousness (Haig and Ruess, 1990; Matsuda et al., 2003, 2005; Krimchansky et al., 2004; Ugoya and Akinyemi, 2010). Moreover, the well-known placebo-controlled randomized study of traumatic DoC patients (Giacino et al., 2012) revealed a significant effect of the indirect dopamine agonist Amantadine.

A recent study (Castro et al., 2015) demonstrated the aforementioned relationship between music, familiarity, and cognition in a sample of DoC patients. The study included the presentation of the subjects' own first name (SON) as a deviant stimulus among other first names as standard stimuli. Listening to excerpts from the patient's preferred music increased the amplitude of ERP components N2 and/or P3 to SON in seven of 13 patients. These seven patients showed a favorable outcome after 6 months following the experiment. The other six patients who did not show any response to the SON remained in the same state or died 6 months later. The existence of music-evoked emotions in DoC might therefore even have a predictive value in DoC and perhaps also the potential to re-activate memory traces associated with musical emotions.

Key messages:

- DoC can be related to damage of the dopaminergic system. Emotionally pleasurable music in turn can activate the dopaminergic system by inducing changes in the limbic system associated with the reward value of music, which could have beneficial effects on consciousness in DoC.

- Music therapy and musically induced positive intra-musical and musicogenic emotions might furthermore stimulate cognitive processes and personal memory activation.
- A hypothesis worth testing is that ERP components, such as the N2 and/or P3 in response to preferred music as well as changes in time-frequency theta amplitudes over frontal midline regions in the EEG, might predict the outcome of DoC in response to emotionally pleasurable music.

Stress Reduction

Influence of stress and the related cortisol level on cognitive functions was shown in numerous studies with healthy participants, where the increased level of cortisol had a negative impact on executive functions, declarative memory, working memory, and language comprehension (McEwen and Sapolsky, 1995; Lupien et al., 1997; Lee et al., 2007). Factors mediating the negative impact of chronic stress are supposed to be dendritic atrophy and synaptic loss in the hippocampus and the prefrontal cortex as well as the decrease of the rate of neurogenesis in the hippocampus (Radley and Morrison, 2005). Chronic stress can also cause changes in the dopaminergic system, reducing dopamine levels in the prefrontal cortex (Mizoguchi et al., 2002), and negatively affect the immune system (Segerstrom and Miller, 2004).

Several studies have emphasized the stress-reducing value of daily music listening, with positive effects being observed on subjective, physiological, and endocrinological parameters (Linnemann et al., 2015). Even short-term exposure to musical stimulation consistently decreases cortisol levels of healthy subjects (for systematic review, see Fancourt et al., 2014) and this effect was particularly large when participants had self-selected the music (e.g., in patients undergoing surgery; Leardi et al., 2007). Moreover, there is also evidence for positive effects of music on the immune system, as indicated by several parameters at cytokine, leukocytes and immunoglobulins levels (Fancourt et al., 2014).

Convincing evidence suggests that traumatic brain injury, stroke, and other frequent neuropathological factors can induce stress reactions in both short-term (Franceschini et al., 2001; Prasanna et al., 2015) and long-term (Sojka et al., 2006; Marina et al., 2015) perspectives. These findings suggest that DoC of traumatic or non-traumatic etiology may also be accompanied by chronic stress, although the available data are inconsistent. While Vogel et al. (1990) obtained an increased level of cortisol in VS using 24 h monitoring, Munno et al. (1998) found a lower cortisol level in VS patients and in a group of exit-VS patients who had been conscious for more than 6 months in comparison with normal parameters. Another study of VS patients in a long-term-care facility (mean disease duration 6.2 ± 5.1 years) did not reveal any significant differences from a control group (Oppl et al., 2014). A case study reported a VS patient whose level of consciousness improved after injections of autologous activated immune cells (Fellerhoff et al., 2012).

Key message:

- Music has the potential to enhance cognitive functions in DoC through a decrease of stress and a related drop of cortisol level together with activation of the immune system.

CONCLUSION

Direct evidence for positive effects of music therapy interventions on cognitive functions in DoC is still very scarce. In this paper we summarized a theoretical justification for the idea that properly organized music stimulation programs can indeed lead to the suggested beneficial effects. At the low-level organization of the (primary and secondary) sensory cortical areas, the auditory modality reveals its particular potential for presenting specific stimulation that combines sufficient complexity with the availability for severely brain-damaged patients. In this context, we strongly suggest the use of complex sounds rather than sine-tones in DoC. Cognitive mechanisms would capitalize the specific psychological and neurophysiological affinity between music and speech processing, based on the great similarity between these two domains of human culture. This entails the identification of auditory objects, which can result in clinically important dissociations between disorders based on the processing of musical syntax and meaning, which are reflected by changes in corresponding ERP components. The neuroplastic associations with music may furthermore lead to functional improvement of memory and attention beyond the language domain, whereas multisensory stimulation based on previously acquired cross-modal plasticity may facilitate electrophysiological responses as well as functional improvement. Moreover, musically stimulated rhythmic processes in the nervous system could serve as a starting point for rehabilitation. A completely different mechanism mediating the hypothesized positive effects of music in DoC runs through music-evoked emotions, which have the potential to activate the dopaminergic system and may thus lead to a suppression of the stress response system. The diagnostic value of musically evoked emotions includes ERP components such as the N2 and/or P3 as well as changes in time-frequency theta amplitudes over frontal midline regions in the EEG. However, more research is needed to address the ecological validity of these suggestions and thus to come to more conclusive results in this patients group, even though the organization and performance of such studies is highly demanding.

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Exploration of Functional Connectivity During Preferred Music Stimulation in Patients with Disorders of Consciousness

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Preferred music is a highly emotional and salient stimulus, which has previously been shown to increase the probability of auditory cognitive event-related responses in patients with disorders of consciousness (DOC). To further investigate whether and how music modifies the functional connectivity of the brain in DOC, five patients were assessed with both a classical functional connectivity scan (control condition), and a scan while they were exposed to their preferred music (music condition). Seed-based functional connectivity (left or right primary auditory cortex), and mean network connectivity of three networks linked to conscious sound perception were assessed. The auditory network showed stronger functional connectivity with the left precentral gyrus and the left dorsolateral prefrontal cortex during music as compared to the control condition. Furthermore, functional connectivity of the external network was enhanced during the music condition in the temporo-parietal junction. Although caution should be taken due to small sample size, these results suggest that preferred music exposure might have effects on patients auditory network (implied in rhythm and music perception) and on cerebral regions linked to autobiographical memory.

Keywords: music, disorders of consciousness, fMRI, functional connectivity, auditory network, external network

INTRODUCTION

Patients with disorders of consciousness (DOC) are a patient population that is very difficult to assess. Following coma, these patients can be in an unresponsive wakefulness syndrome (UWS) where behavior is reflexive, and awareness of the self and surrounding is absent (The Multi-Society Task Force of Pvs, 1994; Laureys et al., 2010), or in a minimally conscious state (MCS) where behaviors indicating awareness are limited, fluctuating but reproducible (Giacino et al., 2002). Various interferences, both physical and cognitive impairments, or medical complications can affect the diagnosis based on clinical assessments of consciousness (Schnakers et al., 2009). This is one of the issues underlying the current misdiagnosis rate of 40% (Schnakers et al., 2009; van Erp et al., 2015). Consequently, numerous research is investigating the neural and cerebral responses of these patients, with the aim to provide unbiased and objective measures complementing bedside evaluation and helping diagnosis (Laureys and Schiff, 2011; Stender et al., 2014).

Previous research has also proposed to increase the sensitivity of clinical tests by using personally relevant stimuli (Perrin et al., 2015). For example, several behavioral studies have shown that a higher number of responses could be observed following self-referential stimuli, like the use of a mirror or the patient's own name, as compared to neutral stimuli (Vanhaudenhuyse et al., 2008; Cheng et al., 2013; Di et al., 2014). Neurophysiological studies have indicated that salient and emotional stimuli increase the probability of observing a cerebral response in patients with DOC. For example, the probability to observe a P300 event-related response (i.e., a brain response reflecting stimulus processing) is enhanced when the deviant stimulus is not a tone stimulus but the patient's own name (Perrin et al., 2006; Cavinato et al., 2011). Very recently, it has also been shown that preferred music (i.e., an autobiographical and emotional stimulus) has an effect on cognitive processes of patients with DOC. Indeed, observing a P300 to one's own name was increased in patients with DOC after having been exposed to their preferred music compared to a control condition (i.e., acoustically similar noise; Castro et al., 2015). This result is in agreement with a study showing increased behavioral responses after preferred music (Verger et al., 2014), and several single-case studies with DOC patients suggesting effects of music on a behavioral level (Magee, 2005; Magee et al., 2014).

Resting state functional MRI allows investigation of several distinct, reproducible and dynamic brain networks (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Laird et al., 2011), without the need for patients' cooperation (Soddu et al., 2011). The auditory network is one of the reliably observed networks, even though not yet extensively studied. This network encompasses primary auditory cortices including Heschls gyri, superior temporal gyri, insula, cingulate, post- and pre-central gyri, and supramarginal gyrus (Beckmann et al., 2005; Smith et al., 2009; Laird et al., 2011). The auditory network can be observed in 81% of healthy subjects, 46% in MCS, and is limited to 21% of UWS patients (Demertzi et al., 2014). In fact, it has strong power to discriminate MCS and UWS patients, making automatic classification possible (Demertzi et al., 2015). Another network that is also related to auditory processing (Brunetti et al., 2008) is the external network. This network is also related to external orientation, goal-directed behaviors, and cognitive processing of somatosensory (Boly et al., 2007), and visual (Dehaene and Changeux, 2005) input. The external network is often named the 'dorsal attention network,' or 'task positive' network (Greicius et al., 2003; Vanhaudenhuyse et al., 2010a). It has been shown to be anticorrelated with an internal/default mode network (Greicius et al., 2003; Vanhaudenhuyse et al., 2010a), implicated in self-awareness and stimulus-independent thoughts in healthy controls (Raichle et al., 2001; Greicius et al., 2009). Interestingly, auditory, external and internal/default mode networks include cortical regions that have been shown to be modulated by emotional sounds. Indeed, as compared to noise, meaningful sounds (infant cries or the patient's own name) are associated to a widespread activation of the auditory cortex and medial cortical structures in DOC patients (Laureys et al., 2004). Thus, the effect of music as reported in Castro et al. (2015) is probably also associated to functional connectivity changes of these regions.

We here aim to explore whether the effect of music in severely brain-damaged patients with DOC is related to functional connectivity changes. Functional MRI scans were acquired while participants were exposed to their preferred music as well as a control condition when they were exposed to the repetitive noise from the scanner (also present in the music condition). Using a functional connectivity parcellation (Gordon et al., 2014), we assessed functional connectivity using seed regions in both primary auditory cortices. We also analyzed network connectivity of the auditory network, the external network, and default mode network. We expect to observe changes, and more specifically increases, in functional connectivity in the auditory and attentional systems in patients with DOC during the music stimulation (vs. the control condition).

MATERIALS AND METHODS

Participants

Eight healthy participants (four female; mean age = 26 years, *SD* = 3), and seven patients (four MCS; three UWS) were scanned between March 2014 and April 2015 for this study. Patients were excluded for this study when any contraindication for MRI was present (e.g., presence of ferromagnetic aneurysm clips, pacemakers), or when patients needed sedation. Chronic patients with DOC were hospitalized for 1 week of assessment at the coma science group, University hospital of Liege, Belgium. Multiple behavioral assessments in the form of the CRS-R were completed, including one the morning before the (f)MRI acquisition. One patient showed drain artifacts on the T1 and functional MRI scan covering more then 40% of the brain, and in one patient the segmentation could not be reliably performed due to the lesion extent. Our patient population consisted thus of five patients (three MCS, two UWS; mean age = 50 years, *SD* = 10; **Table 1**). The ethics committee of the medical school of the University of Liège approved the study.

Music Stimulation and Procedure

Five musical excerpts were selected for each participant from a questionnaire on musical preference completed by family members or loved ones (for the patients) or the participant him/her self (for the healthy participants). These musical excerpts had a mean duration of 2 min and were all dynamic, musically coherent, and representative of the whole musical piece. The five excerpts were combined to create a musical stimulus of a duration of 10 min and 10 s, which overlaps with the duration of the functional scan. Fading in and fading out (around 2 s) was added to avoid rough transitions between the excerpts.

The functional scan was acquired twice during one MRI scanning session. Once with the participants' preferred music (i.e., music condition), and once when participants were exposed to the repetitive noise from the scanner (i.e., control condition). This control condition is the same as used for the investigation of a classical resting state. The order of the conditions was randomized between participants, and the two functional scans

TABLE 1 | Diagnostics of the five patients with disorders of consciousness (DOC).

		DOC1	DOC2	DOC3	DOC4	DOC5
Sex		Male	Female	Female	Male	Male
Age (years)		40	50	39	61	58
Time since injury (months)		12	6	26	13	25
Etiology		Trauma	Anoxic	Trauma	Anoxic	Anoxic
Diagnosis		UWS	UWS	MCS -	EMCS	MCS +
CRS-R score	A.	1	1	2	4	3
	V.	0	0	3	5	0
	M.	2	1	2	6	1
	O.	0	1	1	3	1
	C.	0	0	0	2	0
	Ar.	1	2	2	3	2
	Total	4	5	10	23	7
Structural MRI		Subcortical diffuse axonal injury, moderate enlargement of the ventricles, and atrophy of midbrain and sulci	Cortical and subcortical atrophy with severe post-anoxic leukoencephalopathy	Right lenticular lesion, diffuse axonal injury, and enlargement of the third ventricles	Extensive defects in region of the posterior cerebral artery, thalamus, and enlargement of right lateral ventricle	Global hemosiderosis and ischemic damage, white matter intensities (frontal + temporal), and enlargement of the ventricles
Neuroimaging (PET)		Indicated MCS	Consistent with an UWS	Consistent with MCS	Consistent with EMCS	Consistent with MCS

CRS-R, coma recovery scale revised; A., auditory function; V., visual function; M., motor function; O., oromotor/verbal function; C., communication; Ar., arousal; UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state; EMCS, emergence from minimally conscious state.

were always separated by a delay of 10 min to reduce any potential order effects. Instructions and musical stimuli were delivered through MR compatible Siemens headphones. Participants were instructed to keep their eyes closed, stay awake, avoid any structured thoughts, and listen attentively to the music.

MRI Acquisition and Analysis

Two sets of 300 T2*-weighted images were acquired using a 3T Siemens TIM Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (32 slices; voxel size = 3 mm × 3 mm × 3 mm; matrix size = 64 × 64 × 32; repetition time = 2000 ms; echo time = 30 ms; flip angle = 78°; field of view = 192 mm × 192 mm). The 10 initial volumes were discarded to avoid T1 saturation effects. Data preprocessing was performed using Statistical Parametric Mapping 8 (SPM8[1]). Preprocessing steps included realignment and adjustment for movement-related effects, slice time correction, co-registration of functional onto structural data, segmentation of structural data, spatial normalization of all data to standard stereotactic Montreal Neurological Institute (MNI) space using the normalization parameters which had resulted from the segmentation step. Normalized functional data were then smoothed using a Gaussian kernel with an isotropic 8 mm of full-width half-maximum.

Motion correction was applied using an automatic artifact detection tool for global mean and motion outliers[2]. Outliers in the global mean signal intensity and motion were identified and included in the subsequent statistical analysis as nuisance parameters (i.e., one regressor per outlier within the first-level general linear models). Specifically, an image was defined as an outlier (artifact) image if the head displacement in x, y, or z direction was greater than 0.5 mm from the previous frame, or if the rotational displacement was greater than 0.02 radians from the previous frame, or if the global mean intensity in the image was greater than 3 SD from the mean image intensity for the entire resting session. For our group of patients, the number of motion outlier images did not differ significantly between music and noise sessions (two-sided paired t-test; $p = 0.16$, music condition $m = 16$, $SD = 18$; control condition $m = 3$, $SD = 4$). Healthy participants did not show any movement-affected outlier scans.

Analyses of functional connectivity were performed using the connectivity toolbox "conn," version 15D[3] (Whitfield-Gabrieli and Nieto-Castanon, 2012). As recently recommended (Behzadi et al., 2007; Murphy et al., 2009; Saad et al., 2012; Wong et al., 2012), we used a regression of nuisance effects before bandpass filtering (RegBP; Hallquist et al., 2013). The data were despiked, and white matter (WM) and cerebrospinal fluid (CSF) components were regressed out as nuisance variables according to the aCompCor method. We then applied a linear detrending term. The residual BOLD time series went through a bandpass filter between 0.008 and 0.09 Hz to reduce the effect of low frequency drifts and high-frequency noise. All described steps are part of the standard procedure in the "conn" toolbox (Behzadi et al., 2007; Whitfield-Gabrieli and Nieto-Castanon, 2012). The residual head motion parameters (three rotation and three translation parameters, plus another six parameters representing their first-order temporal derivatives) were regressed out.

[1] www.fil.ion.ucl.ac.uk/spm

[2] http://www.nitrc.org/projects/artifactdetect/

[3] http://www.nitrc.org/projects/conn

One pitfall of the analysis of resting state functional connectivity using seeds is the selection of seeds. The seed placement bias could lead to different and overlapping networks depending on the amount and placement of seeds (Cole et al., 2010). This bias can be reduced through the use of parcellations instead of spheres based on coordinates from the literature. We used a functional connectivity parcellation atlas based on a selection of parcels out of 330 parcels containing highly homogenous signal patterns (Gordon et al., 2014). This parcellation allowed us to perform two different analyses.

We first assessed functional connectivity on a seed based level. Two parcels were taken from the atlas of Gordon et al. (2014), localized at the structurally defined Heschl's gyrus (left and right). These two seeds were chosen for their importance in auditory processing. With these seeds group analysis was performed to assess functional connectivity within both conditions as well as differences between the preferred music and control condition. Furthermore, first level beta maps were extracted (i.e., fisher transformed correlation values) for each participant and used to create individual figures for our *a priori* regions during both conditions (supplementary material). Data of healthy subjects were not directly compared to patients due to age differences, thus the difference between the music and control condition within one patient could not be compared to the range of differences within controls. Therefore, no within-subject statistical analysis was performed.

Although studies in healthy subjects show that single seeds can reveal whole networks, this is not necessarily the case in brain-damaged patients. Network disruption can be expected due to underlying neuropathology excluding regions from overall networks. To assess overall network characterization it is advised to use multiple seeds/regions (Demertzi et al., 2015). All parcels belonging to the auditory network, external network, and default mode network according to Gordon et al. (2014) were assessed for our group of patients in each condition. For all networks, time courses of the parcels were averaged and correlated to the whole brain (Halko et al., 2014; Demertzi et al., 2015). Thus, this averaged time series was used to estimate whole-brain correlation r maps, which were then converted to normally distributed Fisher's z transformed correlation maps to allow for subsequent group-level analysis on the mean network connectivity (comparing music vs. control conditions). For all analyses on the group level (seed based and network based functional connectivity analysis) one sample *t*-tests were used for estimation of functional connectivity in each condition, and two-sample paired *t*-tests were used for between condition comparisons. The results were reported as significant when they exceeded a height threshold of uncorrected $p = 0.001$ with a family wise error corrected extent threshold of $p = 0.05$ at the cluster level. For clusters that showed significant stronger functional connectivity during the music condition contrast estimates (beta values) were extracted (Supplementary Figure S2). We did not compare the healthy group to our patient group due to differences in age, and the possible effects this might have on network integrity, as well as the possible differences in reaction to preferred music in terms of memory or emotion.

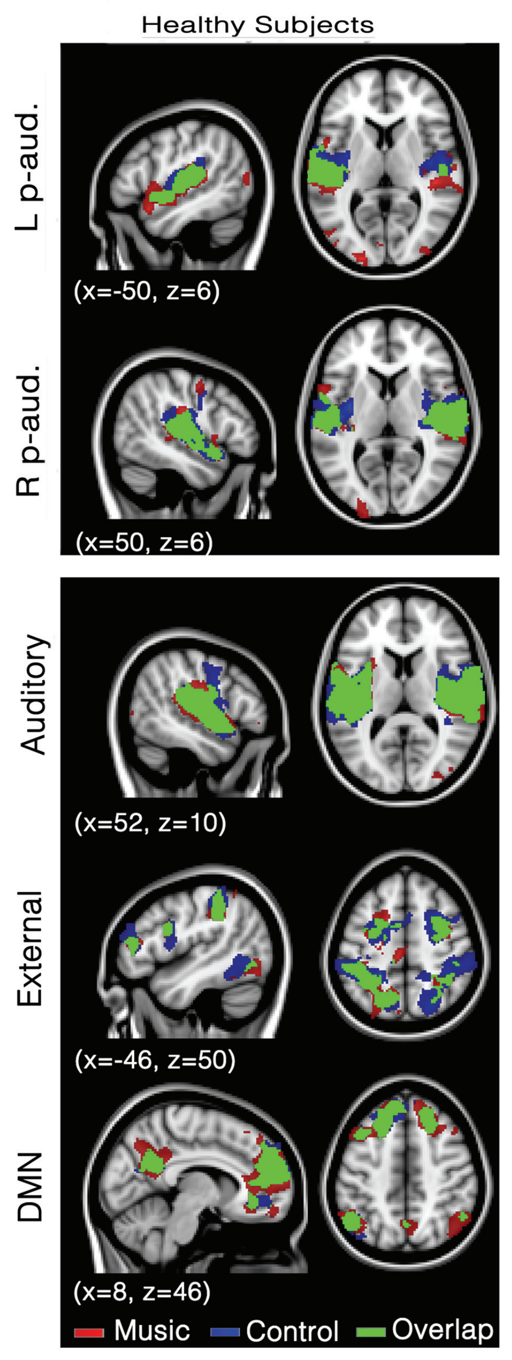

FIGURE 1 | Functional connectivity in healthy subjects during the music condition and the control condition. Maps indicate healthy subjects' ($N = 8$) functional connectivity during favorite music exposure (Red) and the control condition (Blue), and regions where functional connectivity was present in both conditions (Green). The top two panels show seed-based analyses, the lower three panels show mean network connectivity. Note that there is no significant difference between music and control condition. Results were analyzed in a network-based manner and thresholded with a family wise error corrected extended cluster level of $p < 0.05$. Standardized MNI T1 2x2x2 template was used to render results. (x,y,z) value indicates MNI coordinates of represented sections.

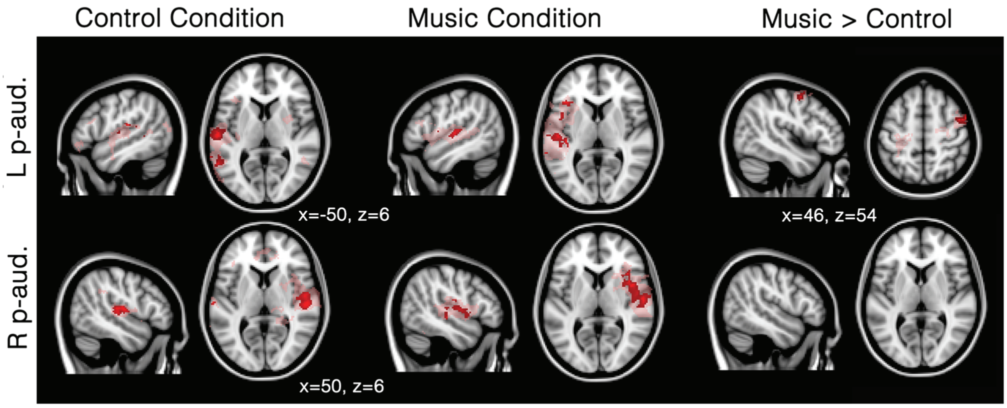

FIGURE 2 | Functional connectivity in patients during the music condition and the control condition using primary auditory seeds. Red/pink maps indicate patients' ($N = 5$) functional connectivity during the control condition (left) and favorite music exposure (middle) for both the left and right primary auditory cortex (L p-aud., and R p-aud.; respectively). Right maps show the regions that show significantly more functional connectivity during music condition compared to the control condition. Results were analyzed in a network-based manner and thresholded with a family wise error corrected extended cluster level of $p < 0.05$ (in red). For visualization a lowered threshold is indicated in pink (0.01 uncorrected height with family wise error corrected extended cluster level of $p < 0.05$). Standardized MNI T1 2x2x2 template was used to render results. (x,y,z) value indicates MNI coordinates of represented sections.

RESULTS

In healthy participants, seed-based analyses of both left and right primary auditory areas showed functional connectivity in areas considered as being part of the auditory network during both music and control conditions. Indeed, functional connectivity with seeds in both primary auditory cortices was observed in bilateral temporal gyri (encompassing Heschl's gyrus, opercular gyrus, insula, planum polare, and superior temporal areas), anterior cingulate, pre- and post-central areas and the occipital pole (**Figure 1**; Supplementary Table S1) in both conditions. No significant difference was observed between the two conditions. Similarly, the auditory network showed activation in bilateral temporal gyri (encompassing Heschl's gyrus, opercular, insula, planum polare, and superior temporal areas). This temporal cluster extended from inferior frontal, to precentral and angular areas. The auditory network also included the anterior cingulate, pre- and post-central areas and the occipital fusiform gyrus and cortex (**Figure 1**; Supplementary Table S2). The external network encompassed regions of bilateral inferior parietal sulcus and lobule, dorsolateral prefrontal, supramarginal, frontal eye field, lateral occipital and precentral, as well as cerebellar and insular areas. The default mode network showed functional connectivity with the precuneus, frontal pole and superior frontal gyrus, angular and lateral occipital gyrus, and middle temporal gyrus. For these three networks, the music condition did not significantly differ from the control condition.

In patients, seed-based analyses of patients showed that functional connectivity was mainly restricted to the areas surrounding each of the two seeds (i.e., left and right primary auditory cortex) for both the music and the control conditions; however, several other clusters of functional connectivity were also observed (**Figure 2**; **Table 2**). The left primary auditory seed showed functional connectivity with the middle temporal gyrus during the control condition, and the left frontal operculum, superior temporal gyrus and cerebellum during the music condition. The right primary auditory seed showed several smaller clusters in the temporal area as well as the supramarginal area during the control condition, and one large cluster of activation in the temporal cortex during the music condition. When the music condition was directly compared to the control condition, the left primary auditory seed showed more functional connectivity in the right precentral gyrus during music. No difference was observed with the right primary auditory seed for this direct comparison. Single subject first level beta values (i.e., Fisher's z transformed correlation values) were used to create individual patient figures for the two primary auditory seed activations during both conditions (Supplementary Figure S1). Correlation values during music and control conditions were mainly restricted to the areas surrounding each of the seeds, but in general, more voxels seemed to be strongly correlated in the music condition than in to the control condition (correlations higher than 0.8 were assessed and shown in the Supplementary Material).

Patients showed a severely limited auditory network of functional connectivity during both conditions (**Figure 3**; **Table 3A**). During the control condition, activation was only seen in bilateral temporal areas. During the music condition, the auditory network consisted of bilateral temporal gyri (only including left Heschl gyrus), as well as small clusters in the right inferior frontal gyrus and the left supramarginal gyrus; these were areas also included in the temporal cluster for the healthy subjects. When the music condition was compared to the control condition, the auditory network showed significantly more functional connectivity with the left precentral gyrus and a region on the junction of the middle frontal gyrus and frontal pole: the left dorsolateral prefrontal cortex.

The external network in patients was restricted to the inferior parietal sulcus and lobule, dorsolateral, middle frontal, and supra marginal areas during both control and music conditions.

TABLE 2 | Results of the seed-based analyses in the patients.

	MNI coordinates (x,y,z)			Cluster size	Cluster p-FWE	p-unc peak	Region	
Left primary auditory cortex								
Music	−40	24	6	223	0	0.000003	Left	Frontal operculum
	−40	−26	6	200	0	0.000023	Left	Heschl/planum temporale
	−68	−36	14	52	0.025011	0.000007	Left	Superior temporal gyrus
	0	−48	−8	50	0.030795	0.000067		Cerebellum
Control	−60	−20	6	403	0	0	Left	Heschl/planum temporale
	−68	−46	4	163	0	0.000003	Left	Middle temporal gyrus
Music > Control	46	0	54	113	0.000007	0.000002	Right	Precentral gyrus
Right primary auditory cortex								
Music	40	26	10	886	0	0.000003	Right	Temporal cortex: insula/central opercular/planum temporale/ Heschl/frontal operculum
Control	44	−16	10	379	0	0.000001	Right	Heschl gyrus/central opercular
	−68	−10	−2	85	0.00046	0.000047	Left	Superior temporal gyrus
	−64	−18	6	50	0.017807	0.000005	Left	Planum temporale
	28	−32	32	47	0.02515	0.000053	Right	Supramarginal gyrus

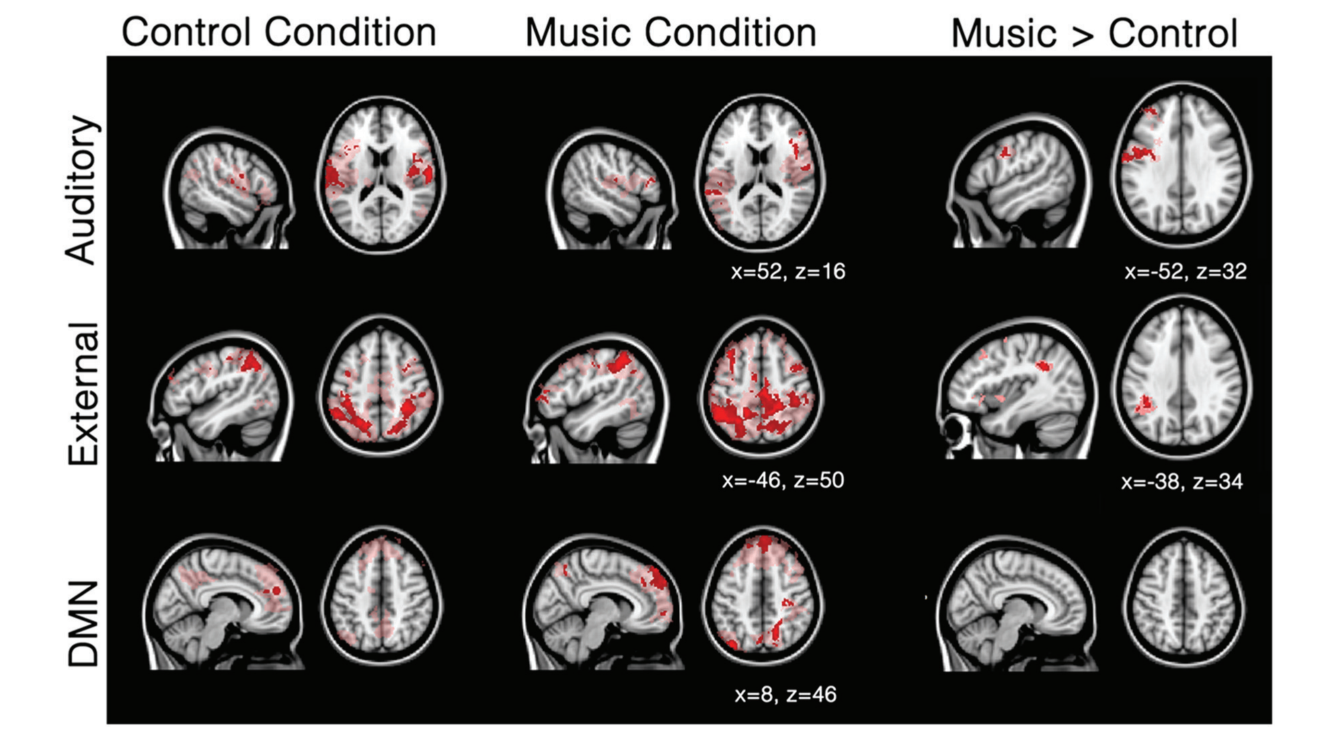

FIGURE 3 | Mean network connectivity in patients during the music condition and the control condition. Red/pink maps indicate patients' ($N = 5$) functional connectivity during the control condition (left) and favorite music exposure (middle) for the auditory network, external network, and default mode network (DMN). Right maps show the regions that show significantly more functional connectivity during music condition compared to the control condition. Results were analyzed in a network-based manner and thresholded with a family wise error corrected extended cluster level of $p < 0.05$ (in red). For visualization a lowered threshold is indicated in pink (0.01 uncorrected height with family wise error corrected extended cluster level of $p < 0.05$). Standardized MNI T1 2x2x2 template was used to render results. (x,y,z) value indicates MNI coordinates of represented sections.

(**Figure 3**; **Table 3B**). Compared to the control condition, music showed more functional connectivity with the supramarginal/ angular gyrus, also referred to as the temporoparietal junction.

The default-mode network in patients seemed disconnected in patients (**Figure 3**; **Table 3C**). The control condition only showed functional connectivity in the frontal pole/paracingulate gyrus. The music condition showed further functional connectivity with the precuneus, post-central gyrus, lateral occipital pole, and middle temporal gyrus. However, no difference could be found between the two conditions.

TABLE 3A | Results of network-based analysis in patients: auditory network.

	MNI coordinates (x,y,z)			Cluster size	Cluster p-FWE	p-unc peak	Region	
Auditory network								
Music	−66	−40	14	161	0.000004	0.000034	Left	Supramarginal gyrus
	40	20	18	109	0.000174	0.000002	Right	Inferior frontal gyrus
	60	−4	12	97	0.000466	0.000032	Right	Temporal, central opercular
	−50	−30	20	48	0.042949	0.000507	Left	Parietal operculum/Heschl
Control	−50	−40	10	1152	0	0.000004	Left	Temporal cortex: planum temporale/central opercular/ superior temporal
	28	6	2	997	0	0	Right	Temporal, central opercular/insula
	−36	20	12	208	0	0.000011	Left	Frontal operculum
	28	−26	26	46	0.046101	0.000094	Right	Parietal operculum
Music > Control	−66	−8	36	319	0	0.000001	Left	Precentral gyrus
	−28	42	30	44	0.028322	0.000019	Left	DLPFC

TABLE 3B | Results of network-based analysis in patients: external network.

	MNI coordinates (x,y,z)			Cluster size	Cluster p-FWE	p-unc peak	Region	
External network								
Music	58	−32	44	4974	0	0	Bilateral	Inferior parietal sulcus/inferior parietal lobule
	−36	24	52	424	0	0.000005	Left	DLPFC
	−52	32	16	122	0.000111	0.000008	Left	Middle frontal gyrus (small part FEF)
	−14	−10	64	116	0.000174	0.000013	Left	SMA
	48	12	56	100	0.000594	0.000021	Right	Middle frontal gyrus (small part FEF)
	30	34	−8	69	0.007915	0.000044	Right	DLPFC
	−38	−54	−12	59	0.019658	0.000013	Left	Lateral occipital/MT
	−56	−58	4	50	0.046263	0.000163	Left	Lateral occipital/MT
Control	−24	−62	48	2072	0	0.000001	Left	Inferior parietal sulcus/inferior parietal lobule
	12	−74	54	1026	0	0.000004	Right	Inferior parietal sulcus/inferior parietal lobule
	−32	14	24	403	0	0.000003	Left	SMA extending to small part FEF
	−42	48	24	104	0.000223	0.000012	Left	DLPFC
	34	8	52	82	0.001473	0.000065	Right	Middle frontal gyrus (small part FEF)
Music > Control	−42	−50	30	103	0.000078	0.000003	Left	Supramarginal/angular gyrus

DISCUSSION

In the present study, we aimed at assessing the potential effect of music on the brain's functional connectivity in patients with DOC. We compared patients' intrinsic brain activation while being exposed to their preferred music and during a control condition. For this purpose, seed-based functional connectivity as well as network-level functional connectivity was assessed. Seed-based functional connectivity analyses of primary auditory cortices showed significant differences in functional connectivity between music and control conditions for the patients. Network-level analyses showed that patients' functional connectivity is increased when being exposed to their preferred music in the auditory and external network (in comparison to the control condition).

In healthy participants, the network of functional connectivity based on both primary auditory regions encompasses large parts of the auditory cortex, superior temporal gyri, insula, cingulate cortex, central areas (pre and post), supramarginal gyrus, and occipital areas (**Figure 1**), in both the music condition and the control condition. These are, as expected, part of the auditory network (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Smith and Tindell, 2009; Laird et al., 2011; Demertzi et al., 2014). To assess network integrity, mean network connectivity was assessed in the auditory network, external network, and default mode network, i.e., networks that are

TABLE 3C | Results of network-based analysis in patients: default mode network.

	MNI coordinates (x,y,z)			Cluster size	Cluster p-FWE	p-unc peak	Region	
Default mode network								
Music	−26	32	34	1247	0	0.000001	Bilateral	Middle frontal gyrus/frontal pole/paracingulate gyrus
	12	−66	62	233	0	0.000004	Right	Precuneus/lateral occipital
	−38	−76	48	150	0.000014	0.000001	Left	Lateral occipital
	−30	52	2	110	0.000264	0.000124	Left	Frontal pole
	−58	−24	−12	81	0.002724	0.000004	Left	Middle temporal gyrus
	8	60	−4	56	0.025536	0.000149	Right	Frontal pole
	28	−24	46	53	0.034	0.000094	Right	Post-central gyrus
Control	−10	48	18	679	0	0.000034	Left	Frontal pole/paracingulate gyrus

respectively linked to auditory processing, external orientation, and internal thoughts.

Network-based second level analysis of functional connectivity showed that the auditory network was clearly replicated in our healthy subjects during both the music and control conditions. This network has consistently been observed in previous resting state studies investigating not only healthy participants but also DOC patients (Demertzi et al., 2014). In healthy participants it encompassed bilateral temporal gyri (including Heschl's gyrus, opercular, insula, planum polare, and superior temporal areas), extending to inferior frontal, precentral and angular areas, as well as clusters in anterior cingulate, pre- and post-central areas and the occipital fusiform gyrus (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Smith and Tindell, 2009; Laird et al., 2011; Demertzi et al., 2014). The external network has also been observed in healthy participants. It encompassed, as consistently observed in previous studies (Fox et al., 2005; Vanhaudenhuyse et al., 2010a), regions of bilateral inferior parietal sulcus and lobule, dorsolateral prefrontal, supramarginal gyrus, the frontal eye field, lateral occipital and precentral, as well as cerebellar and insular areas. The default-mode network showed functional connectivity in regions consistently observed in healthy participants and patient populations (Buckner et al., 2008). Most importantly, music did not show any increases in functional connectivity compared to the control condition for the seed-based and all three network-level analyses. This result is consistent with Castro et al. (2015) who observed that music (in comparison to noise) did not modify the event-related responses in healthy participants (while this was the case for the DOC patients). This observation suggests that the effects of music observed in previous research are possibly not present in healthy subjects (or that the cerebral responses could not be enhanced because they were already at ceiling). This finding could be due to the nature of our experimental material. Indeed Wilkins et al. (2014) have shown functional connectivity differences (in the default mode network and between auditory brain areas and the hippocampus) between two music materials that strongly differ in terms of emotion, i.e., preferred and disliked music (in healthy participants). It is thus possible, that our control condition, which can be considered as rather neutral, was not disliked enough to warrant significant differences in functional connectivity with the preferred music condition.

Seed-based analysis indicated that patients showed strongly limited functional correlations with the primary auditory cortices: activation was only observed around the seed areas and no long distance connectivity emerged within the auditory network. This finding is in line with previous research showing a linear decrease in functional connectivity ranging from healthy participants to unresponsive patients (Vanhaudenhuyse et al., 2010b; Thibaut et al., 2012; Demertzi et al., 2014). In fact, many studies have shown that functional connectivity still exists in DOC patients, and other forms of decreased levels of consciousness (Heine et al., 2012). Low-level activations in primary auditory cortices, without top–down feedback have also been observed in unresponsive patients (Laureys et al., 2000; Boly et al., 2011). In fact, patients seem to have a general disconnection between brain regions, notably missing long range connectivity (Casali et al., 2013). Our results are congruent with this observation as we observe mainly functional connectivity in the hemisphere of the seed. Furthermore, significant differences in the right precentral gyrus are observed during the preferred music condition compared to the control condition (**Figure 2**). This finding is in agreement with a previous study investigating DOC patients and reporting activation in the right superior temporal gyrus during three 10-s blocks of musical stimulation based on a famous song (Okumura et al., 2014).

First-level connectivity maps of each patient suggest larger areas of correlation near the seed during the music condition than during the control condition (Supplementary Figure S1). This difference seems to be present for all subjects, even the subjects clinically diagnosed as UWS (DOC1 and 2). This finding fits with the neuroimaging results observed in DOC1: diagnostic assessment based on PET metabolism suggested MCS (e.g., Stender et al., 2014). However, the second patient who was diagnosed as UWS (DOC2) both clinically and using neuroimaging, also showed more voxels correlated to the seed, indicating that the effect of music as reported here (if replicable in future studies with extended patient samples) might be present for all DOC. It is important to note that stronger correlating voxels were observed during the music condition (as compared to the control condition) in all patients for at least one seed. Also, no clear correlation with etiology, or time since injury can be seen due to the limited sample.

The three network analyses further revealed significant differences in the auditory network and external network, but not the default mode network, during the music condition. Patients showed a severely limited auditory network of functional connectivity during both conditions (**Figure 3**). During the control condition, activation was only seen in bilateral temporal areas. During the music condition, the auditory network was restricted to bilateral temporal gyri (only left including Heschl's gyrus) and small clusters in the right inferior frontal gyrus and the left supramarginal gyrus, areas included in the temporal cluster for the healthy subjects. The right inferior frontal gyrus is implicated in auditory memory as well as the processing of musical syntactic-like structures (Maess et al., 2001; Janata et al., 2002; Koelsch et al., 2002, 2005; Tillmann et al., 2003, 2006; Koelsch and Siebel, 2005; Albouy et al., 2013). When music was compared to the control condition, patients' auditory network showed significantly more functional connectivity with the left precentral gyrus (Note that the seed-based analysis also revealed significant increased functional enhancement in the right precentral gyrus during music; see **Figure 2**) and the left frontal pole. The precentral cluster overlaps with regions of the auditory network in healthy subjects. The lateral prefrontal cortex has also been linked to autobiographical memory (Svoboda et al., 2006; Cabeza and St Jacques, 2007), and has also been implicated in rhythm perception (Zatorre et al., 2007). The finding of increased functional connectivity in music compared to the control condition suggests that music has an effect on the auditory-related network in DOC patients, in whom short-term functional plasticity might appear following the lesions.

In patients, the external network observed during the control condition was restricted to clusters of functional connectivity in inferior parietal sulcus and lobule, dorsolateral, middle frontal, and supramarginal areas. In the music condition, the external network showed besides these regions also connectivity with the region MT and parts of the frontal eye field. When directly compared to the control condition, the music condition showed more functional connectivity with the supramarginal/angular gyrus. This cluster overlaps with the supramarginal regions activated during spatial orienting in healthy subjects (Corbetta and Shulman, 2002). Interestingly, this region overlaps with disconnected areas in UWS patients (Laureys et al., 2000). Laureys et al. (2000) proposed that a lack of integration between primary regions (that activate after simple auditory stimulations in UWS), and higher order regions like the temporoparietal junction and superior temporal gyri (activated in MCS after simple auditory stimuli; Boly and Faymonville, 2004) makes conscious processing unlikely (Laureys et al., 2000; Boly and Faymonville, 2004). Put differently, unconsciousness might be related to a disruption in feedback processing to the auditory regions (Boly et al., 2011).

CONCLUSION

The effect of music on functional cerebral connectivity is reminiscent of previous findings which have shown effects of music in brain-damaged patients (Soto and Funes, 2009; Särkämö and Soto, 2012; Verger et al., 2014; Castro et al., 2015). For example, a recent EEG study investigating DOC patients has shown that the patients' cerebral responses following the presentation of one's own name were increased after having been exposed to their preferred music (Castro et al., 2015). A "Mood and Arousal hypothesis," attributes the beneficial effects of music on cognition to an increase in mood and arousal (Chabris, 1999; Nantais and Schellenberg, 1999). Within this hypothesis, the effects of music in DOC patients might be due to an overall cortical arousal in the cerebral structures that have been reported to be involved in emotional and mood states. A second hypothesis attributes the effect of music to autobiographical priming (Castro et al., 2015). Interestingly, in the present study, an increased functional connectivity during the music condition (vs. the control condition) was shown in cortical structures linked to music perception, autobiographical memory and consciousness for DOC patients. These results need to be confirmed in an extended group of patients, and future studies should also disentangle the general effect of music (because of its acoustic and structural features) from its autobiographical effects (because of its emotional and meaningful contents in relation to the patients' personal memory).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2015.01704

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How Can Music Influence the Autonomic Nervous System Response in Patients with Severe Disorder of Consciousness?

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Activations to pleasant and unpleasant musical stimuli were observed within an extensive neuronal network and different brain structures, as well as in the processing of the syntactic and semantic aspects of the music. Previous studies evidenced a correlation between autonomic activity and emotion evoked by music listening in patients with Disorders of Consciousness (DoC). In this study, we analyzed retrospectively the autonomic response to musical stimuli by mean of normalized units of Low Frequency (nuLF) and Sample Entropy (SampEn) of Heart Rate Variability (HRV) parameters, and their possible correlation to the different complexity of four musical samples (i.e., Mussorgsky, Tchaikovsky, Grieg, and Boccherini) in Healthy subjects and Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) patients. The complexity of musical sample was based on Formal Complexity and General Dynamics parameters defined by Imberty's semiology studies. The results showed a significant difference between the two groups for SampEn during the listening of Mussorgsky's music and for nuLF during the listening of Boccherini and Mussorgsky's music. Moreover, the VS/UWS group showed a reduction of nuLF as well as SampEn comparing music of increasing Formal Complexity and General Dynamics. These results put in evidence how the internal structure of the music can change the autonomic response in patients with DoC. Further investigations are required to better comprehend how musical stimulation can modify the autonomic response in DoC patients, in order to administer the stimuli in a more effective way.

Keywords: disorder of consciousness, vegetative state, autonomic nervous system, central autonomic network, heart rate variability, music therapy, entropy

INTRODUCTION

Music listening is one of the most pleasurable experiences for the human being (Dube and Le Bel, 2003). Music can be defined as the organization of the tone over the time. By mean of the exposure to musical pieces in everyday life, listeners acquire sensitivity to the regularities of the tonal system (Tillmann, 2005). This knowledge creates expectancy in the listeners, with experience of tension, suspense or relaxation, when the rules are confirmed, or violated (Meyer, 2008; Ockelford, 2008). Activations to pleasant and unpleasant musical stimuli were observed within an extensive neuronal network of limbic and paralimbic brain structures. Activations in the ventral striatum, anterior superior insula, and in Rolandic operculum were observed in healthy subjects, during the listening of pleasant music (Koelsch et al., 2006). Moreover, inferior frontolateral cortex, ventrolateral premotor cortex, and anterior part of the superior temporal gyrus were found active in the processing of musical syntax, whereas the processing of musical semantics appears to activate posterior temporal regions (Koelsch, 2005).

Some studies also evidenced a correlation between autonomic activity (modulation of the High frequency component recorded by Heart Rate Variability), and emotion evoked by musical listening (Iwanaga et al., 2005; Orini et al., 2010).

The emotions felt by the listening to music were described as linked to the musical structures (Juslin and Sloboda, 2010). The parameters, defined as Formal Complexity and General Dynamics, provide informations about the relationship between musical structures and emotions (Imberty, 1976). Imberty defines Formal Complexity and General Dynamics, combining musical variables (as note duration, metric interval, density of notes per time unit, loudness, accents, syncopation and other characteristics of melodic, harmonic, and rhythmic structures) associating them to the emotion induced by the music (Imberty, 1976, 1997). In particular, the General Dynamics is defined as the number per time unit of notes played and their relative intensity, while the Formal Complexity as the intrinsic homogeneity of the musical structures (i.e., melodic recorsivity, rhythmic structure, dissonance etc; **Table 1**).

The emotional reactions to four musical samples of different complexity [Boccherini: Minuet; Grieg: Morning; Tchaikovsky: Pathetic (1st movement), and Mussorgsky: Night on bald mountain] were observed in Traumatic Brain Injured (TBI) patients and healthy subjects by mean of the Heart Rate Variability (HRV) analysis, with a classification of reported emotions by the normalized unit of the low frequency (nuLF; Riganello et al., 2008). Successively, it has been possible to infer positive and negative emotional responses in Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) patients (Riganello et al., 2010a), undergone to the same experimental procedure, in particular when they were exposed to the Boccherini's music (positive emotion) and to the Mussorgsky's music (negative emotion).

TABLE 1 | Descriptors of music formal complexity and general dynamics.

Formal complexity	General dynamics
(Hm*t) ± (el*eR)	V*I
(Hm*t) = structure homogeneity index (el*eR) = Heterogeneity index Hm = melodic entropy computed on the epoch of music with melody t = duration of metric interval el = mean variation in intensity of each note over the time eR = mean variation of duration	V = mean number of successive musical note per second I = subjective intensity

Musical structure are characterized by means of the available descriptors of formal complexity and heterogeneity index (or intrinsic homogeneity; FC) and general dynamics (GD). FC describes the intrinsic organization and "predictability" of the music as to rhythm or melody or its lack of perceivable structure and is conventionally regarded as an index of emotional sympathy. GD describes the music in terms of volume, harmony, and rhythms and reportedly accounts for motor involvement. Different degree of FC and GD inducing to different emotional status.

In the HRV analysis, the data are analyzed in time, frequency, and non-linear domains (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996; Riganello et al., 2012b). In the time domain, HRV measures are mainly markers of overall HRV. Detailed informations on the HRV dynamics and frequency components are provided by the analysis in the frequency domain by Fast Fourier Transform (FFT) or autoregressive (AR) models (Malliani, 1999; Montano et al., 2009). The generalized frequency bands, in case of short-term HRV recordings, are the very low frequency (VLF: 0–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.5 Hz). Specifically, normalized unit of Low Frequency (nuLF; Burr, 2007), computed as second step after the initial statistical estimation of the power in the Low Frequency and High Frequency bands [nuLF = LF/(LF+HF)], is deemed indicative of sympathovagal balance.

All frequency domains analyses are based on the recognition of certain predetermined patterns (in FFT the pattern is a sinusoidal wave). A possible alternative to characterize the variability of heart rate is to measure the regularity (or complexity) of the fluctuations. The entropy (non-linear analysis metrics) is a general approach to quantify the regularity or information content of the data, providing "hidden information" related to underlying mechanisms (Richman and Moorman, 2000). The Approximate Entropy (ApEn; Pincus and Goldberger, 1994) determines the conditional probability of similarity between a chosen data segment and the next set of segments of the same duration. ApEn has been developed for measuring the complexity of relatively short time series and the calculations are not based on specific assumptions regarding the internal structure or dynamics of the system. However, ApEn has some known shortcomings, such as bias, relative inconsistency, and dependence on the sample length. Sample Entropy (SampEn) reduces the bias of ApEn (Aboy et al., 2007) is more consistent and easier to compute than ApEn, and provides a more reliable estimate of the complexity of a signal. Moreover, it may be used for considerably shorter time series than the ApEn, ($<$200 points; Batchinsky et al., 2009).

Heart rate complexity data (entropy) reflect overall balance of autonomic outflow, responsiveness, and neuroendocrine mechanisms (Ryan et al., 2011; Riganello et al., 2012a,b). Decreased variability is thought to reflect system isolation and a reduced ability to respond to perturbations. Entropy analysis represents potential powerful methods to use in the care for critically ill patients. In Intensive Care Unit reduced entropy was associated with illness and predicts death (Papaioannou et al., 2006, 2008; Riordan et al., 2009). The changes of entropy rates have been mainly related to aging and disease (Kaplan et al., 1991; Voss et al., 1996). More, it has been suggested that the complexity of short-term recording of heart rate variability might be closely related to cardiac autonomic modulation (Porta et al., 2000).

The decreased entropy of heart rate complexity, associated with Lifesaving Interventions in both prehospital trauma (Cancio et al., 2008) and Cardiac Autonomic Neuropathy patients, suggests a reduced responsiveness of the cardiac control mechanism to external and internal stimuli (Khandoker et al., 2009). The reduced entropy was significantly associated with an increase of mortality, and a relationship between entropy and death was found in patients with isolated severe head injury and with penetrating mechanisms of injury (Riordan et al., 2009).

Reported studies put in evidence the effectiveness of HRV analysis related to the autonomic nervous system (ANS) modifications. The children, who progressed to brain death, had a markedly lower LF/HF ratio, while the patients with more favorable outcomes had significantly higher LF/HF ratios (Biswas et al., 2000). As reported, a worsening of the conditions in TBI patients was correlated to the LF, the severity of neurological dysfunctions and the outcome, as well as the global HRV and parasympathetic tone were found higher in TBI patients, successively died (Goldstein et al., 1996; Rapenne et al., 2001; Norris et al., 2006). On the contrary, an amelioration was correlated to the recovery of autonomic functions, with a decrease of the parasympathetic activity, and a parallel recovery of the consciousness (Keren et al., 2005; Wijnen et al., 2006).

Many studies evidenced the different responses of the ANS, recorded by the HRV analysis, due to the different music styles. Different complex heart dynamics responses were observed, during the listening of different Indian Raga musics, assuming possible different responses based on the different musical patterns (Mukherjee et al., 2015). The effects of Iranian music on the cardiac function has been also studied (Hajizadeh et al., 2015), showing increasing values in the SampEn. Other studies suggest that excitative music decreases the activation of the parasympathetic nervous system in healthy subjects (Iwanaga et al., 2005), as well as the excitatory heavy metal music acutely decreases global HRV (da Silva et al., 2014). Exploring different styles of "relaxing" music, the "new age" music induced a shift in HRV from higher to lower frequencies, independently on the music preference of the listener (Perez-Lloret et al., 2014).

Previous studies (based on the analysis of the first 300 heartbeats recorded) have been designed to verify the possibility to classify positive or negative emotions elicited by different musical stimuli selected for their General Dynamics and Formal Complexity (Riganello et al., 2008), and their possible emotional effect in VS/UWS patients (Riganello et al., 2010a). The aim of this study was to verify the influence of the musical stimuli complexity on the autonomic responses in VS/UWS patients, by the HRV nuLF and SampEn parameters analysis during the listening of the first 3 min of the selected musical samples. The two musical samples (Boccherini and Mussorgsky; Riganello et al., 2010a) have been compared by the nuLF and SampEn parameters, taking in account the possible different effect observed in the VS/UWS patients. The hypothesis is that music with high Formal Complexity and General Dynamics reduces the autonomic response in VS/UWS patients.

MATERIALS AND METHODS

The first 3 min of tachogram (i.e., the series of consecutive intervals between heartbeats) recorded during the listening of four musical samples [Boccherini (Minuet); Grieg (The morning); Tchaikovsky (Pathetic—1st movement); and Mussorgsky Night on bald mountain (**Figure 1**)], by Healthy subjects and VS/UWS patients, were retrospectively analyzed by Kubios HRV version 2.2 (Tarvainen et al., 2014). The selection was characterized by the Formal Complexity and the General Dynamics of the musical samples, as indicated by Imberty (Imberty, 1976, 1997; Juslin and Sloboda, 2010; **Table 1**; **Figure 2**). These descriptors are related to the musical structure and allow to characterize the (induced) emotional status along a continuum from euphoria and well-being to melancholy, severe anxiety etc. In particular an increasing of the Formal Complexity is associated to a major shift from "positive" toward "negative" emotions. In general, positive and negative emotions are associated to relatively simple or complex melodies and regular or irregular rhythms, respectively (Vitz, 1966; Crozier, 1974; Holbrook and Anand, 1990; Smith and Melara, 1990); slow and fast tempi are related to the ratings of subjective sadness and joy (Hodges, 1980; Gabrielsson and Juslin, 1996; Juslin, 1997, 2000). A matrix of the music Formal Complexity and General Dynamics was designed to classify the emotional responses and correlate them with the musical structures (see for detail Riganello et al., 2008; **Figure 2**).

Sixteen healthy subjects (9 women, 24–42 years, mean 31.8 ± 5.2) listened passively the music one time, while 9 patients (6 male, 16–31 years, mean:26 ± 6.0; 3 female, 31–48 years, mean: 39 ± 9) in VS/UWS (**Table 2**) according to current criteria (Giacino et al., 2004; Giacino and Kalmar, 2005), listened the music twice. All patients were assessed by Coma Recovery Scale Revised (CRS-R) administered by an expert neuropsychologist. The experiments took place always at the same time of the day (within 60 days from the injury), in the semi-intensive care unit dedicated to the vegetative state (the VS/UWS subjects' usual environment) and did not interfere with the patients' medical/rehabilitative schedule. VS/UWS subjects and healthy controls were comfortably lying on armchair, with constant 24°C ambient temperature and in absence of transient noises. The baseline was recorded at rest; subjects were exposed binaurally to the four selected music samples, presented via earplugs, balanced for loudness and played in random sequence to minimize carried-over effects. The music samples were presented in randomized sequence with 10 min of interval between each other. The VS/UWS patients were exposed to two music samples per day only in order to avoid overstimulation and excessive fatigue (for procedures detail see Riganello et al., 2010a).

The tachogram was analyzed in the time and frequency domains, by the HRV advanced analysis software developed at the Department of Applied Physics, University of Kuopio, Finland (Niskanen et al., 2004). The HRV nuLF and SampEn parameters were extracted for the analysis. Each couple of listening of the same musical sample administered to the VS/UWS patients, was averaged in one to avoid the error of alpha inflation in the sample size.

Healthy subjects vs. VS/UWS patients were compared between them for baseline and musical samples by Mann-Whitney's exact test. Difference among music samples was analyzed by Friedman's exact test and difference between Boccherini and Mussorgsky's music was analyzed by Wilcoxon's

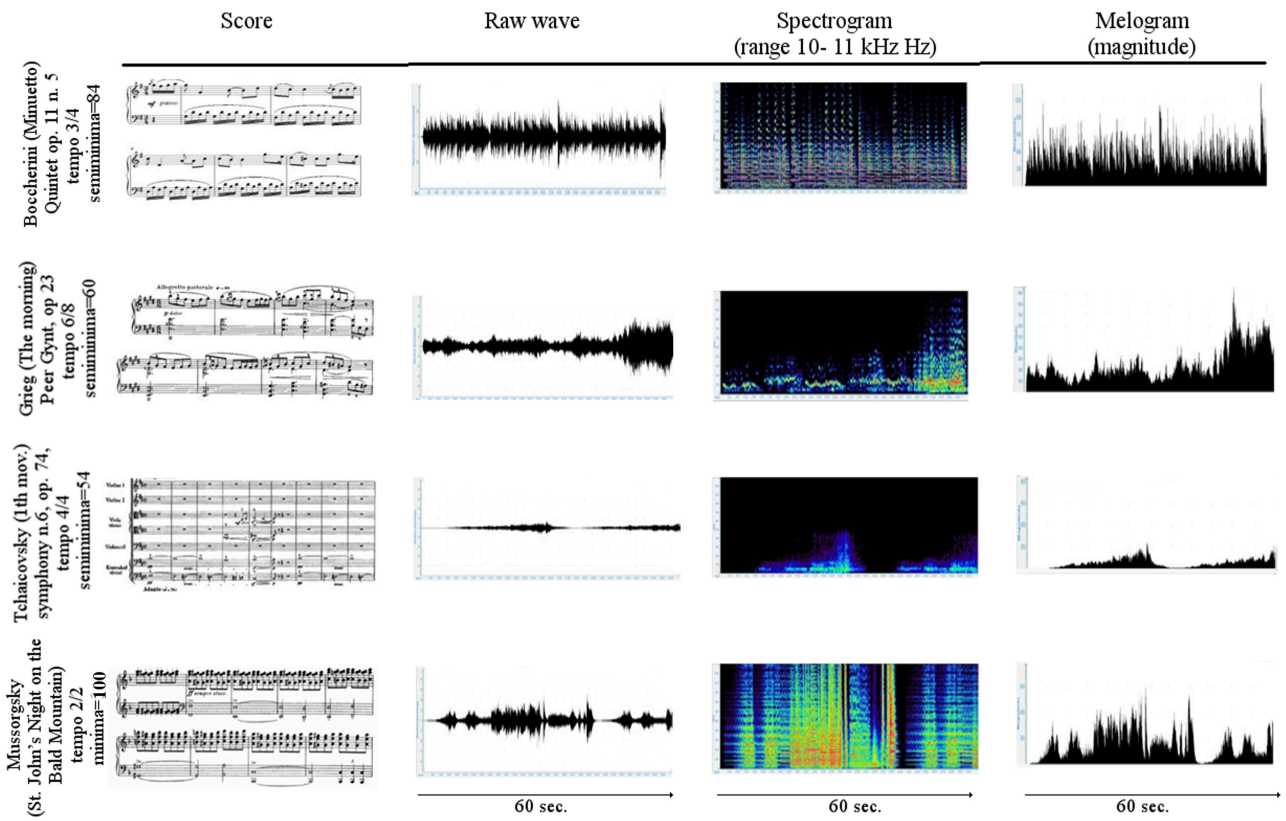

FIGURE 1 | Scores and first 60 s of the raw waveform, spectrogram, and melogram of the selected music. In the 1st column the first bars of the musical score. In the 2nd column the raw wave formgraph displays the unprocessed recorded sound. In the 3rd column the spectrogram plot show the intensity of the frequency content of a signal as it changes over the time. The vertical axis indicates frequency, the horizontal axis indicates time, and the color or gray scales indicate the intensity. Magenta is the color of the highest and dark blue of the lowest intensity. In the 4th column the melogram (or magnitude) graph displays the intensity of the melody relative to a reference sound.

exact test in both groups. The exact test (Siegel, 1956; Gibbons and Chakraborti, 2011) is more accurate in case of small sample, or when the tables are sparse or unbalanced (Tanizaki, 1997; Mundry and Fischer, 1998; Gibbons and Chakraborti, 2011). The effect size (r) i.e., the index measuring the magnitude of difference or change between two conditions, (Rosenthal, 1991) was calculated as the z/square root (N; where N is the number of observations on which z is based) and will be hereafter formally referred to as not relevant ($r < 0.1$), small ($0.1 < r < 0.3$), medium ($0.3 < r < 0.5$), or large ($r > 0.5$; Hemphill, 2003). After the Bonferroni's corrections for multiple comparisons the results of the tests was considered significant for p-value ≤ 0.005.

The ethical principles of the Declaration of World Medical Association (2001) by the World Medical Association were followed.

RESULTS

After Bonferroni correction no significant difference was found in the baseline condition between groups.

The values of nuLF were found different between groups for Grieg (Mann-Whitney's exact test: $Z = -2.887$, $p = 0.001$, $r = 0.58$) and Mussorgsky's music (Mann-Whitney's exact test: $Z = -3.170$, $p = 0.000$, $r = 0.63$), while after Bonferroni correction, SampEn was found different only for Mussorgsky's music (Mann-Whitney's exact test: $Z = -3.453$ $p = 0.000$, $r = 0.69$).

The difference among musical stimuli was significant in VS/UWS group for nuLF (Friedman's exact test: $\chi^2 = 10.733$, $p = 0.009$) and SampEn (Friedman's exact test: $\chi^2 = 16.067$, $p = 0.000$) parameters. Comparing Boccherini and Mussorgsky's music, after Bonferroni correction, a significant difference was found for SampEn (Wilcoxon's exact test: 2.668, $p = 0.002$, $r = 0.63$; **Figure 3**).

DISCUSSION

The HRV analysis, of the previous study, was based on the first 300 heartbeats rate recorded (Riganello et al., 2010a), with different times of recording related to the subjects variability. The listening of Boccherini, compared with the other composers, showed a decreasing of the hearth rate. More, it was observed a difference in the nuLF between the baseline and the music samples listening. The nuLF was linked, by data mining analysis, to the emotions evoked by the different music

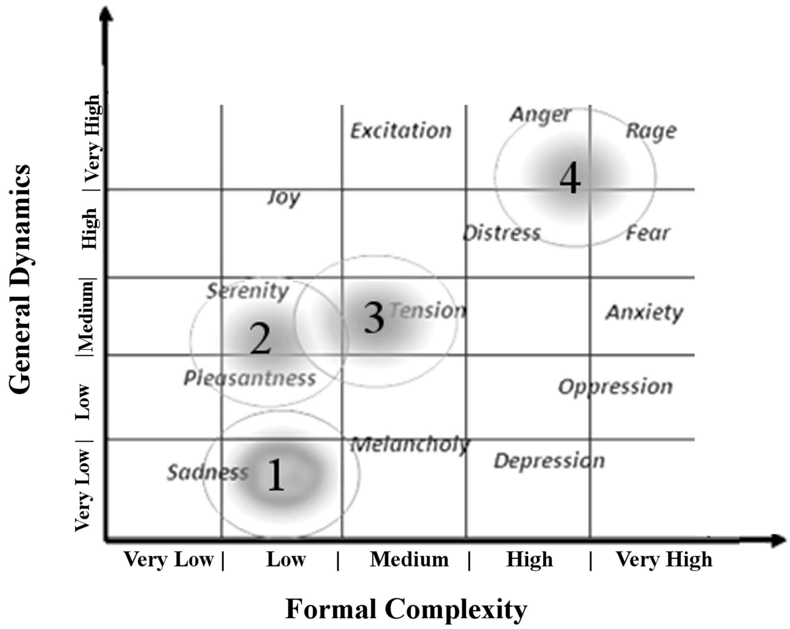

FIGURE 2 | Distribution of reported emotional responses of healthy subjects according to the music *general dynamic* and *formal complexity* (see Table 1). Numbers indicate the position in summary outline of the music samples used as auditory stimuli in the study (1 = Tchaikovsky; 2 = Boccherini; 3 = Grieg; 4 = Mussorgsky). Figure adapted from Riganello et al. (2010a).

TABLE 2 | Demographic data of VS/UWS patients.

	Age	Sex	Etiology	CRS-R	CRS-R sub scores	Follow-up at 6 month
1	16	male	traumatic	6	A = 1 V = 2 M = 1 O = 1 C = 0 Ar = 1	MCS
2	21			5	A = 0 V = 1 M = 1 O = 1 C = 0 Ar = 2	VS
3	30			4	A = 0 V = 1 M = 1 O = 1 C = 0 Ar = 1	dead
4	30			5	A = 1 V = 1 M = 1 O = 1 C = 0 Ar = 1	VS
5	31			5	A = 1 V = 1 M = 1 O = 1 C = 0 Ar = 1	VS
6	27			6	A = 1 V = 1 M = 2 O = 1 C = 0 Ar = 1	VS
7	31	female	hemorrhagic	4	A = 0 V = 1 M = 1 O = 1 C = 0 Ar = 1	VS
8	39			6	A = 1 V = 2 M = 1 O = 1 C = 0 Ar = 2	VS
9	48			5	A = 0 V = 1 M = 2 O = 1 C = 0 Ar = 1	dead

CRS-R subscore: A, Auditory Scale; V, Visual Scale; M, Motor Scale; O, Oromotor/Visual Scale; C, Communication Scale; Ar, Arousal Scale.

(Riganello et al., 2008, 2010a), in particular too high or too low values of nuLF were associated to negative emotions.

In this study we tried to identify possible variations of the autonomic reactivity, specifically to the complexity of the musical stimulus, by analyzing the first 3 min of listening. The results were linked to the same length of the musical stimulation time, unlike the previous study, in which the HRV analysis was dependent also on the length of the tachogram.

The results showed differences between groups for HRV parameters, characterized generally by lower values in VS/UWS patients. This difference was significant for nuLF during the listening of Grieg and Mussorgsky, and for SampEn during the listening of Mussorgsky. Comparing the musical stimuli among them, the autonomic response was characterized by decreasing values in nuLF and SampEn in VS/UWS, when the musical complexity was higher. Such patients showed a shift of HRV parameters toward an increasing of vagal response, and contextually a reduction of heart rate complexity for increasing Formal Complexity and General Dynamics parameters. The different response to the musical stimuli was significant for SampEn, comparing Boccherini and Mussorgsky's musical samples. No similar response was observed in healthy subjects.

The experience of music listening is based on the idea that the music represents and induces emotions, which are, respectively, perceived and felt by listeners, although these two aspects may not coincide (Gabrielsson, 2002). The association of different psychological mechanisms, associated to the physiological correlates of the music listening, were suggested (Harrer and

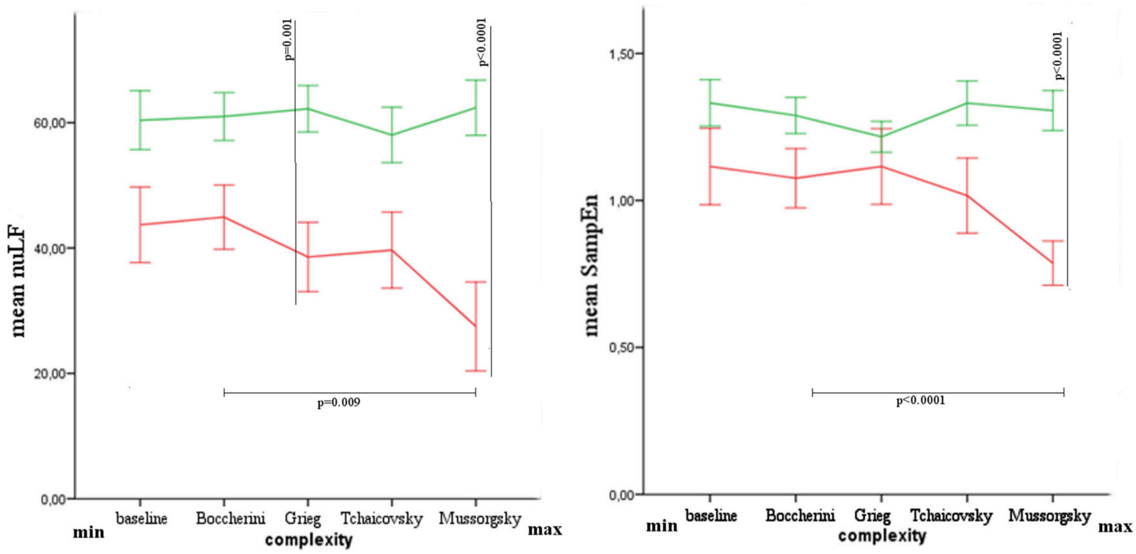

FIGURE 3 | Mean and Standard Error of nuLF and SampEn in healthy (green) and VS/UWS (red) groups. In the axis, from left to right, baseline and musical stimuli with increasing complex structure.

Harrer, 1968). Several modes of music listening were described as associated to conscious (e.g., structural analytic, associative oriented. ect.) or unconscious (e.g., associative emotional, motor-kinetic, etc.) listening (Rauhe, 1975; Rösing, 1985; Behne, 1986). As reported, the music internal structure plays a primary role in the induction of emotions, and rhythmic aspects are considered the major determinants of physiological responses (Gomez and Danuser, 2007). More, the tonal variation was correlated to the psychophysiological happy/sad distinction (Khalfa et al., 2008).

It was shown that the applications of music in medicine can be used to stabilize vital signs and manage symptoms in the short-term (Hanser, 2014). The listening of classical music and of rock music or noise were related to a small variance or an increase/decrease of Mayer Wave components and Respiratory Sinus Arrhythmia components, respectively (Umemura and Honda, 1998). Relaxation and music therapy have been found effective modalities to reduce stress and anxiety in patients of a coronary care unit (Zimmerman et al., 1988; Guzzetta, 1989; Hanser, 2014). Music therapy enhanced parasympathetic activities and decreased Congestive Heart Failure by reducing plasma cytokine and catecholamine levels (Okada et al., 2009).

Changes in the HRV patterns of response indicative of enhanced activity of the cardiovascular system were observed after 14-day music therapy (Lee et al., 2011). Replicable changes in the sympathovagal balance have been identified in DoC patients during the passive listening of symphonic music (Riganello et al., 2008, 2010a,b), allowing to cluster the autonomic responses as indicative of positive or negative emotions in both VS/UWS and awake posttraumatic subjects. Music appears peculiarly efficient in promoting arousal and responsiveness in DoC (O'Kelly et al., 2013). The activation of the superior temporal gyrus, by music, can predict the evolution from VS/UWS (Okumura et al., 2014).

The heart rate reflects the sympathetic/parasympathetic interplay, with a dominant tonus at rest of parasympathetic nervous vagus innervating the intrinsic cardiac nervous system (Scherlag and Po, 2006), and projecting to the sinoatrial node, atrioventricular node, and atrial cardiac muscle. ANS mediates the bidirectional communication between heart function and the Central Nervous System (CNS; Kawashima, 2005; Riganello et al., 2014). This regulation depends on medullar centers, in particular the nucleus of solitary tract and rostroventrolateral medulla (Spyer and Gourine, 2009) that integrate sensory information from proprio-, chemo-, and mechanoreceptors and from the telencephalic and limbic systems. An increase of rate results from reduced vagal activity (Hainsworth, 1995) or sympathetic activity above the intrinsic levels operated by the sinoatrial node (Hainsworth, 1995). An integrated model has been proposed (usually referred to as the Central Autonomic Network, CAN; Benarroch, 1993), in which neuronal structures involved in cognitive, affective, emotional, and autonomic regulation are functionally linked to heart function. This complex brain-heart interaction with the bidirectional links between cortical, midbrain, and brainstem structures (Riganello et al., 2012a) include, among others, the orbitofrontal, ventromedial prefrontal, anterior cingulate, and insular cortices, basal ganglia, central nucleus of the amygdala, nucleus of the solitary tract, nucleus ambiguus, and periaqueductal gray matter. The interplay between autonomic control and the CNS is modeled as a functional setup connecting through feedback and feed-forward loops the brainstem solitary tract nucleus with forebrain structures (Napadow et al., 2008; Lane et al., 2009; Riganello et al., 2012a).

Most of studies on HRV and music have been experimental rather than interventional, reporting significant changes in HRV as a function of musical mood (Etzel et al., 2006), genre

(Bernardi et al., 2006), familiarity (Iwanaga et al., 2005), or tempo(Ellis, 2009; Fukumoto and Matsuo, 2010). Few reports exist of musical interventions that have included HRV as an index of autonomic function (Kemper et al., 2008; Okada et al., 2009; Ellis and Thayer, 2010; Roque et al., 2013a,b), and very few on musical stimuli and HRV in VS/UWS patients (Riganello et al., 2010a,b; Yen et al., 2010; Lee et al., 2011). However, it was suggested that the effect of music on cerebral processes in patients might reflect its capacity to act both on the external and internal neural networks supporting consciousness (Perrin et al., 2015). Again, it has been shown the benefit of classical and meditation music on patients hospitalized in intensive care medicine, whereas heavy metal or techno music were found not only ineffective, but possibly dangerous (Trappe, 2012). In these frames, it is important to define the correlations between musical structures and autonomic response to the musical stimuli, in order to have a correct approach to the stimulation of patients with DoC.

CONCLUSIONS

The music listening is a complex experience and the responsiveness to the musical stimuli is constituted by a strong individual variability (Hanser, 2014). However, the study of the musical parameters can help to define and make hypothesis about musical stimuli and modification of ANS.

The close relationship between the CAN structures and the music listening could play an important function in the use of music in DoC patients (Magee, 2005; O'Kelly and Magee, 2013; O'Kelly et al., 2013). Complex musical stimuli could reduce the effectiveness of the response too. In order to improve the approach by the musical stimulation, further investigations are required to better comprehend how the musical structures can modify the autonomic response in DoC patients.

AUTHOR CONTRIBUTIONS

All Authors equally contributed to the study design and preparation of the protocol as well as to the manuscript preparation. FR also performed the statistical analyses. The work reported in this paper has not been published previously, is not under consideration for publication elsewhere, and if accepted will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder. Its publication is approved by all authors and by the responsible authorities where the work was carried out. All Authors are employees of the Institute S. Anna–RAN and the study was supported by the Institute itself, without external funding.

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OPINION
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Electroencephalography (EEG) Measures of Neural Connectivity in the Assessment of Brain Responses to Salient Auditory Stimuli in Patients with Disorders of Consciousness

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Disorders of consciousness (DOC) present a clinical challenge in diagnosis, prognosis and defining appropriate treatments that aim at improving the patient's care and quality of life. As there is no universally accepted definition of consciousness, DOC are difficult to define, elucidate and diagnose (Giacino et al., 2014; Schiff et al., 2014).

Modern neuroscience has facilitated a multitude of advanced approaches, models of brain connectivity and techniques, to develop a deeper understanding of the states of consciousness and their transitions, as well as more robust, objective assessment and interventions to be adopted in the clinical environment (Liberati et al., 2014). These could not only enhance and complement diagnosis and assessment but also assist the validation of appropriate rehabilitation interventions, including music therapy.

THE MESOCIRCUIT MODEL OF THALAMOCORTICAL CONNECTIVITY AND ITS APPLICATION IN DOC

The mesocircuit model (Schiff, 2010; Giacino et al., 2014) hypothesizes that the highly dynamic and integrated thalamocortical network is driven by complex and synchronized neuronal firing patterns associated with depolarization of cortical, thalamic and striatal membrane potentials (Giacino et al., 2002, 2014). To illustrate, following a traumatic brain injury (TBI), synchronous activity diminishes across long distance thalamocortical pathways between the prefrontal and parietal cortices, and large-scale dysfunction is seen at the circuit level due to global decreases of excitatory neurotransmission, producing overall changes in cerebral activity levels and reduction in arousal levels (Schiff, 2010; Leòn-Carriòn et al., 2012; Giacino et al., 2014).

This model assumes the key role of the thalamus in integrating thalamocortical pathways, as the thalamus is a central processor not just a simple relay center and performs complex information processing and integration that underlies different mammalian behaviors through corticothalamic feedback input with a high reciprocal connection across cortical areas. The relationship between the thalamus and cortex is bidirectional as the cortex receives thalamocortical inputs and itself projects to the thalamus via corticothalamic fibers (Sherman and Guillery, 2013).This frontocortico-thalamacortical loop responds to the level of synaptic activity; it receives sensory inputs and projects them to the appropriate cortical areas depending on the type of sensory stimulation (e.g., auditory). Such projections are able to regulate cortical states and behaviors: perception and learning and cognition, what we know to be elements of "consciousness" (Tononi and Koch, 2008).

In DOC, structural and functional abnormalities in these pathways reduce the ability to integrate and synchronize cortical areas to process sensory input and couple with executive cognitive functioning (Schiff, 2010; Bagnato et al., 2012; Giacino et al., 2014). Thalamic integrity is related to the severity of DOC in acute and chronic settings (Luckenhoff et al., 2013). DOC states could therefore be interpreted as a "disconnection syndrome" because of impairment in specific cortico-thalamo-coritcal circuits (Monti et al., 2015).

When considering restorative mechanisms in DOC and intra and inter transitioning states, these pathways are implicated in rehabilitation (Laureys et al., 2000; Schiff, 2010; Bagnato et al., 2013). A model of recovery which focuses on connectivity between and within frontal and parietal regions influenced by specific circuit modifications of the thalamocortical pathways is proposed (Laureys and Schiff, 2012; Crone et al., 2014). Evidence for this model comes from studies that show disrupted functional connectivity in a widespread frontoparietal network in patients with impaired consciousness (Luckenhoff et al., 2013; Schiff et al., 2014; Monti et al., 2015) and studies which emphasize the important role of the thalamus (Laureys and Schiff, 2012). Across the network, thalamocortical plasticity may occur through different mechanisms, such as sensory stimulation or deprivation: auditory, visual, cognitive, or somatosensory, impacting thalamocortical arborisation and dendritic spine density (e.g., Bagnato et al., 2013). This has considerations regarding the impact of rehabilitation interventions which could induce neuroplasticity and therefore the functional network of the brain required for synchronized connectivity across the thalamo–cortical network to identify changes and characteristics associated with transitional states of a DOC.

The mesorcicuit model and concept of thalamocortical connectivity in DOC has led to research models which aim to measure brain dynamics in response to different stimulation and at rest states. The aim of this is not only to elucidate the condition but also to develop standardized and robust objective assessment methods that can be adopted in the clinical environment (Liberati et al., 2014).

APPLICATIONS OF ELECTROENCEPHALOGRAPHY (EEG) TO STUDIES OF BRAIN CONNECTIVITY IN DOC

Modern neuroimaging and recording techniques such as MRI, fMRI, PET, and electroencephalography (EEG) have facilitated the integration of structural and functional methods enabling a greater understanding of the variation in different states and transitions of a DOC, as well as some individual differentiators within the spectrum (Laureys et al., 2004; Liberati et al., 2014). EEG serves as a direct measure of neuronal activity, which is independent of overt motor communication responses; this is particularly pertinent to studies on DOC where these very functions are severely impaired (Laureys et al., 2004). Thanks to these characteristics, EEG has become a global standardized technique widely used in both clinical and research settings with well-defined criteria for interpretation.

EEG can measure brain signals of neuronal activity over bandwidths of frequency ranges recorded with dozens or hundreds of scalp locations over different timescales; it has particular relevance when considering brain dynamics and the mesocircuit model in DOC. Brain dynamics are measured through signal oscillations which act as communication connections integrating brain functions. They are important for the mediation and distribution of higher functional and synchronized processes in the human brain (Sauseng et al., 2005). Moreover, it has been proposed that brain oscillatory systems act as possible communication networks with relationship to integrative brain functions (Fingelkurts et al., 2013). The advent of EEG digital technology has led to quantitative computational models which analyse dynamic internetwork connectivity within DOC in response to different stimuli—auditory, visual, cognitive, motor, and resting state (Lehembre et al., 2012; Malinowska et al., 2013).

EEG COHERENCE IN DOC

The most accepted measure of interaction and connectivity is that of coherence, a generalization of correlation to the frequency domain. Coherence is used to study the relationship and interactions between EEG channels and between brain regions (Nolte et al., 2004). Coherent neuronal oscillations are seen to correlate with cognitive and behavioral functions, mediating long, and local range communication, impacting synaptic plasticity (Maris et al., 2007; Plankar et al., 2013). EEG coherence is computed between pairs of electrodes, providing information on the extent of synchronization between two time series. A high coherence between signals at different sites of data collection indicates an increased functional connectivity between the regions of interest within the neuronal network, thus identifying a circuit of neural activity; such measures have a temporal definition as they can be collected at various time points (Cohen, 2014). Apart from the obvious advantages of such information, there are also limitations as scalp-recorded EEG measures of coherence do not provide insights into the discrete anatomical and physiological factors that underpin circuit activity (Chorlian et al., 2009).

In DOC, coherence is used to study connectivity and synchronization between brain regions. Correlated activities amongst brain areas or electrodes can determine patterns of functional connectivity, which is known to be impaired in DOC (Noirhomme and Laureys, 2014). Although a wide range of EEG patterns are present in brain injured patients, there are broad regularities that are identifiable across the power spectrum for coma, DOC states and normal wakefulness (Malinowska et al., 2013).

One of the main limitations of this approach is that coherence values must be interpreted carefully, as they can be contaminated by artifacts between electrodes caused by reference and by volume conduction which is pertinent to the DOC population. Volume conduction can impact interelectrode connectivity results due to the spatial autocorrelation between electrodes which measures connectivity between the two brain regions where the electrodes are placed, this is further impacted by skull injury and craniotomy following a TBI (Cohen, 2014). This has been addressed by a modified measurement of coherence that takes into account only the imaginary part of coherence (iCoh; Nolte et al., 2004). Although some neural information may be lost due to removing the real part of coherency, the benefit is that the imaginary part explains only true brain interactions (Lehembre et al., 2012; Cohen, 2014).

Research using the modified imaginary coherence across difference frequency ranges and brain regions in DOC using resting state and diverse stimuli has expanded significantly over the last few years (e.g., Leòn-Carriòn et al., 2012, 2013; Höller et al., 2013; Chennu et al., 2014; Bagnato et al., 2015).

EEG studies of coherence can be used to assess the effects of auditory stimuli in DOCs. One of the most reliably tested methods is using salient auditory stimuli either through music therapy or music intervention that is meaningful or personal to the patient. DOC studies have identified that auditory stimulus with personal and/or emotional meaning produces meaningful results compared to unrelated auditory stimuli (e.g., O'Kelly et al., 2013; Magee et al., 2014; Okumura et al., 2014; Heine et al., 2015).

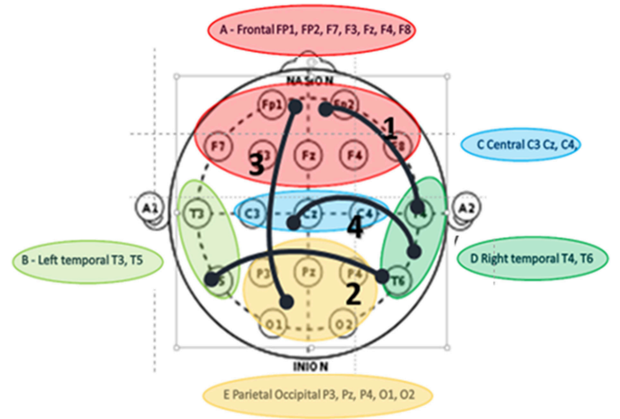

FIGURE 1 | Interregional Theta connectivity using i-coherence values to represent connections following music therapy intervention in DOC. Values of coherence not shown as diagram for illustrative purposes only. Paired electrodes groups into 5 anatomical brain regions: "1" indicates strongest regional coherence from right temporal to frontal electrodes; "2" is second coherence from right to left temporal regions; "3" is the 3rd strongest from frontal to parietal/occipital regions and "4" is the fourth level of i-coh between right temporal and central regions. There is no indication of connectivity direction, only interconnectivity (Lord, 2015).

EEG COHERENCE FOLLOWING SALIENT AUDITORY STIMULI IN DOC—CURRENT AND FUTURE DIRECTIONS

Music therapy is an established rehabilitation intervention in DOC (Magee et al., 2014; Raglio et al., 2014; Magee and O'Kelly, 2015). While there is a large body of literature regarding the brain responses to music (e.g., review by Koelsch, 2014) and music rehabilitation in DOC, as recently reviewed by Kotchoubey et al. (2015), there is a paucity of reports on EEG coherence and music therapy in DOC. A first of this kind of clinical research (O'Kelly et al., 2013) has evaluated the effects of salient auditory stimuli in patients with minimally conscious and vegetative states; which demonstrated theta increases in the frontal and temporal discriminatory activity in response to salient music stimuli. There is an obvious need for longitudinal DOC clinical studies, which analyse synchronized connectivity in response to salient auditory stimuli by means of EEG coherence. To address this, and following on the work by O'Kelly et al. (2013), a current clinical study evaluates the effects of music therapy on regional coherence in patients with DOC in a clinical rehabilitation setting during a course of music therapy applied over 6–18 months (**Figure 1**) (Lord, 2015). This collaborative research uses the mesocircuit model and thalamocortical synchronization to explore whether increased synchronization in brain connectivity across thalamocortical pathways can be considered as an indicator of increased awareness or consciousness, evaluating the responses to salient auditory stimuli over time.

More research is needed on the mesocircuit model and thalamocortical synchronization to develop an EEG regional coherence methodology in order to analyse and compare cortical regional connectivity in response to rehabilitation interventions, including music therapy. The application of these models in a clinical setting could help develop an EEG regional coherence methodology to analyse and compare cortical regional connectivity in response to music rehabilitation interventions.

It is important to understand if an increase in connectivity across the mesocircuit pathways could be an indicator of the conscious state and neuroplasticity, and whether such a change could monitor the functional recovery in line with the earlier works (Schiff, 2010; Leòn-Carriòn et al., 2012; Bagnato et al., 2013; Chennu et al., 2014; Crone et al., 2014). This approach could also facilitate the assessment of thalamocortical neuroplasticity as a possible effect of music intervention, by analysing regional coherence levels as indicators of awareness and arousal in response to salient auditory stimuli.

CONCLUSIONS

The application of the mesocircuit and thalamocortical connectivty models using EEG coherence measures could lead to a more objective determination of the state of consciousness in patients with DOC and any transitions that may happen across the continuum within the different states through the trajectory of rehabilitation with the contribution of music therapy. It is hoped that the development and adoption of such clinically applicable and complementary tools across DOC patient populations will enhance the existing practizes to provide more translational and differential evaluation of post-injury diagnosis and throughout rehabilitation.

AUTHOR CONTRIBUTIONS

VL is the lead author. Both VL and JO contributed to the conception and design of this work. VL drafted the manuscript and JO revised it critically for intellectual content. Both authors approved the final version of manuscript. Both VL and JO agree to be accountable for all aspects of the work.

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OPINION
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Sensory Stimulation and Music Therapy Programs for Treating Disorders of Consciousness

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INTRODUCTION

Until now, no treatment has shown its efficacy in patients with severe brain injury, with the exception of one pharmacological agent (i.e., Amantadine; Giacino et al., 2012). Recovery of consciousness is therefore one of the biggest challenge facing clinicians (Whyte, 2014). For years, sensory stimulation programs have been the most frequently applied treatment during patients' neurorehabilitation (Tolle and Reimer, 2003). These programs are based on the idea that an enriched environment benefits brain plasticity and improves recovery of injured brains.

Theories of brain plasticity, which suggest that an adult injured brain has the capacity to reorganize itself to compensate for affected regions, have broadly been accepted for several years (Hummel and Cohen, 2005). The most famous case illustrating this phenomenon is the case of Terry Wallis (Voss et al., 2006). This patient remained in a minimally conscious state for 19 years after a traumatic brain injury and yet recovered functional verbal and motor activities. A study of this case revealed a neural change, mainly involving the precuneus which is related to consciousness, suggesting that this spectacular recovery could be explained by brain plasticity. These results stress the importance of developing therapeutics that intensify brain plasticity in severely brain-injured adults to reach full recovery of consciousness.

Providing sensory stimulation may potentially stimulate affected neural networks, accelerate brain plasticity, and avoid a sensory deprivation that could slow down the patient's recovery. The efficacy of such intervention is, however, still currently debated. Recently, music therapy has been presented as another potential way to stimulate those patients and may constitute a promising alternative to sensory stimulation programs (Magee and O'Kelly, 2015).

SENSORY STIMULATION: THEORETICAL PRINCIPLES

Rosenzweig and colleagues introduced "environmental enrichment" in the field of animal research four decades ago to investigate the influence of environment on brain and behavior, and showed that the morphology and physiology of the brain can be altered by modifying the quality and intensity of environmental stimulation (Rosenzweig, 1966). An enriched environment is an environment with enhanced novel and complex stimulation relative to a standard environment, providing the animals with optimal conditions for enhanced exploration, cognitive activity and physical exercise (Rosenzweig et al., 1978). It has been associated with an increase in cortical thickness and weight (Rosenzweig et al., 1964; Beaulieu and Colonnier, 1987), size of the cell soma and nucleus, dendritic arborisation, length of dendritic spines (Holloway, 1966; Greenough et al., 1973; Kozorovitskiy et al., 2005) and synaptic size and number (Diamond et al., 1964; Mollgaard et al., 1971; Turner and Greenough, 1985). In animal models, exposure to such environment has shown to be beneficial for nervous system disorders, including brain injury (Johansson, 1996; Koopmans et al., 2006; Sale et al., 2009). Indeed, evidence suggests that the recovery of cognitive (e.g., learning and memory) and motor functions following experimental brain lesion is enhanced by this technique (Farrell et al., 2001; Hicks et al., 2002; Rönnbäck et al., 2005). Enriched environment following brain injury also has beneficial effects on the brain, such as decreasing lesion size or enhancing dendritic branching (Kolb and Gibb, 1991; Passineau et al., 2001; Nithianantharajah and Hannan, 2006).

SENSORY STIMULATION PROGRAMS

Numerous studies investigated the impact of sensory stimulation programs on the recovery of patients with disorders of consciousness (DOC). However, when reviewing studies published from 1966 to 2002, Lombardi reported only three studies with adequate methodologies (Kater, 1989; Mitchell et al., 1990; Johnson et al., 1993), the other ones mostly being non-controlled designs or descriptive case reports. The results from this small number of studies could not confirm the efficacy of sensory stimulation programs (Lombardi et al., 2002). Indeed, besides an insufficient description of the program applied, the results were contradictory, the types and dosage of interventions but also the primary outcomes examined differed, making any study comparison difficult. Another bias was the role of spontaneous recovery. Indeed, these studies were mainly performed in the acute or subacute stage, a period during which spontaneous recovery has the highest probability to appear. Due to small sample sizes, none of these studies could ensure a dissociation between improvements attributed to the sensory stimulation treatment and improvements due to spontaneous recovery.

Since 2002, several studies investigated whether the improvements observed after treatment exceeded spontaneous recovery (Oh and Seo, 2003; Lotze et al., 2011; Di Stefano et al., 2012). Time-series designs were used since the treatment was compared to baselines (see **Figure A1**). Results showed more complex behavioral responses in the presence of treatment than in its absence, suggesting that sensory stimulation programs have truly an impact on the improvement of consciousness in patients recovering from coma. These studies nevertheless included a small number of patients ($n < 15$). Finally, only one study investigated the changes in brain activity related to treatment. Pape and colleagues examined the effects of a unimodal (auditory) stimulation program (Pape et al., 2015). They found better neurobehavioral performance in the treated group as compared with the control group. fMRI recordings performed before and after treatment demonstrated higher activation in the language network in the treated group as compared to the control group, suggesting an impact of the sensory stimulation program on the patients' brain recovery (see **Figure A2**). Such findings indicate that supplementing behavioral measures with neuroimaging may expand our understanding of the impact of sensory stimulation with such complex populations (see **Table A1** in Appendix).

A NEW POTENTIAL OPTION: MUSIC THERAPY

Music therapy interventions use live music that can be modified according to patient responsiveness "in the moment." Musical parameters (e.g., tempo, rhythm) are manipulated according to changes in a patient's attention or arousal, incorporating salient content, such as the patient's name, in musical material. Salient auditory stimuli, such as family members' voices, increase the probability of observing brain and behavioral responses in DOC patients (Perrin et al., 2015). However, music listening may offer a superior auditory stimulus as it is believed to involve key areas supporting consciousness (Vanhaudenhuyse et al., 2010). Music's self-referential and autobiographical properties, in combination with stimulation of cognitive functions such as attention and mental imagery, may also act on these areas (Perrin et al., 2015). Previous studies with DOC populations showed that music enhanced arousal and attention when compared to white noise or disliked music (O'Kelly et al., 2013) or when compared to a control non-musical auditory stimulus (Castro et al., 2015), suggesting a potential impact of music therapy on consciousness recovery.

Research into music therapy with DOC has been limited due to the lack of behavioral measures that are sensitive to the complex needs of this population (Bradt et al., 2010; Magee and O'Kelly, 2015). For this reason, single subject designs and case reports prevail, reporting on behavioral and neurophysiological outcomes. A single case study assessed the effects of recorded music on a learned behavior through operant conditioning. Results demonstrated that music could be a motivating reward and could help when detecting signs of consciousness (Boyle and Greer, 1983; see **Figure B1**). Indeed, in another study patients had an increased cerebral response to their own name following a music condition in comparison to a control condition, suggesting that music can increase arousal and/or awareness (Castro et al., 2015; see **Figure B2**). Music stimulation activated superior temporal gyri in healthy adults ($n = 21$), minimally conscious patients ($n = 2$) and one patient in a vegetative state who recovered consciousness 4 months later, suggesting music's potential prognostic capacity in detecting conscious brain activity (Okumura et al., 2014).

Interventions using live music, typical in music therapy intervention, provide more promising data. Improvements in arousal and cognition during music therapy were noted in one study with 21 patients in DOC (O'Kelly et al., 2013). Personally salient live music resulted in significantly more eye blinks in VS patients when compared with baseline silence suggesting increased arousal. In the same study, *post-hoc* EEG amplitude increases were found for frontal midline theta and frontal alpha during the live presentation of personally salient music across both VS and MCS cohorts signaling greater cortical activity than responses to auditory stimuli of a non-salient nature (white noise and recordings of disliked music). Differential responses to live music vs. white noise indicated more intact cognitive processes suggestive of selective attention in the MCS cohort than the VS cohort where differentiation was less evident (O'Kelly et al., 2013). Another case report using standardized DOC

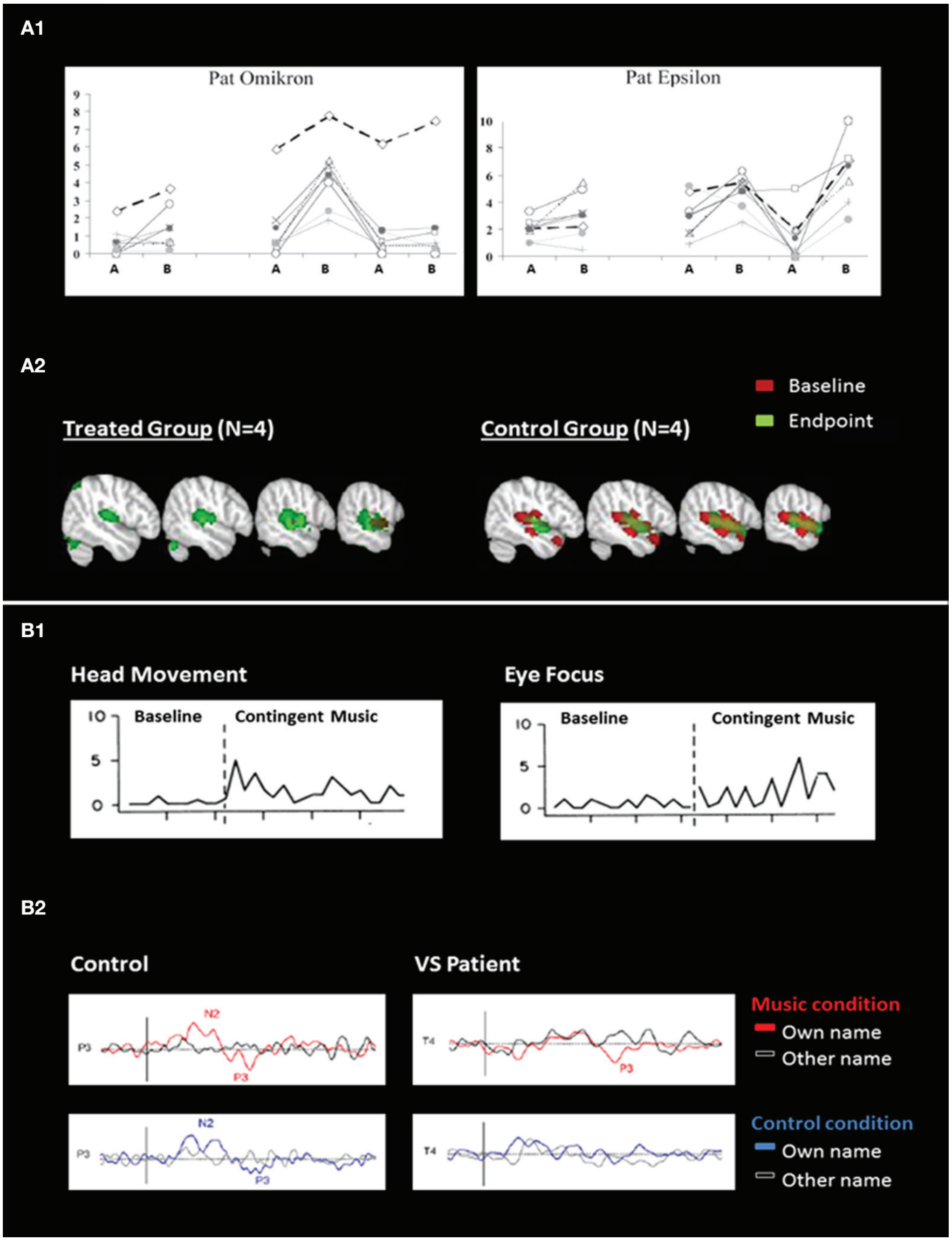

FIGURE 1 | Behavioral and neuroimaging responses to sensory stimulation (A) and music (B). (A1) Illustrates averaged behavioral scores from blinded independent raters during multimodal sensory program in two patients. The x-axis describes time (ABABAB design where *A* = baseline and *B* = treatment) and the y-axis represents the rating scores (0 = no movement, 10 = voluntary movements; adapted from Lotze et al., 2011). **(A2)** Illustrates brain activation in response to unimodal sensory (auditory) stimulation, at the baseline and at the end of the study (adapted from Pape et al., 2015). **(B1)** Illustrates behavioral responses during baseline and music stimulation for head movements and eye focus in one patient (adapted from Boyle and Greer, 1983). **(B2)** Illustrates event-related potentials in response to the subject's own name and to other names in music and control conditions, in one control subject and in one patient in a vegetative state (VS) (adapted from Castro et al., 2015).

behavioral measures compared responses in a DOC patient during neuropsychological evaluation with those measured during live music therapy interventions (Lichtensztejn et al., 2014). The results indicated that music therapy interventions at both baseline and post treatment elicited higher level responses involving behaviors demonstrating greater complexity, particularly within the auditory and language domains. These results are important in contributing to differential diagnosis in DOC patients. Music therapy interventions using live music may optimize the promising benefits that music as a stimulus in the auditory modality offers DOC patients (See **Table A1** in Appendix).

LIMITATIONS AND PERSPECTIVES

The beneficial effects of enriched environment on brain plasticity and cognitive functioning have been demonstrated by animal research. Its impact on human subjects is nevertheless much more challenging to show. The first difference is the control of the environment. Medication, changes in therapy, medical status or spontaneous recovery are among the variables the most difficult to control. Although, they are not impossible to account for, most studies examining sensory stimulation have been performed in an acute setting where those variables are in constant change. The inclusion of a chronic population would be a way to manage this bias as these patients are more stabilized. Indeed, changes in treatment or spontaneous recovery are not inexistent at a chronic stage but occur way less frequently.

The other weakness of these studies is the sample size. Most of them are case reports or descriptive case series which do not allow a generalization of the results. A longitudinal approach is useful when assessing the efficacy of treatment but such design require an important investment in time, making difficult for an isolated center to follow more than 30 cases simultaneously while finishing the study within a reasonable time-frame. A solution would be to develop an international initiative involving a significant amount of centers. This is not impossible since it has been done before for demonstrating the effect of Amantadine on the recovery of patients with severe brain injury (Giacino et al., 2012). This study was performed with the participation of 11 clinical sites and resulted in the recruitment of 184 patients which were followed during 6 weeks. The study used a randomized double-blind placebo-controlled design. Such sample size and such design represent a phase II clinical trial and allowed to establish the efficacy of the treatment.

The use of a controlled design may be more efficient when considering large samples since it requires a shorter follow-up. The use of a randomized (rather than matched) control group allows bias allocation to be minimized, balancing both known and unknown prognostic factors, in the assignment of treatments and is an optimal choice when dealing with such a heterogeneous population. Finally, one aspect that has been found useful in several preliminary studies (Castro et al., 2015; Pape et al., 2015) and should be considered in the future is the use of neuroimaging techniques (e.g., fMRI or electrophysiology; Giacino et al., 2014; Gosseries et al., 2014; Hannawi et al., 2015). Indeed, showing that treatment-related changes are observed using objective methods is essential to prove that sensory stimulation programs and music therapy are efficient in improving brain plasticity in patients with DOC.

CONCLUSION

Initiating such a big project is challenging but is crucial since effective treatment options are limited. The combination of all these scientific findings will certainly help the clinicians to treat more efficiently patients with severe brain injury.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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APPENDIX

TABLE A1 | Summary of previous studies investigating sensory stimulation program and music interventions.

Treatment	References	Sample size	Cause of injury	Time since injury	Level of consciousness	Design	Main findings after/during treatment
Sensory stimulation program	Kater, 1989	30	TBI	2 weeks	Mix (GCS 3-14)	Non randomized controlled	Better outcome at 3 months post-injury
	Mitchell et al., 1990	24	TBI	4–12 days	Mix (GCS 4–6)	Non randomized controlled	Shorter duration of coma and increase in the GCS
	Johnson et al., 1993	14	TBI	<24 h	Mix (GCS =8)	Randomized controlled	No significant changes in the GCS, brainstem reflexes or physiological measurements
	Oh and Seo, 2003	5	TBI/NTBI	<3 months	Mix (GCS 3-7)	Time-series	Increase in the GCS
	Lotze et al., 2011	8	TBI/NTBI	16–126 months	Mix (VS/MCS)	Time-series	Improvements in behavioral responses (e.g., response to command)
	Di Stefano et al., 2012	12	TBI/NTBI	> One 1 month	Mix (VS/MCS)	Time-series	Greater range of behavioral responses based on the Wessex Head Injury Matrix
	Pape et al., 2015	15	TBI	Average of 70 days	Mix (VS/MCS)	Randomized controlled	Improvements in behavioral responses based on the Coma Near Coma Scale and in brain activity based on fMRI recording. Effect size: d = 1.88.
Music interventions	Boyle and Greer, 1983	3	TBI/NTBI	6–38 months	Mix (VS/MCS)	Operant conditioning	Changes in behavioral responses
	O'Kelly et al., 2013	21	TBI/NTBI	2–14 months	Mix (VS/MCS)	Multiple baseline within-subjects with randomized treatment order	Significant increases in blink rate to liked music in VS cohort; significant post hoc EEG amplitude in frontal midline theta and alpha for liked music in both VS and MCS cohorts
	Lichtensztejn et al., 2014	1	TBI	32 months	Mix (VS/MCS)	Case study	Changes in behavioral (including musical) responses
	Okumura et al., 2014	7	NTBI	12–72 months	Mix (VS/MCS)	Cross-sectional	Based on fMRI recording, activation of the superior temporal gyri to music in all MCS patients and in one of five VS patients who recovered consciousness 4 months later.
	Castro et al., 2015	13	TBI/NTBI	20 days to 3 years	Mix (VS/MCS)	Cross-sectional	Better cerebral (electrophysiological) responses in response to music and related to the outcome at 6 months

TBI, Traumatic Brain Injury; NTBI, Non-Traumatic Brain Injury; GCS, Glasgow Coma Scale; VS, Vegetative State; MCS, Minimally Conscious State; fMRI, functional Magnetic Resonance Imaging; EEG, Electroencephalogram.

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REVIEW
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Promoting the use of personally relevant stimuli for investigating patients with disorders of consciousness

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Sensory stimuli are used to evaluate and to restore cognitive functions and consciousness in patients with a disorder of consciousness (DOC) following a severe brain injury. Although sophisticated protocols can help assessing higher order cognitive functions and awareness, one major drawback is their lack of sensitivity. The aim of the present review is to show that stimulus selection is crucial for an accurate evaluation of the state of patients with disorders of consciousness as it determines the levels of processing that the patient can have with stimulation from his/her environment. The probability to observe a behavioral response or a cerebral response is increased when her/his personal history and/or her/his personal preferences are taken into account. We show that personally relevant stimuli (i.e., with emotional, autobiographical, or self-related characteristics) are associated with clearer signs of perception than are irrelevant stimuli in patients with DOC. Among personally relevant stimuli, music appears to be a promising clinical tool as it boosts perception and cognition in patients with DOC and could also serve as a prognostic tool. We suggest that the effect of music on cerebral processes in patients might reflect the music's capacity to act both on the external and internal neural networks supporting consciousness.

Keywords: disorders of consciousness, music, autobiographical memory, self-processing, internal and external networks, vegetative state, minimally conscious state, coma

Using Stimulation to Evaluate and Restore Cognitive Functions and Awareness in Disorder of Consciousness (DOC) Patients

Survivors of severe brain injury generally transit through different states of decrease or loss of awareness (both of their environment and of their self), named coma, vegetative state (VS) –or unresponsive wakefulness syndrome (UWS)– and minimally conscious state (MCS). Evaluating cognition, probing consciousness, and predicting recovery are critical clinical issues. Currently, repeated behavioral clinical examination provides the main approach to establish diagnosis in clinical practice. However, these behaviors are often fluctuating and their detection can be unreliable. Indeed, some studies have observed that up to 40% of MCS patients are erroneously diagnosed as vegetative by non-expert teams, this being explained by arousal fluctuation, motor disabilities, poor expertise in behavioral assessment, or the use of insensitive behavioral assessment scales (e.g., Schnakers et al., 2006). One additional important issue concerns the difficulty of the correct recognition of affective behaviors that is part of the definition of MCS (Giacino et al., 2002). Indeed, the detection of subtle, but potentially meaningful affective behaviors remains difficult and hard to differentiate from purely automatic responses. Moreover, a part of subjectivity and interpretation of behavioral responses is often difficult to avoid because of facing dramatic situations and family expectations. As misdiagnosis has consequences on treatment and end-of-life decisions, developing additional methods in order to improve the detection of signs of consciousness is therefore crucial.

Over the last 20 years, neurophysiological studies have been developed, both at rest or using sensory stimulations, to better evaluate the preserved cerebral functions in patients with disorders of consciousness (DOC). General brain network organization has been explored using functional connectivity analyses at rest, i.e., when patients are not perceptively solicited. This allows evaluating spontaneous brain activity, including networks that probably serve basic functions related to consciousness (Boly et al., 2008). Indeed, this method helps understanding whether information processing can be locally amplified and distributed on a long-distance, whole-brain scale (e.g., Tononi et al., 1994), with the latter one being probably a prerequisite for conscious access (Dehaene and Naccache, 2001). Using resting state functional magnetic resonance imaging connectivity analyses, it has been shown that the default mode network connectivity was negatively correlated with the degree of clinical consciousness impairment, ranging from MCS patients over VS patients to coma patients (Vanhaudenhuyse et al., 2010; Stender et al., 2014). Using ^{15}O-radiolabeled water PET measurements of regional cerebral blood flow performed at rest, Silva et al. (2010) have also identified an impaired functional connectivity between the ascending reticular activating system and the precuneus during persistent VS.

Most frequently, evaluations rest on sensory stimulations. In this case, specific cerebral activations are investigated, from sensory detection to higher order cognitive processes, sometimes also including stimulus awareness. Most importantly, these neurophysiological studies have shown that patients with little or no behavioral evidence of conscious awareness may retain critical cognitive capacities (for a review, see for example Laureys and Schiff, 2012). For example, the primary and secondary auditory cortices are often activated by auditory stimuli in DOC patients. It has also been shown that an acoustically deviant stimulus (such as an infrequent high pitch tone compared to frequent low pitch tones) can evoke an early event-related potential (ERP) referred to as MisMatch Negativity (MMN), thus demonstrating that an automatic echoic memory can still be preserved in these patients (e.g., Fischer et al., 2010). Interestingly, the presence of the MMN is a predictor of awakening and precludes comatose patients from moving to a permanent VS (Fischer et al., 2004). Furthermore, the preservation of linguistic functions has been also investigated. While ERP studies showed that the cerebral signatures to the detection of incongruous speech, i.e., the N400 potential, is still observed in some VS and MCS patients (Schoenle and Witzke, 2004; Kotchoubey et al., 2005; Rämä et al., 2010; Steppacher et al., 2013), fMRI studies suggested that the cortical structures associated to speech processing (notably the temporal lobe) are also activated in these patients (Schiff et al., 2005; Coleman et al., 2007; Fernández-Espejo et al., 2008).

More recently, active paradigms (i.e., paradigms in which patients are asked to follow the researcher's instructions) have been developed to investigate the preservation of the patient's voluntary brain functions. A new MMN paradigm has been developed to test the ability to actively maintain mental representations in working memory and to use these informations strategically, by measuring cerebral responses to violations of local or global temporal regularities (Bekinschtein et al., 2009). Faugeras et al. (2011) have shown that two patients who developed the neural signature of long-term violation detection showed unequivocal clinical signs of consciousness within the 3–4 days following the ERP recording. In another active paradigm, Schnakers et al. (2008) have evaluated the ability for DOC patients to count their own first name. They showed that the P300 potential, which indicates that the individual discriminates her/his own name (Perrin et al., 1999), was greater in an active condition than in a passive condition (i.e., without any instruction to count) in both controls and MCS patients. This finding suggests that MCS patients can direct active attention to an auditory target when asked to follow instructions. Finally, a neuroimaging study has also shown that a presumably VS patient was still able to understand and follow verbal instructions, such as "imagine you are walking around in your house" or "imagine you are playing tennis," although clinical evaluation failed to detect her as conscious (Owen et al., 2006). However, the number of VS patients who could actually pass that test was extremely low: in a more recent study testing 54 DOC patients with this paradigm, only five patients were able to perform both mental activities on request and only one patient was able to associate these activities with a yes-or-no response and communicate with the researchers (Monti et al., 2010). Thus, although the achievement of this kind of sustained mental imagery tasks offers a specific criterion to detect patients that are conscious and highly functioning, one major drawback of this criterion is its lack of sensitivity. These tests cannot detect patients who are in the process of recovering awareness, but who are unable to understand complex verbal commands and/or to produce the mental effort required by sustained mental imagery tasks.

In addition to its use in evaluating the patient's state and diagnosis, sensory stimulation has been also proposed as an intervention strategy to enhance the patient's engagement with the immediate environment and to increase her/his consciousness level (Canedo et al., 2002). The background tenets for supporting stimulation initiatives include (a) the general fear that sensory deprivation connected with the virtual isolation of the person after severe brain injury may have additional negative effects on her/his condition (Oleson and Zubek, 1970) and (b) the view that the plasticity of the central nervous system could definitely benefit from a rich stimulation regimen (Canedo et al., 2002; Lombardi et al., 2002; Elliott and Walker, 2005). The use of sensory stimulation for DOC patients has gained popularity during the 1980s, but beliefs and opinions about its effectiveness vary substantially among health professionals. Canedo et al. (2002) and Bekinschtein et al. (2005) tested the effect of multisensory stimulation (auditory, visual, tactile, gustatory, and olfactory stimulation) on DOC patients. They both showed clear progress for the patients with consistent responses to stimulations and progressively the ability to respond to yes/no questions. Di Stefano et al. (2012) have also used multisensory stimulation and showed that familiar stimuli elicited a greater range of behavioral responses. However, other studies could not bring reliable evidence to support beneficial effects of multisensory stimulation (for reviews, see Formisano et al., 2001; Lombardi et al., 2002; Rigaux and Kiefer, 2003; Lancioni et al., 2010). Sensory stimulation approaches are thus still controversial, notably because of the absence of control conditions and/or statistical analyses, but also because the fatigability of these particular patients is not considered (Wood et al., 1992). In clinical practice, sensory regulation approaches are preferred over these sensory stimulation programs, that are programs in which salient and significant stimuli are delivered, but in which resting periods are also required.

Personalized Stimuli Enhance the Probability to Observe a Response in DOC Patients

Most of the clinical tests are standardized protocols in which well-controlled stimuli (such as pure tones) are used. While neutral stimuli facilitate comparisons between patients' data, they might also be associated with a high number of false negatives because they cannot personally engage patients with disorders of consciousness. In line with this hypothesis, it has been shown that, in contrast to neutral stimuli, personalized stimuli enhance the probability to observe a cerebral response in DOC patients.

Familiarity has been frequently used to capture the patient's attention and to evoke an emotional reaction. For example, Bekinschtein et al. (2004) have shown, in one MCS patient, an extended brain activation of the emotional network (amygdala, insula, inferior frontal gyrus) in response to his mother's voice reading a story, as compared to a non-familiar voice. Similarly, familiar faces (but not unfamiliar faces) succeed in eliciting activations in face-selective brain areas (with further limbic and cortical activations) in VS patients (Sharon et al., 2013). Personal significance also increases the probability to observe a brain response in DOC patients. Enhanced cognitive responses evoked by emotional and salient (personal) stimuli were first demonstrated with ERP methodology (for a review, see Perrin, 2004). While the P300 component to rare tones is observed only in a few patients (Harris and Hall, 1990; Yingling et al., 1990; Gott et al., 1991; Rappaport et al., 1991; De Giorgio et al., 1993; Glass et al., 1998), its probability of occurrence is enhanced with relevant and meaningful stimuli. Indeed, Signorino et al. (1997) have shown that the P300 to tones is more frequently observed when a short phrase spoken by a member of the family is presented simultaneously. Similarly, the P300 response is enhanced and can be analyzed, even on an individual level, when the deviant stimulus is not a tone stimulus but the patient's own name. Perrin et al. (2006) have shown that, when the subject's own name (SON) is presented in series of equiprobable unfamiliar first names, the P300 can be observed in all MCS patients, and in certain VS patients (see also the studies of Mazzini et al., 2001; Fischer et al., 2008; Höller et al., 2011; Risetti et al., 2013 in which the SON is used as a novel stimulus). As compared to the P300 to rare tones, the P300 to the SON is elicited more frequently (Cavinato et al., 2011). This is in agreement with behavioral assessments in which patients show more localization to the SON as compared to neutral sound (Cheng et al., 2013), and with fMRI studies in which a widespread activation in the temporal structures was observed for meaningful sounds (infant cries and SON) as compared to meaningless noise stimuli (Laureys et al., 2004).

The cerebral response following the presentation of the SON has been interpreted, in both healthy participants and DOC patients, as an index of a discriminative processing to a very salient and emotional word (Perrin et al., 1999, 2006) and might be associated to the enhancement of both top–down attentional and/or arousal mechanisms (for a review see Chennu and Bekinschtein, 2012), as well as of self-processing (Laureys et al., 2007). These functional hypotheses are supported by neuroimaging studies in which it has been shown that SON processing is associated, in controls and DOC patients, with regional cerebral blood flow changes in the superior temporal gyrus and in the medial (both in frontal and parietal) cortical structures (Laureys et al., 2004; Perrin et al., 2005; Northoff et al., 2006; Staffen et al., 2006; Di et al., 2007; Qin et al., 2010; Crone et al., 2013; Huang et al., 2014; Nicholas et al., 2014).

Music Evokes Attention, Emotion, Autobiographical, and Self-Processing in Healthy Subjects

One of the most emotional and salient stimulus of our environment is probably music. Neuroimaging studies have shown that music listening activates a vast bilateral network related to attention, semantic processing, memory, and the sensori-motor system (for a review, see for example Zatorre, 2013), but also to emotion. Indeed, the entire limbic/paralimbic system, including the amygdala, the hippocampus, the parahippocampal gyrus, the nucleus accumbens, the ventral tegmental area, the anterior cingulate, and the orbitofrontal cortex have been shown to be activated when listening to music (for a review, Koelsch, 2010). Music also evokes autobiographical memories (e.g., Janata et al., 2007). Indeed, neuroimaging studies suggest that the dorsal medial prefrontal cortex (MPFC) plays a central role when we experience episodic memories that are triggered by familiar songs from our personal past. MPFC (as part of an internal network) might act in concert with more lateral brain structures, such as the lateral prefrontal and posterior cortices (as part of an external network) both in terms of overall responsiveness to familiar and autobiographically salient songs and tonality tracking and musical structure processing (Janata, 2009a).

Autobiographical memory is recognized as being multifaceted, containing a body of general knowledge (shared with other individuals), as well as unique experiences specific to an individual, which have been accumulated since childhood, and which allow ourselves to construct a feeling of identity and continuity (Conway and Pleydell-Pearce, 2000; Piolino et al., 2009). Tulving's (1993) conception of memory emphasizes the episodic aspects of the self, defending the role of a phenomenological self in the construction and maintenance of subjective continuity in time and personal identity. Constructing autobiographical memories involves search, monitoring, and self-referential processes that are associated with activations in different regions in the prefrontal cortex (Cabeza and St Jacques, 2007). This is accordance with studies investigating music perception and emotion; these studies reported that the amount of activation in the MPFC depends on the likelihood of experiencing a chill while listening to self-selected music (Blood and Zatorre, 2001; Janata, 2009a).

Music perception thus requires complex processing, including numerous cognitive functions, some of them being specific to music, and others being shared with other materials or functions (Zatorre, 2005). Consequently, it has been proposed that music listening can convey beneficial effects on cognitive processes (e.g., Schellenberg, 2006; Thaut, 2010). For example, it has been shown that listening to music daily over a 2-month period leads to an enhancement of cognitive recovery (memory, attention, language) and mood, as well as long-term plastic changes in early sensory processing (as indexed by the MMN), after cerebral artery stroke (Särkämö et al., 2008). An enhancement of visual attention has been also described in patients with visual neglect when the tasks are performed while listening to preferred music relative to unpreferred music (Soto et al., 2009). Listening to a short musical excerpt improves subsequent linguistic syntax processing in patients with basal ganglia lesions (Kotz et al., 2005), patients with Parkinson disease (Kotz and Gunter, 2015) as well as in patients with developmental language disorders (Przybylski et al., 2013). Recently, it has been shown for conscious patients from intensive care units that music exposure resulted in greater reduction of sedation frequency, in comparison to usual care or noise-canceling conditions (Chlan et al., 2013). The beneficial effects of music have been attributed to the stimulation and recovery of cerebral networks required for the processing of different information (e.g., music and language), but also to the emotional characteristics of music, which are able to increase arousal (Thompson et al., 2001) and to activate the reward system (Salimpoor et al., 2011).

Music Boosts Cognition in DOC Patients

From the research reviewed here above (but see also Bigand et al., 2015), music appears to be one of the best candidates to stimulate cerebral processes in DOC patients. This particular stimulus could engage patients and helps them to reach a higher level of cognition.

In DOC patients, music has been mostly used in therapy up to now. Formisano et al. (2001) have used active music therapy in 34 severe brain-injured patients. This music therapy approach consisted in activities related to musical improvisation between the patient and the therapist by singing or by playing different musical instruments, according to the vital functions, the neurological conditions and the motor abilities of the patients. Formisano et al. (2001) showed an improvement of the collaboration capacity of the patients and a reduction of undesired behaviors, such as inertia (reduced psychomotor initiative) or psychomotor agitation. Magee (2005, 2007) reported an increased participation of a VS patient following exposure to live music and to familiar songs, changing the diagnosis to MCS. Similar effects have been also described in other behavioral single-case studies (e.g., Bower et al., 2013). However, it is difficult to draw firm conclusions from these studies as they did not use quantified measures and were missing control conditions/groups (for a review, see Lancioni et al., 2010). Recently, the beneficial effect of music has been started to be investigated in more experimental approaches for DOC patients. For example, the effect of preferred music on performance to the Coma Recovery Scale-Revised (CRS-R) was compared to that of a control condition using a noise stimulus (a meaningless, non-aversive, acoustically matched sound stimulus) in six MCS patients (Verger et al., 2014). Qualitative and quantitative analyses showed in 66.6% of the assessments a better result for the music condition than for the control condition. Thus, this study suggests that preferred music, as compared to the control condition, has a beneficial effect on the cognitive abilities of MCS patients.

The effect of music therapy on physiological parameters has been also explored in DOC patients. Lee et al. (2011) have observed in a VS patient the enhancement of the cardiovascular activity following 14-day stimulation with a musical stimulus (i.e., Mahler's Second Symphony). Autonomic changes with possible emotional value were also observed in both healthy controls and six VS patients while they passively listened to music samples (Riganello et al., 2010). Finally, alterations in oxygen saturation, breathing frequency and facial expression were found following preferred music in 30 DOC patients (Puggina et al., 2011).

Up to now, only few studies have used neurophysiological methodologies to assess the effect of music on DOC patients' cerebral responses. Using power spectra analyses, O'Kelly et al. (2013) have shown an increased EEG amplitude in alpha and theta bands when listening to the patients' preferred music in six VS and four MCS patients (see also Aldridge et al., 1990). To investigate auditory perception of comatose and post-comatose patients, Jones et al. (2000) measured the MMN responses following tones that were either played with complex synthesized instrumental timbres or with simple pure tones (Jones et al., 2000). It has been shown that the harmonically richer musical tones elicited an MMN more frequently and with larger amplitude than did the simple sine wave tones (Kotchoubey et al., 2003). Very recently, Castro et al. (2015) have demonstrated that music boosts cognition in comatose and post-comatose patients. In this study, the patient's names were presented after either an excerpt of the patient's preferred music (music condition) or a meaningless noise stimulus (control condition). Seven of the 13 patients showed a significant discriminative ERP (N200 and/or P300) to the patient's own name, whereas, in the control condition, only one patient showed this response. Furthermore, the results showed that the presence/absence of the cerebral response was associated with, respectively, good/bad outcomes.

Recently, two neuroimaging studies have also explored the effect of music on the brain functioning of DOC patients. Okumura et al. (2014) showed that a famous, generally well-known music, which should thus probably be also familiar to the patient ('Les Toreador' from 'Carmen' Suite No. 1 by Bizet) activated the bilateral superior temporal gyri in 2/2 MCS and 1/5 VS patients. Interestingly, although DOC patients generally lose long-range functional connections, listening to music elicits increased functional connectivity, as compared to a noise condition, in regions belonging to the auditory network (see Heine et al., personal communication).

The Effect of Music on Consciousness

The beneficial effects of music on cognitive functions of patients with DOC might be explained by an overall cortical arousal and/or an awareness enhancement. This is in agreement with "the arousal and mood hypothesis," suggesting that the effect of music listening on cognitive abilities can be attributed to changes in listeners' arousal and mood (Nantais and Schellenberg, 1999). The beneficial effects of music might be also associated to its "engagement" properties. Indeed, two types of brain networks interact when listening the music (Janata, 2009b). An external network and an internal network. The network for external engagement is generally associated with cognitive functions of language processing (including semantics), working memory, mental imagery, attention, etc. (for a review, see Cabeza and Nyberg, 2000). This network could be conceptualized as the perception/action cycle that implies the lateral posterior part of the brain in sensation and perception and the lateral anterior part in action (Fuster, 2009). The network for internal engagement is anticorrelated to the previous one (when one is activated, the other is generally deactivated) and encompasses mainly medial brain areas (Vanhaudenhuyse et al., 2011). It is engaged in various forms of self-referential (Wicker et al., 2003; Northoff et al., 2006) and autobiographical re-experiencing processes (Cabeza and St Jacques, 2007), which both support the "default-mode" hypothesis (Raichle et al., 2001). In summary, the internal network would be associated to awareness of the self, while the external network would be involved in awareness of environment (Vanhaudenhuyse et al., 2011). Both networks would be particularly coupled in listening to familiar or preferred music (for a review, see Janata, 2009b). This proposal of internal and external engagement when listening to music can be connected to the proposal of internal and external networks related to consciousness, providing a hypothesis for the neural basis of the beneficial effects of music in DOC patients. The connectivity within an external fronto-parietal network (i.e., between primary cortices and "higher-order" associative cortices), as well as the connectivity inside the nodes of an internal network (precuneus/posterior cingulate, mesas-frontal/anterior cingulate, and temporo-parietal cortices), has been shown to have a correlation that is decreasing with an increasing level of consciousness (Laureys and Schiff, 2012). Thus, it could be suggested that the effect of music on cerebral processes in DOC patients might reflect the music's capacity to act on these two major networks supporting consciousness.

Conclusion and Clinical Perspectives

This review strongly suggests that personally relevant stimuli are associated with enhanced behavioral responses and/or cerebral responses indicating perception in DOC patients, as compared to irrelevant or neutral stimuli. Preferred music appears to be a promising clinical tool, as it seems boosting some cognitive processes and/or awareness in patients with DOC, and could further serve as a prognostic tool as well. Future studies should identify what kind of cognitive and/or conscious processes could be enhanced following the presentation of preferred music, for example whether attention and awareness could be boosted in active paradigms or whether word processing be enhanced also for common names (as observed for the SON). Future studies should also disentangle a general effect of music (because of its acoustic and structural features) from its autobiographical effects (because of its emotional and meaningful contents in relation to the patients' personal memory). The beneficial effects of the preferred music could be indeed due to its sound complexity (rhythm, melody, tempo, syntactic-like structural organization, etc.), as well as to familiarity, emotional, episodic/autobiographical, and self-related features. For example, it would be interesting to contrast familiar and unfamiliar music or to compare the effect of preferred music with either fast or slow tempo, as previous studies have shown that these features can modulate cognition (e.g., Gomez and Danuser, 2007; Nombela et al., 2013; Tillmann et al., 2014).

The challenge is also to incorporate personally relevant stimuli into standardized assessments that will be comparable across patients. This issue appears even more critical as one of the current diagnostic criteria for MCS is the detection of "affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity" (Giacino et al., 2002). Although this criterion is used to define MCS, the assessment of affective behavior is poorly addressed (in the supplementary items) by the CRS-R that is the current gold standard clinical scale. Moreover, the method to assess this very important criterion is based on the observation or the reports from family and clinician of affective behaviors like smiling, laughing, frowning, crying that occur spontaneously or in response to a specific stimulus. The incorporation of personally relevant stimuli in clinical practice is difficult, but it could be done with success: indeed, more and more hospitals now use SON protocols even though they request a personalized voice recording. For music, one perspective for future development would be to test whether similar effects could be obtained with familiar music (and not only with personally preferred music). If it is the case, then one could imagine developing (for a given country or culture) a set of musical pieces (selected per age group) that could be used to stimulate cognition in DOC patients before the behavioral or the neurophysiological assessments.

Finally, this review also point to a potential role of music in rehabilitation, i.e., for a long-term effect of music on cognition and consciousness in patients with DOC. It is not possible to assert that the presentation of the music was responsible for a long-term increase of the level of arousal and awareness, but it has been previously shown that music can induce long-term cognitive improvement. For example, for patients after cerebral stroke, listening to music daily during a 2-month period has improved significantly verbal memory and focused attention 6 months after (Särkämö et al., 2008, 2010). Furthermore, it has been previously demonstrated that listening music after neural damage can induce long-term plastic changes in early sensory processing, which, in turn, may facilitate the recovery of higher cognitive functions (Särkämö et al., 2010). Thus, these data encourage testing in future research the potential long-term role of music listening on cerebral plasticity in DOC patients.

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Music in the Treatment of Children and Youth with Prolonged Disorders of Consciousness

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INTRODUCTION TO THE POPULATION

Children and youth with disorders of consciousness (DOC) are defined as those under 18 years of age who show wakefulness, but with absent or reduced awareness. This condition is considered to be prolonged when this state lasts for longer than four weeks. Hence, the term prolonged disorders of consciousness (PDOC) (Royal College of Physicians, 2013). Children and youth with DOC need care that can meet their highly complex needs. This care includes careful stimulation to elicit purposeful responses in assessment and evaluation, and managing an individual's environment optimally to meet their sensory needs. Accuracy in determining awareness is paramount due to several factors. First, ethical issues surround the provision of appropriate care (Ashwal, 2013) regarding the design and use of the type of sensory stimulation and the intensity of the intervention. Second, admission to rehabilitation programmes is affected by accurate diagnosis (Eilander et al., 2005), as this would ensure that those who could benefit are not excluded from admission to these programmes. Third, end-of-life decisions are critically dependent upon correct diagnosis (Ashwal and Cranford, 2002), when clinicians, families, and the legal system consider continuation or withdrawal of intervention in the light of the patients' pain and suffering and their prognosis for recovery.

Although guidance for working with adults with PDOC is available (Royal College of Physicians, 2013), there are no specific clinical guidelines for working with children and youth with PDOC. Recovery following brain injury in adults is better understood than in pediatric populations (Anderson and Yeates, 2010; Ponsford, 2013). This has resulted in theories about recovery of consciousness being based on adult brains, despite neurodevelopmental differences between child, and adult brains (Ashwal and Cranford, 2002; Perner and Dienes, 2003), particularly within the frontal lobes (Nicholas et al., 2014). This poses several problems for clinicians. Evaluation and treatment guidelines for rehabilitation with pediatric PDOC are adapted from those used with adults. However, guidance on adaptation is limited and dependent on clinicians' specialist knowledge, which is likely to be highly variable. The dearth of knowledge regarding neurological recovery from PDOC in childhood positions some theorists to argue that the immature brain is less susceptible to damage due to its plasticity, whereas others propose that the developing brain is more vulnerable to injury (Bower and Shoemark, 2012). Hence, more must be understood about recovery from brain injury in the pediatric population.

SENSORY STIMULATION WITH PEDIATRIC DOC

Sensory stimulation activates affected neural networks, maximizing the potential for neural reorganization through brain plasticity (Di and Schnakers, 2012; Pham et al., 2014). Sensory stimulation programs provide enriched environments that optimize stimulation to encourage experience-dependent changes to the brain at neuroanatomical and biochemical levels (Renner and Rosenzweig, 1987; Nithianantharajah and Hannan, 2006; Schreiber et al., 2014). When working with children and youth with PDOC, developmental factors must be considered. These include pre-morbid neurological development that influences the acquisition of fundamental skills in motor functioning and cognitive functioning, for example attention, memory, choice-making, and command-following capabilities. There are also significant differences in comprehension and expressive language development across ages, and these have important implications for the presentation of verbal and written commands as well as expectations of the patient's vocalizations. Educational level may also be important to consider when working with children and youth with PDOC, as this can also influence cognitive functioning and language development. Neurological changes related to emotional development and the importance of attachment at different stages must also be considered. The presence of parents can have a significant impact on children's anxiety and emotional states, and children with PDOC have been known to respond more effectively to parental voice above other voices (Machado et al., 2007). A final point to consider is that life/cultural experiences may have influenced the memories and templates that have been stored at earlier stages of development. So, specific life or cultural experiences could provide useful sources of stimuli for assessment and treatment of children and young people with PDOC. The developmental factors described above should inform clinical decisions about the stimuli used to elicit responsiveness and methods of presentation (Amari et al., 2012). A child's developing sensory processing system might demand the use of stimulation that raises arousal sufficiently but does not overwhelm the sensory or cognitive systems that process this information. A number of studies have discussed the use of music as a sensory stimulus with children with DOC. The suggested benefits include the provision of enriched environments through increasing arousal and maximizing the patients' potential to respond through supporting opportunities for fundamental interpersonal interaction (Bower et al., 2014). Researchers have postulated that the use of familiar songs in music therapy intervention compared with unfamiliar songs reduces agitation and cognitive load on the patients by increasing organization and orientation. This is supported by other research that suggests that familiar songs may reduce agitation and enhance orientation in adults suffering from post-traumatic amnesia (Baker, 2001). Presented live (rather than in recorded format), the use of familiar songs provides opportunities and invitations for interaction and development of social integration (Bower and Shoemark, 2012).

The loudness, number of instruments/voices, mood, tempo, and rhythmic complexity, and the meaning/familiarity of the music to the patient might all be key factors in providing optimal stimulation. Music, as a stimulus, can be manipulated using fine changes across wide ranges in intensity, complexity, and other musical parameters. As pre-linguistic children are biologically predisposed to attend to the musical elements of speech prosody, such as melodic contour and rhythmic patterning, these elements can be emphasized in musical interactions with the non-verbal typically developing or brain-injured child (Bower and Shoemark, 2012). Despite these promising factors, there have been no studies to date examining the effectiveness of music as a therapeutic intervention with children and youth with PDOC.

MUSIC AND PDOC POPULATIONS

Music can be particularly salient as a stimulus depending on the patient's exposure to music. The factors of saliency (Magee and O'Kelly, 2015) and familiarity (van den Bosch et al., 2013) position music as an ideal stimulus for attaining optimum arousal (O'Kelly et al., 2013) and eliciting awareness (Rosenfeld and Dun, 1999) in children and youth with PDOC. Recent guidelines advise that evaluative stimulation used with patients with PDOC should maximize stimuli that are familiar to the patient, highlighting the use of the patient's favorite music (Royal College of Physicians, 2013). One study comparing auditory conditions with varying levels of saliency showed that music with known saliency improved arousal and attention in vegetative state (VS) patients and revealed indications of improved discriminative attention in minimally conscious patients (MCS) (O'Kelly et al., 2013). This study examined physiological and electroencephalography (EEG) responses in patient and healthy cohorts during five auditory conditions: silence, patient-preferred salient music, improvised music entrained to the subject's breathing, patient disliked music, and white noise. The findings suggest that patient responsiveness to different musical conditions is comparable to responsiveness in healthy subjects: both patient and healthy cohorts show a range of significant responses corresponding to arousal and attention during preferred music i.e., music with personal saliency. Healthy responses included globally enhanced EEG power spectra across frequency bandwidths with distinct discriminatory responses across the frontal and temporal regions. During exposure to patient preferred music, frontal alpha frequencies peaked in the MCS patient cohort, and frontal midline theta increased during the preferred musical condition for VS and MCS cohorts. Familiarity is a key factor in inducing emotional responses: Pereira et al. (2011) found that familiar music triggered greater emotion-related brain activity than music that was "liked" but not necessarily "familiar."

These findings reflect research with other adult neurologically impaired populations such as dementia, Alzheimer's and stroke, where music was shown to improve attention and memory functioning (Särkämö et al., 2013; Baird and Samson, 2014). These two cognitive processes are targeted when assessing and treating people with PDOC. The evidence regarding the use of salient stimuli with people with PDOC supports the notion that memory systems are activated in people with PDOC. However, less is known about the effects of music therapy with children with PDOC. This lack of research is surprising given music's role in healthy development (Trehub, 2005) as well as its widespread use in therapy and education for youth with developmental challenges.

A detailed understanding of the neural effects of music on children and youth with PDOC is lacking due to the cost and technical difficulties in conducting imaging studies with these patients (Ashwal, 2013). Therefore, some assumptions must be made drawing from knowledge about music with non-brain damaged populations. Music is used as a meaningful stimulus with children with normal development to activate emotional responses, to prime cognitive responses, and to facilitate cross-modal learning (Trehub, 2005; Miendlarzewska and Trost, 2013). It recruits neural activity from the early stages of development. Behavioral, physiological, and neural responses to music and vibroacoustic stimuli have been reported in utero, in premature infant and in neonate populations (Shetler, 1990; Woodward et al., 1992; Panthuraamphorn, 1993). Music has also been shown to activate memory function in newborns through recognition tests of familiar music following a two-week delay (Ilari and Polka, 2006). The ubiquitous use of music in human development implies an innate salience to music as a principal activating stimulus and suggests that it has strong ecological validity as a tool for stimulating developing brains. Observations of parent-infant interactions are described in terms of their musical qualities (Stern, 2000). The musical structure of the caregiver's responses supports the development of the infant's brain within this relationship, underpinning later development, and epigenetic expression. There is historical use of musical structure to encode, store, and recall narratives and lessons to pass between generations within social groups (Blacking, 1974). Educators use music and song to aid learning in the classroom in mainstream and specialist schools (Ockelford, 2010), as music can influence learning (Gold et al., 2013). Music is perhaps such a powerful tool for eliciting responses in humans due to its ability to arouse emotions (Blood and Zatorre, 2001) and communicate immediate feeling states from our earliest days of infancy (Malloch and Trevarthen, 2009).

Neurological theories about the nature of consciousness, i.e., theories from anesthesia studies, suggest that consciousness is the complex combination of neural activity in multiple brain areas with the interaction between these brain areas (Vanhaudenhuyse et al., 2011; Di Perri et al., 2014). Musical experience recruits multiple parts of the brain (Bower and Shoemark, 2012; Särkämö et al., 2013) suggesting that it is perhaps an ideal stimulus for maximizing recovery from PDOC. In recent studies researchers have gathered evidence to hypothesize that the pleasure from musical experience is derived from the complex interaction between brain areas known to be involved in cognitive and affective processing (Salimpoor et al., 2013; Zatorre and Salimpoor, 2013). Perhaps music is highly suited to working with both adult and pediatric PDOC patients because of this phenomenon, i.e., that it activates areas of the brain involved in cognitive and emotional processing and that it fosters the interaction between them.

FUTURE DIRECTIONS

Given its utility in the context of typical development, using music with children with PDOC may be appropriate for a number of reasons. The auditory modality has been established as the most sensitive for diagnosing awareness in adults in vegetative state (Gill-Thwaites and Munday, 1999). The prevalence of visual impairment in pediatric PDOC populations (Huo et al., 1999) suggests that auditory stimulation may be more appropriate in assessment and intervention. Musical stimulation, therefore, has the potential to meet a child's developmental needs and match his/her abilities regardless of language development, sensory impairment, or communication disorder stemming from profound damage. Music provides a powerful tool that is well suited to the needs of children with PDOC for sensory stimulation. It can be individually tailored and offers a powerful stimulus for maximizing the patient's potential to respond (Bower et al., 2014). Music therapy has been shown to provide some degree of benefit in improving consciousness (Meyer et al., 2010). However, the paucity of clinical research warrants further empirical inquiry in order to develop an evidence base for using music as a stimulus in assessment and intervention with pediatric PDOC.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Feasibility of the music therapy assessment tool for awareness in disorders of consciousness (MATADOC) for use with pediatric populations

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Measuring responsiveness to gain accurate diagnosis in populations with disorders of consciousness (DOC) is of central concern because these patients have such complex clinical presentations. Due to the uncertainty of accuracy for both behavioral and neurophysiological measures in DOC, combined assessment approaches are recommended. A number of standardized behavioral measures can be used with adults with DOC with minor to moderate reservations relating to the measures' psychometric properties and clinical applicability. However, no measures have been standardized for use with pediatric DOC populations. When adapting adult measures for children, confounding factors include developmental considerations for language-based items included in all DOC measures. Given the lack of pediatric DOC measures, there is a pressing need for measures that are sensitive to the complex clinical presentations typical of DOC and that can accommodate the developmental levels of pediatric populations. The music therapy assessment tool for awareness in disorders of consciousness (MATADOC) is a music-based measure that has been standardized for adults with DOC. Given its emphasis on non-language based sensory stimuli, it is well-suited to pediatric populations spanning developmental stages. In a pre-pilot exploratory study, we examined the clinical utility of this measure and explored trends for test-retest and inter-rater agreement as well as its performance against external reference standards. In several cases, MATADOC items in the visual and auditory domains produced outcomes suggestive of higher level functioning when compared to outcomes provided by other DOC measures. Preliminary findings suggest that the MATADOC provides a useful protocol and measure for behavioral assessment and clinical treatment planning with pediatric DOC. Further research with a larger sample is warranted to test a version of the MATADOC that is refined to meet developmental needs of pediatric DOC populations.

Keywords: pediatric, disorders of consciousness, brain injury, child, music therapy, assessment, measure, awareness

Introduction

Disorders of consciousness (DOC) refer to a compromised level of awareness of self and the environment, which manifests as coma, vegetative state (VS), or minimally conscious state (MCS). Consciousness is comprised of the dual dimensions of wakefulness and awareness (The Multi-Society Task Force on PVS, 1994), both of which are lacking in a coma state. Individuals who achieve wakefulness, but continue to lack awareness may be considered to be in a VS, "a clinical condition of complete unawareness of the self and the environment, accompanied by sleep–wake cycles with either complete or partial preservation of hypothalamic and brain-stem autonomic functions" (The Multi-Society Task Force on PVS, 1994, p. 1500). The nomenclature 'VS' remains contentious, and the European Task Force on DOC have made a proposal to replace this term with the term 'unresponsive wakefulness syndrome' (UWS: Laureys et al., 2010). However, as 'UWS' is not yet adopted internationally and is yet to receive recognition from authoritative sources (Royal College of Physicians, 2013), we use the term 'VS' in this paper. Individuals who emerge from a VS and demonstrate "minimal but definite evidence" of awareness of themselves or their environments may achieve a *MCS* (Giacino et al., 2002). Prolonged disorders of consciousness (PDOC) is a more recent term representing conditions of DOC that persist for more than 4 weeks following sudden acquired profound brain injury (Royal College of Physicians, 2013).

It is particularly challenging for clinicians to differentiate between VS and MCS. Despite the development and widespread dissemination of diagnostic criteria for VS and MCS, recent evidence of the rate of misdiagnosis of VS in adults (41%) corroborates previous estimates and suggests that a significant number of adults with consensus-based diagnoses of VS may actually be in MCS (Schnakers et al., 2009). Differential diagnosis is important for prognosis and treatment planning, including understanding an individual's level of consciousness and potential for pain perception (Boly et al., 2008).

Disorders of Consciousness in Pediatric Populations

Differential diagnosis may be particularly challenging in children, especially those who have developed DOC prior to the acquisition of foundational language and motor skills. Accurate worldwide estimates of the prevalence and incidence of VS and MCS in both adults and children are difficult to obtain due to variations in diagnostic criteria used within different geographic regions and across treatment settings (Pisa et al., 2014). Ashwal (2003, p. 537) estimates the prevalence of MCS in children under the age of 18 to be between 44 and 110 per 100,000 children, based on U.S. census data from 2000, when the overall population of children in the U.S. was 72,293,812. The estimated worldwide incidence of children (defined here as younger than 15 years of age) in a VS is approximately 93,000 (range 11,365–151,536), with an estimated 3,000 (range 367–4,897) children in a VS in the U.S. (Ashwal, 2004). Considerable variation exists between estimates of the prevalence and incidence of DOC in adults and children worldwide (Pisa et al., 2014), making the interpretation of these estimates challenging.

Children most commonly experience a DOC as a result of congenital or developmental disorders, acquired brain injuries (either traumatic or non-traumatic), or central nervous system degenerative and neurometabolic disorders (Ashwal, 2003). For example, in a group of 5,075 children diagnosed in VS or MCS, approximately 43% had an etiology of perinatal/genetic conditions, 15% had acquired brain injury, 2% had various degenerative diseases, and 40% were of unknown or unspecified etiology (Strauss et al., 2000). The specific presentation of DOC in children versus adults remains elusive, as there are very limited published data on the pediatric population demonstrating vegetative or MCS (Ashwal, 2005, 2013; Nicholas et al., 2014). Children with DOC may present differently than adults, especially when the DOC is acquired congenitally, and the child subsequently experiences developmental delays in all domains.

Diagnosis of DOC in children is challenging, particularly among those younger than 3 years of age, and those with significant developmental delays, due to immaturities in language and motor development. Lack of mature language and motor development confounds the assessment of cognitive function in this population, as such children are not able to complete tasks related to command following, verbal expression, or purposeful movement that are a part of existing assessment tools (Giacino et al., 2002). Without premorbidly developed language and motor skills, it becomes difficult to discriminate between children who are minimally conscious in a way that precludes motor ability, versus those who are fully conscious, but present as being minimally responsive due to compromised ability to execute motor or speech-based tasks required of assessments (Ashwal, 2003). Thus, the measures used for assessment and diagnosis of young children with DOC, or in children with significant developmental delays, must discriminate between minimal consciousness and minimal responsiveness.

Clinical guidelines established in the mid-1990s by the American Academy of Neurology and the Child Neurology Society defining aspects of the VS have largely retained their utility, though such guidelines may soon be updated due to recent advances in functional neuroimaging (Ashwal, 2013). Neuroimaging technologies have demonstrated that in isolated cases, some adults presenting as vegetative are able to activate areas of the brain in response to specific commands (Ashwal, 2013). Research exploring neurocognitive functioning in children has only recently commenced, and preliminary evidence of a single pediatric case report shows both consistencies and inconsistencies with brain imaging evidence from adults with DOC (Nicholas et al., 2014). At a minimum, children with DOC should receive "appropriate medical, nursing, or home care to maintain their personal dignity and hygiene" (Ashwal, 2013), but recent brain imaging evidence supports the need for more sophisticated forms of treatment and assessment for individuals with DOC. Evidence from neuroimaging may be particularly helpful in discriminating when a child is minimally conscious versus when he or she is minimally responsive (conscious, yet physically unable to complete physical or communicative acts; Ashwal, 2003).

Despite the challenges associated with diagnosis of DOC in pediatric populations, there are important clinical reasons for achieving accurate diagnosis. Accurately assessing the presence or absence of a particular disorder of consciousness and understanding typical trajectories of recovery serve as prerequisites for formulating appropriate treatment goals and providing family support and advisement for appropriate expectations (Ashwal, 2003; Pham et al., 2014). For example, in acute care and short-term rehabilitation settings, comprehensive interdisciplinary efforts can improve outcomes for children who experience a DOC as a result of an acquired TBI (Ashwal, 2003; Pham et al., 2014). The careful tracking of level of consciousness and responsivity over time can help demonstrate the impact of treatment. Children in MCSs, especially those meeting the criteria for "MCS+" (Bruno et al., 2011) have emerged to conscious states when given intensive multidisciplinary therapeutic intervention in the setting of acute inpatient rehabilitation (Pham et al., 2014). The relationship among diagnosis, prognosis, and treatment planning may take on different dimensions in long-term care settings, where children may receive comprehensive care services to promote quality of life and support families, regardless of a child's particular DOC diagnosis. In palliative care settings, differential diagnosis may provide families with reassurance of the likely absence or presence of fluctuating awareness, which may provide insight as to what the child may be experiencing. Thus, the relevance of diagnosis in pediatric DOC may be partially dependent upon the care environment in which the child is situated.

Measures of Awareness for DOC Populations

Establishing valid and reliable behavioral measures that are sensitive to the complex disabilities typical in DOC populations is of central concern due to the implications for treatment, care, and decisions around withdrawal of tube feeding (Seel et al., 2010). Although the Glasgow Coma Scale (GCS, Teasdale and Jennett, 1974) is a powerful predictor of mortality and morbidity in the acute phase (Zafonte et al., 1996), the behavioral domains tested in acute care and rehabilitation differ. In acute care the behaviors of interest are those concerning prognosis of survival, whereas rehabilitation is more concerned with diagnostic assessment, outcome prediction, projection of disposition needs, interdisciplinary treatment planning, and monitoring treatment effectiveness (Giacino et al., 2004). A number of DOC measures validated as diagnostic assessments assess responsiveness across the motor, auditory, and visual domains, measuring arousal and responses to verbal commands as well. Whilst each have different strengths, only the Coma Recovery Scale (Revised; Giacino and Kalmar, 2004) may be used with minor reservations to assess awareness in the person with DOC (Seel et al., 2010).

One of the problems with the existing behavioral measures of responsiveness for DOC is the reliance on language within assessment protocols. Following profound brain injury, receptive language is typically severely impaired which calls into question the value of language based assessments (Laureys and Schiff, 2012). This is further complicated by the high incidence of acquired impairments with the visual and/or motor domains that can limit a patient's capacity to respond to verbal commands (Andrews et al., 1996). As the auditory modality has been found to be most sensitive in diagnosing awareness (Gill-Thwaites and Munday, 1999; Owen et al., 2005), attention has turned more recently to the importance of auditory stimuli in DOC assessments. Given its non-language basis and potential for emotional saliency, there is increasing interest in using music as a stimulus within DOC protocols for diagnosis (Okumura et al., 2014) and treatment (Verville et al., 2012; O'Kelly et al., 2013). The music therapy assessment tool for awareness in disorders of consciousness (MATADOC, Magee et al., 2014) is a measure used for assessment of awareness and intervention that uses a music-based protocol to stimulate responsiveness in DOC populations. A wide range of live musical stimuli is presented and behavioral responsiveness is rated across the motor, communication, arousal, visual, and auditory domains. Its Principal Subscale is reported to have good interrater reliability (mean = 0.83, SD = 0.11), good test–retest reliability (mean = 0.82, SD = 0.05), with good internal consistency ($\alpha = 0.76$) with a strong first principal component (Magee et al., 2014). Rasch analysis confirmed it as a reliable, unidimensional and homogenous scale. Its performance against another validated sensory assessment as an external reference standard found excellent agreement (100%) for diagnostic outcomes of awareness states (Magee et al., 2014). The purpose of the MATADOC is to contribute to interdisciplinary clinical assessments of awareness in DOC patients by providing a rigorous and detailed assessment of auditory responsiveness. Although validated for use with adults, its value for use with a pediatric DOC population has not yet been tested.

Pediatric DOC Measures

Valid pediatric specific DOC measures for accurate diagnosis of awareness and evaluation of treatment are lacking at the current time and there is no agreed gold standard for pediatrics (Cohen, 2009). Pediatric measures need to be developmentally appropriate, considering development milestones, such as the expectation to reliably follow verbal commands (Pham et al., 2014) or to localize painful stimuli (Durham et al., 2000). The existing rehabilitation measures for adult DOC cannot be adapted simply for children due to the reliance on language in their protocols. These require the child to have a fully developed use of language which is questionable when working with children who acquired brain damage prior to 5 years of age. Also, given that children most commonly experience a DOC as a result of congenital or developmental disorders rather than as a result of acquired conditions (Strauss et al., 2000), it is possible that youth with DOC will not have reached any developmental markers in the language domain. This highlights the complexity of developing appropriate measures for youth with DOC, and the need to develop measures that are not language-dependent. Thus, language specific items in adult measures compromise the validity of using such measures with children and require testing with children to meet the evidence-based criteria for clinical measures for DOC populations.

A number of behavioral coma measures have been developed to assist with nursing care of children in intensive care following catastrophic brain injury (Durham et al., 2000; Birse, 2006; Czaikowski et al., 2014), however, establishing reliability and validity for most of these measures remains outstanding (Cohen, 2009). Pediatric coma measures tend to have been developed for nursing staff to plan care and identify interprofessional collaboration where the child's needs indicate it is required (Birse, 2006) although many require motor and verbal responses that are not appropriate for children under 2 years of age (Durham et al., 2000).

Some adult coma scales have been adapted for pediatric patients following recommendations that the verbal components of adult scales be modified when using these with children under the age of 4 years (American College of Surgeons, 1997, cited in Durham et al., 2000). For example, The Full Outline of UnResponsive Score Coma Scale (Wijdicks et al., 2005) was adapted in a pediatric version (the PFSS) by including age appropriate responses inclusive of all developmental milestones and age appropriate respiratory rates (Czaikowski et al., 2014). The Infant Face Scale (Durham et al., 2000) adapts elements of the adult GCS, basing its scoring on infant appropriate behaviors. Although reliability has been established to varying degrees for some of these measures (Durham et al., 2000; Birse, 2006; Cohen, 2009; Czaikowski et al., 2014), the existing pediatric coma scales are more suited to prediction of survival than prediction of functional outcome. There remains a need for rehabilitation measures that are valid for youth with DOC.

Sensory stimuli that promote purposeful responsiveness, without requiring previous acquisition of language, would seem to be indicated for assisting in the differential diagnosis of children with DOC. Misdiagnosing individuals as VS when they are in fact in MCS is most often a result of the inability to detect purposeful eye movement (Schnakers et al., 2009). However, due to the high incidence of cortical visual impairment observed in the pediatric DOC population (Huo et al., 1999; Hoyt, 2003), measurement tools that optimize the use of the auditory modality may increase the likelihood that clinicians can discriminate a child's purposeful responses to sensory stimuli.

In human development, pre-linguistic communication is formed upon musical parameters such as pitch, dynamics, melodic contour, articulation, timing, and phrasing (Papousek, 1996; Trevarthen, 1999, 2002). In interactions with their environment, infants communicate immediate feeling states through varying these musical parameters, expressed through motor and vocal actions. The neurophysiological effects of music on children, either with brain damage or who are normally developing, is limited due to the practical and ethical complexities of researching this vulnerable population. However, there is some evidence that music can enhance neural processing of language mechanisms in at-risk children (Kraus et al., 2014). Brainstem assessments of children with Rett Syndrome have shown that music elicited responses comparable to normal neurophysiological responses suggesting that musical processing remains intact despite compromised neurological functioning (Bergström-Isacsson et al., 2014). Partially preserved brain activation patterns were found in response to salient auditory stimuli in one case of a child with PDOC (Nicholas et al., 2014), supporting the role for presenting stimuli with valence in the auditory modality. A model for using music with these children is therefore proposed given its role in normal child development, its neural effects with neurologically compromised populations, and the importance of optimizing environmental stimuli with personal saliency to enhance arousal in children with DOC (Amari et al., 2012).

Providing auditory stimuli in the form of musical sounds and interactions enables the clinician working with children with PDOC to provide a sound stimulus that is more intrinsically motivating than the noise stimuli frequently used in standardized neurobehavioral assessments of consciousness. The clinician can also make use of familiar and preferred sounds and music in order to promote the triggering of learned, cognitively mediated responses. Live musical stimuli may be presented with increasing complexity and stimulative qualities at a pace tolerated by the child with DOC, to enable the modulation to optimal arousal states for purposes of assessment. Thus, a standardized behavioral assessment tool for DOC that maximizes the use of musical stimuli, like the MATADOC, may promote the differential diagnosis of children with DOC.

Although the MATADOC is a standardized tool suitable for adult DOC populations, its utility with pediatric populations is not yet known. Understanding the importance of music in human development and its intrinsic motivating forces, it may similarly offer a valuable clinical measure for pediatric DOC. Its items need examining to determine their sensitivity to the developmental needs of pediatric populations and the appropriateness of the one language based item in particular. Following refinement of the measure, its reliability and validity need testing with a substantial pediatric sample. The purpose of this pre-pilot exploratory study was to examine the clinical utility of the MATADOC with a pediatric DOC cohort, explore trends for test–retest and inter-rater agreement, and compare the measure's performance with that of external reference standards.

Materials and Methods

Recruitment

Children with PDOC were recruited from inpatient admissions to a pediatric long-term care facility providing specialized medical and therapeutic services to children with complex medical challenges. The pediatric skilled nursing facility provides residential care to children from birth to 21 years of age within a major metropolitan area. Participants between the ages of 2–18 years of age, who were assessed as having a DOC, were recruited from multidisciplinary treatment team referrals. Formal diagnoses of VS/MCS/Emerging had not been determined at the time of referral to the study. Children with known hearing impairments and profound visual impairments were excluded, as we wished to ensure that the clinical utility of these MATADOC items could be explored fully. Children with known musicogenic epilepsy were excluded due to the contra-indication of treatment, and children with seizure disorders that cause frequent and/or prolonged seizures were also excluded due to the complexity of behaviors and the risk of collecting skewed data.

This study involved only children who could not communicate using language, and potentially involved children who had acquired their brain injury before language skills were fully developed. As language development was a variable of specific interest in this study, only children whose first language was English were included in this pilot study. For the purposes of examining whether language dependent items impact upon the validity and reliability of the MATADOC, recruitment aimed to include 50% participants who had never developed language skills (i.e., those who had acquired a DOC prior to the age of 3 years) and 50% that had developed language skills prior to acquiring a DOC (i.e., those who had acquired a DOC from the age of five and older). Consent for involvement was gained from the children's legal guardians. This study received ethical approval from the Behavioral and Social Sciences Committee of the Institutional Review Board at Temple University, Philadelphia, as well as from a research advisory committee at the clinical facility.

Procedure

Each child received a MATADOC assessment that involved four individual clinical contacts. Clinical sessions were scheduled at a time of the day to suit the child's usual schedule of school and treatment. The MATADOC protocol was implemented by a Board Certified Music Therapist who was experienced in work with children with DOC and had been trained to a recognized level of competency in delivering the MATADOC. The MATADOC protocol involves the use of live music in a process of at least five tasks that aim to determine the patient's awareness of and responsiveness to musical stimuli. The tasks include musical entrainment to the child's breathing whilst singing the child's name; presenting a song known to be preferred or at least familiar to the child; and presenting musically related visual and auditory stimuli (Magee et al., 2012). If the child demonstrated responses during these tasks that indicated higher level responsiveness (e.g., attempts to vocalize to music; attempts to touch or play an instrument), the protocol's tasks were adapted and extended in the moment to assess the child's responsiveness within a particular domain of functional behavior.

In order to enhance comfort and promote familiarity with the setting, clinical interventions consistently took place in the child's individual room or in a specific music therapy clinical room, depending upon which setting offered the most controlled and appropriate environment for the child. Distractions (e.g., interruptions; environmental noise) were minimized as much as possible. Children were physically positioned to enhance wakefulness and physical comfort. This was usually in their wheelchair or in their bed, following the recommendations of each child's care team.

Data Collection

Measures

The MATADOC has 14 items that measure responsiveness across auditory, visual, arousal, physical, cognitive, communication, and emotional behavioral domains. The MATADOC data collectors (assessors) were four Board Certified Music Therapists who were experienced at working with children with DOC (mean = 8.5 years; range = 5–12 years). They were all trained to a specified level of competence in delivering the MATADOC protocol and rating responses.

MATADOC data were collected for each child during four individual clinical contacts that took place over an 8 day period. Data were collected using the MATADOC rating form for each clinical contact by two assessors: one who delivered the protocol (therapist rater) and one who observed the clinical intervention (observer rater). Assessors remained blind to each other's ratings. MATADOC clinical contacts were video recorded. This allowed for raters to perform a further rating at a later date from the video. In this way, we captured performance trends for test–retest ratings in addition to inter-rater ratings.

Selecting appropriate measures as external reference standards in this study was problematic given the lack of measures validated for pediatric DOC that are suitable for rehabilitation settings. With no "gold standard" measure, expert opinion and common clinical practice with pediatric DOC was sought by surveying two global networks specializing in neuro-rehabilitation. From the 11 measures that are reportedly used in pediatric acute and rehabilitation settings, two were selected considering existing evidence-based recommendations for adults (Seel et al., 2010), the relevance of each measure to assessing sensory responsiveness, measures used in previous studies of children with DOC and local practices in the facility at which this study took place. The Coma Recovery Scale (Revised; CRS-R, Giacino and Kalmar, 2004), the COMA/Near Coma Scale (CNC, Rappaport et al., 1992), and the Pediatric Center Criteria Persistent VS (described later) were used as external measures to compare with the MATADOC (Magee et al., 2014). All non-MATADOC data were collected by an attending physician at the facility who was experienced with children with DOC and was blind to MATADOC ratings.

The CRS-R is a measure used to estimate the incidence of selected neurobehavioral signs in patients admitted to rehabilitation with a diagnosis of DOC (Giacino et al., 2004). It has 25 items that are hierarchically arranged items comprising six subscales addressing auditory, visual, motor, oromotor, communication, and arousal processes. It was selected for this study as, although not validated for pediatric populations, it is recommended for use with adult DOC with only "minor reservations" (Seel et al., 2010). It has also been used in previous studies with children with DOC caused by acquired brain injury (Patrick et al., 2000; McMahon et al., 2009).

The Coma/Near Coma Scale was designed to measure subtle changes in responsiveness in individuals with severe brain injury and consists of eleven items assessing responses to auditory, visual, olfactory, tactile, pain, and reflexive stimuli as well as vocalizations and response to commands (Rappaport et al., 1992). The presented stimuli include a range of verbal commands, sounds, olfactory, and tactile stimuli including unpleasant stimuli. It has been found to have high inter-rater reliability and validity for use with a DOC population (Rappaport et al., 1992). Although not validated for use with pediatric populations, it has been used in previous studies with children with DOC caused by acquired brain injury (Patrick et al., 2000; McMahon et al., 2009; Pham et al., 2014).

The Pediatric Center Criteria for Diagnosing a Persistent Vegetative State (PCC) is a measure that was designed within the facility at which this study took place and was regularly used in routine clinical care. It is a checklist designed as a series of yes/no questions that would differentiate a persistent VS from a MCS. It was based on the definition of MCS proposed by the Aspen Neurobehavioral Conference Workgroup in 2002 (Giacino et al., 2002). Recognizing that most children in the facility were either congenitally affected, or acquired their brain injury prior to the acquisition of language skills, this checklist did not require any specific validated assessment tool that relied on language comprehension. Instead, an interdisciplinary team would reach a consensus based on subjective assessments of five criteria: presence of voluntary actions or behavior, voluntary language or expression, sustained eye tracking, cognitive responses, or specific responses to commands. If any one of the criteria were reliably observed by a member of the interdisciplinary team, then a diagnosis of MCS was made. The interdisciplinary team consisted of the physician and might include any number of the following: nursing, social work, physical therapy, occupational therapy, speech/language pathology, music therapy, art therapy, child life, and/or recreation therapy. Staff was educated by the physician regarding the nature of spinal, brainstem, and limbic reflexes as well as other non-volitional movements such as seizures and myoclonus.

Non-MATADOC data were collected in single assessments that occurred within the same time period as the MATADOC ratings. All assessors (MATADOC and non-MATADOC) remained blind to all other ratings.

Results

Four children were recruited over a 3 month period from residents admitted to the facility for continuing care. We had hoped to recruit a further two participants, however, a number of potential participants were excluded due to a diagnosis of visual impairment and/or lack of English as a primary language. All the children had acquired brain damage sustained after birth, resulting in profound physical, cognitive, and communication impairments and were fully dependent for all activities of daily living. All the participants had been screened to have DOC but had not received diagnoses through formalized assessments, e.g., VS/MCS/Emerging. Data were collected using paper forms of the four study measures and then entered into an Excel spreadsheet by an independent research assistant, and double checked for accuracy by the principal investigator.

Data were analyzed by two of the investigators by means of descriptive statistics as the sample size precluded the use of inferential statistical analysis. Initially, we calculated the frequencies of each assessor's ratings for all MATADOC items for the live condition and the video condition to examine trends within each child's MATADOC results. Mean percentage agreement between raters was then calculated for combined conditions within each participant's data. We then examined ratings from both assessors across the four participants' ratings to look at the performance of each MATADOC item. To examine the overall performance of the MATADOC, mean percentages of agreement and disagreement in inter-rater and test–retest ratings were calculated. In inter-rater comparisons, we explored whether one of the assessors in the different roles (therapist rater vs. observer rater) rated responses higher or lower more consistently. We also paid particular attention to patterns of ratings made during live sessions versus video recorded sessions in order to make recommendations for the optimal design of further research with this measure. All MATADOC outcomes for each child were calculated by pooling the ratings from both live and video conditions of that child's assessment. This was done in order to balance occasional discrepancies in outcomes between the live and video conditions, as we anticipated that live ratings might provide more favorable outcomes than ratings from the video condition. For both inter-rater and test–retest comparisons, we considered mean agreement in the upper quartile (75–100%) only as "good," in line with rating schemes for agreement drawn from those used by the DOC task force (Seel et al., 2010). Data were analyzed by the first author (WM) and then checked by the second author (CG) for accuracy and assessment of the level of agreement. Where there was disagreement, the authors reviewed the data until agreement was reached.

Comparisons of Items Across Measures

Patterns of diagnostic outcome across comparable items of the four measures were examined to explore divergence and similarities between the MATADOC items and more widely used measures. This comparison was undertaken to identify potential sensitivities or weaknesses in MATADOC items so as to assist with refining the MATADOC for further testing with a pediatric cohort.

All four measures test visual responsiveness, although the CNC has two items for this domain (labeled Visual items 1 and 2 in the tables). Only the MATADOC, CRS-R, and CNC test auditory responsiveness. A second item in the MATADOC called "Awareness of musical stimuli" also falls under the auditory domain, where raters record behaviors that "evidence... the patient's awareness of the music" played in the patient's environment (Magee et al., 2012). Thus the outcomes of this item are provided with the label of "Auditory item 2." All four measures rate responses to verbal commands. The MATADOC, CRS-R, and PCC rate responsiveness in the motor domain. The MATADOC and CNC rate vocalization, the PCC rates "voluntary language or expression," and the CRS-R rates "Oromotor/Verbal Function": these items are compared with each other under the category "Expression." The CNC does not rate this item when a tracheostomy is in place. Although all four measures rate arousal, these ratings are not associated with diagnosis and so have been omitted from the results reported here.

Because this study aimed to explore the clinical utility of the MATADOC and make recommendations for its refinement and future research, we examined inter-rater agreement for the MATADOC within each of the live and video conditions as well as overall agreement across conditions. A pattern of difference in rating emerged early in analysis between ratings made by each rater (i.e., one rating higher than the other consistently) and by condition. Therefore we examined these trends in detail. Test–retest agreement is also reported.

As we were interested in how the MATADOC performed with both children who had acquired language prior to DOC ($n = 2$) and those who had not ($n = 2$), we present the results in a case by case form as the results were widely divergent across the four participants. The scores of comparable items for all measures are presented in tables for each individual.

Case 1

This 8-years-old female had sustained an anoxic brain injury from a cardio-pulmonary attack 2 years prior to data collection following normal development including normal language development (see **Table 1**). She demonstrated minimal responsiveness for all items across all four measures, resulting in a diagnosis of VS. Inter-rater agreement on MATADOC ratings was generally weak (66%), influenced by the therapist–rater rating responses during the live condition higher than those rated by the observer–rater 38% of times. This compared with the video condition where the therapist–rater ratings were higher than the observer–rater 's only 13% of times. Inter-rater agreement was best for items that rated clearly observable behaviors (e.g., Arousal: 87.5%; Change in Eye Contact/Direction: 75%) and also for items that rated cognitively mediated behaviors that were plainly absent in such a minimally responsive patient (e.g., Verbal Command: 100%; Choicemaking: 100%). Overall, the level of agreement between and within raters was best when a behavior was rated as "absent" or "VS." Of particular note is the disagreement between the two raters on the child's sensory responsiveness in both live and video conditions, i.e., Visual responsiveness: Item 1; Auditory responsiveness: Item 2. Overall test–retest agreement was mixed (79%) due to the therapist–rater's higher ratings during the live condition. There was better test–retest agreement for items rating behaviors that were unambiguously absent, with one exception for the item "Attention to task" where there was 87.5% test–retest agreement for responses categorized as "MCS." The observer–rater's ratings demonstrated excellent test–retest agreement (10 items at 100%; 5 items at 75%) although the child's minimal responsiveness, resulting in many items rated as "0/VS," assisted with this test–retest agreement.

TABLE 1 | Participant 1: demographic information and results from four disorders of consciousness (DOC) measures.

Age	8 years
Gender	F
Diagnosis	Anoxic brain injury and encephalopathy. Seizure disorder. Spastic quadriparesis
Time since injury	2 years
Language prior to brain damage	Yes
Average session duration	19.25 min
Inter-rater agreement	66%
Test–retest agreement	79%
Gender	F

	Measures			
	MATADOC	CRS-R	PCC	CNC
Diagnostic outcome	VS	VS	PVS	Marked coma*
Visual item 1	VS	VS	VS	VS
Visual item 2	–	–	–	VS
Auditory item 1	VS	VS	–	VS
Auditory item 2	VS	–	–	–
Verbal command	VS	VS	VS	VS
Motor	VS	VS	VS	–
Expression	VS	VS	VS	NA**

*Inconsistently responsive to stimulation presented to one sensory modality and not responsive to simple commands. No vocalization. **Not assessed due to tracheostomy in situ.*

Case 2

An 8.5 years-old boy had been developing normally prior to acquiring profound brain damage from a viral infection, which occurred over 7 years prior to data collection (see **Table 2**). Given the age he acquired his brain damage (1.5 years of age), he was considered not to have full language development. Diagnostic outcomes provided by DOC measures were not in agreement: although the CRS-R, PCC, and CNC all gave a diagnosis of VS, this contrasted with the MATADOC outcome of MCS. A closer examination of the item comparisons revealed that the MATADOC ratings differed on three items across the visual and auditory domains, rating the participant's responsiveness as "MCS" rather than "VS" as rated in the other three measures. In particular, auditory responsiveness was rated higher on the MATADOC (Item 2) during the live condition, albeit at the "inconsistent" response level. Ratings at MCS level for "Awareness of Musical Stimuli" (Item 3) across both live and video conditions support the observations of the child's responses to his auditory environment. All other items across all four measures rated his responses at VS level.

Similar to Participant 1, inter-rater agreement was best for items that rated clearly observable behaviors (e.g., Arousal: 100%) and also for items that rated cognitively mediated behaviors that were evidently absent in a patient whose responses are minimally responsive (e.g., Verbal Command: 100%). However, inter-rater agreement was high for a further seven items (at 75% for each item), including three on the Principal Subscale that contribute to higher diagnosis (Visual responsiveness; Auditory responsiveness; Awareness of Musical Stimuli). Overall inter-rater agreement was 78%, with comparable agreement rates between the live condition (81%) and the video condition (79%). Both raters rated higher than the other one at a rate of 16% in the live condition and 9% in the video condition. Although inter-rater agreement was higher for absent responses generally, there

TABLE 2 | Participant 2: demographic information and results from four DOC measures.

Age	8.5 years			
Gender	M			
Diagnosis	Encephalopathy due to bacterial meningitis. Spasticity. Seizure disorder			
Time since injury	>7 years			
Language prior to brain damage	No			
Average session duration	23.25 min			
Inter-rater agreement	78%			
Test–retest agreement	79%			
	Measures			
	MATADOC	**CRS-R**	**PCC**	**CNC**
Diagnostic outcome	MCS	VS	PVS	Marked coma*
Visual item 1	MCS	VS	VS	VS
Visual item 2	–	–	–	VS
Auditory item 1	MCS	VS	–	VS
Auditory item 2	MCS	–	–	–
Verbal command	VS	VS	VS	VS
Motor	VS	VS	VS	–
Expression	VS	VS	VS	VS

**Inconsistently responsive to stimulation presented to one sensory modality and not responsive to simple commands. No vocalization.*

TABLE 3 | Participant 3: demographic information and results from four DOC measures.

Age	15 years			
Gender	M			
Diagnosis	Hypoxic ischemic encephalopathy. Spasticity			
Time since injury	1 year			
Language prior to brain damage	Yes			
Average session duration	23.75 min			
Inter-rater agreement	67%			
Test–retest agreement	73%			
	Measures			
	MATADOC	**CRS-R**	**PCC**	**CNC**
Diagnostic outcome	MCS	MCS	MCS	Near coma#
Visual item 1	MCS	MCS	VS	VS
Visual item 2	–	–	–	MCS
Auditory item 1	MCS	MCS	–	MCS
Auditory item 2	MCS	–	–	–
Verbal command	VS	VS	VS	MCS
Motor	VS	VS	VS	–
Expression	VS	VS	MCS	NA**

*#Consistently responsive to stimulation presented to two sensory modalities and/or partially responsive to simple commands. **Not assessed due to tracheostomy in situ.*

was agreement on ratings of responses that were present (i.e., indicative of MCS) in Item 7: Musical responses. These agreed ratings were to behaviors observed relating to musical stimuli categorized as "Timbre" and "Dynamics." Overall test–retest agreement was the same as for Participant 1 at 79%.

Case 3

A 15 years-old male had been developing normally prior to acquiring profound anoxic brain damage through asphyxiation, which occurred less than 1 year prior to data collection (see **Table 3**). A diagnostic outcome of MCS was agreed across all four measures. Items within behavioral domains show some differences between different measures.

Inter-rater agreement for MATADOC data overall was at 67%. However, differences between raters for the different conditions reflect those seen in Participant 1 to a great degree: the therapist–rater rated higher on twice as many occasions as the observer–rater in both conditions (therapist–rater live: 24%, video: 18%; observer–rater live: 12%, video: 9%). There is some agreement between raters for items that are rated as present/MCS/above "0" across the items rating responsiveness to musical stimuli, (Items 3 and 6, both 87.5%). Of note is the inter-rater agreement (87.5%) for an item rating "Attention to task" where responsiveness is agreed at MCS. There was poorest inter-rater agreement for the item rating responses to Verbal commands. Test–retest agreement was strongest on items rating the auditory domain (item 2) and behavioral responsiveness to musical stimuli (items 3 and 6) notable as responses were rated as present or MCS. Test–retest agreement tended to be strong otherwise only for absent/VS ratings, aside from behavioral responses to "Dynamics" (i.e., a response for a change in the volume of music played) in item 6, where there was 75% test–retest agreement for behaviors that were present. Overall test–retest agreement was at 73%.

Case 4

A male aged 5.9 years-old had been developing normally prior to acquiring hypoxic ischemic encephalopathy following a cerebral vascular accident that occurred 2.9 years prior to data collection (see **Table 4**). He demonstrated minimal language development at the time of his acquired brain injury. As with participant 3, a diagnostic outcome of MCS was agreed across all four measures, however, items within behavioral domains show widely divergent outcomes across the different measures. MATADOC provided higher ratings than all other measures on two items: Visual responsiveness (Emerging) and Verbal commands (MCS). The CRS-R rated auditory responsiveness lower (VS) than the CNC and MATADOC (MCS). The PCC measure rated motor responses higher (MCS) than the other two measures that rated this domain. Agreement between authors for the MATADOC motor item was difficult to reach as the ratings were highly variable between and within raters, suggesting that the child's responsiveness bordered somewhere between VS and MCS levels. Inconsistent responses are a typical clinical presentation in DOC populations. We reached consensus on the more conservative rating of "VS" by giving greater weight to inter-rater and test–retest agreement across all possible rating occasions for this item.

TABLE 4 | Participant 4: demographic information and results from four DOC measures.

Age	5.9 years			
Gender	M			
Diagnosis	Hypoxic ischemic encephalopathy status-post cerebral vascular accident. Spastic quadriparesis			
Time since injury	2.9 years			
Language prior to brain damage	No (minimal)			
Average session duration	19.25 min			
Inter-rater agreement	73%			
Test–retest agreement	80%			
	Measures			
	MATADOC	**CRS-R**	**PCC**	**CNC**
Diagnostic outcome	MCS	MCS	MCS	Near coma#
Visual item 1	Other (emerging)	MCS	MCS	MCS
Visual item 2	–	–	–	MCS
Auditory item 1	MCS	VS	–	MCS
Auditory item 2	MCS	–	–	–
Verbal command	MCS	VS	VS	VS
Motor	VS	VS	MCS	–
Expression	VS	VS	VS	VS

#Consistently responsive to stimulation presented to two sensory modalities and/or partially responsive to simple commands.

The participant's responses can be seen to be highly variable across behavioral domains, spanning VS, MCS, and Emerging.

Overall inter-rater agreement was 73%. Unlike the other cases presented here, the observer–rater rated much higher than the therapist–rater in both live and video conditions: Live: observer–rater 17% higher compared to therapist–rater rating higher for just 5% occasions; Video: observer–rater rated higher 18% than the therapist–rater who rated higher for just 4% of opportunities. Test–rest agreement was 80% overall. The principal subscale items performed particularly well for both inter-rater and test–retest agreement: Visual responsiveness and arousal: 100%; Auditory responsiveness and Awareness of musical stimuli: 87.5% in both agreements. It is significant that these agreements were reached for behaviors that spanned across VS, MCS, and even Emerging. "Choicemaking" (Item 10) performed well on both inter-rater and test–retest agreement (75% for each). Other items that performed well for test–retest agreement were items rating "Emotional response" (Item 14) and "Choicemaking" (Item 10), both at 75% rating behaviors across VS and MCS. "Musical response" (Item 7) also had high agreement however mostly for absent responses, aside from ratings for "Timbre" which were for both mixed level responses.

Summary of the Results

Analysis of the MATADOC's utility, overall and item by item, in relation to three external reference standards and how it was used by two independent raters with children with DOC produced widely varying results. It produced diagnostic outcomes that were in agreement with all other measures in three of the cases. In the fourth, it provided a diagnosis of a higher awareness state than the external reference standards (See **Table 2**). The MATADOC items provided similar ratings for responsiveness as comparable items for the same domains from the other measures (e.g., auditory, visual, verbal command, motor, expression), with three exceptions where it produced ratings of responsiveness higher than that found by the other measures in the visual and auditory domains (see **Tables 2** and **3**). Agreement between MATADOC raters overall ranged from 66 to 73% (mean = 71%) with greater agreement during video ratings than rating of live sessions. In three of the cases, the therapist–rater rated higher than the observer–rater and this occurred to a greater degree during the live condition. Agreement for test–retest was slightly higher ranging from 73 to 80% (mean 78%). Overall, there was greatest agreement where the child's responsiveness was absent or indicated a VS response although some items performed reasonably well when there were responses over a range of diagnostic categories.

Discussion

The results are promising for the clinical utility of the MATADOC as a measure for pediatric PDOC. The trends found in the agreement for inter-rater and test–retest ratings reflect those of the larger study to standardize the measure with adults with DOC (Magee et al., 2014). Its performance against external reference standards was also promising, although differences in individual item outcomes require further exploration. It is notable that scores for verbal command items across all measures and cases were overwhelmingly "VS," with two exceptions that could be anomalies. This highlights the questionable relevance of items that rely on preserved language in pediatric brain-injured patients, and particularly whether language dependent items should contribute to diagnosis in children with PDOC given the issues of language development. Discrepancies between the outcomes of MATADOC items in the visual and auditory domains when compared to other measures (see Cases 2 and 4) are notable. These may be explained as the MATADOC producing false positives, or conversely may suggest that using music as a stimulus may generate greater responsiveness than non-musical stimuli. Higher ratings overall in the auditory domain (item 3) for MATADOC outcomes also occurred in Case 1. However, agreement was not consistent enough between raters or for test–retest ratings to provide an unequivocal score of "MCS." This picture reflects the inconsistent behavioral patterns typical of a patient with PDOC who might fluctuate between VS and MCS levels of responsiveness, particularly when starting to make functional recovery. The possibility of recovery should not be discounted in this particular case given the patient was within 2 years of injury. A decision to score the patient more conservatively as "VS" on this MATADOC item was made given the inconsistent agreements for MATADOC ratings on this item and the outcome of "VS" on all the comparable items in the auditory domain on the external reference measures. However, the higher level behaviors observed for this item might be explained once more by the use of musical stimuli facilitating greater responsiveness than non-musical stimuli. Clearly further investigation is warranted of item sensitivity in the visual and auditory domains with children, as the MATADOC has been found to have greater sensitivities in the auditory and visual domains than another standardized DOC measure in adults with DOC (O'Kelly and Magee, 2013).

Differences between raters suggest that in three of the cases, the therapist–rater observations were influenced by other factors causing them to rate behaviors at levels indicating greater responsivity. The prevalence of these "over" estimates cannot be explained solely as recall inaccuracies, although it may be that physical proximity afforded the therapist opportunities to see and hear behaviors that were not audible or visible by the observer. This could also explain why both observers tended to rate responses higher within the live condition. The interaction established by a therapist delivering this protocol is a highly intimate one, where the child's responses are stimulated and then incorporated into musical responses, much as occurs in intimate caregiver–child interactions. Professionals delivering interventions to children who have such profound disabilities invest heavily in tiny responses observed in the child. Providing objective observations for such a subjective experience with a child where treatment teams have so few responses to work with may explain the pattern in therapist ratings for the live condition. This has implications for future testing, where video observations alone may help to enable greater objectivity in ratings. However, until the reasons for discrepancies between ratings in live and video conditions are better understood, further research should continue to consider including both conditions.

Clinical Utility of the MATADOC Protocol

The current exploratory study has illuminated several logistical considerations for future research and clinical uses of the MATADOC with children. Obtaining optimal levels of arousal for each child was challenging. The children engaged in this study were part of long-term care therapeutic and educational programming, which included participation in sensory-based experiences within an on-site school. Some children were more alert and responsive when seated in their personalized wheelchairs for MATADOC sessions, though this depended upon how long the child had been in his or her chair during educational or therapeutic programming that day, along with other factors that impacted sleep and comfort. Though concerted efforts were made to assure that MATADOC research sessions occurred when the child was in his or her optimal physical positioning, timing of the sessions to promote optimal alertness was difficult to ascertain in advance. Thus, it is recommended that in future research, efforts are made to have daily consultation with the care team to identify the best combination of timing and physical positioning to promote alertness and responsiveness.

Individual children in this study demonstrated unique responses to the music therapist's voice, sounds delivered via the musical instruments, and to the directives inherent in the assessment sessions. The music therapists engaged in the study had been trained to use music to promote alertness and responsiveness while implementing the protocol; however, some children responded at times to mildly stimulative music and interactions with pacification and sleep. Thus, instead of serving to stimulate arousal, as might be expected due to the acoustic features of the music or the arousing use of the therapist's voice, the musical stimuli inadvertently served to sedate the child. It would be informative to further explore this relationship to determine if certain children become overstimulated with any form of sensory stimuli, even when experiencing very minimal and progressively presented auditory stimuli.

Some children in the current study appeared to orient and respond best to the novelty of the spoken voice, when the spoken voice contrasted with the musical environment experienced during the implementation of the MATADOC. This finding highlights the alerting capacity of novel sensory stimuli, and the challenge of teasing out which responses are purposeful in nature and which responses are reflexive responses to novel stimuli. Other children alerted to the therapist's sung voice with guitar accompaniment when they did not alert to isolated musical sounds (such as the playing of a tubular bell as an isolated auditory stimulus). Elements that constitute "stimulative" auditory stimuli may vary from child to child, depending upon his or her history and sensory processing abilities. It is therefore imperative that the MATADOC protocol is presented via live music, so that auditory stimuli and interpersonal interactions may be presented in a way that promotes optimal arousal and purposeful, discriminant responses to stimuli. Such presentation requires a skilled music therapist who is able to provide stimuli in fluid relation to the patient's unfolding responses.

In order to promote purposeful responsiveness, the MATADOC includes the use of familiar and preferred music. Determining the musical preferences of children with DOC is challenging, especially with those who experienced significant cognitive impairment at birth or early in life. In such cases, it is difficult to determine which music is familiar, salient, and preferred. One must rely on family or caregiver reports or observations of a child's responses to music, which ultimately may be inaccurate or misinterpreted. Ascertaining musical preference may sometimes rely on the factor of "familiarity," considering a child's history of "exposure" to certain music, i.e., television program theme tunes, rather than a direct demonstration of "preference." During administration of the MATADOC, therapists are encouraged to use a song that is acknowledged as being preferred and familiar to the child. The child's responsiveness to such a piece of music may fluctuate, and thus, the protocol also allows for therapists to use improvisational exchanges with the child to promote volitional responses.

The current pre-pilot exploratory study has demonstrated the complexity inherent in the assessment of DOC in the pediatric population. Recruitment of the target sample size for this study was challenging due to the frequency of children being diagnosed with cortical visual impairment or not having English as a primary language, an aspect that was tied to the demographic of this urban setting. Following some refinement of the measure, expansion of the research protocol to a multi-site study would provide a larger sample size and enable the testing of reliability and validity of the MATADOC for children and youth.

Future Directions

There is a demonstrated need for sensory assessment tools that contribute to differential diagnosis of PDOC in pediatric populations with a broad range of etiologies including traumatic and non-traumatic brain injury, perinatal/genetic conditions, and degenerative or neurometabolic disorders (Ashwal, 2003). Since a significant number of children have PDOC as a result of perinatal/genetic conditions (Strauss et al., 2000), a multi-site study with a larger sample size may help distinguish whether the MATADOC is more diagnostically useful for children who have acquired PDOC later in life, versus PDOC from congenital conditions. Considering the potentially high number of children with no language development prior to PDOC, it remains imperative to determine if PDOC can be accurately diagnosed without relying upon language-dependent items. Children who experience severe neurologic injury or dysfunction early in life may demonstrate extensive developmental delays in all areas. Given the complex presentation of such children, it will be important to assess whether the MATADOC reliably discriminates between children who are minimally responsive but conscious versus those who are minimally conscious due to PDOC.

It is possible that additional forms of sensory stimuli not specifically evaluated in the MATADOC may contribute to discriminating purposeful responsiveness in children with PDOC. For example, since children who have acquired PDOC congenitally may have never developed full capacity for sensory integration, the ability to process certain forms of sensory stimuli may be compromised. Some children may demonstrate sensitivities to certain sensory modalities, such as to tactile stimulation, yet may be more tolerant of others, such as vibroacoustic stimuli. Assessor clinicians engaged in the current study anecdotally reported instances of children with PDOC demonstrating increased alertness and responsiveness to vibroacoustic stimuli, delivered via deeply resonant wooden instruments. Such stimulation provides paired auditory and tactile stimulation via low frequency soundwaves, and may promote proprioceptive awareness when placed alongside or beneath the child's body. Empirical examination of the use of vibroacoustic stimulation for individuals with PDOC is indicated, and is a prerequisite of such stimuli being incorporated into further refinement of the MATADOC protocol as it is tested with a larger cohort.

Conclusion

The MATADOC provides a sensitive measure of responsiveness to sensory stimuli and early indications suggest that it may contribute to differential diagnosis and enable ongoing evaluation of progress for children with PDOC. Refinement of the measure in alignment with the outcomes of this study, and replication with a larger pediatric sample will strengthen the measure and establish its relevance for this unique population.

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Neuroscientific and neuroanthropological perspectives in music therapy research and practice with patients with disorders of consciousness

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A growing understanding of music therapy with patients with disorders of consciousness (DOC) has developed from observing behavioral changes and using these to gain new ways of experiencing this research environment and setting. Neuroscience provides further insight into the effects of music therapy; however, various studies with similar protocols show different results. The neuroanthropological approach is informed by anthropological and philosophical frameworks. It puts emphasis on a research *with* and not just *on* human beings concerning the subject/object question within a research process. It examines relational aspects and outcomes in the context of working in an interdisciplinary team. This allows a broader view of music therapy in a reflective process and leads to a careful interpretation of behavioral reactions and imaging results. This article discusses the importance of the neuroanthropological perspective on our way of obtaining knowledge and its influence on therapeutic practice. It is important to consider how knowledge is generated as it influences the results. Data from two cases will be presented to illustrate the neuroanthropological approach by comparing quantitative PET data with qualitative results of video analyses.

Keywords: music therapy, neuroanthropology, disorders of consciousness (DOC), unresponsive wakefulness syndrome (UWS), Positron Emission Tomography (PET)

Introduction

A growing understanding of music therapy with patients with disorders of consciousness (DOC) has developed from observing behavioral changes and using these observations to gain new ways of experiencing the research environment and setting. Music therapy has been used to support the neural and behavioral rehabilitation of individuals with unresponsive wakefulness syndrome (UWS) for over 20 years now. An increase in music therapy research points to its importance (Gustorff and Hannich, 2000; O'Kelly et al., 2013; Magee et al., 2014; Raglio et al., 2014; Magee and O'Kelly, 2015) and is additionally supported by research on the neurological impact of music on patients with DOC (Okumura et al., 2014; Verger et al., 2014; Castro et al., 2015).

Where the aim of music therapy is to support the rehabilitation of patients with DOC, studies of behavioral changes are crucial for detecting reactions to music therapy. Still, the simple observation of behavior poses a risk for misinterpretation and misdiagnosis (Andrews et al., 1996; Giacino et al., 2009) because behavioral responses can be limited by cognitive dysfunctions and masked by the inability to execute movement and reactions (Giacino et al., 2009; Fingelkurts et al., 2014; Stender et al., 2014). Neuroscience helps music therapy gain knowledge of the physiological effects of musical elements, which is useful for the theoretical foundation of music therapy. However, images of the brain do not capture the meaning of music therapy for the patients and the impact on their daily life (Nettleton et al., 2014). Although neuroscience is a valuable complement to music therapy research, especially with patients with DOC, it is an illusion that everything can be seen in the brain (Cohn, 2004; Nettleton et al., 2014). It is essential for us to note that we see music therapy as something beyond the simple act of listening to music. It is a complex process built around a therapeutic relationship between the patient and therapist. Therefore, research on music therapy needs a broader approach and interpretation of results, especially when working with patients who cannot communicate their experience verbally, where special attention is required and it is important to find indications for the effect of music therapy.

In an attempt to bridge the gap between research and practice we introduce a neuroanthropological perspective to music therapy research.

The Neuroanthropological Approach

The neuroanthropological approach should be seen as a response to challenges occurring within an interdisciplinary research setting, which includes the use of neuroimaging techniques and multidisciplinary methods. Daniel Lende and Greg Downey, who are the key actors within this field, have pointed out a holistic approach, trying to bridge brain and environment, drawing on insights of anthropology and psychology regarding individual-environment interaction (Lende and Downey, 2012). Although it is basically an anthropological approach (Roepstorff and Frith, 2012), we use the prefix "neuro" to emphasize the neuroscientific research, the neurorehabilitation environment and the interdisciplinary approach of our work.

An important, epistemological question, also within disciplinary borders, is how knowledge is generated and, in particular, how this influences the research results. The task was to challenge the research practice itself and simultaneously collect objective data on changes in brain activity.

The field of neuroanthropology is also described as a humanistic science (Domínguez et al., 2009). Within the whole research process each patient is seen as a human subject and not as an object of the study. We want to conduct research *with* the patient and not *on* the patient. This attitude mirrors the approach of music therapy itself, which can be seen as a *relational medicine*, in which the therapist opens up to the individual needs of every patient and tries to meet them at an egalitarian level.

An Anthropological Approach to Music Therapy

Our concept of music therapy (Tucek, 2014; Tucek et al., 2014) derives from an anthropological perspective, which historically developed from the models of traditional oriental music therapy and ethno music therapy to the current model of music therapy in Krems. We are oriented toward an individual, bio-psycho-social approach, asking for individual needs of patients and their personal meaning of music therapy. Inspired by theories of embodiment (Csordas, 2002; Storch and Tschacher, 2014), which describe the engagement of culture and individuals through sensual perception and experience, we believe that the meaning of music in therapy develops within the therapeutic session as a specific tool of communication between the patient and the therapist. In contrast to the theories describing communication as an exchange of certain messages between sender and receiver, we assume that the meaning of communication, as well as of music and music therapy, develops in an interaction between humans and their environment. To paraphrase Simon Rattle (2004), "music is not just what it is, but is that what it means to the people."

The basic aim of music therapy is to encourage the individual resources of the patients and an allostatic regulation (Schulkin, 2004), helping them regain a mental and physical stability. Therefore, music therapy can be activating on the one hand, e.g., by moving the patient's hand on an instrument or along with a rhythm. On the other hand, it can encourage balance and relaxation by playing improvisations in e.g., playing to the rhythm of the patient's breath. However, as the needs and meaning of interventions differ from person to person, the central concern is to meet and approach each patient individually.

For a positive outcome it is essential to establish a relationship between the patient and the music therapist. Music therapists not only work with musical interventions but also via a human relationship in which music creates a special kind of frame for this intervention. Within this framework music therapy tries to find new ways of connecting with the patient and to establish a communication beyond words; i.e., a way of communicating on a very emotional and relational level which is based on patients' needs and capabilities. From an anthropological perspective, the aim of music therapy is to transform the foreign, clinical environment (*Umwelt, "around-world"*) of patients to their contemporaries (*Mitwelt, "with-world"*) (Binswanger, 1963; Prinds et al., 2013). By addressing the patient individually and opening up to individual needs and reactions, music therapy is formed not only *for* the patient but *with* the patient.

Amidst a hospital setting with technical apparatus and noise, one always runs the risk of losing sight of the human being. According to our understanding of music therapy, as it is applied in Krems, one essential aim of music therapy, especially within intensive care units, is to *humanize*, also in terms of existential orientation. Music therapy tries to build a connection to the patient on an individual, relational level. Being aware of the patient's biography and their new and constantly changing context, the therapist approaches with an inquiring attitude.

It is important for the music therapist to get an understanding of this patient's culture and include it in their therapeutic considerations. In this context, culture is not the idea of "*isolated societies with shared cultural meanings*" but rather one's own "*local world,*" as e.g., the environment of the patient and their family. This culture comprises, among others, the patients' relatives, musical preference, ability to play an instrument and personality, and affects all aspects of their experiences (Kleinman and Benson, 2006). This leads us to the point why anthropology, its core methodology (i.e., ethnography) and its interpersonal, intersubjective nature are important for a music therapist. They help us appreciate and humanly engage with the differentness of a patient, particularly with DOC, and get a deeper understanding of the patient's needs. Nevertheless, we are aware of the fact that, however confident our interpretations might seem to us, they are always limited by the analytic tools and research methods we use and by the epistemological limits of what we actually mean by intersubjectivity (Willen and Seeman, 2012).

Patients with DOC do not only have their "local world," but they are in a very special situation in a "liminal period" (Turner, 1967) in which familiar norms are absent and received notions of personhood are destabilized (Nettleton et al., 2014). Without the possibility of verbal conversation they have to readapt to a new situation of life by mourning about the loss of their former life and by regaining confidence in their current and future situation. The same holds true for the family members who cannot share their experience with the patient in the way they are used to, and have to go through this reorientation process regarding a life under completely new conditions. The therapist has to be aware of changes caused by this reorientation syndrome (Steinhoff, 2012) and has to consider the individuality of each person involved. In order to connect with a person in such a transition it is important to empathize with the lived human experience of the patient's situation and to approach the patient as an individual human being "facing danger and uncertainty" (Kleinman and Benson, 2006). To help the patient regain certainty and stability, building trust can be seen as a basis for therapeutic relationship. For this, the therapist needs flexibility which is also required in research with human beings.

Neuroanthropological Perspective in Music Therapy Research

When it comes to carrying out research within a therapeutic setting with human interaction as we do in music therapy, many important aspects happen on a subjective level which cannot be sufficiently illustrated in objective terms. Domínguez argues that subjects, subjectivity and understanding are not only absent but obscured and marginalized in favor of the scientific process and its results (Domínguez, 2012), and that subjectivity has a negative attribution *per se*. But why do we need such a radical omission?

Neuroanthropology takes up the idea that knowledge is neither built on objective data nor subjective perception alone (Domínguez, 2012). It does not need an "either/or" nor an "and" but a "with" in terms of interaction between them. The data generated by the PET scanner shows the neural changes during music therapy, but it does not explain the reason for this effect. While it is important to look at this data, an increase in brain activity does not tell us much about the patient's situation. When and how does a patient actually benefit from music therapy and what exactly does he benefit from? To answer these questions we need a more detailed and careful intersubjective interpretation of interactions between the patient and the therapist (Nettleton et al., 2014). Qualitative data collected within the therapeutic setting is essential for our understanding of the effect of music therapy, as it provides more details on it and strengthens the interpretations of the results.

We have tried to jump onto this ontology-epistemology rollercoaster and use insights gained from intersubjective communications and reflective processes to adapt the experimental script design. This helps us to ask novel questions for improving the research process as well as the therapeutic setting.

To give an example, we would like to describe part of our pilot study in which we tried new ways of examining the effect of music therapy on patients with UWS. In a pre-post method spanning 5 weeks, the neurological effect was measured by positron emission tomography, the vegetative effect by heart rate variability and behavioral changes by qualitative microanalysis of video sequences of the therapy sessions. Four patients were randomly enrolled either into the music therapy group ($n = 2$) or the control group ($n = 2$) by drawing lots. We want to illustrate two cases of patients in the music therapy group for this article to describe the neuroanthropological approach in a concrete example.

PET results of these two patients show that the brain activity during music therapy increased after 5 weeks of music therapy in three observed regions, which are the frontal areas (31/47%), the hippocampus (28% both) and the cerebellum (31/47%). These results show that the increase is quite high in both patients. Considering these results, we could assume that patients may have shown similar conditions too. But in fact they were different. Each patient has to be seen as a unique human being with their own resources and requirements for an individual path to recovery. This also means that the outcome of music therapy is often subjective and difficult to generalize. Therefore, we want to give a description of two of our patients, their music therapy sessions and the respective outcomes.

The first patient was a 70 year old man, who had been living with UWS after cardiac arrest for 3 years. His wife came to visit him at least every second day and provided a lot of information about his musical biography, preferences and interpretation of his physical conditions. When she saw the harp that the therapist brought for the first session, she mentioned that harp music had always been one of their favorites ever since they had had a wonderful vacation in Ireland with lots of happy memories and had wanted to go back there. Therefore, the therapist often worked with the harp during the first few weeks and played to him and also with him by guiding his hands and fingers through the strings. As the patient seemed to be more attentive in the course of the weeks, the therapist adapted the music to another piece of biographical information by singing songs of the 1950s, which the patient used to play in a band in his youth. In addition to singing the songs to the patient, the therapist guided his hands in the rhythm of the songs on a frame drum. The tempo and dynamics were adapted to the rhythm and condition of the patient, like, for example, breath and movement. All steps were described verbally to him.

The second patient was a 60 year old woman. She had been living with UWS for 4 years. In the first few sessions the patient experienced a high physical tension, had problems with secretion and seemed to be too stressed to listen or react to the music therapy. In a conversation with the patient's daughter the therapist found out that she liked to sing, especially traditional folk songs. As it was Christmas time, the therapist took up this information and sang Christmas and winter songs to her in a calm and rhythmic way and reduced verbal speech to a minimum. This was meant to give her the opportunity to calm herself down and regulate her physical tension. After rhythmicity came back into her breathing, the songs were often adjusted to this rhythm and included deep breaths or pauses.

The therapist constantly observed the patients attentively and tailored the therapy as well as the research setting to the present condition and needs of the patient. The therapy was, for example, adapted to the posture of the patient and the intensity of the light in the room was changed to fit the patient's individual sensitivity. The interpretation of the patient's needs, conditions and sensitivity was based on signs like facial expression, tonicity or breath. By acting attentively and describing everything that happened to or around the patients, the therapist guided them through the whole research process turning it into a reciprocal act.

After 5 weeks of music therapy various changes in the condition of both participants were observed in video micro analysis using the transcription software "Feldpartitur," which allows an examination of video data by creating a score with various self-selected levels in intervals of 1 s. In a master's thesis these observed levels such as eyes, viewing direction, breathing of the patient and therapeutic intervention were evaluated in outcome categories (e.g., wakefulness, attention, tonus, communication) to gain insight into the behavioral changes after 5 weeks of music therapy. However, these changes differed in the two patients. While the subsequent video analysis indicated that the first patient's eyes were more open in the fifth week and he seemed to be more attentive, the second patient had her eyes closed most of the time and showed less movement. One could assume that she fell into a deeper state of the UWS. However, this is a rather limited perspective on a patient. Due to the individuality of the two patients and the contact in therapy, the changes are not comparable. From the beginning, the focus of the therapy was influenced by the behavior and condition of the patients and the intention of therapy was adapted to their capabilities and resources. Hence, the therapy with the first patient followed a more active approach and embraced his resources by engaging his wakefulness and attention. Due to the high tension of the second participant and her problems with secretion, an active approach would not have been appropriate and possibly even an excessive demand. The goal of music therapy for the second patient was to support her responses of relaxation and regulation.

The results show a positive outcome of music therapy with both patients. Music therapy helped the first patient to increase his wakefulness and attention. Several levels of observation in the video analysis represent this outcome: his eyes are more open in the fifth week, he looks at the instruments and his eyebrows are raised, indicating concentration. His breath, which had a constant rhythm in the first week, varies depending on the activity or intervention in the therapy. Guiding his hands on a drum or the harp helped him increase his attention and focus on the instruments. Therefore, therapy changed from a rather receptive approach to active interventions. Also, more interaction between the patient and the therapist can be observed in the video analysis. This is shown by an increase in verbal explanations and requests by the therapist as well as in the increase of attention by the patient himself. For the wife of the first patient this increase in attention was recognizable as well. She described that her husband started to look around, that more eye contact was possible and she felt that the music made him more alert than just talking to him. She also made use of the possibility to be around during the PET measurement sessions, where she was allowed to be in the same room as the radial assistants which had a very calming effect on her, being close to her husband.

The goal to support relaxation and regulation was also met for the second patient as the tonus in her body and her face decreased. The video analysis showed that in the fifth week secretion and stertorous breathing started to subside shortly after the beginning of the music therapy and ended completely after a few minutes. Her breathing even became constant and rhythmic again. At first glance her wakefulness and attention appeared to be reduced, having her eyes closed, lying relaxed and without movement. However, we interpreted the changes in her condition as positive, as she seemed to be more relaxed and physically stable. But how do we know if this is really true? Our interpretation does not only derive from video analysis, which poses as a snap-shot of single therapy sessions, but also from interdisciplinary exchanges within our research group, with care givers, relatives, therapists and neurologists and from the perception of the therapist during the therapy sessions. An important perspective and source of knowledge is the view of the patients' relatives, since they are usually very close to them and can provide valuable information about their behavioral change.

All of this information was recorded in protocols and a research diary which supported the analysis with qualitative data. According to Csordas (2004), "*Perception* becomes *data* when it is used as *evidence* to establish *facts*, which are subsequently elevated to the status of *truths* and *certainties*." Subjective perception can be valuable and fruitful for research, especially if patients are not able to communicate their perception directly. Using it in a reflective process, it complements data by conveying the individual environment of a human being.

Therefore, we argue that important knowledge is not only generated via an objective machine but also via human interaction throughout the whole research process and in the therapeutic setting at the bedside. Whenever individuals come together, experience and knowledge are exchanged, which in turn creates new kinds of knowledge (Roepstorff, 2001).

However, working in an interdisciplinary team can also lead to difficulties, since people do not always share the same research background and framework of thoughts. Coming from different traditions, they are facing a shared process of knowledge creation (Roepstorff, 2001) and need to find a way to attune. Being confronted with the common tensions between ideals of methods and the realities of research (Roepstorff and Frith, 2012), we tried to identify these tensions and reflect on them. From a neuroanthropological perspective the aim is not to avoid these tensions but to be aware of them and to discuss their influence on the research results. Moreover, conflicts and tensions can bear chances of creativity, as they provide room for improvement. Tensions can be valuable, as they lead to a dialog between different professions and help consider a broader view.

The benefit of neuroanthropology lies in the open approach to the complexity of music therapy. The multidisciplinary proceedings in research allow us to capture various different processes within this complexity. But still, as in music therapy practice, the human individual is at the center of the whole research process. Additionally, it allows the acknowledgment of the qualitative value of music therapy.

Conclusion

Neuroscience supports the understanding of the effect of music therapy at the level of brain activity of people with DOC. However, brain images, like PET, cannot sufficiently determine the *local world* and the impact on the patients' life. An additional behavioral observation, e.g., video analysis, can give information on a patient's condition. However, it is static and inflexible as it captures only a short period of time. As a patient with DOC is not able to express himself with the familiar means of communication, both neuroscience and behavioral observations pose a risk of misinterpretation. Neuroanthropology can help bridge this gap by reflecting on the information collected in the environment of the patient, which is necessary for a careful interpretation of data.

We suggest taking the entire research project including the experiences, sensation, meaning, and perception into consideration as an important source of knowledge, to bring together the different inner and outer worlds of every individual involved and to realize the importance, not only of the objective data but also of the lived experience, relationship aspects and all the social interactions.

When dealing with humans, and especially patients with DOC, the question should be how we can improve their situation. Is it the ideal to have tightly controlled experiments and behave like a personalized robot in order to collect "objective" data or could it be different? Could the research process itself be more open, fluent and flexible according to the individual and the situational needs? Another question that still needs consideration is: How would we then deal with the amount of data collected and measure a successful research result?

We know that in reality a research process can never be 100% controllable (Roepstorff, 2001). Why not take this finding and use it for research itself?

Combining anthropological methods like the ethnographic investigation with neuroscientific quantitative data collection and behavioral measures can provide further understanding of what is really happening during the music therapy interventions. In particular ethnographic insights can help us with the interpretation of research results and inspire us to ask novel questions (Domínguez et al., 2009).

The fact that an observed and described phenomenon is difficult to confirm does not provide sufficient evidence against its authenticity or importance. Nevertheless, we need to develop more powerful methods with which to study such phenomenon and thus make them comprehensible and valuable for a music therapist in daily clinical practice. DOC pose many unanswered questions due to the inability of the patients to communicate their own perceptions and views. However, considering not only snap-reading methods but a broader view of the patients' environment could help us gain more knowledge on music therapy and approach the patients directly.

To achieve this, an intense self-reflecting process of the therapist and researcher is required. The University of Applied Sciences Krems encourages and supports this self-reflecting process from the beginning of its music therapy program in order to impart the importance of a neuroanthropological perspective to future generations of music therapists and researches. This will hopefully help improve the neuroscientific research on music therapy and lead us toward a deeper comprehension of our work with the patients.

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