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Original article

Electrodermal reactivity to emotional stimuli in healthy subjects and patients with disorders of consciousness

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ABSTRACT

Objectives: After a coma, one major challenge is the detection of awareness in patients with disorders of consciousness. In some patients, the only manifestation indicative of awareness is an appropriate emotional response. Preferred music is a powerful medium to elicit emotions and autobiographical memory. Furthermore, music has been shown to improve cognitive functions both in healthy subjects and patients with neurological impairment. We hypothesized that signs of awareness could be enhanced in some patients with disorders of consciousness under appropriate emotional stimulation such as preferred music and also probably preferred odors.
Methods: To investigate an objective, easily recordable marker of emotions at the patients' bedside, electrodermal activity (skin conductance level, SCL) was assessed with stimulations in auditory and olfactory modalities, notably with preferred music, neutral sound, preferred odors, and neutral odors. The study was conducted in 11 patients with disorders of consciousness (DOC) and 7 healthy participants.
Results: In healthy subjects, the mean amplitude of the SCL was increased during exposure to preferred music as compared to neutral sounds (respectively: 0.00037 ± 0.0004 vs. -0.00004 ± 0.00019 μS). No significant difference between conditions was detected in patients.
Conclusion: The results of this study suggest that electrodermal activity could be a useful marker of emotions induced by music in healthy controls. However, it failed to show any significant difference between conditions in patients with DOC.

1. Introduction

Since the definition of the minimally conscious state (MCS) [1], one of the major issues has become the detection of markers of consciousness in patients waking from a coma. If it is possible to know the content of a healthy individual's consciousness (i.e. awareness) by asking them to say what they think or feel (i.e. "conscious reporting", [2]), in the patient waking from a coma, communication is altered and "reporting" therefore limited. Thus, in clinical practice, the standard way to assess the content of consciousness is to ask a person to reply to questions or to carry out simple instructions (close your eyes, shake your hands, show me your index finger, what is your name etc.). Some behaviors show intentionality and are considered signs associated with a minimal state of consciousness. In particular, these are oriented or finalized movements (e.g.: following a gaze, movements of a limb directed towards stimulation), intelligible verbalization or adapted emotional responses. Reproducibility is an essential criterion for giving observed clinical manifestations a value in terms of regaining awareness. Clinical scales such as the Coma Recovery Scale – Revised (CRS-R) have been developed to look for these subtle manifestations of regaining consciousness [3]. The development of functional explorations of the central nervous system makes it possible to study brain activity during more or less complex tasks. These approaches may be useful in patients with disorder of consciousness (DOC) to search for a neuronal signature of awareness in the absence of behavioral response (for a review see [4]). The evaluation of brain activity provides additional

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information that improves the clinical examination [5]. Whatever the technique used, an important challenge is to improve the sensitivity of the markers of consciousness.

1.1. Music: a way to "boost" the detection of markers of consciousness

Several studies have shown that music has a positive impact on cognitive performance in both healthy participants and brain-damaged patients [6,7]. This suggests that music may facilitate the detection of cognitive activity in patients with altered states of consciousness. Music is also a powerful medium that could help to restore non-verbal communication. In fact, in several case studies or case series, a positive effect of preferred music on the relational awakening of patients with a consciousness disorder has been stressed [8,9]. Nevertheless, interpretation of the results is difficult in the absence of monitoring and quantitative evaluation conditions. In a recent study we showed that the detection of an evoked response to the patient's own name was significantly improved when stimuli were preceded by a preferred range of music over noise [10]. Functional imaging has made it possible to target a reinforcement of the auditory network of patients with a consciousness disorder when they were exposed to a preferred musical stimulation compared to noise (control condition) [11]. In a preliminary behavioral study of 5 minimally conscious patients, we also showed that the score on some CRS-R items was better when the assessment was preceded by preferred music compared to noise ("control" conditions) [12]. The results of this study raised the question of the mechanism at the origin of the observed effects: characteristics of the music (linked to tempo, rhythm or harmonic structures) versus the auto-biographical and emotional dimension of the stimulus. In order to more accurately evaluate the auto-biographical value of music, a new study was performed to investigate whether there is an effect of preference on the observed response [13]. Thirteen patients with a vegetative state or a minimally conscious state participated in the study. In this protocol, 4 CRS-R items were assessed under 4 different conditions: preferred sound (music), neutral sound (noise), preferred odor, neutral odor. The most discriminating CRS-R items to differentiate the vegetative state and the minimally conscious state were used: sound localization at the first name, visual tracking in the mirror reflection, and two reproducible movements on request. The first two items are called "self-relevant" because they were the most biographically charged. The score of each item was standardized as a percentage of the maximum score and an analysis of variance with a Friedman test was performed to look for any difference between the conditions. The results obtained for the CRS-R items were derived from a rating based on videos (blinded by two independent experimenters) and without knowing the type of stimulation. Previously published behavioral results have shown that CRS-R is higher after auditory stimuli compared to olfactory stimuli. CRS-R is also higher after preferred musical stimulation compared to "preferred odour" and "neutral odor" stimuli. In an ancillary study, in addition to behavioral responses, we were interested in the electrodermal response under the four selected conditions. The results of these studies are presented below.

1.2. Consciousness, emotions and electrodermal response

Emotions are an integral part of the construction of self-awareness and of the outside world [14]. In some patients in a minimally conscious state, the only manifestation of regained consciousness is an appropriate emotional response (i.e.: smiling, laughter, frowning, crying) [1]. In order to be considered as intentional, the response must occur significantly more often in reply to a specific stimulus (smiles after a joke; crying when a loved one departs etc.), than in the absence of a stimulus. In healthy subjects, in addition to facial expressions, the existence of a peripheral response mediated by the vegetative system, concomitant with the perception of an emotion, has been the subject of major literature since the founding works of William James (for a review see [15]). Electrodermal activity is a biological electrical activity of the skin linked to the activity of the sweat glands controlled by the sympathetic system. This electrodermal activity is a good candidate to study the emotional response for example during a sad or happy musical stimulation [16]. In a study conducted in 31 healthy subjects, it was shown that the electrodermal response was more important as a function of arousal during the presentation of pleasant music but not during the presentation of noise [17]. It is a non-invasive technique that is relatively easy to implement, inexpensive and can be performed without any specific instructions or behavioral responses from the participant. In addition, the measurements collected are objective and quantifiable. The demonstration of a significantly greater electrodermal response in terms of amplitude, after a preferred musical or olfactory stimulation compared to a neutral stimulation, could represent a means of studying emotional responses more objectively in patients with a consciousness disorder.

2. Materials and method

2.1. Ethics

This study was validated by the local Ethics Committee (CPP Lyon South-East II n°2014-A01062-45; Favorable opinion of the Personal Protection Committee Sud-Est II n°2014-A01062-45, on 08/10/2014; Authorization was approved by the National Agency for Medication Security and Health Products on 30/09/2014). An information document and informed consent were read, completed and signed by the patient's support person and healthy participants. The study was reported in clinical trials as NCT02759068.

2.2. Experimental design

This was a case-control study whose main objective was to evaluate the response of the autonomic system during stimulation with an emotional valence compared to neutral stimulation in patients with a consciousness disorder and in healthy participants.

In patients, the total duration of the study was 5 weeks from inclusion. Once a week during 4 weeks, an experimental session was conducted. The session began with a 30-minutes period of silence with the objective of standardizing the conditions of stress in terms of fatigue, attention availability. One of four sensory solicitations (preferred music, PM; neutral sound, NS; preferred odor, PO; neutral odor, NO) was presented for 5 minutes then one of the 4 CRS-R items (e.g. visual tracking) was evaluated for approximately 2 to 3 minutes. Four stimulation/item combinations were presented during a session, so that the 4 types of stimulation (preferred music, neutral sound, preferred odor, neutral odor) and the 4 CRS-R items (sound location of the first name, visual tracking in the reflection of the mirror, reproducible movements) were presented during the same session. The 16 stimulation/item combinations were evaluated during the 4 experimental sessions. The order of presentation of the stimulation/item pairs was established randomly, with the limitation that an item and a stimulation were evaluated only once per session. The 4 items were tested after each of the 4 stimulation categories. Over all 4 sessions, each of the conditions (preference and neutral) was tested 32 times independently of the sensory modality. Similarly, the sound condition (preferred music and neutral sounds) was tested 32 times and the olfactory

Table 1
Demographics.

Patient	Sex	Age	Time since injury (months)	Etiology	Diagnosis (CRS-R)	A	V	M	O	C	Ar	Total	EDA
1	M	54	15	Encephalitis	MCS	3	3	0	1	0	1	8	N
2	M	28	6	TBI	MCS	4	5	4	1	0	1	15	Y (2)
3	M	37	7	TBI	MCS	0	3	3	0	0	2	8	Y (3)
4	F	23	6	TBI	MCS	3	3	5	1	0	2	14	Y (3)
5	M	38	6	TBI	MCS	3	3	3	0	0	2	11	Y (4)
6	M	42	14	TBI	MCS	1	1	0	0	0	1	3	Y (4)
7	F	54	23	Anoxic (hemorrhage)	UWS	0	0	0	2	0	1	3	Y (4)
8	M	53	90	TBI	UWS	1	0	0	0	0	1	2	N
9	F	53	15	Anoxic (cardiac arrest)	UWS	0	0	2	1	0	1	4	Y (4)
10	F	63	45	Anoxic (hemorrhage)	UWS	0	0	2	1	0	1	4	Y (3)
11	M	58	36	Anoxic (cardiac arrest)	UWS	0	0	2	1	0	2	5	Y (4)
12	M	30	81	TBI	UWS	0	0	2	1	0	2	5	Y (1)
13	M	34	50	TBI	MCS	2	3	1	0	0	1	7	Y (1)

Abbreviations: F: female; M: male; MCS: minimally conscious state; TBI: traumatic brain injury; UWS: unresponsive wakefulness syndrome; CRS-R: Coma Recovery Scale-Revised; A: auditory; V: visual; M: motor; O: oromotor; C: communication; Ar: arousal; EDA: electrodermal activity assessment: N: No; Y: Yes (number of sessions analyzed).

condition (preferred and neutral odors) 32 times, all preference values combined.

For healthy subjects, only one session was performed which included the 4 experimental conditions with the same stimuli exposure procedure as that used for patients.

2.3. Participants

2.3.1. Patients

Patients included in the study had to be between 18 and 80 years of age and have a consciousness disorder (vegetative state, VS also named unresponsive wakefulness syndrome, UWS, or minimally conscious state, MCS) based on the coma recovery scale-revised (CRS-R) as a result of a non-evolving acquired brain injury. The diagnosis of MCS was retained if intentional behavior was observed (items with a star on the CRS-R scale) [3]. Exclusion criteria included comatose patients, patients with locked-in syndrome, anosmic or deaf patients, and patients with uncontrolled epilepsy or neuro-vegetative crisis, and patients with an unstable medical condition.

2.3.2. Healthy subjects

A control group was included only to provide normative values for electrodermal activity.

2.4. Criteria and evaluation procedure

2.4.1. Sound and olfactory stimuli

From a list drawn up with the family, six favorite songs and 6 smells were selected. One hundred seconds of each favorite music was selected (this was the most recognizable part of the song that most often corresponded to the beginning of the song or the chorus), making sure to cut off the songs at the end of a musical phrase using a fading effect. The preferred odors were selected from a pre-defined list of 51 food odors. Controlled stimuli should not be something familiar (no prior exposure), preferred or hated (no marked hedonic value). Six "neutral" sounds were elaborated from a mixture of songs known in different musical styles (rap, rock, reggae, popular). The sounds obtained were complex monotonous sounds without rhythmic or melodic characteristics but sharing the same frequency characteristics as the music. The "neutral" odors were unidentifiable and unfamiliar mono molecular chemical extracts from pre-tests conducted in healthy participants. Six neutral odors were thus subsequently produced. The duration of the sound stimuli was 5 minutes (3 favorite songs in a series or 3 neutral sounds). The sounds were presented via an MP3 player and two speakers installed 1 meter apart, at the level of the bed legs on two mobile tables, 1.60 m from the patient's pillow. The sound level of the music was clearly audible and less than 80 dB (i.e. at a sound equivalent to that of a conversation). The odors were presented at the lower lip of the participant with a metal arm to avoid any olfactory interference and for 5 minutes (3 odors of 30 seconds each repeated 3 times).

2.4.2. Electrodermal responses

Electrodermal responses were obtained with Biopac equipment (Biopac©). It consisted of two non-polarizable silver chloride electrodes. These electrodes were applied to the anterior surface of the second phalanx of the second and third fingers of the left hand with a distance of two centimeters between the two electrodes. The electrodes were connected to a case attached to the patient's wrist that recorded skin conductance. This equipment was set up five to ten minutes before the start of the recording until the gel of the electrodes softened the skin and the conduction took place under optimal conditions. This material is used to measure skin conductance (in microsiemens or μS), which corresponds to the opposite of skin resistance (Conductance = 1/Resistance). The signal consists of two components: the tonic component or Skin Conductance Level (SCL) which corresponds to the baseline, it decreases gradually when the subject is at rest, and slowly increases again when the subject is stimulated, this component varies from one individual to another and for the same individual between two recordings and; the phasic component or Skin Conductance Response (SCR) which corresponds to rapid variations in skin conductance in response to a stimulus. In this study, we were only interested in the tonic component (see: analysis of electrodermal responses below).

Table 2
Electrodermal activity (skin conductance level) related to each condition.

	Mean	sd	Min	Max
Controls				
PM	0.00037	0.00040	0.00005	0.00111
NS	−0.00007	0.00019	−0.00004	0.00016
PO	−0.00007	0.00025	−0.00055	0.00018
NO	−0.00523	0.01572	−0.04083	0.00183
Patients				
PM	0.21446	0.60537	−0.09163	1.97560
NS	−0.03965	0.19312	−0.40901	0.39711
PO	0.05789	0.10269	−0.03504	0.31793
NO	−0.19894	0.44592	−1.32513	0.02259

Mean amplitude (micro siemens, μS) of the tonic response (skin conductance level [SCL]) comparatively to the baseline for each condition (Preferred music [PM]; neutral sound [NS]; preferred odor [PO]; neutral odor [NO]). sd: standard deviation; min, minimal and max, maximal SCL values (μS).

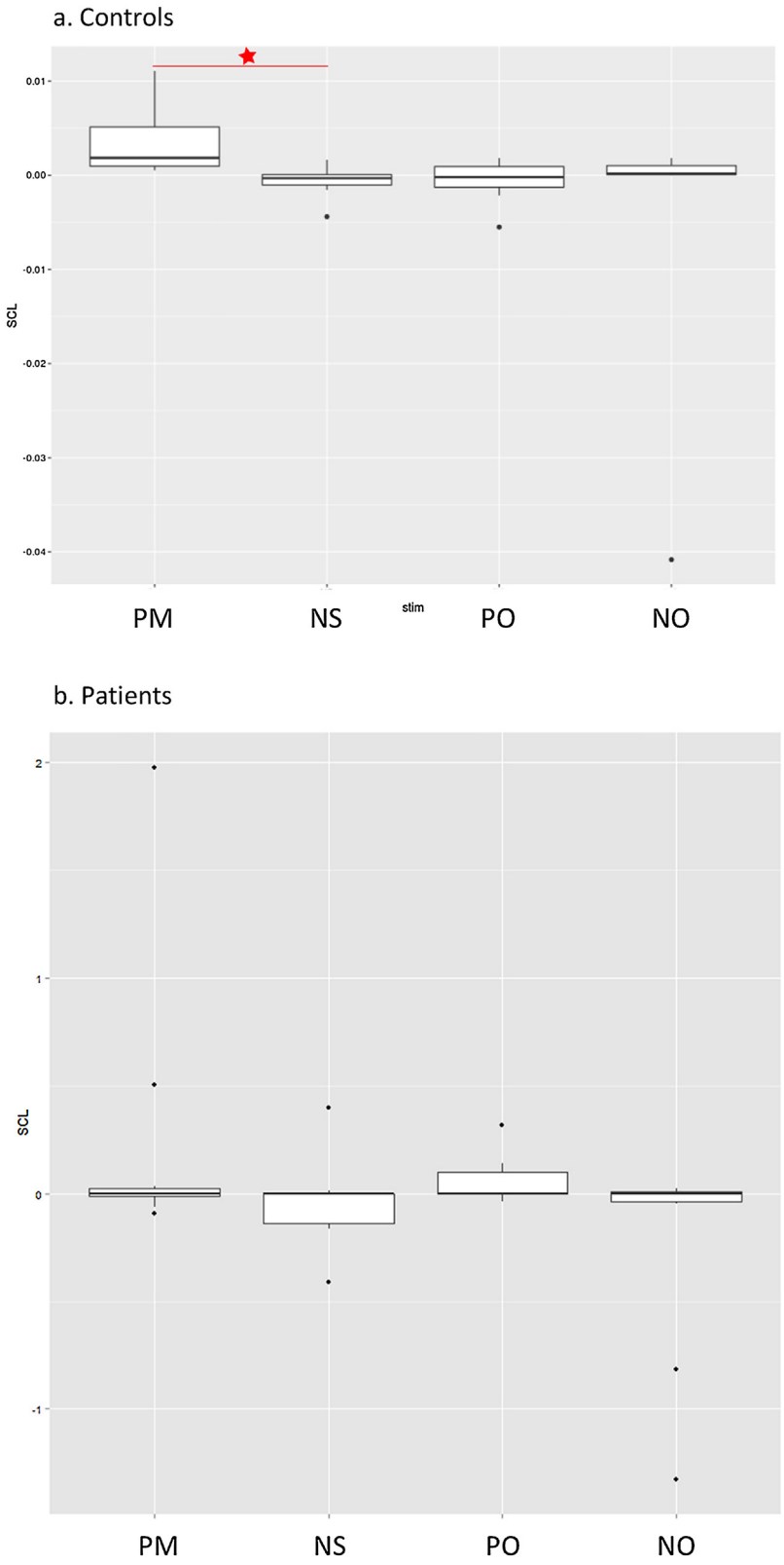

Fig. 1. Electrodermal activity related to stimuli, a: controls; b: patients. Abbreviation: SCL: skin conductance level. For controls subjects (Fig. 1a) and patients (Fig. 1b), the tonic response (skin conductance level [SCL]) (comparatively to the baseline) is displayed for each condition; preferred music (PM), neutral sound (NS), preferred odor (PO), neutral odor (NO). The horizontal line of each plot represents the mean amplitude (microSiemens, μS) of the SCL; the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The dots are outliers.

2.4.3. Analysis of electrodermal activity

We were only interested in the amplitude of the tonic component (SCL) measured by Acknowledge® 4.2 software. The average amplitude of the tonic response in microsiemens (μS) was calculated for each condition (music, noise, preferred odor, neutral odor). Due to inter-individual and inter-session variability, the reported value is the difference between the mean values for each condition compared to the value obtained at baseline at the beginning of the session. Standard deviation and extreme values are also reported. The same procedure was applied for healthy subjects with the main difference that there were no multiple sessions.

2.5. Statistics

For control subjects and patients a one-sided Friedman test was performed to search for a difference between the measurements obtained under the 4 conditions. If the test was positive ($P < 0.05$), post-hoc *t*-tests were performed to look for a significant difference between the different conditions (PM vs. NS, PO vs. NO, PM vs. PO, NS vs. NO).

3. Results

Thirteen patients with a consciousness disorder were included in this study (7 MCS patients and 6 patients in vegetative state or UWS). Of these 13 patients, 11 received an electrodermal response recording in at least one session with the 4 different conditions (see Table 1 for population demographics). Seven healthy subjects (4 women and 3 men) aged from 21 to 44 years (average age: 28.7 years) had an electrodermal recording under the 4 predefined conditions (music, neutral sounds, preferred odors, neutral odors).

3.1. Electrodermal activity

The mean amplitude of the tonic response in microsiemens (μS), compared to the baseline, standard deviation and extreme values are reported for each condition preferred music (PM); neutral sound (NS); preferred odor (PO); neutral odor (NO) in Table 2 and Fig. 1 for both control subjects (Fig. 1a) and patients (Fig. 1b).

For control subjects, the Friedman test was significant with a Chi^2 value equal to 11.74 ($P = 0.008318$). Post-hoc *t*-tests show a significant difference between preferred music and neutral music ($P = 0.0078$). The other comparisons (PO vs. NO, PM vs. PO, NS vs. NO) were not significant.

For patients, the Friedman test showed no significant difference between the 4 conditions (Chi^2 equals 0.273; $P = 0.97$).

4. Discussion and conclusion

Previously published behavioral results indicate that consciousness content (assessed by performance on the 4 CRS-R items) was highest when the assessment was performed after a period of preferred music compared to preferred odors and neutral odors. These results confirm that it is possible to improve the detection of a conscious state with music [8,10,12]. The effect of music could improve the detection of a conscious state by revealing emotional responses. Other mechanisms can also participate and notably the auto-biographical value of the musical stimulus (for a review see: [18]) and also the effect of music on the awakening and alert level of the patient [6].

Interestingly, the analysis of the electrodermal responses showed that the average amplitude of the tonic response was higher in the music condition compared to "neutral sounds" conditions in the control subjects. The amplitude of the electrodermal response could thus vary in a proportional manner to the intensity of the emotion induced by stimulation.

These results were not reproduced in patients. It should be noted that the variation in tonic electrodermal responses (SCL) between different conditions was very small, usually less than 0.1 μS. The skin conductance response (SCR) is probably a better marker than the tonic response (SCL) to study a modification in the vegetative system in connection with a specific stimulation [19]. The protocol of this study, which was originally designed to study behavioral responses, did not consider this phasic response due to insufficient stimuli. Indeed, for the preferred music and neutral sounds condition, a maximum of 3 phasic responses could be retained during a stimulation (1 response during each song change), i.e. a maximum of 12 phasic responses for the 4 "preferred music" stimuli and 12 responses for the 4 "neutral sounds" stimuli. For odor conditions, a maximum of 9 responses could be retained per stimulation (1 response at each odor change), i.e. a maximum of 36 phasic responses for the 4 "preferred odors" stimulations and 36 responses for the 4 "neutral odors" stimulations. Under these conditions, the tonic response, which incorporates the phasic response, appeared the most appropriate in the present study. Future studies are required to include more stimuli per condition to study phasic response. The interpretation of the electrodermal response to emotions will require further work to better understand the links between the different characteristics of the electrodermal response and emotions. It is possible that other measurements of vegetative activity are more sensitive than the electrodermal response to study emotional responses. Several other physiological measurements such as respiratory rate, heart rate, pupillary reactivity or facial heat have previously been studied. It has been shown that music induces pupillary dilation [20], an increase in the heart rate, respiratory rate and body temperature in addition to a modulation of electrodermal activity [21]. It has also been shown that the more pleasant and auto-biographical the smell, the higher the electrodermal conductance [22], inspiratory volume, heart rate and pupillary dilatation [23]. In addition, it would be interesting to carry out a concomitant measurement of brain activity to study the modulation of the vegetative response by the brain centers involved in the control of emotions. In fact, an important argument for linking consciously felt emotions and vegetative response is the existence of vegetative system control by brain structures involved in emotions and decision-making (the amygdala, prefrontal cortex and striatum) [24]. Several recent studies in patients with residual consciousness have shown that detecting a rule violation can alter both brain activity [25] and cardiac activity [26].

In clinical practice, an already substantial amount of reported literature shows that there are sufficient arguments to collect the musical preferences of patients with a consciousness disorder, to target stimuli or the sound environment in their room, in order to improve their well-being and better detect signs of regained consciousness.

Disclosure of interest

The authors declare that they have no competing interest.

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