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Music processing deficits in Landau-Kleffner Syndrome: Four case studies in adulthood.

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Music processing deficits in Landau-Kleffner Syndrome: Four case studies in adulthood.

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Abstract.

Verbal-auditory agnosia and aphasia are the most prominent symptoms in Landau-Kleffner syndrome (LKS), a childhood epilepsy that can have sustained long-term effects on language processing. The present study provides the first objective investigation of music perception skills in four adult patients with a diagnosis of LKS during childhood, covering the spectrum of severity of the syndrome from mild to severe. Pitch discrimination, short-term memory for melodic, rhythmic and verbal information, as well as emotion recognition in music and speech prosody were assessed with listening tests, and subjective attitude to music with a questionnaire. We observed amusia in 3 out of 4 patients, with elevated pitch discrimination thresholds and poor short-term memory for melody and rhythm. The two patients with the most severe LKS had impairments in music and prosody emotion recognition, but normal perception of emotional intensity of music. Overall, performance in music processing tasks was proportional to the severity of the syndrome. Nonetheless, the four patients reported that they enjoyed music, felt musical emotions, and used music in their daily life. These new data support the hypothesis that, beyond verbal impairments, cerebral networks involved in sound processing and encoding are deeply altered by the epileptic activity in LKS, well after electrophysiological normalization.

Keywords:

Acquired epileptic aphasia - Musical perception disorders- Musical short-term memory - Pitch discrimination - Auditory agnosia

Declarations of interest: none

Music processing deficits in Landau-Kleffner Syndrome: Four case studies in adulthood.

1. Introduction

Developmental or acquired impairments of musical abilities (referred to as amusia) have been increasingly recognized and studied in recent years with the availability of standardized tests to dissociate components of music perception (e.g., Dalla Bella, Farrugia, Benoit, Begel, Verga, Harding, and Kotz, 2017; Peretz, Champod, and Hyde, 2003; Stewart, von Kriegstein, Warren, and Griffiths, 2006). A unique epilepsy syndrome with a major genetic component, the Landau-Kleffner syndrome (LKS), mainly manifests in childhood as an acquired aphasia and impaired central auditory perception (Deonna & Roulet-Perez, 2016). Whereas language processing has been extensively studied at all stages of LKS (including adulthood), there are no systematic data on potential auditory non-verbal impairments, notably in the music domain, as long-term consequences of this condition.

1.1 Landau-Kleffner syndrome

LKS was first described by Landau and Kleffner (1957). It is a rare childhood epilepsy syndrome associating speech and language regression with sleep activated focal epileptiform activity in the perisylvian regions of the cortex reflected in the electroencephalogram (EEG). Continuous spike-waves during sleep are frequently observed, but seizures are not always reported. Age of onset of LKS is typically between 3 and 7 years of age, a crucial period for language development. Verbal auditory agnosia (VAA) and progressive deterioration of expressive language are the main clinical signs. Central auditory and language impairments usually occur while non-verbal intelligence and peripheral hearing, as tested by tonal audiometry or brainstem auditory evoked responses, are normal. There is no structural abnormality on anatomical brain MRI, but regional alterations of brain metabolism are found in the acute phase. LKS is now considered to be at the more severe end of a spectrum of childhood focal epilepsies; the mildest end being childhood epilepsy with centro-temporal spikes (CECTS, also called rolandic epilepsy; Deonna & Roulet-Perez, 2016).

The pathophysiology of LKS is complex and still poorly understood. It differs from the classical link established between seizures and ictal or postictal cognitive deficits observed in other epilepsies. Temporal correlations between language symptoms and EEG abnormalities are often not observable in the short-term but only on a broader time scale,

suggesting a prolonged neural dysfunction linked to the sleep-related epileptic activity. In severe cases, epileptiform discharges seem to alter developing language networks, including long-term consequences persisting into adulthood (Deonna & Roulet-Perez, 2016; Roulet-Perez, 1995; Takeoka, Riviello, Duffy, Kim, and Kennedy, 2004).

Epileptiform abnormalities spontaneously decrease at puberty and language progressively improves, but impairments frequently remain. Their severity depends on the age of symptom onset, with worst outcomes for children with LKS onset before 5 years of age (Dulac, 1983; Bishop, 1985, Cockerell, Bolling, and Nakken, 2011) and with the longest durations of the EEG abnormalities during childhood (Smith & Hoepfner, 2003).

1.2 Central auditory disorders in LKS

Previous studies investigating LKS have shown a large spectrum of central auditory disorders in the acute phase of the disease. Concerning language processing, alterations of phonological discrimination seem to be the core disorder, resulting in impairments in speech comprehension (Majerus, Linden, Poncelet, and Metz-Lutz, 2004; Metz-Lutz, 2009; see Titus, 2017, for a review). Syntax processing and semantic lexicon might be altered independently, but they remain difficult to evaluate given the severe phonological alterations and the absence of baseline assessments in these young children. Prosody processing seems relatively spared (Kim Dufor, Ferragne, Dufor, Astésano, and Nespoulous, 2012). Clinical observations report that environmental sound identification is altered in the acute phase of the disease in the most severe cases (e.g., global auditory agnosia, see Cockerell et al., 2011), and that it recovers earlier than does word identification (Kaga, 1999; Korkman, Granström, Appelqvist, and Liukkonen, 1998). Timbre discrimination may be affected, for instance with a difficulty distinguishing male from female voices (Kaga, 1999, case 2). Auditory verbal short-term memory, working memory, and attention are severely impaired (e.g., Cockerell et al., 2011). Auditory and verbal impairments may be so severe that the child may behave as if he/she was profoundly deaf (Chevrie-Muller et al., 1991). Out of 19 patients described in Cockerell et al. (2011), 37% showed auditory agnosia (agnosia for speech and environmental sounds), 10% a verbal agnosia and 53% auditory discrimination deficits (impaired verbal processing in noise or with distraction). Although mild forms of LKS can fully recover, long-term consequences frequently include impairments in phonological processing, verbal short-term memory and working memory (Majerus et al., 2003). Lexico-semantic short-term memory is generally found intact (Majerus et al., 2004). Using a dichotic listening task, several studies reported

extinction of one ear, reflecting an auditory attention deficit (Majerus et al., 2003; Metz-Lutz et al., 1997, 2001). For instance, in the study by Rejnö-Habte Selassie, Hedström, Viggedal, Jennische and Kyllerman (2010), 100% of the patients tested in adulthood ($n=19$) showed one ear extinction on a dichotic test (implemented with disyllabic words). Twelve out of the 19 adult patients also displayed speech comprehension difficulties in a noisy environment. However, up to now, investigations of potential long-term deficits beyond verbal skills are scarce, and a full picture of the late consequences of the syndrome on auditory perception and cognition as well as the definition of the core deficits are still missing.

1.3 Musical disorders in LKS and aim of the present study

To our knowledge, no published research has investigated musical skills in LKS with a systematic approach, either in the acute phase or at follow-up. However, some clinical reports suggest that music perception or production are affected. Among four LKS patients with auditory agnosia described by Kaga (1999), three demonstrated deficits of musical abilities at the most severe stage of their disease. Case 1 was unable to identify or did not even react to environmental sounds, including instrumental sounds; case 2 was described as committing rhythmic, harmonic and tempo errors when playing the piano, with normalization at follow-up (adulthood); and case 4 was impaired in song recognition and in song melody and rhythm discrimination, without normalization at follow-up. Deonna and Roulet-Perez (2016) also report the testimony of Christine, who complained about an aversion to music and her difficulty carrying a tune during the acute phase of her LKS in childhood. At follow-up (age 29), her aversion to music had decreased, but singing performance remained poor.

These scarce clinical data suggest that, when located in the superior temporal regions, the epileptic dysfunction may alter not only phonological processing, but also lower levels of sound processing, such as pitch processing. This hypothesis is supported by an EEG study in six LKS adults (Seri, Cerquiglini, and Pisani, 1998), revealing a delay in the N1 component recorded over lateral temporal cortex both to tones and speech sounds.

While language often recovers significantly and sometimes even fully in children with LKS, notably thanks to antiepileptic drugs and language therapy, it is unclear whether musical disabilities persist at long-term follow-up and what consequences they may have on the patients' quality of life. For instance, pitch processing deficits might affect speech prosody processing even in the long-term.

In the present study, we aimed to investigate music perception in four adult patients with a childhood diagnosis of LKS. These patients had been fully investigated during childhood and had follow-up examinations in adulthood. Our hypothesis, based on the cases reported above, was that musical abilities might remain impaired in adulthood (thus years after EEG normalization), as an unrecognized consequence of LKS.

Our main aims were to 1) obtain a detailed assessment of music perception with a set of tests investigating pitch discrimination, short-term memory for melodic, rhythmic and verbal information, as well as emotion recognition in music and speech prosody; 2) investigate the potential impact of impaired music perception on patients' attitude to music (including the use of music in daily life and feelings evoked by music listening) with a questionnaire; and 3) link the observed impairments of music perception with the severity of LKS during childhood (as defined by age of onset, language impairments, and age of EEG normalization; see Bishop, 1985; Cockerell et al., 2011).

2. Material and methods

2.1 Participants

Four adults diagnosed with LKS as a child and ten matched control subjects (see below) participated in the study. All participants gave written informed consent. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

2.1.1 Patients

We included four French-speaking patients treated for LKS at the Centre Hospitalier Universitaire Vaudois (CHUV) Lausanne, Switzerland. Inclusion was determined by a history of clinical language symptoms, typical epileptic EEG abnormalities (including activation of the discharges during sleep, see Deonna & Roulet-Perez, 2016), normal brain imaging (CT or MRI) and gradual improvement of symptoms during follow-up without evidence of any other brain disorder or intellectual deficit. All adult patients followed and studied at the CHUV since 1987 were included. No patient was excluded after being tested. The four patients illustrate the full range of severity of LKS: Patient 1 and Patient 2 had a long duration of the disease with incomplete language recovery, Patient 3 had a moderate duration of the disease and almost complete recovery, and Patient 4 had a short duration of the disease and full recovery. Non-verbal intelligence was preserved for all patients, as tested by the Wechsler Intelligence Scale for Children (Wechsler, 1991) or the Raven's 38 Matrices (Raven, 1960).

Patients had no musical education background (i.e., formal choral or instrumental training; see the Results section 3.5 for details about their musical background). EEG normalization occurred at least 10 years before the current tests. The main clinical and EEG data are shown in Table 1. A tonal audiometry (250-8000Hz) and a dichotic listening test with forced choice responses were performed as pre-tests at the beginning of our assessment. The dichotic listening test consisted of a list of 12 pairs of bisyllabic nouns to test central processing of verbal materials.

Patient 1

Patient 1 was a right-handed 30-year-old man (Roulet-Perez et al., 2001). He presented with severe language regression at the age of 3.5 years after previously normal language development. LKS was diagnosed 2 years later. EEG anomalies lasted 2 years, and VAA gradually improved from 8 years to adolescence. The patient attended a school for the deaf, was fluent in sign language and received a high school diploma in a technical domain. Receptive and expressive language abilities recovered with intensive speech and language therapy at age 16, but phonological and syntactic impairments were still present at the time of testing. Auditory acuity in the left ear decreased after a blast trauma at adolescence. Our audiometric examination revealed a mild auditory loss in the left ear between 1000 and 6000Hz, while acuity was normal for the right ear. The dichotic listening test could not be interpreted due to the mild unilateral hearing loss.

Patient 2

Patient 2 was a right-handed 28-year-old woman who presented with severe LKS at the age of 3 years, diagnosed shortly after onset. VAA persisted for 6 years with very slow improvement, and at the time of testing, language still revealed phonological, lexical and syntactic impairments; however, these were efficiently compensated in conversations. The patient attended a regular school and was working as a classroom assistant at the time of testing. She was following intensive speech and language therapy up to the time of testing. Auditory acuity was normal in the tested frequency range. The dichotic listening test revealed a left-ear extinction.

Patient 3

Patient 3 was a right-handed 18-year-old man who presented with moderate LKS at the age of 4 years, diagnosed a few months later. VAA lasted 1.5 years and EEG anomalies lasted 6 months (normalization after medication). He attended a regular school and worked as a waiter at the time of testing. Neuropsychological testing at the age of 12 years described persistent impairments in verbal auditory short-term memory, with normal performance in visuo-spatial short-term memory. At assessment, an impairment for speech perception in noise was still present, as well as subtle perceptual phonological deficits. Auditory acuity was normal in the tested frequency range. The dichotic listening test revealed a right-ear extinction.

Patient 4

Patient 4 was a left-handed 26-year-old man, who presented with mild LKS at the age of 6.5 years, diagnosed a few months after onset. Occasional rolandic seizures on awakening were still present at 9 years of age without affecting verbal expression. He attended a regular school and was working as an accountant at the time of testing. Auditory acuity was excellent (+5 and +10dB between 1000 and 8000Hz) in the tested frequency range. The dichotic listening test revealed a right-ear extinction. The patient commented he could hear some noise in his right ear without being able to understand it, even when paying attention to it.

Please insert Table 1 about here

2.1.2 Control participants

Ten male participants were included in the study. One was excluded because of psychiatric symptoms. A last participant was included in order to reach a sample of 10 control participants, aged between 18 and 30 years-old (mean age: 20.3 ± 2.5). Six were right-handed and 4 were left-handed. They had a maximum of 2 years of musical education (mean years of formal instrumental training \pm standard deviation (SD) = 0.4 ± 0.7) and a maximum of 3 years of graduate studies at university to be globally matched to the patients. All participants were native French speakers without any history of neurological or psychiatric illness. Their auditory acuity was normal in the tested frequency range (250-8000Hz), except one participant who had a moderate deficit in one ear for 6000Hz (-30dB) and 8000Hz (-50dB).

This high-frequency and unilateral deficit was not likely to alter performances in the tests performed.

2.2 Procedure

Patients performed a series of audiometric tests (tonal and vocal audiometry in silence and in noise, dichotic listening, and the “Speech, Spatial and Qualities of Hearing Scale” questionnaire) as well as prosodic and musical tests. Residual language deficits and audiometric findings for patients are outlined in section 2.1.1 above, but full details of the audiometric tests are not reported in the present manuscript, which focuses on musical skills. Controls performed the same tests, except the prosodic tests, for which we used the published norms provided in the test battery, including pathological cut-off scores (see below, section 2.2.1).

2.2.1 Musical tests: standard evaluation of basic perceptual and mnemonic skills

MBEA Scale subtest

The Scale subtest is the first and most sensitive subtest from the Montreal Battery of Evaluation of Amusia (MBEA, Peretz et al., 2003; see Peretz et al., 2008), an international and standardized neuropsychological test battery used to diagnose amusia in adults. In each trial, participants were asked to compare two melodies and indicate whether they were identical or different. In the “different” pairs, one note from the second melody was out-of-tune. This subtest is composed of 30 items (15 identical and 15 different pairs). Performance of our control group was used as a reference to evaluate the patients’ performance. Note that, with reference to the data of an adult population (18-75yo, $N= 421$ participants, <http://www.peretzlab.ca/publications/2003/page2> , 2013 updated norms following the publication of Peretz et al., 2003), a score equal or inferior to 70% correct answers ($-2 SD$ from the mean) on the Scale subtest is generally considered as an indicator for amusia.

	P1	P2	P3	P4
<i>Language development prior to VAA</i>	normal	“simple speech delay” (3y)	normal	normal mild articulation disorder
<i>Age at onset of symptoms</i>	3y6m	3y2m	4y	6y6m
<i>Age at diagnosis</i>	5y6m	3y5m	4y9m	6y8m
<i>Epilepsy (active phase of the disease)</i>	Rare, exclusively nocturnal seizures with focal onset	No documented seizures	Rare “absences” at onset + hemifacial seizures	Rare Rolandic seizures before onset and after recovery of VAA
<i>Total duration of VAA</i>	5y	6y	15-18 months	4 months
<i>Main EEG findings</i>	Bilateral temporo-posterior foci, asynchronous, markedly increased by sleep	Bilateral temporo-posterior, asymmetrical, increased by sleep	Bilateral temporo-posterior, markedly increased by sleep + independent centro-temporal	Bilateral, independent centro-temporal, markedly increased by sleep
<i>Duration of abnormal EEG</i>	2years	5years	6months	Bilateral: 2months Unilateral (rare) at 9yo
<i>Treatment</i>	CBZ, STM: no effect Prednisone at 6y4m for 18 months	VPA, CLB: no effect Hydrocortisone for 4y	CLB, VPA: for 6 months, partial effect Prednisone at 5y6m for 2 years	CLB: 2 months Prednisone for 6 months

VAA = Verbal auditory agnosia. EEG = Electroencephalogram. CBZ = carbamazepine. STM = sultiame. CLB = clobazam. VPA = valproic acid

Table 1: Clinical and EEG Data for the 4 Patients.

MBEMA Rhythm subtest

The rhythm subtest was taken from the child version of the MBEA (MBEMA, Montreal Battery of Evaluation of Musical Abilities, Peretz et al., 2013) to lower the difficulty of the task and avoid possible floor effect in patients’ performance. Participants were asked to compare two short melodies and indicate whether they were identical or different. The “different” pairs included a rhythmic change. This subtest was composed of 20 items (10 identical and 10 different pairs). There are no norms for the age range of our patients (norms are provided up to 16 years). Performance of our control group was thus presented in the Results section and used as a reference to evaluate the patients’ performance.

Pitch Discrimination Task

We used an adaptive pitch discrimination test enabling computation of the finest pitch difference a participant can perceive (relative pitch discrimination threshold). The protocol was based on the presentation of two pairs of tones, one pair with identical pitches, the other pair with a small pitch difference. The participant indicated whether the pitch difference was in the first or in the second pitch pair. The procedure is described in detail in Tillmann, Schulze, and Foxtan (2009). The higher the threshold, the lower the performance in pitch discrimination. Performance of our control group is presented in the Results section and used as a reference to evaluate patients' performance.

2.2.2 Auditory short-term memory

We created two short-term memory tests, adapted from Tillmann et al. (2009), one with tones, the other with spoken syllables (similar to Hirel et al., 2017). One trial was composed of two sequences of four sounds (tones or syllables, each sound with a duration of 500 milliseconds (ms), presented with an inter-stimulus-interval of 40 ms) separated by a silent delay of 1 second. The syllables were formed by a consonant followed by the French vowel /u/. The two sequences were either the same or different. In the "different" pairs, one tone was changed for the tonal test (yielding an inverse interval direction from ascending to descending or the reverse), and one syllable was changed in the verbal test. Participants were asked to indicate whether the two tone sequences or the two syllable sequences were identical or different. This test was composed of 32 items (16 identical and 16 different pairs) for each material. Results of the control group are presented in the Results section and used as reference to evaluate patients' performance. This auditory memory test aimed to evaluate tonal short-term memory, while comparing performance to a verbal task composed of items of the same duration and presentation speed.

2.2.3 Prosodic tests

Patients performed the two subtests of the receptive prosody test from the Montreal Evaluation of Communication (MEC) protocol (Joanette, Ska, and Côté, 2004). For the Emotional Prosody test, participants had to indicate whether spoken sentences (played from audio files) expressed joy, anger, or sadness, and for the Linguistic Prosody test, whether spoken sentences were said with an affirmative, interrogative, or imperative intonation. Semantic content was emotionally neutral, and syntax was not informative. The Emotional and Linguistic Prosody subtests both contained 12 items. Published norms are available in

Joanette, Ska, and Coté (2004) for the age range 18-29 years. In the Linguistic Prosody test, the pathological cut-off is established at 8/12 correct responses (mean score = 10.7, $SD = 1.46$) when education is 11 years or lower, and at 10/12 correct responses (mean score = 11.27, $SD = 1.55$) when education is above 11 years. In the Emotional Prosody test, the pathological cut-off is established at 10/12 correct responses for both education levels (mean score = 11.6, $SD = 1.46$ for education of 11 years or less, mean score = 11.27, $SD = 1.55$ for education over 11 years).

2.2.4 Emotion perception in music and faces

Participants performed two emotion categorization and quantification tests, as described in detail in Leveque et al. (2018): one with musical excerpts and one with pictures of faces for comparison (taken from a classical set of black and white pictures; Ekman & Friesen, 1976). After having listened to one musical excerpt or seen one face, participants were asked to indicate the emotion that was evoked by the item amongst four emotions: joy, sadness, fear, or serenity (for music) or joy, sadness, fear or neutral (for faces). Participants were then asked to rate the intensity of the emotion on a subjective scale from 1 (*weak*) to 5 (*strong*), except for the ‘neutral’ judgment for faces. When the response “neutral” was chosen, the emotion intensity rating was not presented. Results of the control group are presented in the Results section and used as reference to evaluate patients’ performance.

2.2.5 Questionnaire about the patients’ attitude to music

Patients filled out a questionnaire of 90 items, dealing with their attitude to music (based on questionnaires of McDonald & Stewart, 2008; Peretz, Brattico, Järvenpää, and Tervaniemi, 2009, and Sloboda, Wise, and Peretz, 2005). The questionnaire was completed with the help of the experimenter, checking that questions were correctly understood. Questions covered different domains, such as self-assessment of musical skills (e.g., *Do you sing accurately?*), exposure to music in childhood (e.g., *As a child, how often were you exposed to music at home?*), use of music in daily life (e.g., *How often do you listen to music when you are doing sport?*), musical emotions (e.g., *Indicate how much you agree with the following sentence: “music can evoke memories”*), and self-assessment of other central auditory skills (e.g., *How often are you able to correctly identify a famous voice?*). Responses were given on scales (ranging from 1 to 5) or with a binary choice (yes/no), but patients’ additional comments were also noted.

2.3 Data analyses

When published norms were available (tests from the MBEA and the MEC), they were used to determine the pathological cut-off. Otherwise, patients' performance was considered impaired when inferior to the mean of the control group by at least 2 *SD*, except for the pitch threshold where the pathological zone was 2 *SD* superior to the mean of the control group. Information on patients' attitude to music extracted from the questionnaire will be presented in a qualitative way.

2.4 Availability of data

The conditions of the informed consent signed by our participants do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author Yohana Lévêque, at the Lyon Neuroscience Research Center. Access will be granted to named individuals for research projects or meta-analyses, with no further conditions applied.

We were not the owners of most of the stimuli we used in the study. Readers seeking access to the stimuli may contact Yohana Lévêque to obtain the contacts of the research teams who originally created the stimuli and collaborated with us either in the present study or a previous one or have made public access already. Material and stimuli for the MBEA Scale (Peretz et al., 2003) and MBEMA Rhythm (Peretz et al., 2013) subtests are accessible on https://www.peretzlab.ca/knowledge_transfer/. The Pitch Discrimination test has been developed by Jessica Foxton and used in the following collaborative publication: Tillmann, Schulze, and Foxton (2009) and several others of our team (e.g., Hirel et al., 2017; Lévêque et al., 2018). Individual sounds used in the auditory short-term memory tests were created by Schulze and Tillmann for a previous study (Schulze, K. & Tillmann, B., 2013) and assembled in sequences with new characteristics for the present study. Stimuli from the MEC protocol are commercialized by Ortho Edition (Joanette, Y., Ska, B., & Côté, H., 2004, Protocole Montréal d'évaluation de la communication. Isbergues, France: Ortho-Edition.). Musical stimuli for the emotion categorization test have been selected by Emmanuel Bigand and Philippe Lalitte (University of Burgundy, LEAD - CNRS 5022, Dijon, France), and used in the following collaborative publications: Leveque et al., 2018; Belfi et al., submitted. Copyright for face stimuli (Ekman & Friesen, 1976) is held by Paul Ekman Group.

3. Results

3.1 Musical tests: evaluation of basic perceptual skills

Out of the four patients, the 3 more severe cases presented impaired performance in the MBEA Scale subtest and the MBEMA Rhythm subtest (see Figure 1). Patients 1 and 2 were close to chance level (50%). Patients 1 and 3 also complained about the length of the tests.

We also analyzed performance with signal detection theory (Macmillan & Creelman, 1990), using d' as an indicator of discrimination sensitivity and c as an indicator of response bias. This analysis is based on calculation of the proportion of hits (i.e., correct responses for “Different” trials) and false alarms (i.e., errors for “Same” trials). d' corresponds to $z(p[\text{hits}]) - z(p[\text{false alarms}])$ and c to $-0.5(z(p[\text{hits}]) + z(p[\text{false alarms}]))$. The results are as follows: controls average $d' = 2.84 \pm 0.54SD$, $c = -0.14 \pm 0.26SD$; Patient 1 $d' = -0.35$, $c = 0.26$; Patient 2 $d' = -0.37$, $c = 0.44$; Patient 3 $d' = 1.46$, $c = 0.11$; Patient 4 $d' = 2.12$, $c = 0.44$. (Note that a negative c indicates a tendency to answer “different”). This analysis confirmed that the 3 more severe cases were below the pathology cut-off (-2SD from the controls' mean) for the discrimination sensitivity at the Scale test.

Pitch discrimination thresholds of these 3 patients were increased (see Figure 1), with a pitch threshold of 3.6 semitones for Patient 1, 4.79 semitones for Patient 2, and 0.92 semitones for Patient 3 in comparison to a mean of 0.27 ± 0.18 semitones for controls.

Patient 4 performed within the range of controls for performance on the Scale and Rhythm subtests, and pitch discrimination threshold.

These results provided indicators for strong amusia in Patients 1 and 2 (scores more than 6 SD from the control group for the Scale, Rhythm and Pitch discrimination threshold tests), moderate amusia in Patient 3 (scores more than 2 SD from the control group on the same tests), and no amusia in Patient 4 (scores less than 2 SD from the control group), in line with the severity of the LKS they had presented with.

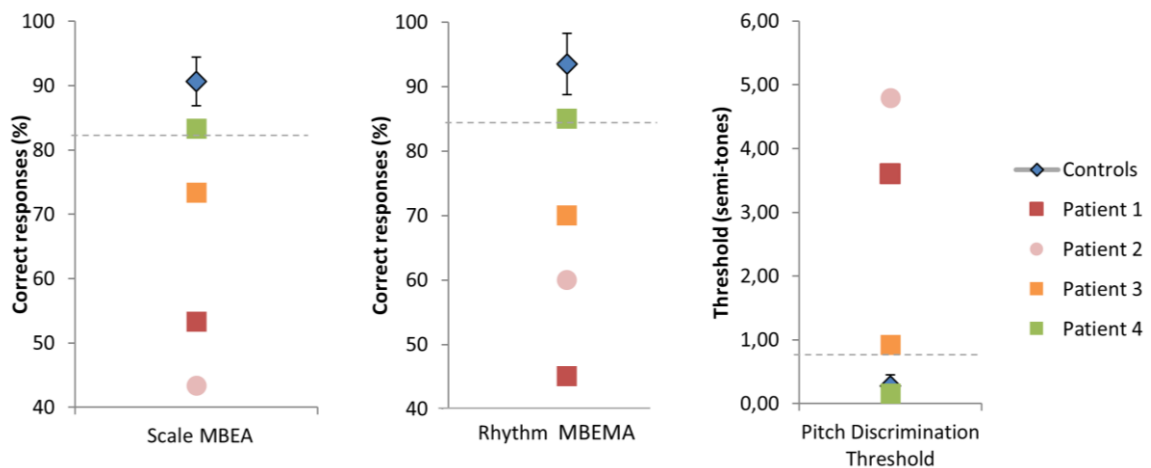


Figure 1. Controls' and patients' performance on the Scale subtest of the Montreal Battery of Evaluation of Amusia, the Rhythm subtest of the Montreal Battery of Evaluation of Musical Abilities, and the Pitch Discrimination Threshold test. The dashed line indicates -2 standard deviations from our controls' mean for the MBEA and the MBEMA subtests, and $+2$ standard deviations from the mean for the Pitch Discrimination Threshold test. Error bars indicate the standard deviation. Note that higher values on the Pitch Discrimination Threshold test represent poorer performance.

3.2 Auditory short-term memory

Performance on the musical short-term memory task was impaired in Patients 1, 2 and 3, with respective performance at -15 SD, -13 SD and -10 SD from the mean of our control group. Patients 1 and 2 were close to chance level (see Figure 2). The verbal short-term memory task revealed a similar pattern, with Patients 1, 2 and 3 being impaired, respectively at -6 SD, -6 SD and -3 SD from the control group mean. Patients 1 and 2 were close to chance level. Patient 3 had a lower score in the musical task than the verbal task. Note that both tasks were easy for the control participants, with the musical task (correct responses: $92.5\% \pm 3.34$) being slightly easier than the verbal task ($88.5\% \pm 7$; difference statistically non-significant, $p = .15$).

Performance of Patient 4 fell within the range of controls.

The results of the analysis according to the signal detection theory are as follows: controls average $d' = 2.88 \pm 0.34$ SD, $c = 0.05 \pm 0.14$ SD for tones, $d' = 2.48 \pm 0.62$ SD, $c = 0.007 \pm 0.21$ SD for syllables; Patient 1 $d' = -0.48$, $c = 0.08$ for tones, $d' = -0.31$, $c = 0$ for syllables; Patient 2 $d' = -0.33$, $c = 0.32$ for tones, $d' = 0$, $c = 0.15$ for syllables; Patient 3 $d' = 0.52$, $c = 0.42$ for tones, $d' = 1.54$, $c = 0.36$ for syllables; Patient 4 $d' = 3.01$, $c = -0.36$ for tones, $d' = 2.42$, $c = 0.32$ for syllables. With these indicators, the patients reported as being -2 SD from the controls' mean

were still inferior to -2SD and patient 4 performance was still similar to controls. d' scores were higher for music than for words in controls and Patient 4, while Patient 3 showed the reverse pattern, as reported with the percent of correct response. Patients 1 and 2 were at floor (negative d' or close from 0 for tones and words) as reported with the percent of correct responses. This analysis thus confirmed the effects previously reported.

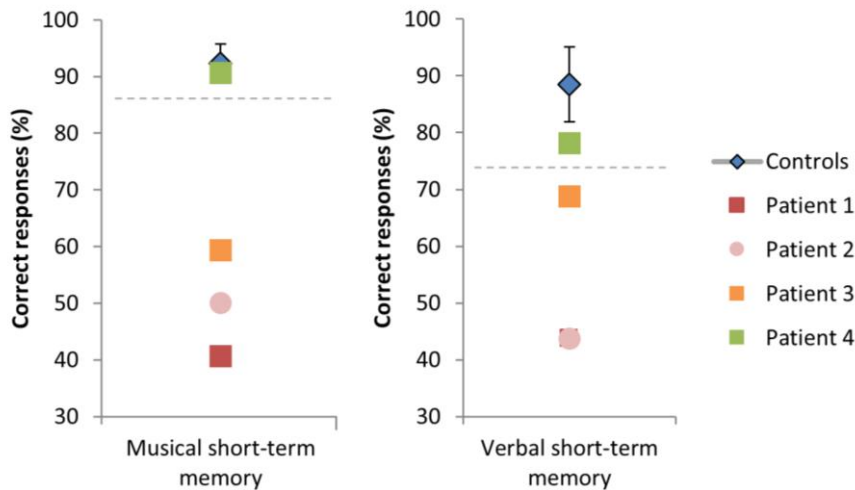


Figure 2. Controls' and patients' performance on a musical and verbal short-term memory test based on the comparison of pairs of tone or word sequences. The dashed line indicates the pathological cut-off, set up at -2 SD from the controls' mean. Error bars indicate the standard deviation.

3.3 Prosodic tests

Patient 1 showed pathological performance in the understanding of emotional (8/12 correct responses) and linguistic (7/12 correct responses) prosody, in reference to the pathologic cut-off reported in the MEC norms (see section 2.2.3). Patient 2 had normal understanding of emotional prosody (12/12), but impaired understanding of linguistic prosody (7/12). Patients 3 and 4 showed normal performances (both 12/12 for emotional prosody and both 11/12 for linguistic prosody).

3.4 Emotions

3.4.1 Music

Patients 1 and 2, who had the most severe syndromes, were impaired in categorizing musical emotions (see Figure 3). Note that Patient 2 had a score below the cut-off for the negative valence emotions (sadness and fear) but control-like scores for positive valence emotions (joy and serenity). Patients 3 and 4 performed within the range of controls. Emotional intensity was evaluated at a similar level by patients and controls, except for sadness for Patient 1 (Figure 3). Thus no patient had musical anhedonia (i.e., an incapacity to feel musical emotions and enjoy music), which would have been reflected by decreased scores in this emotion intensity judgment (e.g., Hirel et al., 2014).

3.4.2 Faces

All patients had scores in the normal range for the recognition of emotion on faces and associated intensity ratings, thus excluding generalized emotional deficits as the cause of impaired performance on the musical task for Patients 1 and 2.

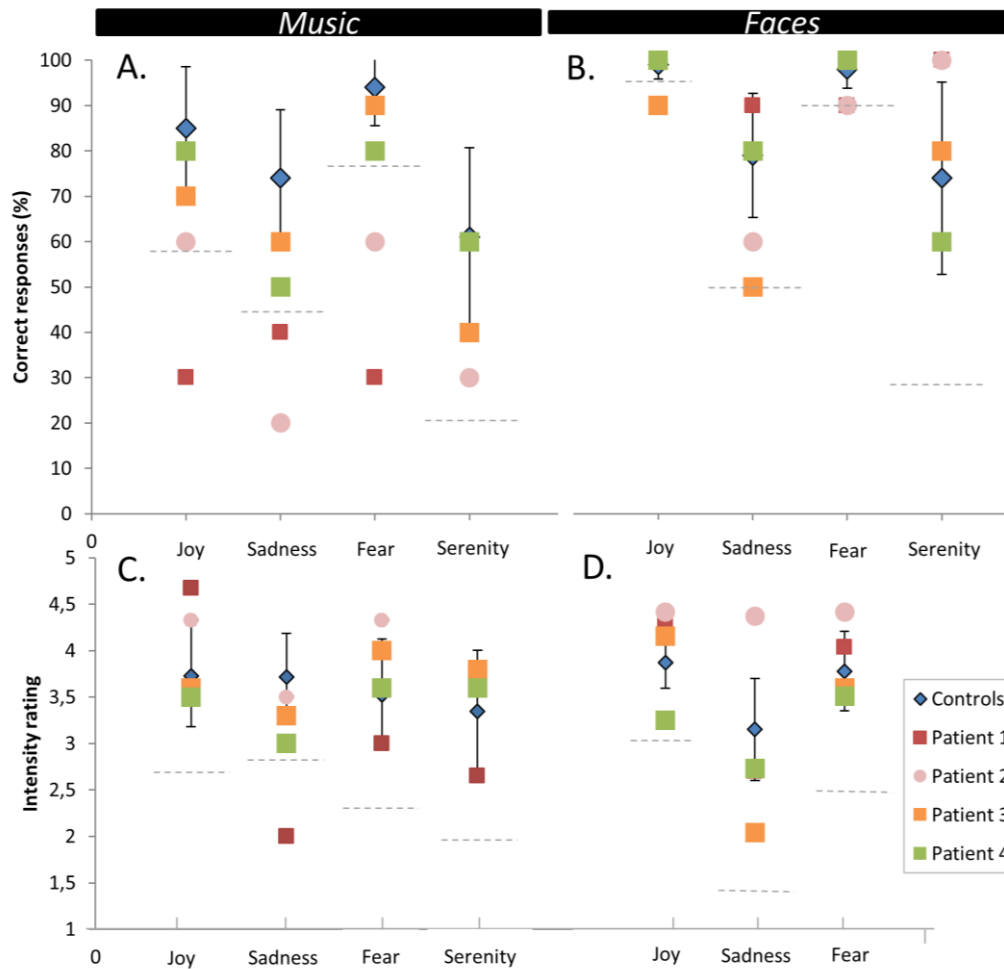


Figure 3. Controls' and patients' performance on the emotion categorization test for music (A) and faces (B) and their mean emotion intensity ratings for music (C) and faces (D). The dashed line indicates the pathological cut-off, set at - 2 standard deviations from the controls' mean. Error bars indicate standard deviation.

3.5 "Attitude to music" questionnaire

Patient 1 has not received musical training (note that he went to a school for deaf children). He never sings, even for his children, and rarely dances. He rates his skills in singing and dancing as very bad and reported being rarely able to detect an out-of-tune note, to recognize a familiar tune or to identify a famous voice. He indicates that understanding song lyrics is very difficult. Music, however, generates emotions, evoking personal memories or "motivating and reinforcing" him. He does not find concerts enjoyable, but appreciates listening to music when he is alone and able to concentrate. He reports that music accompanies numerous moments of his daily life (sports, reading, working and driving "except when it is a sports car because the exhaust pipe makes music"!).

Patient 2 has not received musical training at school or at home. Music was temporarily used as a therapeutic tool in a disability center, and she attended a choir for 3 months as part of her National Vocational Qualification, but as a child and teenager, her motivation toward these musical activities was low. She reports listening to music and dancing frequently. She considers herself unable to carry a tune accurately, but to dance well, being able to follow the rhythm of music, detect an out-of-tune note and recognize a familiar tune. She reports feeling emotions when listening to music (enthusiasm, sadness...). She finds rap music irritating, but music is globally a pleasure and accompanies active moments of her daily life (in particular, sports and driving).

Patient 3 has received basic musical training at school¹. He sings sometimes in private, but never in public, and is never dancing. He considers himself unable to carry a tune accurately and being a poor dancer, not able to follow the rhythm. However, he reports being able to detect an out-of-tune note and to recognize familiar tunes. He reports feeling emotions with music and listens to music very frequently (when taking a bath, eating alone, reading, doing sports, homework, housework, etc.)

Patient 4 has received basic musical training at school¹. He never sings in public and almost never in private, and reports being unable to carry a tune accurately. He almost never dances, but considers himself able to dance and follow the rhythm of music. He reports being able to detect an out-of-tune note and to recognize familiar tunes. Music generates diverse emotions for him, and he often listens to music when doing housekeeping, but more rarely for other activities.

Overall, patients report poor production skills (i.e., singing), but good perceptual skills (except for Patient 1). Most importantly, all patients report feeling emotions when listening to music and fully integrate music in their daily life.

4. Discussion

In this study, which is, to our knowledge, the first to investigate musical skills with objective measures in adults diagnosed with Landau-Kleffner syndrome in childhood, we observed amusia in three out of four patients, and overall, musical abilities were linked to the severity

¹ One hour a week maximum of musical education generally led by a non-specialized teacher in primary school; followed by more specialized teaching in secondary school, but without any extensive training to practice an instrument or acquire technical vocal skills.

of the disease in its acute phase. Amusia, defined as the inability to discriminate and memorize musical sounds, was shown at a rarely observed level of severity in two patients (Patients 1 and 2) and was milder in one patient (Patient 3).

Our pre-tests showed one-ear extinction on dichotic listening for the three patients where we could interpret the test results (Patient 1 was excluded for acoustic trauma), as described previously in the literature (Metz-Lutz et al., 2001; Wioland, Rudolf, and Metz-Lutz, 2001). None of the patients had significant peripheral auditory impairment that could have altered music perception. We here provide evidence for poor pitch discrimination, poor pitch and rhythmic change detection, and impaired short-term tonal memory in Patients 1, 2 and 3. Patient 4, who had a mild form of LKS, showed control-like performance. For the two patients with more severe forms of LKS (Patients 1 and 2), the amusia extended to speech prosody recognition as well as to musical emotion categorization, in line with findings in participants with congenital amusia (Leveque et al., 2018; Pralus et al., 2018).

In contrast to these perceptual and cognitive disorders of music processing, none of our patients showed musical anhedonia. They reported feeling pleasure and emotions when listening to music, and to listen to music on a daily basis; they also evaluated the emotional intensity of musical excerpts with control-like ratings, similarly to findings observed in congenital amusia (Leveque et al., 2018).

4.1 Brain correlates and impact of syndrome severity

In the four patients, the severity of musical impairment was proportional to residual language deficits and to the age of onset of LKS and/or duration of the clinical symptoms. The importance of age of onset on follow-up outcomes is in agreement with previous studies, which have focused on the investigation of language skills (Bishop, 1985; Cockerell et al., 2011). In focal temporal epilepsy, Bird, Jackson, and Wilson (2019) also found a significant correlation between longer disease duration and poorer tonal working memory, when age of onset was controlled.

Neural networks underlying auditory perception and cognition are probably altered by continuous interictal epileptiform discharges over months and years (Deonna & Roulet-Perez, 2016). Normal synaptogenesis and pruning, which are necessary to build auditory processing circuits in children younger than 8 years, are likely to be disturbed by epileptic activity in the bilateral temporal posterior regions (Smith & Hoeppeppner, 2003). Anatomical MRI measurements have previously shown volume reduction in the bilateral superior temporal

regions in four children with LKS (Takeoka et al., 2004). After recovery from LKS, unilateral amplitude reduction of late auditory evoked potential signals generated by the associative cortex contralateral to the extinct ear in dichotic listening also reflects a permanent dysfunction in this specific region (Wioland et al., 2001). The difficulty to correctly process (Seri et al., 1998; Vance, Dry, and Rosen, 1999), organize (Cockerell et al., 2011; Majerus et al., 2003), and interpret (Kaga, 1999; Korkman et al., 1998) sounds during this critical period of development could also explain why later development of musical abilities is limited in LKS, even a long time after EEG normalization. The longer the epileptiform activity lasts, the less neural plasticity can compensate for auditory deprivation, spontaneously or with therapy (Deonna & Roulet-Perez, 2016). However, the question of whether developmental or acquired abnormalities in language and musical skills could precede the onset of LKS instead of being its consequence has been raised in literature (e.g., Overvliet, Aldenkamp, Klinkenberg, Vles, and Hendriksen, 2011). Although this hypothesis appears unlikely, in this study we cannot ascertain that participants had normal musical skills prior to language regression.

4.2 A window to further our understanding of the relation between music and language processing

Regarding short-term memory, the comparison of performance between tonal and verbal material was limited by a floor effect for Patients 1 and 2, with scores close to chance level. Such a severe impairment reflects the fact that an auditory short-term memory deficit is a core and persistent after-effect in LKS, even in adulthood. Patient 3 demonstrated lower performance with tonal than with verbal material, while control participants (and Patient 4) showed the reverse pattern. This finding might be explained by the speech therapy Patient 3 was engaged in during childhood, which may have benefitted verbal short-term memory (without reaching normalization). Speech therapy may also have familiarized the patient with this type of verbal task, but with a weak impact on musical short-term memory. Note that, contrary to the case of Patient 3, musical skills were found more resistant than verbal skills to the damaging consequences of epilepsy in focal temporal epilepsy (Bird et al., 2019). However, a longitudinal approach would be necessary to fully address this question, regardless of the epilepsy type.

Regarding prosody processing, our data are in favor of partially shared processes for emotion recognition in speech and music, as deficits in both materials seem to be associated in LKS.

This finding complements the observation of deficits in emotional prosody recognition in congenital amusia (Pralus et al., 2019; Thompson et al., 2012), and, on the other end of the spectrum, the observation of improved emotional prosodic skills with musical expertise (Lima & Castro, 2011). The processing of emotions in both domains may share cerebral resources.

4.3 Dissociation between objective deficits and subjective reports

The dissociation between major difficulties in music/pitch processing and the self-reported, very positive attitude to music, with preserved feeling of musical emotions, is striking. The pitch discrimination thresholds of 3.6 to 4.8 semitones found in our two most severe cases (Patients 1 and 2) are exceptionally elevated compared to average thresholds in a young non-musician population. They were well above the pitch thresholds supposed to be necessary to capture a melodic phrase in classical or pop music. They also exceed average thresholds reported in congenital amusia. Only 1 out of 34 amusic patients had a pitch threshold over 3 semitones in our review based on the same threshold test as in the current study (Tillmann, Lévêque, Fornoni, Albouy, and Caclin, 2016). The severe impairments we observed in the present study contrasts with self-reported appreciation of music, frequent use of music in daily life (section 3.5), and control-like quantification of emotional intensity in the Emotion tests (section 3.4). Our findings thus suggest a potential partial dissociation between perceptual processes and emotional feelings in the music domain. An impoverished musical access in the perceptual and/or cognitive domain does not seem to prevent the patients from enjoying music. In congenital amusia, a dissociation between cognitive deficits in processing music (perception/memory, verbal categorization of emotions) and the preservation of emotional access to music has also been described (Lévêque et al., 2018). The general profile of these individuals is similar to LKS patients, with impaired pitch discrimination and impaired tonal short-term memory, slight prosody processing deficits (Pralus et al, 2019; Thompson et al., 2012), and partially impaired musical emotion categorization, but without systematic musical anhedonia (Lévêque et al., 2018). Musical anhedonia is nonetheless present in some subjective reports of cases of congenital amusia (McDonald & Stewart, 2008) as well as in an anecdotal report of LKS (the case of Christine, Deonna & Roulet-Perez, 2016). Underlying neural correlates of anhedonia and the factors determining its presence in LKS are unknown. Objective measures such as autonomic responses to music (Mas-Herrero, Zatorre, Rodriguez-Fornells, and Marco-Pallarés, 2014) will also be necessary to further investigate the relationship to music in LKS beyond subjective statements. For example, self-reports concerning attitude to music in young adults may be influenced by sociocultural

factors. Implicit measures like autonomic responses or paradigms where the participant is not conscious to process emotions in music are thus relevant to further investigate this apparent dissociation.

It is notable that 2 of our 3 amusic patients with LKS were not aware of their pitch processing impairment, and 1 patient was not aware of her rhythm processing impairment. The fact that they have access to musical emotions and pleasure may hide their perceptual and cognitive music processing deficits. Nonetheless, all patients reported being poor singers and some reported being poor dancers as well. This does not mean they can perceive their own inaccurate singing, but may have been told they were poor singers by their families or friends (see Sloboda et al., 2005, for discussion around self-assessment in tone-deafness). Musical and prosodic production skills should be evaluated in future studies, in particular to investigate whether strongly altered perceptual skills might also impact vocal pitch control.

4.4 Clinical perspective

The management of a child with LKS focuses on the preservation of communication (verbal and/or gestural) and on remediation of oral language as soon as possible (Deonna & Roulet-Perez, 2016). Using music in remediation could be an enjoyable way to work on temporal sound organization (Stefanatos, 2011), auditory memory, attention, and other pitch, timbre, and rhythmic characteristics shared by speech and music (Bigand, Tillmann et al., 2015; Fujii & Wan, 2014). However, in clinical practice, it is important to also remember that some children with LKS may show aversion to sounds and music.

4.5 Conclusion

The current study reveals amusia at long-term follow-up in four LKS patients with moderate and severe LKS, but not in a patient with mild LKS. Our data suggest that verbal deficits reported in clinical and research contexts to characterize LKS are only one dimension—the most obvious—of generalized alterations affecting networks responsible for sound processing and encoding. Future studies should further investigate auditory nonverbal skills, including music processing, aiming to reach a more complete picture of consequences of LKS in the acute phase and at follow-up (even in adulthood). A longitudinal approach would also be valuable to distinguish primary and secondary impairments and the impact of therapies. Finally, the subjective reports of our patients suggest that musical pleasure and emotions are paradoxically preserved, at least at adulthood. This means that music might be an interesting tool to support language remediation after the acute phase. Even though explicit processing is

impaired, music provides an enjoyable material to enhance acoustic processing and/or auditory working memory. Our findings also provide perspectives for a larger research question: As LKS is a severe variant of CECTS (Deonna & Roulet-Perez, 2016), one might wonder whether subtle music processing disorders also occur in more common types of childhood epilepsy. Up to now, studies on music processing in epileptic patients have been the source of rich data for music neurosciences and psychology (see for instance Maguire, 2017, for a review). However, they have been essentially based on patients with refractory epilepsy after surgical resections (Maguire, Altenmüller, Finger, and Boller, 2015; Stewart et al., 2006, for reviews) or during intracranial EEG recordings (Dellacherie et al., 2009; Omigie et al., 2015, 2019), with the notable exception of the study of Bird et al. (2019) in focal epilepsy. Explorations of potential deficits in music processing in CECTS with a comparative approach are needed to complete this literature and further investigate the consequences of epilepsy on the brain.

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Transparency statement: The manuscript reports how sample size was determined, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

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