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Pleasurable Emotional Response to Music: A Case of Neurodegenerative Generalized Auditory Agnosia

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Abstract

Recent functional neuroimaging studies implicate the network of mesolimbic structures known to be active in reward processing as the neural substrate of pleasure associated with listening to music. Psychoacoustic and lesion studies suggest that there is a widely distributed cortical network involved in processing discreet musical variables. Here we present the case of a young man with auditory agnosia as the consequence of cortical neurodegeneration who continues to experience pleasure when exposed to music. In a series of musical tasks the subject was unable to accurately identify any of the perceptual components of music beyond simple pitch discrimination, including musical variables know to impact the perception of affect. The subject subsequently misidentified the musical character of personally familiar tunes presented experimentally, but continued to report the activity of "listening" to specific musical genres was an emotionally rewarding experience. The implications of this case for the evolving understanding of music perception, music misperception, music memory, and music-associated emotion are discussed.

Introduction

> "The music in my heart I bore
>
> Long after it was heard no more…"
>
> William Wordsworth, *The Solitary Reaper*

Emotional responses to music have been quantified with psychophysiology (Khalfa, Isabelle et al. 2002; Baumgartner, Esslen et al. 2005), lateralized with neurophysiology (Tsang, Trainor et al. 2001), and localized with functional neuroimaging (Blood, Zatorre et al. 1999; Blood and Zatorre 2001); Khalfa, Schon et al. 2005; Koelsch, Fritz et al. 2005). In lesion studies preservation of an emotional response to music after the development of severe deficits in music processing has been reported (Peretz, Gagnon et al. 1998). Conversely, preserved cognitive processing of music with loss of the emotional response to music has also been demonstrated (Griffiths, Rees et al. 1997). This double dissociation supports the possibility of separate neural circuits functioning in parallel during the musical experience, as asserted by the many current theoretical models of music processing (Baeck 2002; Koelsch and Friederici 2003; Peretz, Champod et al. 2003; Peretz and Coltheart 2003).

Here we describe a young man with an idiopathic, chronic, progressive cortical neurodegenerative disorder who developed functional deafness but reported retention of his ability to experience pleasure when listening to his favorite musical genres, jazz and classical. We determined that the patient had developed auditory agnosia based on his preserved ability to recognize the onset of acoustic stimuli in association with a relative inability to interpret auditory input. The bilateral hemispheric representation of tonotopic maps throughout the auditory pathway renders such deficits rare, although, confusion generated by the complex terminology and the inherent difficulty in adequately and uniformly evaluating these syndromes continue to contribute to an underreporting of such deficits (Polster and Rose 1998).

Auditory Agnosia

A brief review of the nosology of auditory agnosia is pertinent to our description of this patient. Generalized auditory agnosia refers to a rare condition in which subjects demonstrate impairment in the ability to recognize sounds in spite of adequate hearing as measured by standard audiometry (Mendez 2001). Bitemporal cortical lesions have been reported as the neuroanatomic substrate of the condition, most frequently as the result of cerebrovascular disease (Vignolo 2003), but also in association with neurodegeneration (Pinard, Chertkow et al. 2002), herpes encephalitis (Kaga, Kaga et al. 2003), and traumatic brain injury (Hattiangadi, Pillion et al. 2005). Lesions with a similar distribution involving the primary auditory cortex (BA 41) and auditory association cortex (BA 42 & 22) bilaterally may also result in cortical deafness, a distinct condition which yields an abnormal pure tone audiogram and, therefore, impairs the perception of sounds preceding the assignment of their meanings (Mendez and Geehan 1988; Szirmai, Farsang et al. 2003).

Selective auditory agnosias are encountered in which the interpretation of specific categories of sounds is impaired. These disorders include pure word deafness and nonverbal auditory agnosias for environmental sounds and music. The selective auditory agnosias may result from less widely distributed bitemporal lesions, or unilateral right or left temporal lesions, often involving the white matter tracts traversing from the contralateral hemisphere (Auerbach, Allard et al. 1982; Takahashi, Kawamura et al. 1992; Griffiths, Rees et al. 1997; (Mendez 2001).

Perhaps the least-well characterized and likely the most widely neuroanatomically distributed of the selective auditory agnosias is music agnosia. In a review of 175 published reports of auditory perceptual disorders published from 1883–2001, Vignolo cited the cases of 13 right-handed stroke patients in which there was dissociation between agnosia for music and for environmental sounds. Although there was no consistent lateralization of the lesions (most of the patients demonstrated bihemispheric involvement), music agnosia was reported more frequently than a deficit in environmental sound processing, with a ratio of 11:2. A subsequent systematic assessment of 40 unihemispheric stroke patients confirmed dissociation between the selective auditory agnosia subtypes in 19 patients (Vignolo 2003).

Music agnosia may also be subdivided as referable to a deficit in melodic perception (apperceptive music agnosia) or in musical memory (associative music agnosia), similar to the schema used for other forms of sensory agnosia (Ayotte, Peretz et al. 2000). Importantly, studies in music agnosia suggest lateralization of function, with melodic deficits resulting from right hemisphere lesions and temporal and associative deficits resulting from left hemisphere lesions (Ayotte, Peretz et al. 2000; Vignolo 2003; Zatorre and McGill 2005).

We hypothesized that our patient had a selective auditory agnosia for words and possibly environmental sounds based on the history provided by his informant. Given the higher frequency of music agnosia compared to environmental sound agnosia in the literature, we also hypothesized that there was a deficit in music perception, with the patient responding emotionally to one or more of the specific attributes of music. We used both standardized and novel stimuli in an attempt to determine at which level of auditory processing the reported emotional response occurred.

Case Report

JS, a right-handed man with a master's degree in urban architecture, presented for assessment at our medical center in September 2001 at the age of 30. His medical and developmental history prior to the onset of his neurological symptoms was significant only for mild psoriasis. Due to his auditory processing deficit, his mother provided the collateral history which was supplemented by extensive medical records from evaluation at other tertiary-care medical centers. The patient developed his first symptom of an acute-onset right paracentral scotoma in March of 1997. A brain MRI at that time revealed subtle signal abnormality in the left occipitotemporal region, but no obvious cause for the lesion or visual deficit was found during routine cerebrovascular disease screening evaluation.

JS experienced no further symptoms other than a persistent visual deficit until March 1999, when the intensity of his experiences of smell and taste decreased. The following month he developed the acute onset of left homonymous hemianopsia and subsequent gait instability. Repeat brain MRI demonstrated superior vermian and bilateral occipital pole T-2 weighted signal hyperintensities thought to be the imaging correlates of ischemic infarcts. The patient underwent an extensive inpatient evaluation at another institution for potential causes of cerebrovascular disease in young adults without classic risk factors. Studies included lumbar puncture, transesophageal echocardiogram, MR and conventional cerebral and cervical angiogram, laboratory screening for inflammatory conditions/infection and laboratory evaluation for predisposition to hypercoaguable states. Consecutive CSF studies revealed 8 and11 white blood cells/mms without associated elevations in protein or red blood cells. Other studies were unremarkable. The patient was dismissed from the hospital on clopidigrel, enteric-coated aspirin, and verapamil with a diagnosis of idiopathic vasoconstrictive disease.

In July of 1999, JS became concerned with "hearing loss", although a precise description of his auditory perceptual experience is not documented in his medical record. An audiogram revealed only minimal high frequency (8000 Hz) hearing loss with preservation of audition for pure tones between 125 and 4000 Hz, suggesting a possible central disorder of auditory processing. Due to his earlier history of cerebrovascular disease, the patient was immediately started on empiric anti-inflammatory therapy with prednisone 80 mg daily for possible central nervous system vasculitis and was subsequently transitioned to cyclophosphamide. JS developed no new symptoms while on these medications, but his deficits did not improve, so the therapy was discontinued.

In February 2000 the patient developed abdominal and paraspinal myoclonus that resolved after initiation of low-dose valproic acid and clonazepam therapy. MRI of the cervical and thoracic spine were normal, and no EEG correlate to the movement disorder was identified. A repeat audiogram in early 2000 revealed similar pure tone thresholds with normal tympanometry and word recognition scores; however, the ability of JS to recognize words was noted to deteriorate significantly as the intensity of the auditory stimulus was increased.

In the two months preceding his evaluation at our medical center, JS recognized progression of his difficulty understanding spoken language. Findings in September 2001 included a requirement of written instructions for most portions of the examination and prominent visual field deficits, sparing only the right superior quadrant bilaterally. As part of his evaluation, JS underwent brain, nerve, and muscle biopsy. The specimens revealed normal right frontal cortex and white matter with multiple staining techniques. The right sural nerve biopsy demonstrated changes consistent with a mixed demyelinating and axonal neuropathy with occasional abnormal mitochondria in Schwann cells on electron microscopy. A right quadriceps muscle biopsy demonstrated slightly increased numbers of mitochondria on both

NADH and SDH staining and subtle mitochondrial hyperplasia and hypertrophy associated with increased glycogen. All biopsy specimens were non-diagnostic. Genetic testing for the presumptive diagnosis of mitochondrial disease was unrevealing.

JS was next seen in September 2002 as which time he had developed depressed mood in association with frustration with his functional decline. A repeat audiogram completed prior to a follow-up visit in May 2002 revealed no significant change in pure tone thresholds but a dramatic reduction in the word recognition score to zero. Tympanometry was normal. Acoustic reflexes were normal in the frequency range of most human speech (500–2000 Hz). Brainstem auditory evoked responses were normal, although there was some asymmetry in amplitude suggestive of a more prominent abnormality in the left ear. Formal visual field testing remained stable without evidence of retinal or optic nerve pathology. Subsequent to this visit JS successfully learned American Sign Language (tactile) in an effort to compensate for his multimodal communication deficits.

In June 2005, JS returned to the neurology clinic with his mother; she provided the majority of the interim history due to the progression of his inability to comprehend spoken language. New symptoms included mild word-finding difficulty and impairment in comprehending the meaning of low frequency words (examples given included: “pedestrian”, “confirmatory”, and “khaki”.) JS had developed a shaving compulsion and a tendency to spit frequently. A choreiform and tic-like movement disorder was apparent in the head and neck. Functionally, the patient continued to use his computer avidly and participated in outdoor activities including skiing, cycling, and swimming. On examination, JS was minimally interactive and appeared to be more anxious than had been documented previously. He was able to communicate by reading instructions written in large block letters positioned near his face in the right superior visual field. He was noted to process such information more slowly than had been observed during prior visits. Pertinent findings on the examination included: reduced blink frequency, diminished upgaze, rotatory nystagmus on far lateral gaze, increased right upper extremity tone with activation of the contralateral upper extremity. There was persistence of the visual field defects and auditory processing deficit detailed on prior examinations.

Remarkably, he still enjoyed listening to his CD collection of jazz and classical music, acquired prior to the onset of his neurological symptoms. He preferred listening to music over other hobbies such as gardening. He preferred to attend concerts rather than non-musical social activities. He spoke with excitement about his favorite performers and discussed his music listening with his mother in great detail. According to his mother’s report, he continued to enjoy music despite progressive difficulty in responding purposefully to other noises in his environment (i.e. voices, telephone, doorbell, etc.).

Methods/ Results

General Neuropsychological Evaluation

JS underwent a comprehensive neuropsychological evaluation in 2001. General intellectual function was assessed at each subsequent visit using the Mini-Mental State Examination (MMSE; Folstein, Folstein et al. 1975) with variable modifications for advancing multi-modal sensory deficits. Assessment of visuospatial ability included a modified version of the Rey-Osterrieth figure copying task with an associated measure of nonverbal episodic memory assessed by measuring free recall ability for this figure after a delay of 10-minutes. Using the California Verbal Learning Test-Mental Status version (CVLT-MS) (Delis, Kramer et al. 2000) verbal memory was assessed. Language testing included confrontational naming with a 15-item modified Boston Naming Test. Executive function was tested with digit span backward, a modified version of the Trailmaking task, the Stroop test, and the

Design Fluency subtest of the Delis-Kaplan Executive Function Scales (Delis, Kaplan et al, 2001). Verbal fluency was assessed with both category and phonemic cues. Further testing included abstract reasoning with three proverbs and three tests of similarity, and five calculations. Results are presented in Table 1.

In summary, JS demonstrated executive dysfunction, with multiple intrusions on verbal memory testing as well as errors and rule violations on fluency measures. Initial MMSE score was 25/29; repeat MMSE was undertaken in coordination with the language and psychoacoustic evaluation described below. On that occasion, a total score of 29/30 was obtained, with a single point deducted for incorrect phrase repetition. The improvement was deemed referable to the modifications of the instructions and written format of presentation of the material to accommodate the progressive decline in auditory and visual processing.

MRI

MRI scans were obtained on a 1.5 Magnetom VISION system (Siemens Inc., NJ, USA) equipped with a standard quadrature head coil. Structural MRI sequences were obtained within three months of the testing battery to be described. Selected images are presented in Figure 1 with findings summarized in the accompanying caption.

Audiometry

Hearing sensitivity was assessed using insert headphones and standard audiometric techniques (Hattiangadi, Pillion et al. 2005) with results compared to prior evaluation completed in 2002 at the same facility. Results were determined to represent fair reliability in the context of known multi-sensory deficits. Pure tone testing of the right ear revealed normal hearing 250–2000 Hz sloping to a mild to moderate hearing loss in the 3000–8000 Hz range. Pure tone testing in the left ear revealed normal hearing 250 Hz sloping to mild to moderate hearing loss in the 500–8000 Hz range. Tympanometry demonstrated bilaterally normal mobility, middle ear pressure, and ear canal volume. Acoustic reflexes were present bilaterally with negative reflex decay, consistent with a normal reflex arc with the exception of the 2000Hz frequency ipsilaterally on the left. Distortion Product Otoacoustic Emissions were present 750–6000 Hz on the right and 750–4000 Hz on the left providing evidence of normal or near-normal outer hair cell cochlear function for much of the speech spectrum bilaterally. Word recognition ability was 0% during the audiometric examination in 2002 and was not repeated.

Language Testing

Standardized language and sound testing was undertaken when possible; however, due to the severity of visual impairment in combination with auditory processing deficits and mild inattention, the majority of the tasks required modification or were administered in a truncated form. Several tasks were adapted at the time of the evaluation by the authors to investigate specific skills or aspects of auditory processing. Therefore, normative data is unavailable or of limited value. The subsequent testing, described below, probed the distinction between certain impaired versus preserved skills in JS.

Confrontational naming was re-evaluated using the 15-item Boston Naming Test (BNT) on which JS correctly identified 11 of 15 items by scanning the photos in the right superior quadrant of his visual field. He transcribed his correct answers with two spelling errors, in addition to the four items misidentified or not identified. The subject correctly identified each of the remaining four items with written multiple choice options. The Auditory Word Recognition subtest of the Western Aphasia Battery (WAB; Kertesz, 1980) was modified with written instructions requesting that the subject to “Point to the_____.” He made no errors in the tested categories: *real objects*, *forms*, and *colors*. Two subtests of the Curtiss-

Yamada Comprehensive Language Evaluation-Receptive (CYCLE-R; Curtiss and Yamada, 1988) representing the most complex sentence structures (negative passives and object relative clauses with relativized objects) were administered in modified form, containing 5 sentences each. Modifications included providing written instructions rather than verbal instructions and identification with written word gender specification due to difficulty in interpreting the line drawings of human forms. The subject was unable to visually interpret one stimulus, but completed the remaining 9 items without difficulty or error. Syntax and grammar in spontaneous speech were not formally quantified but were perceived as within normal limits during multiple clinical encounters. On motor speech examination, dysarthria was prominent with hypernasality and diminished articulation. In sum, language testing revealed subtle anomia, potentially referable to visual impairment impeding identification of line drawings, and dysarthria, possibly secondary to a lack of auditory feedback from speech, but no frank aphasia.

Psychoacoustic Testing

All auditory stimuli were binaurally presented at moderate volume using speakers placed 2 feet or less from the patient when feasible. Twelve pre-recorded environmental sounds (categories: animal, human, musical instrument, tools/equipment; matched for difficulty) were selected from a previously described battery (Marcell, Borella et al. 2000). Multiple-choice picture matching was deferred as picture choices were deemed unidentifiable secondary to the subject’s visual impairment. JS accurately identified the onset of each environmental sound but was uncertain when the sound ended and failed to accurately name any of the stimuli. Subsequent presentation of environmental sounds selected for presumed variability in emotional valence and arousal characteristics (i.e. clapping, laughing, hammer, siren, and windchime (Gomez and Danuser 2004) demonstrated identification of paired stimuli as “same” or “different” at chance level (3/6). Also, he misidentified sounds as positive versus negative in valence. For example, the subject identified clapping as both positive and negative on consecutive trials and consistently misidentified and reported the most arousing negative stimulus, a siren, as moderately positive in valence using a Likert scale. In combination, the ability to respond to environmental sound onset but lack of recognition of the sounds regardless of emotional content was consistent with auditory agnosia for environmental sounds.

Non-standard sound localization testing was undertaken by requesting that the subject identify the location of a cellular telephone ring. Although JS was unable to name the sound, he reproducibly and correctly recognized the onset and localized the tone to three of six possibilities, each anterior to his location (left, right, and center.) He consistently misidentified the sound presented posterior to his position as originating from the right anterior sextant. Thus, JS was deemed deficient in sound localization in addition to sound interpretation.

Music testing was undertaken at three separate one to two hour encounters. During the initial session, pitch discrimination, melodic discrimination, and recognition of highly familiar tunes was assessed. The pitch discrimination task consisted of a series of 20 paired tones played consecutively. The subject correctly identified 13/20 as either “same” or “different.” Melodic discrimination was assessed using the stimuli from the Montreal Battery of Evaluation of Amusia (MBEA;(Peretz, Champod et al. 2003) scale task. The subject responded correctly to 3/10 items presented before he asked that the test be discontinued because his answers represented “guessing.” High frequency American patriotic and folk tunes (i.e. “Happy Birthday” and “My Country ‘Tis of Thee”) performed on piano and compiled as MIDI files for identification (Johnson et al, 2007) were then presented. JS was unable to correctly name or recognize as familiar any of the 12 selections. Subsequently, he was unable to identify a 3-minute orchestral excerpt of the United States National Anthem.

On further questioning, he was unable to name the instruments used in the recording nor could he reproduce the rhythm of this selection while it was presented aurally. In aggregate, the first music testing session revealed a pitch discrimination score slightly better than chance (potentially consistent with the relative preservation of pure tone audiogram) with an inability to recognize melody and timbre, to name highly familiar tunes, and to reproduce a presumably overlearned rhythm.

A subsequent testing session further investigated perception of rhythm as well as vocal melody production of the familiar tunes “Happy Birthday” and “Jingle Bells.” The meter task of the MBEA was attempted but aborted at the subject’s request after he was unable to interpret the example stimuli. Perception of rhythm was investigated serially by first asking the subject to tap the beat on the examination table in coordination with an unidentified tune selected from the highly familiar tunes. The tunes were then revealed as “Happy Birthday” or “Jingle Bells” and again the subject was asked to tap in rhythm with the clip. JS was unable to successfully complete the task in either format for either song. Likewise, melody and rhythm were unrecognizable during the subject’s attempts to sing each tune although the lyrics were correctly reproduced.

The patient’s perceived affective response and subjective pleasure while playing his personal music selections prompted a further investigation using favorite compact disc recordings from his own collection, including performances by Miles Davis, Dave Brubeck, Yo-Yo Ma, and The Russian National Symphony Orchestra performing selections of Wagner. He was unable to correctly identify the genre of randomly selected tracks from these limited choices in a series of 10 trials. Similarly, he could not correctly name solo instruments, and appeared to have no appreciation of variation in instrumental timbre. Surprisingly, with each example from his personal collection JS described the sound of the instruments he was hearing in detail and gesticulated the tempo of the piece he was describing by miming a performer or tapping his feet. There was never concordance between the selection being presented aurally and the track being described verbally and demonstrated physically. He appeared to recognize the onset of musical selections, but he appeared unaware of the offset. As a result of this testing session, vocal music production and rhythm production were revealed to be impaired, as was the recognition of meter. Rhythm identification without production was not formally investigated. Recognition of timbre and genre of music were impaired even when given a limited sample of personal selections, and the patient described and appeared to experience sounds distinctly different from those presented by the examiner.

Due to the prominent change in the patient’s affect when musical excerpts were presented, additional testing was undertaken styled after published accounts of assessing responsiveness to variables seemingly related to the perception of affect in music (Gosselin, Peretz et al. 2005); (Peretz, Gagnon et al. 1998); (Dalla Bella, Peretz et al. 2001). Four sample stimuli (available for download at http://www.brams.umontreal.ca/peretz/; (Gosselin, Peretz et al. 2005) were presented in random order with instructions to identify the excerpt as happy, sad, peaceful, or scary. JS tolerated the presentation of nine excerpts, correctly matching the intended emotion on 4/9 excerpts, a score slightly greater than expected by chance, but with no pattern to suggest more accurate positive or negative emotion identification. Complex musical stimuli intended to denote happiness or sadness (Peretz, Gagnon et al. 1998) were subsequently presented, and JS scored below chance level, appropriately identifying 4/10 excerpts with 3 correct “happy” responses compared to 1 correct “sad” response. A single musical stimulus with tempo, mode, and both variables manipulated was presented (available for download at http://www.brams.umontreal.ca/peretz/; (Dalla Bella, Peretz et al. 2001) to determine if the subject perceived any change in the affective valence of the stimuli. He rated the original stimulus as affectively neutral rather than happy, and unlike even young children, JS did not appreciate a change representing sadness with associated change to minor mode, slower tempo, or a combination of both changes, scoring 0/4 on this modified task. Combining these investigations of the patient's ability to determine the affective intent of musical stimuli, he demonstrated a marked deficit in perceiving changes to musical variables such as mode and tempo, but demonstrated a trend toward better emotion discrimination than melodic discrimination observed in music testing session #1.

Discussion

Our patient JS suffered from generalized auditory agnosia, yet showed remarkable sparing of his ability to appreciate and emotionally respond to music. The diagnosis of generalized auditory agnosia in JS is confirmed by the near-normal pure tone audiometry with an inability to recognize words, environmental sounds, familiar music or discreet musical variables. The bitemporal injury suspected with the clinical syndrome was corroborated by neuroimaging evidence; however, the neural substrate of the preserved emotional response to music remained as elusive as the etiology of the neurodegeneration.

Recent studies suggest that attribution of affect in music arises early in development with tempo and mode as the most important determinants of happy versus sad judgments of musical excerpts (Dalla Bella, Peretz et al. 2001; Dalla Bella, Peretz et al. 2001). This skill is probably distinct from identification of other separable musical variables such as pitch, melodic contour, melodic interval, rhythm, or meter (Liegeois-Chauvel, Peretz et al. 1998; Peretz, Gagnon et al. 1998). JS was unable to identify either of the affective variables or the intended results of their manipulation, emphasizing a distinction between the identification of the affective character of music and the resultant emotional experience associated with music. For example, a tragic aria is typically perceived as conveying negative affective valence but many listeners derive pleasure from the experience (Siegwart and Scherer 1995), which may even result in a positive musical emotion, “thrills” and “chills” (Blood and Zatorre 2001; Panksepp and Bernatzky 2002). Thus, it is plausible that one might not recognize the affective intent of music but still possess the capacity to experience an emotional response.

Investigations of the neural correlates of pleasurable responses to music with PET imaging demonstrate activation of reward circuitry (Cardinal, Parkinson et al. 2002) including the ventral striatum, midbrain, amygdala, orbitofrontal cortex, and ventral medial prefrontal cortex (Blood, Zatorre et al. 1999; Blood and Zatorre 2001). In particular the nucleus accumbens (NAc), ventral tegmental area (VTA), hypothalamus, and insula have demonstrated increased perfusion when subjects reported experiencing music-related pleasure in a fMRI paradigm (Menon and Levitin 2005). This neural circuit implies involvement of the dopaminergic and opioid neurochemical systems, with dopamine release in the VTA having been associated with NAc opioid transmission (Kelley, Bakshi et al. 2002; Zhang, Balmadrid et al. 2003).

Interestingly, the potential role for opioid mediation in music-associated pleasure was suggested prior to modern functional imaging techniques as subjects reported a decrease in their positive emotional reaction to musical stimuli after administration of a known opioid antagonist, naloxone (Goldstein 1980). Involvement of the endogenous opioid system may be further implicated by opioid receptor prominence in the inferior colliculus, a rudimentary yet important component of the auditory processing system in humans, that has been implicated in mediating affective responses related to non-musical sound perception (Panksepp and Bernatzky 2002). Deep brain structures not pathologically involved in our patient or other reported cases of generalized auditory agnosia may therefore contribute to the emotional experience of sounds, even in the absence of the capacity to identify specific characteristics of those sounds.

While such evidence may be compelling, an attempt to explain the emotional response of JS to music by invoking only subcortical structures seems insufficient. Subcortical sound processing in the thalamus and brainstem is observed in other species (Kanwal and Rauschecker 2007) with evidence of pre-processing extrapolated to humans (Boatman 2006). Indeed, the acoustic startle response (arguably the most primitive human emotional response to sound) localizes to the brainstem across species (Pissiota, Frans et al. 2002). While such explanations may begin to explain the preservation of the awareness of music onset for JS, they fail to account for the vivid, yet clearly erroneous, descriptions of the music JS experienced when confronted with auditory stimuli cognitively primed as selections from his personal music collection.

Importantly, the expectation that musical excerpts were to be extracted from his personal favorites may have been a determinant in the pattern of response that emerged when asking JS to describe his auditory experience during music testing session #2. Subjects rate musical taste as one of the most revealing preferences or activities in attributing personal qualities to themselves and others (Rentfrow and Gosling 2003). Further experimental evidence suggests that subjects are more likely to experience musically and emotionally induced “chills” when listening to personally preferred and familiar tunes (Panksepp 1995). Such preliminary evidence highlights experience as an important contributor to the emotional response to music, and suggests why one might strive to maintain a musical identity congruent with social expectations, even in the absence of adequately functioning auditory cortex. However, JS failed to correctly identify even the genre of music being presented, describing the classical writings of Wagner during Brubeck’s jazz stylings and later mistaking the examiner’s surprise sample of Johnny Cash for world renowned cellist, Yo-Yo Ma.

Understanding the musical experience of JS becomes even more challenging if one attempts to characterize the neurophysiological source of his experience, which is objectively a misperception of auditory stimuli. Musical hallucinosis is a well-described, albeit rare, disorder of the processing of sound, requiring a mental representation of high-level sound patterns (Berrios 1991). Functional imaging with PET has demonstrated activity in the posterior temporal lobes, right basal ganglia, cerebellum, and inferior frontal cortices in several patients actively experiencing continuous musical hallucinations of specific tunes following acquired peripheral deafness. Based on this evidence a modular representation of sound perception was formulated that suggests the potential for generation of spontaneous neural activity in the absence of the perception of pattern in segmented sound as depicted at the top of Figure 2 (Griffiths 2000). While the aforementioned model was created to describe musical hallucinosis in acquired deafness rather than auditory agnosia, it does allow for “triggering” of spontaneous activity which may be extrapolated to the experience of JS as depicted at the bottom of Figure 2.

On the contrary, all of the subjects contributing to the development of this particular model experienced musical hallucinations as distressing. This is in concordance with a review of the literature on musical hallucinations where 41% of subjects experienced the hallucinations as frightening, compared to only 10% of cases that were described as pleasant. More consistent with the experience of JS, 78% of the patients reported in the literature described hallucination of familiar tunes (Evers and Ellger 2004). This consistency in the familiarity of tunes has prompted other authors to suggest “neuronal irritation” resulting in stimulation of the relevant neuronal circuit with resultant re-experience of stored perceptual (in this case *musical*) experiences (Keshavan, Davis et al. 1992) Analogously, deafferentation resulting in visual hallucinations is well-known in the medical community and can result from pathology at any point along the visual system pathway (Eustache, Lambert et al. 1995). We speculate that JS experiences personally preferred music and his associated positive emotions by a similar mechanism. Using more precise terminology, such experience would represent a type of musical *illusion* rather than *hallucination*, as an auditory stimulus is actually presented and subsequently misperceived.

Alternatively, Keshavan and colleagues suggest the "concept of parasitic memory", or an unchangeable memory that can be experienced spontaneously or with some unidentified triggering mechanism. This theoretical occurrence may fit with recent functional neuroimaging data to explain the musical experience of JS and a common anecdotal experience, having a tune "stuck in one's head." The PET study identifies distinct neuroanatomic regions activated by semantic versus episodic musical memory tasks (Platel, Baron et al. 2003). The experience of JS would presumably involve activation of the episodic memory network triggered at the earliest auditory perceptual level (he denied experiencing music spontaneously when directly questioned) coupled with the musical expectation generated by presentation of the personally preferred compact discs and associated discussion or recollection of previous circumstances in which the familiar music was heard. Both explanations remain equally speculative given the available data in this case.

Although the mysteries of the emotional response to music in this case may not be unraveled during the lifetime of JS or his clinicians, reflection on current models of musical processing is demanded by the unusual attributes of the experience of this patient. Proposed revision to current musical models is represented in Figure 3, emphasizing the emotional response module as accessible from brainstem and subcortical regions active early in musical perceptual processing. Similarly, such early auditory processing may demonstrate previously unrecognized connectivity to an associative memory module in music.

Continued theoretical modeling of musical perception may move the study of the cognitive and affective neuroscience of music forward, but the therapeutic potential of music due to its intimate association with human emotion deserves future attention, as well. For example, an animal model exposed to daily music demonstrated significantly increased brain norepinephrine levels when compared to control animals (Panksepp 1986) suggesting music as a potential for treatment of attentional deficits and mood disorders. Similarly, after presentation of stressful stimuli salivary cortisol levels were noted to decline more rapidly in human subjects exposed to pleasant music when compared to subjects exposed to silence (Khalfa, Bella et al. 2003) suggesting the potential for music to modulate harmful effects of chronic stress on the brain (Sapolsky 1996). While it is not known what medical benefits, if any, JS may reap as a result of his persistently rewarding emotional experience of music, his case of neurodegenerative generalized auditory agnosia provides a unique opportunity to envision the positive consequences of exposure to music, or perhaps even more primarily, the mental rehearsal of music in health and disease.

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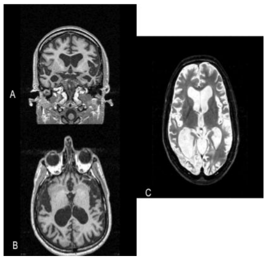

Figure 1.

A) T1coronal MRI demonstrating prominent bilateral temporal, insular, and inferior frontal atrophy

B) T1 axial MRI demonstrating dramatic superior temporal and insular atrophy bilaterally

C) T2 axial MRI demonstrating right occipital infarct and gliosis with compensatory change in occipital horn of lateral and generalized atrophy.

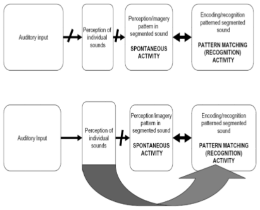

Fig. 2.

(*Top*) Griffiths' (2000) proposed basis for musical hallucinations due to spontaneous activity in the module for the perception and imagery of pattern in segmented sound
(*Bottom*) Modification to Griffiths' (2000) model to account for musical hallucinations/misperceptions with adequate perception of individual sounds

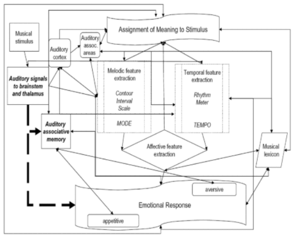

Fig. 3.

Proposed comprehensive psychoacoustic model for music perception based on musical modules described by Peretz et al. (2003). See text for details of rationale for departures from current theoretical models as highlighted with bold dashed connectors and italicized text.

Table 1

Neuropsychological Test Scores 2001

MMSE 25/30 (instructions given verbally; points deducted for following a 3-step command, repetition of a phrase, and spelling “world” backward)
Verbal Memory
CVLT learning trials: 4/9(2 intrusions), 4/9 (1 intrusion), 6/9 (1 intrusion), 8/9 (1 intrusion)
CVLT 30 sec delay recall 7/9 (2 intrusions)
CVLT 10 min recall 9/9 (1 intrusion)
CVLT 10 minute recognition 8/9
Visual Memory
Modified Rey figure recall 16/17
Visuospatial Construction
Modified Rey figure copy 16/17
Language
Modified Boston Naming Test 12/15
Working Memory
Digits span backward 4
Calculations 5/5
Fluency
“D” words in 1 minute 5 (2 rule violations)
Animals in 1 minute 16
Designs 6 (2 repetitions, 1 rule violation)
Set-shifting/ Inhibition
Modified Trails 41 seconds/ 14 correct lines
Stroop Interference condition 50/ 1 min (1 error)
Abstraction
Similarities & Proverbs 6/6