Apathy alters emotional arousal in chronic schizophrenia.

Thibaut Dondaine, Pierre Philippot, Jean-Marie Batail, Florence Le Jeune, Paul Sauleau, Sophie Drapier, Marc Verin, Bruno Millet, Dominique Drapier, Gabriel Robert

▶ **To cite this version:**

HAL Id: hal-01943955

https://univ-rennes.hal.science/hal-01943955

Submitted on 4 Dec 2018

Apathy alters emotional arousal in chronic schizophrenia

Thibaut Dondaine, PhD; Pierre Philippot, PhD; Jean-Marie Batail, MD;
Florence Le Jeune, MD, PhD; Paul Sauleau, MD, PhD; Sophie Drapier, MD;
Marc Vérin, MD, PhD; Bruno Millet, MD, PhD; Dominique Drapier, MD, PhD;
Gabriel Robert, MD, PhD

Background: Within the heterogeneity of schizophrenia, apathy constitutes an independent cluster of negative symptoms associated with poor outcomes. Attempts to identify an emotional deficit in patients who have schizophrenia with negative symptoms have yielded mixed results, and studies that focus on the relationship between apathy and emotional disorders are lacking. **Methods:** We set out to remedy this shortcoming using a validated battery of film excerpts to induce positive and negative emotions in patients with chronic schizophrenia with ($n = 20$) or without ($n = 20$) apathy, and in controls ($n = 20$) comparable for age, sex and socioeconomic status. We assessed emotions using an innovative but validated technique to evaluate tonic and phasic electrodermal activity and subjective feelings using a standardized visual analogue scale. **Results:** Using a qualitative measure of apathy, we did not find a specific decrease in tonic activity during the induction of positive emotions. However, we did observe that patients with apathy showed reduced tonic activity independent of valence (i.e., for both positive and negative emotions) compared with controls and patients without apathy. Moreover, the quantitative measure of apathy (Apathy Evaluation Scale) was the only significant factor, explaining 24% of the variance in tonic activity during induction of positive emotions after controlling for confounding factors. **Limitations:** Electrodermal activity was the only physiologic measure we acquired. We induced several emotions sequentially that might have overlapped with each other, but we added an emotional "washout" period and randomized the order of each film excerpt to limit this possibility. **Conclusion:** Taken together, these results suggest that apathy in schizophrenia could impair tonic activity during positive emotions. Treatments aimed at enhancing positive emotions may help alleviate apathy in schizophrenia.

Introduction

Schizophrenia induces emotional impairments, causing social dysfunction.[1] Negative symptoms in schizophrenia are heterogeneous, but can be grouped into 2 independent clusters: apathy/avolition and diminished emotional expression.[2] Apathy is defined as a lack of motivation that reduces the emotional, cognitive and behavioural components of goal-directed behaviours in daily life.[3,4] It accounts for the largest proportion of poor functioning in daily life and overall outcomes in schizophrenia, independent of cognitive impairment[5] and diminished emotional expression.[6] People with schizophrenia and apathy show steeper reward devaluation in relation to physical effort than patients without apathy.[7] However, emotional deficits in schizophrenia with apathy have been unexplored. This is unexpected, because motivation is a key component of emotional processing in contemporary models,[8] and altered emotional processing has been highlighted in Parkinson disease with apathy,[9,10] suggesting that apathy might impair emotional processes.

Previous investigations into subjective emotional experiences in schizophrenia have opted for laboratory-based eliciting of emotion, using a wide variety of stimuli (e.g., odours, food, emotional faces or pictures).[11] Despite such methodological heterogeneity, most studies have found that patients with schizophrenia experienced positive emotions in a similar way to healthy controls.[1,12] However, some results have suggested exacerbated negative emotional experiences in response to positive or neutral stimuli,[13,14] or impaired neural response to positive stimuli in schizophrenia.[15,16] One approach to explaining preserved hedonic capacity in schizophrenia separates goal-directed emotions into reward anticipation and intact positive emotions during reward reception.[1,17] The results of previous studies support the

Correspondence to: T. Dondaine, Faculté de Médecine, Pôle Recherche, Service de Pharmacologie Clinique, 1, place de Verdun, 59045 Lille CEDEX, France; thibaut.dondaine@univ-lille2.fr

hypothesis that apathy in schizophrenia and in healthy people with psychotic-like symptoms is associated with blunted striatal response during reward anticipation, but not during reward reception.[18–20]

Emotional processes include electrodermal activity (EDA) as a marker of emotional arousal.[21] Few studies have explored the link between subjective emotional experiences and EDA during emotional induction in schizophrenia, and results have been mixed: studies found greater, equal or reduced EDA in response to emotional pictures.[22–24] Electrodermal activity reflects autonomic nervous system activity and can be divided into tonic (slow variations) and phasic (rapid variations) activity.[25] More specifically, tonic EDA activity refers to skin conductance level, and phasic activity corresponds to a skin conductance reaction (SCR) evoked by a stimulus.[25] A recent review found that tonic and phasic activities can be increased during emotional episodes using various methods of emotion induction (film excerpts, music or pictures) and across all emotional categories (joy, fear, anger, surprise).[21] Phasic activity is a rapid and event-related feature of EDA, but tonic activity is associated with anticipation of an outcome during conditional paradigms of long duration.[26] Moreover, reduced tonic EDA has been related to apathy in a population with brain injuries.[27]

Because apathy has been related to the decreased ability to anticipate positive emotions in schizophrenia, and because anticipation of an outcome is associated with tonic EDA, our primary objective was to test for reduced tonic activity during the induction of positive emotions in patients with schizophrenia and apathy, compared to patients with schizophrenia without apathy and healthy controls. Our secondary objective was to examine whether quantitative apathy scores were associated with tonic activity during positive emotion when controlling for confounding factors in patients with schizophrenia.

To this end, we induced discrete positive and negative emotions using a validated battery of film excerpts[28] and extracted tonic activity from EDA recordings in comparable groups of patients with schizophrenia with and without apathy, and in a control group.

Methods

Participants

We recruited 20 outpatients who had stable chronic schizophrenia (fewer than 3 positive items scored 4 or above on the Positive and Negative Syndrome Scale[29] [PANSS] and no medication changes during the previous 2 months) and apathy (Scz-A), and 20 patients who had schizophrenia without apathy (Scz-NA), all from Rennes University Hospital in France. All participants were native French speakers. We recruited healthy controls using local advertising. Eight patients refused to participate in our study. We recruited participants to build 3 groups that were comparable in terms of age, socioeconomic status, sex, handedness and disease duration. We also recruited patients so that the chlorpromazine-equivalent dose was similar between both groups. All patients were ambulatory.

Schizophrenia had been diagnosed according to the French version of the Mini International Neuropsychiatric Inventory,[30] based on DSM-IV-TR criteria.[31] Exclusion criteria included psychotic depression, severe extrapyramidal symptoms and low-order visual and auditory impairments. Patients were allocated to the Scz-A or Scz-NA group according to the diagnostic criteria for clinical apathy.[6] Apathy was assessed quantitatively using the Apathy Evaluation Scale (AES).[32] The clinical criteria and the AES have been validated in schizophrenia.[4]

All patients were being treated with medication at the time of testing. In the Scz-A group, 16 patients were receiving atypical antipsychotics and 4 were receiving both atypical and typical antipsychotics; 4 were receiving benzodiazepines. In the Scz-NA group, 19 patients were receiving atypical antipsychotics and 1 was receiving a typical antipsychotic; none were receiving benzodiazepines.

Twenty healthy controls received €50 for their participation and were not taking any medications. Patients did not receive monetary compensation, following French ethics recommendations.

Exclusion criteria for all participants were neurologic and systemic illness, previous head injury, severely impaired vision or auditory acuity, and mental retardation (Mattis Dementia Rating Scale[33] score below 120). As well, any diagnosis of a mental disorder according to the Mini International Neuropsychiatric Inventory led to exclusion in the control group.

Written informed consent was obtained from each participant, and the study met the ethical standards of the Declaration of Helsinki. The study was approved by the local ethics committee (CPP Ouest II-Angers Number: 2012/16).

Psychopathological and neuropsychological assessment

We used the PANSS[29] to assess the stability and severity of schizophrenia. We assessed overall negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS)[34] and depressive symptoms using the Calgary Depression Scale for Schizophrenia.[35] We used the Abnormal Involuntary Movement Scale[36] to assess extrapyramidal symptoms.

The executive function battery included phonemic and semantic fluency tests, an adapted version of the Stroop paradigm, the Trail Making Test (TMT) and the digit span and digit symbol coding subtests of the Wechsler Adult Intelligence Scale IV. See a study by our group[37] for a complete description of the battery.

Emotion elicitation procedure

Film excerpts are effective, valid and powerful for eliciting intense and specific target emotions.[38–40] We used a battery of 5 film excerpts, selected from a larger validated battery[28] according to their likelihood to induce a specific subjective emotional experience: happiness, anger, fear, sadness or disgust. All excerpts were in French, lasted 1 to 4 minutes, and were displayed on a 22-inch colour screen. The film excerpts had been edited to produce the apex of emotional intensity as

they ended (Philippot P., personal communication, Nov. 15, 2017). To capture the emotional peak and standardize excerpt length, we analyzed the EDA recordings for only the last minute of each excerpt. We randomized the order of presentation for each participant so that no one experienced them in the same order. Before each excerpt, participants went through a 3-minute relaxation procedure to "wash out" previous emotions. After the washout period, we captured EDA for 1 minute to obtain a baseline before eliciting the next emotion (Fig. 1).[41]

Assessment of subjective emotional experience

After each relaxation and presentation phase, participants reported the intensity of their emotional experiences on the Differential Emotions Scale,[41] which consists of 10 visual analogue scales: 1) interested, concentrated, alert; 2) joyful, happy, amused; 3) sad, downhearted, blue; 4) angry, irritated, mad; 5) fearful, scared, afraid; 6) anxious, tense, nervous; 7) disgusted, turned off, repulsed; 8) disdainful, scornful, contemptuous; 9) surprised, amazed, astonished; 10) warmhearted, gleeful, elated. Each scale ranged from 0 (no subjective emotional experience at all) to 7.5 (very intense subjective emotional experience).

Assessment of EDA

We acquired EDA following the recommendations of the Society for Psychophysiological Research.[42] Two surface bipolar finger electrodes (Model MLT 118F; ADIntruments) were placed on the pad of the left forefinger and middle finger, without isotonic paste to preserve the natural condition of the skin. We recorded EDA using an isolated amplifier (ML116 GSR Amp; ADInstruments) connected to a PowerLab/4SP system (ADInstruments) using constant-voltage excitation ($22\ mV_{rms}$ at 75 Hz). The signal was recorded continuously using Labchart v7.4.1 software (ADInstruments) at a sampling rate of 10 Hz. The temperature of the room was constant (approximately 20°C). Before the emotion elicitation procedure, EDA was recorded during a training session with the relaxation procedure to calibrate the EDA recording and train the participant on filling out the DES. Participants were excluded if the EDA recording did not meet the criteria for data quality (many artifacts, low or high EDA, or no SCR).

We performed analyses on the final 60 seconds of each relaxation and film excerpt phase to control for differential stimulus lengths. We removed artifacts (body movements, speech, irregular breathing or disruptions of the skin electrode interface) by visual inspection. We imported data using Ledalab V3.4.3 toolbox (www.ledalab.de/) running on MATLAB 7.7 (MathWorks, Inc.). We ran continuous decomposition analysis (CDA). This method, based on deconvolution, works on the principle that an impulse is followed by a biexponential function (i.e., increased skin conductivity). The automated CDA identifies the impulse and detects the EDA shape, physiologic deviation and interindividual differences. Based on this method, phasic EDA (SCR) can be differentiated more accurately from tonic activity. Moreover, the CDA method is more suitable for long-lasting stimuli and less sensitive to artifacts than other deconvolution methods.

The minimum amplitude criterion for an SCR was 0.05 µS. We summed the amplitudes of the SCRs (i.e., the phasic
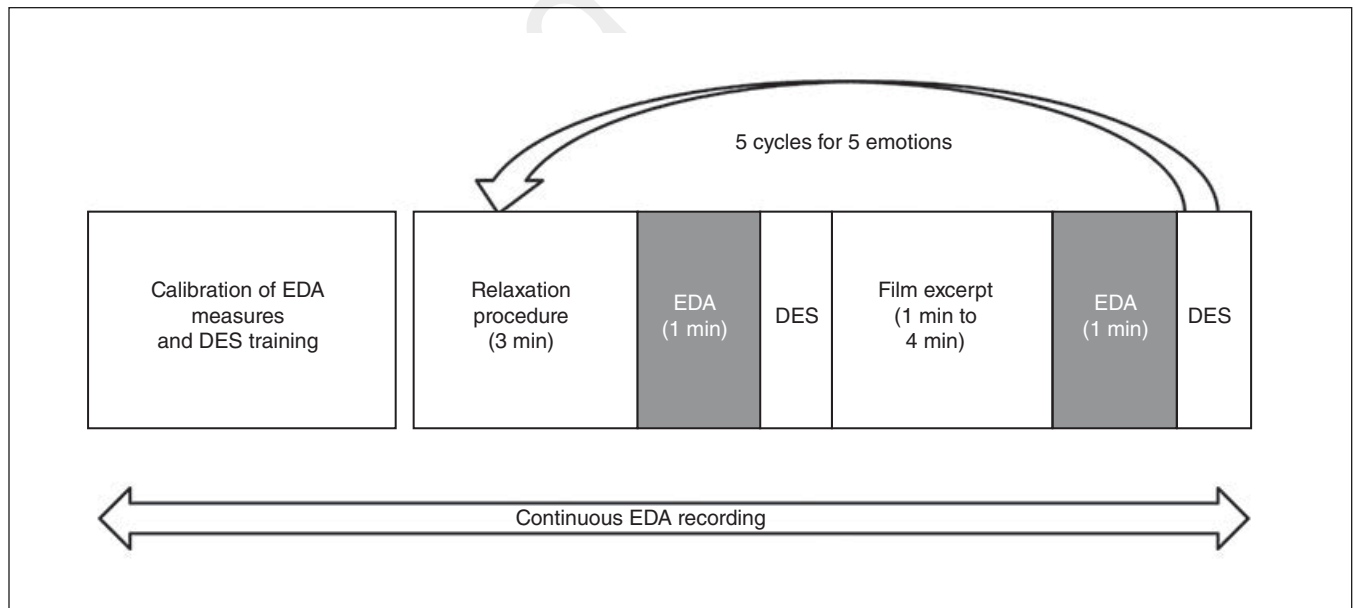
Fig. 1: Procedure for emotional induction. First, we performed a calibration of EDA measures using a period of relaxation. Then, we ran 5 cycles using 5 different film excerpts that targeted 5 emotions in random order, with continuous recording of EDA. Each cycle began with a relaxation procedure (3 min), followed by acquisition of a baseline EDA value and a first subjective emotional rating using the DES. Then, a target emotion was induced using a film excerpt. We used the final minute of the film excerpt for EDA processing, and then a second subjective emotional rating (DES) was performed. DES = Differential Emotion Scale; EDA = electrodermal activity.

activity) and extracted the tonic activity. We applied a logarithmic transformation ($y = \log [1 + x]$) to the phasic and tonic data to account for the positive skewed distributions of SCR amplitudes.[25] We expressed electrodermal measures using log µS. Because our hypothesis was that apathy would be related to decreased arousal during induction of positive emotion, we assigned positive emotion to tonic and phasic activity during the induction of happiness. In contrast, we had no a priori arguments for choosing specific negative emotions, and were constrained by the small sample sizes. Therefore, we chose to assign negative emotions to the mean of tonic and phasic activities during induction of sadness, fear, anger and disgust. By doing so, positive emotions were related to what is experienced as "pleasant," and negative emotions were related to what is experienced as "unpleasant."

Target and nontarget subjective emotional experiences

Positive emotions (e.g., joy) were target items for happiness induction. Negative target items were those that best described the discrete emotion being induced (e.g., "disgusted, turned off, repulsed" was the target item for induction of disgust). Each film excerpt had only 1 target item from the 10 items on the DES; the other 9 were nontargets. For the positive film excerpt, we used the mean of the 9 nontarget items for comparison. For the negative film excerpts, we used the mean of all nontarget items across all 4 negative film excerpts (fear, anger, disgust and sadness). We used the mean of all 4 negative target and nontarget items to score negative subjective emotional experiences. We computed these scores before and after participants viewed the film excerpts.

Statistical analysis

We compared sociodemographic and neuropsychological variables using 1-way analyses of variance (ANOVA; 3 groups). We supplied post hoc comparisons (using a Dunnett test) if main or interaction effects were significant. We compared clinical variables for the Scz-A and Scz-NA groups using a Student t test.

We subjected tonic and phasic EDA measures to repeated-measures ANOVAs (RM-ANOVAs). Two within-participant factors had 2 levels (valence [positive and negative] and induction [relaxation and film viewing]), and 1 between-participant factor had 3 levels (group [controls, Scz-A and Scz-NA]). When RM-ANOVA main effects involving group differences were significant, we ran planned comparisons (defined a priori) for reduced emotional EDA measures in the Scz-A group compared with the other groups. To perform these planned comparisons, we first computed the differences between emotional measures (i.e., tonic and phasic) at baseline[38,43] and during the induction phase: for example, emotional measure$_{\text{film excerpts}}$ – emotional measure$_{\text{baseline.}}$ We then used independent t tests to compare the mean of the variables between the Scz-A group and the control and Scz-NA groups. Planned comparisons increase statistical power by limiting the number of statistical tests that might result from complex factorial designs. As long as the planned compari-

sons rely on a priori hypotheses and are limited, it is not necessary to adjust for multiple comparison testing.[44,45]

We performed a multiple linear regression to test for significant association between quantitative apathy measures (AES score) and tonic activity during induction of positive emotions, while accounting for confounding factors.

We used an RM-ANOVA to test for the effectiveness of the battery in individuals and groups in inducing subjective emotional experiences. We used an RM-ANOVA with 3 within-participant factors that had 2 levels (induction [before and after the film excerpt], valence [positive and negative] and item [target and nontarget]), and 1 between-subject factor with 3 levels (group [Scz-A, Scz-NA and control]). For group differences, we tested the main effects of the RM-ANOVA for induction × item × group and induction × item × group × valence. We tested the effectiveness of the battery using the main effect of induction × item. We did not perform post hoc comparisons.

Finally, we used an RM-ANOVA with 1 within-participant factor that had 5 levels (happiness, anger, fear, sadness, disgust) to test for an influence of film excerpt order on EDA measures during relaxation phases in controls.

We performed statistical analysis using SPSS version 22 (IBM Inc.).

Results

Table 1 displays the sociodemographic, clinical and neuropsychological characteristics for each group. We found no statistical differences between groups for age, sex, handedness, educational level or disease duration. We found no significant chlorpromazine-equivalent differences between the Scz-NA and Scz-A groups.

The findings for tonic and phasic activity, as well as target and nontarget item ratings for each group, are displayed in Table 2.

Executive function

Although it was not part of our working hypothesis, we found selective executive impairment in initiation (categorical fluency), mental flexibility (TMT), inhibition (Stroop) and strategy switching (Modified Wisconsin Sorting Test) in the Scz-A group compared with the control and Scz-NA groups. Attention was also impaired in the Scz-A and Scz-NA groups (Table 1).

Effectiveness of emotion elicitation procedure

We found a significant induction × item contrast ($F_{1,53} = 118.6$, $p < 0.001$), suggesting a satisfying effect of the battery on the target items, independent of group (i.e., across all individuals; $n = 60$). We found no group differences in target subjective emotional experiences for induction × item × group ($F_{2,53} = 1$, $p = 0.7$) or induction × item × valence × group ($F_{2,53} = 1.9$, $p = 0.2$). These results suggest that the targeted subjective emotional experiences did not differ between groups after emotional induction (Table 2).

Influence of film order on relaxation phase in controls

To verify that previous emotions did not alter baseline EDA recordings, we ran an RM-ANOVA with 1 within-subject factor that had 5 levels (happiness, anger, fear, sadness, disgust) for both the tonic and the phasic measures. We found no significant effect of emotion for the tonic ($F_{4,16} = 0.7$, $p = 0.6$) or phasic ($F_{4,16} = 0.3$, $p = 0.8$) measure. These nonsignificant results suggest that the order of the film excerpts had no influence on the EDA recordings.

EDA activity

Tonic activity

We found significant effects of induction ($F_{1,57} = 12$, $p = 0.001$), induction × valence ($F_{2,57} = 16.1$, $p < 0.001$) and group × induction ($F_{2,57} = 3.3$, $p = 0.04$). We found no effect of valence ($F_{2,57} = 2.4$, $p = 0.1$) or group × valence ($F_{2,57} = 1.3$, $p = 0.3$). We also found no effect of induction × valence × group ($F_{2,57} = 2.2$, $p = 0.1$). To test whether the Scz-A group had reduced tonic activity across valence (i.e., both positive and negative), we first

Table 1: Participant sociodemographic, clinical and neuropsychological characteristics

Characteristic*	Control (n = 20)	Scz-A (n = 20)	Scz-NA (n = 20)	Statistical test	p value
Age, yr	35.5 ± 7.6	33.4 ± 9	33.8 ± 7.3	$F_{2,57} = 0.4$	0.7
Sex, male/female, *n*	14/6	15/5	14/6	$F_{2,57} = 0.9$	0.6
Educational level	13.3 ± 1.9	11.9 ± 2.1	13.2 ± 2.6	$F_{2,57} = 2.4$	0.1
Handedness, right/left, *n*	17/3	15/5	17/3	$F_{2,57} = 0.9$	0.6
Chlorpromazine equivalent, mg	—	729.6 ± 451.1	528.3 ± 412.2	$t_{38} = 1.4$	0.2
Disease duration, yr	—	11.6 ± 5.9	10.5 ± 6.9	$t_{38} = 0.6$	0.6
Neuropsychological test scores					
Calgary Depression Scale for Schizophrenia	—	3.15 ± 2.4	2.2 ± 1.7	$t_{38} = 1.4$	0.2
Abnormal Involuntary Movement Scale	—	0.2 ± 0.5	0.6 ± 0.9	$t_{38} = -1.6$	0.1
Apathy Evaluation Scale	—	50 ± 5.4	32.6 ± 4.3	$t_{38} = 11.3$	< 0.001
Scale for the Assessment of Negative Symptoms	—	63.9 ± 16.7	28.4 ± 11.2	$t_{38} = 7.9$	< 0.001
PANSS, overall	—	73.7 ± 12.2	54.6 ± 14.8	$t_{38} = 4.4$	< 0.001
PANSS, positive subscale	—	10.1 ± 1.8	10.5 ± 4.1	$t_{38} = -0.4$	0.7
PANSS, negative subscale	—	29.1 ± 6.2	16.9 ± 4.6	$t_{38} = 7.1$	< 0.001
PANSS, general psychopathology subscale	—	34.5 ± 6.2	27.2 ± 7.5	$t_{38} = 3.4$	< 0.001
Digit span test, forward	5.75 ± 0.97	5.7 ± 1.3	6.1 ± 1	$F_{2,57} = 1.09$	0.3
Digit span test, backward	4.5 ± 1.4	4 ± 1.2	4.6 ± 1.2	$F_{2,57} = 1.2$	0.3
Verbal fluency test, categorical	31.1 ± 7.6	21.1 ± 8.7	28.2 ± 7.6	$F_{2,57} = 8.5$	< 0.001†‡
Verbal fluency test, lexical	20.8 ± 7.1	17.1 ± 6.3	20.6 ± 6.7	$F_{2,57} = 1.9$	0.2
Stroop, interference	4.3 ± 7.6	−2.1 ± 9.1	1.8 ± 7.8	$F_{2,57} = 3.1$	0.05†
Trail Making Test, B–A time	34.1 ± 14.7	78.6 ± 57	40.1 ± 23.3	$F_{2,57} = 8.7$	< 0.001†‡
Digit symbol coding test	72.1 ± 17.7	49.3 ± 12.8	56.7 ± 13.5	$F_{2,57} = 12$	< 0.001†§

PANSS = Positive and Negative Syndrome Scale; Scz-A = schizophrenia with apathy; Scz-NA = schizophrenia without apathy.
*Results are shown as mean ± standard deviation unless otherwise indicated
†Significant post hoc Dunnett test between Scz-A and controls.
‡Significant post hoc Dunnett test between Scz-A and Scz-NA.
§Significant post hoc Dunnett test between Scz-NA and controls.

Table 2: Tonic and phasic EDA and emotion ratings on target and nontarget scales for positive and negative films*†

Variable	Control (n = 20)	Scz-A (n = 20)	Scz-NA (n = 20)
Tonic activity, positive emotion, μS	0.086 ± 0.155	0.016 ± 0.056	0.123 ± 0.133
Tonic activity, negative emotion, μS	0.033 ± 0.128	−0.019 ± 0.076	0.006 ± 0.093
Phasic activity, positive emotion, μS	0.344 ± 0.347	0.087 ± 0.333	0.377 ± 0.433
Phasic activity, negative emotion, μS	0.034 ± 0.316	0.016 ± 0.245	0.089 ± 0.286
Target scale ratings, positive film	2.798 ± 2.039	2.230 ± 2.398	3.138 ± 2.345
Nontarget scale ratings, positive film	0.018 ± 0.078	−0.174 ± 0.55	−0.136 ± 0.628
Target scale ratings, negative film	1.678 ± 1.074	1.969 ± 1.310	1.512 ± 1.364
Nontarget scale ratings, negative film	0.350 ± 0.433	0.300 ± 0.612	0.358 ± 0.702

EDA = electrodermal activity; Scz-A = schizophrenia with apathy; Scz-NA = schizophrenia without apathy.
*Mean ± standard deviation.
†We have displayed findings for only the emotional induction procedure, such as elicitation = emotional variable_film excerpts − emotional variable_relaxation. Each value is the difference between the 2 conditions.

calculated the mean tonic activity between the positive and negative emotions for each participant, and then used planned comparisons to compare tonic activities across emotions between groups. We found decreased tonic activity across emotions (i.e., both positive and negative emotions) in the Scz-A group (mean ± standard deviation [SD] −0.002 ± 0.053) compared with the Scz-NA group (mean ± SD 0.065 ± 0.083, $t = 3$, $p = 0.004$) and the control group (mean ± SD 0.06 ± 0.12, $t = 2.04$, $p = 0.048$). This revealed significant reduced tonic activity in the Scz-A group across the emotions (i.e., both positive and negative) compared with the Scz-NA and control groups (Fig. 2).

Phasic activity
We found significant effects of induction ($F_{1,57} = 20.7$, $p < 0.001$) and induction × valence ($F_{2,57} = 19.8$, $p < 0.001$). We found no effect of valence ($F_{1,57} = 2.4$, $p = 0.1$). We also found no effect of group × valence ($F_{1,57} = 2.6$, $p = 0.08$), group × induction ($F_{2,57} = 2.5$, $p = 0.09$) or induction × valence × group ($F_{2,57} = 2.3$, $p = 0.1$).

Quantitative apathy as a predictor of tonic EDA activity during induction of positive emotion

Disease severity, medications and executive dysfunction can confound the relationship between apathy and EDA in schizophrenia. The AES score was highly correlated with the PANSS total score ($r = 0.8$, $p < 0.001$), and with the SANS score ($r = 0.9$, $p < 0.001$). We did not control for these variables in the linear regression, because it would have violated the assumption of noncollinearity. Instead, we used the PANSS positive subscore to control for the severity of positive symptoms. We conducted a multiple linear regression; the dependent variable was tonic activity during induction of positive emotions, and the independent variables were AES, chlorpromazine equivalent, Wechsler Adult Intelligence Scale digit symbol coding, TMT B–A, categorical fluency (the 3 tests with significant differences between the 3 groups; Table 1) and
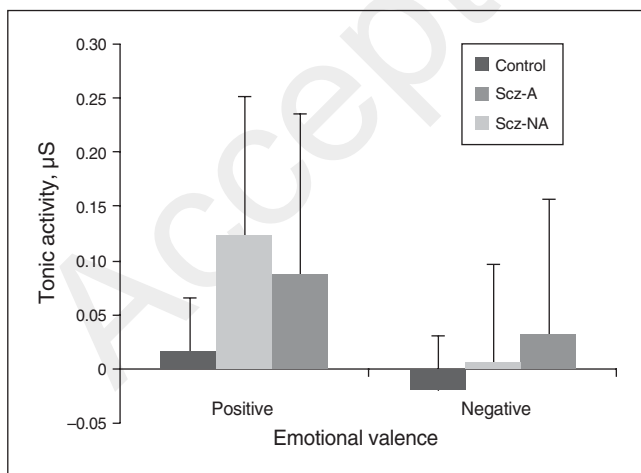
PANSS positive subscore in the total sample of patients with schizophrenia. Apathy was significantly associated with tonic activity during positive emotions ($t = −3.5$, $p = 0.001$), accounting for 24% of the variance (Fig. 3).
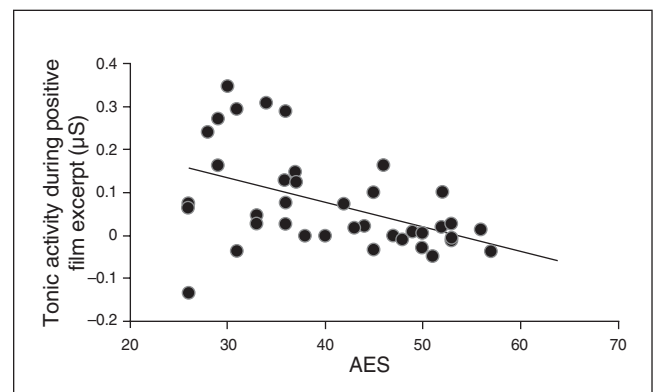
Discussion

Using an innovative method to extract tonic and phasic activity from EDA recordings, we tested primarily for decreased tonic activity during induction of positive emotion in Scz-A patients compared with Scz-NA patients and controls. We did not find specific decreased tonic activity during induction of positive emotion in the Scz-A group compared with the Scz-NA group and controls. However, RM-ANOVA revealed a significant effect of group × induction, with decreased tonic activity in Scz-A compared with Scz-NA and controls, independent of valence (i.e., across both positive and negative emotions). Although it was not part of our a priori hypothesis, this result suggested decreased emotion-induced arousal in the Scz-A group versus the Scz-NA group and controls. Using a quantitative measure of apathy in the total sample of schizophrenia patients, we also found that apathy was significantly associated with tonic-related emotional EDA during induction of positive emotion, accounting for 24% of the variance. Our results were consistent with the suggestion that apathy in schizophrenia is associated with reduced emotional experience, especially positive emotion.

We also found impaired executive function in the Scz-A group, in line with previous reports of apathy-related executive impairment in both chronic schizophrenia[46] and first episode of psychosis.[47] These results support the assessment of apathy in our sample.

Limitations

The first limitation of this study was the lack of a priori estimation of sample size. Indeed, the negative results (i.e., the valence × induction × group interaction) from our primary

Fig. 2: Tonic EDA (µS) in each group during positive and negative film excerpts. Error bars represent standard error of the mean. EDA = electrodermal activity; Scz-A = schizophrena with apathy; Scz-NA = schizophrenia without apathy.

Fig. 3: Decreased tonic EDA (µS) during the positive film excerpt was associated with higher AES scores. Controlling variables were chlorpromazine equivalents, executive dysfunction and positive PANSS score; β was the standardized estimated coefficient for the AES score. AES = Apathy Evaluation Scale; EDA = electrodermal activity; PANSS = Positive and Negative Syndrome Scale.

hypothesis may have stemmed from lack of power, because the quantitative measure of apathy was significantly associated with tonic activity during induction of positive emotion. We are not aware of previous work trying to identify deficits in subjective emotional experiences in schizophrenia relative to apathy, so we were unable to estimate a specific sample size. We based our hypothesis on previous studies that induced emotion in people with schizophrenia using film excerpts and used EDA activities to measure subjective emotional experiences.[48]

We used only EDA as a physiologic measure of arousal, limiting our conclusions. Future confirmation studies should combine different modalities to quantify arousal.

We induced several emotions sequentially that might have overlapped with each other. This limitation is inherent in all emotion-elicitation paradigms. We added an emotional "washout" period and randomized the order of the film excerpts to limit this possibility. Moreover, post hoc analyses showed no influence of film excerpt order on tonic and phasic measures during relaxation phases in controls. Despite our efforts to reduce the possible overlap of emotion induction, the possibility of overlap should be kept in mind when interpreting our results.

We deliberately avoided assessing apathy in healthy young adults because, from our experience, the AES shows only small variability in this population (data not published).

Participants with schizophrenia were taking antipsychotic and antidepressant medications that might have affected the EDA recordings.[49] Antipsychotics can cause hypohidrosis with an antimuscarinic effect and induce lower EDA activity. Antidepressants can cause hyperhidrosis, leading to a noisy signal during EDA recordings. Our ethics committee did not authorize a drug washout period, such as the one in a previous work.[48] To limit the potential effect of this issue, we carefully inspected EDA recordings and applied a conservative method of artifact rejection. Moreover, we included the measure of chlorpromazine equivalents in the linear regression, and it was the least significant predictor of tonic activity during positive emotion, explaining only 6.5% of the variance ($p = 0.8$). This finding suggests that the antimuscarinic effect associated with antipsychotic medications could not explain the difference in EDA recordings during emotion induction in this sample.

We induced more discrete negative emotions (anger, fear, sadness and disgust) than positive emotions (happiness). We averaged the scores for the negative film excerpts and used single scores for the positive excerpt. As a result, the general category of positive emotion was restricted to happiness, and positive emotions were measured with a single estimator, while negative emotions were measured with 4 estimators. Using this approach, we could not form conclusions about differences between positive tonic EDA emotional components and a specific discrete negative tonic EDA emotional component in schizophrenia patients with apathy. As well, we arbitrarily assigned anger, fear, sadness and disgust as "negative" emotions and happiness as a "positive" emotion. Although this seemed intuitive, it was a limitation for the present study.

Conclusion

With the above limitations in mind, the present study yields new insights into the emotional component of apathy in schizophrenia. Alongside the specific cognitive deficits associated with apathy in chronic schizophrenia, our findings provide further arguments for an independent cluster of negative symptoms, namely apathy, associated with altered positive emotions in schizophrenia. Therapeutics that enhance the anticipation of positive emotions could offer new strategies for alleviating apathy in schizophrenia. Our results also point to the need to assess apathy in future studies using EDA (and possibly other psychophysiological recordings) during emotional induction in schizophrenia.

Affiliations: From the University Department of Psychiatry, Guillaume Régnier Hospital, Rennes, France (Batail, D. Drapier, Robert); University of Lille, Inserm, CHU Lille, U1171, Degenerative and Vascular Cognitive Disorders, F-59000, Lille, France (Dondaine); Behaviour and Basal Ganglia Laboratory (EA 4712), University of Rennes, Rennes, France (Batail, Le Jeune, Sauleau, S. Drapier, Vérin, D. Drapier, Robert); Eugène Marquis Centre, Rennes, France (Le Jeune); Neurophysiology Department, Rennes University Hospital, Rennes, France (Sauleau); Movement Disorders Unit, Rennes University Hospital, Rennes, France (S. Drapier, Vérin); Psychiatry Department, Pitié-Salpêtrière Hospital, Paris, France (Millet); University of Louvain-la-Neuve, Louvain-la-Neuve, Belgium (Philippot).

References

1. Kring AM, Elis O. Emotion deficits in people with schizophrenia. *Annu Rev Clin Psychol* 2013;9:409-33.
2. Kirkpatrick B. Developing concepts in negative symptoms: primary vs secondary and apathy vs expression. *J Clin Psychiatry* 2014;75:3-7.
3. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243-54.
4. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* 2011;26:158-65.
5. Konstantakopoulos G, Ploumpidis D, Oulis P, et al. Apathy, cognitive deficits and functional impairment in schizophrenia. *Schizophr Res* 2011;133:193-8.
6. Strauss GP, Horan WP, Kirkpatrick B, et al. Deconstructing negative symptoms of schizophrenia: avolition–apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res* 2013;47:783-90.
7. Hartmann MN, Hager OM, Reimann AV, et al. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. *Schizophr Bull* 2015;41:503-12.
8. Sander D, Grandjean D, Scherer KR. A systems approach to appraisal mechanisms in emotion. *Neural Netw* 2005;18:317-52.

9. Robert G, Le Jeune F, Dondaine T, et al. Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: a PET study with conjunction analyses. *J Neurol Neurosurg Psychiatry* 2014;85:1153-8.

10. Martínez-Corral M, Pagonabarraga J, Llebaria G, et al. Facial emotion recognition impairment in patients with Parkinson's disease and isolated apathy. *Parkinsons Dis* 2010;2010:930627.

11. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull* 2008;34:819-34.

12. Cohen AS, Minor KS, Najolia GM. A framework for understanding experiential deficits in schizophrenia. *Psychiatry Res* 2010;178:10-6.

13. Trémeau F, Antonius D, Cacioppo JT, et al. Anticipated, on-line and remembered positive experience in schizophrenia. *Schizophr Res* 2010;122:199-205.

14. Trémeau F, Antonius D, Cacioppo JT, et al. In support of Bleuler: objective evidence for increased affective ambivalence in schizophrenia based upon evocative testing. *Schizophr Res* 2009;107:223-31.

15. Pankow A, Friedel E, Sterzer P, et al. Altered amygdala activation in schizophrenia patients during emotion processing. *Schizophr Res* 2013;150:101-6.

16. Cassidy CM, Brodeur MB, Lepage M, et al. Do reward-processing deficits in schizophrenia-spectrum disorders promote cannabis use? An investigation of physiological response to natural rewards and drug cues. *J Psychiatry Neurosci* 2014;39:339-47.

17. Moran EK, Kring AM. Anticipatory emotion in schizophrenia. *Clin Psychol Sci* 2018;6:63-75.

18. Wynn JK, Horan WP, Kring AM, et al. Impaired anticipatory event-related potentials in schizophrenia. *Int J Psychophysiol* 2010;77:141-9.

19. Simon JJ, Biller A, Walther S, et al. Neural correlates of reward processing in schizophrenia — relationship to apathy and depression. *Schizophr Res* 2010;118:154-61.

20. Simon JJ, Cordeiro SA, Weber M-A, et al. Reward system dysfunction as a neural substrate of symptom expression across the general population and patients with schizophrenia. *Schizophr Bull* 2015;41:1370-8.

21. Kreibig SD. Autonomic nervous system activity in emotion: a review. *Biol Psychol* 2010;84:394-421.

22. Hempel RJ, Tulen JH, van Beveren NJ, et al. Physiological responsivity to emotional pictures in schizophrenia. *J Psychiatr Res* 2005;39:509-18.

23. Volz M, Hamm AO, Kirsch P, et al. Temporal course of emotional startle modulation in schizophrenia patients. *Int J Psychophysiol* 2003;49:123-37.

24. Schlenker R, Cohen R, Hopmann G. Affective modulation of the startle reflex in schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci* 1995;245:309-18.

25. Boucsein W. *Electrodermal activity.* Berlin: Springer Science & Business Media; 2012.

26. Lovibond PF. Tonic and phasic electrodermal measures of human aversive conditioning with long duration stimuli. *Psychophysiology* 1992;29:621-32.

27. Andersson S, Finset A. Electrodermal responsiveness and negative symptoms in brain injured patients. *J Psychophysiol* 1999;13:109.

28. Schaefer A, Nils F, Sanchez X, et al. Assessing the effectiveness of a large database of emotion-eliciting films: a new tool for emotion researchers. *Cogn Emotion* 2010;24:1153-72.

29. Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261.

30. Sheenan DV, Lecrubier Y, Sheenan K, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59:22-33.

31. American Psychiatric Association. *DSM-IV-TR: Diagnostic and statistical manual of mental disorders.* 4th ed, text revision. Washington (DC): American Psychiatric Association; 2000.

32. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143-62.

33. Mattis S. *Dementia rating scale.* Odessa (FL): Psychological Assessment Resources, Inc.; 1988.

34. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). *Br J Psychiatry Suppl* 1989;7:49-58.

35. Addington D, Addington J, Maticka-Tyndale E, et al. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res* 1992;6:201-8.

36. Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. *Hosp Community Psychiatry* 1988;39:1172-7.

37. Dondaine T, Robert G, Péron J, et al. Biases in facial and vocal emotion recognition in chronic schizophrenia. *Front Psychol* 2014;5:900.

38. Gross JJ, Levenson RW. Emotion elicitation using films. *Cogn Emotion* 1995;9:87-108.

39. Philippot P. Inducing and assessing differentiated emotion-feeling states in the laboratory. *Cogn Emot* 1993;7:171-93.

40. Westermann R. Stahl G, Hesse F. Relative effectiveness and validity of mood induction procedures: analysis. *Eur J Soc Psychol* 1996;26:557-80.

41. Vicente S, Péron J, Biseul I, et al. Subjective emotional experience at different stages of Parkinson's disease. *J Neurol Sci* 2011;310:241-7.

42. Society for Psychophysiological Research Ad Hoc Committee on Electrodermal Measures, Boucsein W, Fowles DC, et al. Publication recommendations for electrodermal measurements. *Psychophysiology* 2012;49:1017-34.

43. Vicente S, Biseul I, Péron J, et al. Subthalamic nucleus stimulation affects subjective emotional experience in Parkinson's disease patients. *Neuropsychologia* 2009;47:1928-37.

44. Saville DJ. Multiple comparison procedures: the practical solution. *Am Stat* 1990;44:174-80.

45. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1:43-6.

46. Roth RM, Flashman LA, Saykin AJ, et al. Apathy in schizophrenia: reduced frontal lobe volume and neuropsychological deficits. *Am J Psychiatry* 2004;161:157-9.

47. Faerden A, Vaskinn A, Finset A, et al. Apathy is associated with executive functioning in first episode psychosis. *BMC Psychiatry* 2009;9:1.

48. Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *J Abnorm Psychol* 1996;105:249.

49. Cheshire WP, Fealey RD. Drug-induced hyperhidrosis and hypohidrosis. *Drug Saf* 2008;31:109-26.