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Specific mechanisms underlying executive and emotional apathy: A phenotyping study

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ABSTRACT

Apathy is a behavioral symptom prevalent both in neuropsychiatric pathologies and in the healthy population. However, the knowledge of the cognitive and neural mechanisms underlying apathy is still very limited, even if clinical and fMRI data support the existence of three forms of apathy (executive, emotional, initiative). These forms could be explained by the alteration of specific mechanisms. This present study's aim is to specify the cognitive and neuronal mechanisms of executive and emotional apathy. We used an EEG study conducted on 68 subjects comprising two groups of young people with specific executive or emotional phenotypes of apathy and one group with no apathy. Despite having symptom of apathy, participants were free of any neurological, metabolic, or psychiatric diagnoses and with high education. Two tasks were used: the DPX for cognitive control and the MID for motivation. Our results showed that distinct mechanisms underlie these two forms of apathy, and, for the first time, we specified these mechanisms. A deficit of the proactive control mode, reflected by a reduced probe-N2 amplitude in AY trials, underlies the executive form of apathy ($p < .03$), whereas liking motivational blunting, highlighted by a reduced LPP amplitude for financial loss, characterizes the emotional form ($p < .04$). The main limit of the results is that generalizability to the general population may be reduced since the apathetic samples were chosen for having a specific form of apathy. To conclude, better knowledge of these mechanisms informs new, more targeted treatments, both pharmacological and non-pharmacological, necessary for reducing the debilitating consequences of apathy.

1. Introduction

Apathy is a clinical symptom defined by a quantitative decrease in an individual's goal-directed activity compared to their previous level of functioning (International consensus group - Robert et al., 2018). This symptom is transnosographic, prevalent in many neurological, neurodegenerative, and psychiatric pathologies. For example, apathy affects about 40–50% of patients suffering from stroke, multiple sclerosis, Parkinson, Alzheimer or schizophrenia (Manera et al., 2019; Mulin et al., 2011). It is also a significant personal and professional burden (Tsang et al., 2010; van Reekum et al., 2005). Apathy can also occur in the healthy population, where it is less frequent but associated with the same debilitating consequences in all spheres of daily life. Indeed, about 2% of young people and 6% of older people have apathy scores similar to those of patients (i.e., scores higher than two standard deviations from the population mean) (Brodsky et al., 2010; Pardini et al., 2016). Furthermore, along a continuum from healthy behavior to apathetic

symptom, milder apathy trait, often described as subclinical apathy (i.e., scores higher than one standard deviation from the population mean), has even been reported in about 30%–40% of the general population, stable at one-year intervals (Ang et al., 2017; Lafond-Brina and Bonnefond, 2022). Despite apathy's high prevalence and negative consequences, the scientific knowledge of the cognitive and neural mechanisms underlying apathy is very limited (Radakovic and Abrahams, 2018; Robert et al., 2018). However, its improvement is essential for the development of new, more targeted treatments, both pharmacological and non-pharmacological, in order to help to reduce the debilitating consequences of apathy.

The limited knowledge we have about the mechanisms of apathy is undoubtedly linked to the prevailing one dimensional concept of apathy (Dickson and Husain, 2022). However, clinical and fMRI data, mainly collected from studies on patients suffering from brain damage and neurodegenerative diseases (Bhatia and Marsden, 1994; Cummings, 1993; Dickson and Husain, 2022; Pagonabarraga et al., 2015; Radakovic

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and Abrahams, 2018; Stuss et al., 2000), support the existence of at least three forms of apathy: executive/cognitive, emotional and initiative/auto-activation apathy. The alteration of specific mechanisms could underly these different forms of apathy (Levy and Dubois, 2006). Executive apathy manifests as difficulty in planning new action, switching between tasks, or focusing on an activity. It is related to dysfunctions of the dorso/ventrolateral prefrontal cortex and cognitive territory of the basal ganglia (mainly the dorsal caudate nucleus) and may be caused by executive/cognitive control disorders (Miller and Cohen, 2001; Nejati et al., 2018). Emotional apathy is characterized by difficulty in experiencing and expressing emotion, empathy, and interest. It is associated with dysfunctions of the orbital and ventromedial prefrontal cortex, and the limbic territories of the basal ganglia (especially the ventral striatum) and may be underpinned by motivational deficits (Kringelbach, 2005; Kringelbach and Rolls, 2004; Zald, 2007). Finally, initiative apathy is often described as mental emptiness with difficulty in thinking of new things, being spontaneous, and initiating social contact. It is associated with dysfunctions affecting interconnected regions associated with executive and emotional apathy and/or the anterior cingulate cortex and it may be a mixed form of apathy (Le Heron et al., 2018). This hypothesis for specific mechanisms underlying each form of apathy has never been directly tested.

To date, only studies using neuropsychological tests, known to have strong psychometric properties but low process specificity, and/or validated questionnaires have confirmed that impairments of specific cognitive processes underpin executive and emotional forms of apathy, whereas initiative apathy is underpinned by the sum of the cognitive processes altered in the two other forms [in patients suffering from neurodegenerative diseases (Perri et al., 2018), schizophrenia (Raffard et al., 2016), and in subclinical apathy in the healthy population (Cuvillier and Bayard, 2021; Lafond-Brina and Bonnefond, 2022)]. Only the unidimensional approach of apathy has been used to explore neural mechanisms of apathy. Yet, several electrophysiological correlates of cognitive control or motivational processes, and more precisely cognitive event-related evoked potentials (ERP), have previously been linked to the severity of unidimensional apathy. In cognitive tasks allowing the exploration of cognitive control processes, especially the proactive and reactive modes, some specific ERP, like the cue-P3b and probe-P3a, had seen their amplitude negatively correlated with the severity of unidimensional apathy (Daffner et al., 2000, 2001; Mathis et al., 2014; Yamagata et al., 2004). However, the P3b results were heterogeneous between the pathologies (Davis et al., 2022; Vignapiano et al., 2016; Yamagata et al., 2004). In the same way, in motivational tasks allowing the exploration of wanting and liking motivational processes, relatives respectively to the anticipation of a rewarded cue and the hedonic treatment of a rewarded feedback, the amplitude of two ERP had been linked to the severity of unidimensional apathy: the feedback-P3a in healthy subjects (Takayoshi et al., 2018) and the LPP in Parkinson disease (Dietz et al., 2013). Finally, the heterogeneity of the ERP linked to unidimensional apathy could be due to differences between pathologies, but also to specificities associated with each form of apathy (Kos et al., 2016).

Therefore, this present study's main aim is to specify the cognitive and neuronal mechanisms underlying executive and emotional forms of apathy using experimental cognitive and motivational paradigms combined with EEG. We hypothesize specific altered processes in the executive and emotional forms of apathy: a specific impairment of the proactive control process in executive apathy and a specific impairment of the wanting and/or liking motivational components in emotional apathy.

2. Method

2.1. Subjects

68 university students', native French speakers aged between 18 and

28 years, were recruited based on their specific phenotypes of multidimensional apathy. Three groups of participants were created: one group of 22 participants with an executive apathy phenotype, one group of 22 participants with emotional apathy phenotype, and one group of 24 participants with non-apathy. Participants with a history of neurological, metabolic, sensorial, or psychiatric disorders; a history of psychiatric disorders in first-degree relatives; consumption of psychoactive drugs and cannabis during the last three months; or general anesthesia in the past three months were excluded based on a self-administered clinical questionnaire and then, a short interview with a certified neuropsychologist. Moreover, students with mild or severe depressive symptoms, as determined by the self-report Beck Depression Inventory II (BDI-II; score ≥ 16) (Beck et al., 1996), were excluded. No participant dropped out. The study protocol was approved by the local ethics committee (University review board: UNISTRA/CER/2020-13) and the selected subjects were paid for their participation.

The executive and emotional apathy participants were included because they specifically presented one form of apathy but not the two other forms of apathy (see Table 1 for the criteria). To do that, participants completed the self-report Dimensional Apathy Scale (DAS) (Radakovic and Abrahams, 2014). The DAS is a 24-item scale assessing the severity of executive, emotional, and initiative apathy. Items are scored on a 4-point Likert scale based on the frequency of occurrence of apathy symptoms in the previous month (1 = "hardly ever"; 4 = "almost always"). For each subscore, a cut-off based on the mean and the standard deviation of the total sample was calculated (Lafond-Brina and Bonnefond, 2022). Cut-offs were +1 standard deviation from the mean for trait apathy and +2 standard deviation from the mean for symptom apathy, as recommended (Angus et al., 2017; Muneaux, 2018).

A part the DAS and the BDI, they also completed another self-report questionnaire: the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006). The TEPS is an 18-item scale designed to measure motivational trait dispositions in both anticipatory and consummatory experiences of pleasure. For a brief neuropsychological measure of their working memory, the digit span task from the WAIS-III was realized by a certified neuropsychologist (Wechsler, 1997).

2.2. Tasks and behavioral measures

The participants completed in a counterbalanced order the Dot Pattern Expectancy (DPX) task (MacDonald et al., 2005) and the Monetary Incentive Delay (MID) task (Knutson et al., 2000). The DPX is a dot-pattern cue-probe detection task that allows for the exploration of cognitive control processes in a dual time framework, proactive and reactive modes, corresponding respectively to anticipatory and adaptive control modes (Boudewyn et al., 2019; Braver et al., 2009). The MID task is a simple detection task that allows the study of the motivational "wanting" and "liking" components, which reflect, respectively, the anticipation of a reward and the feeling of pleasure when obtaining that reward (Angus et al., 2017; Berridge et al., 2009; Gard et al., 2006). Both tasks lasted about 30 min and were divided into three blocks of 100 trials. These blocks were separated by short breaks and preceded by a training of a few minutes until the participants achieved success in six consecutive trials.

Table 1

Criteria for the constitution of the three groups of participants. Values are the cut-offs used for each questionnaire (the DAS, the Dimensional Apathy Scale; the BDI-II, the Beck Depression Inventory II).

	Controls	Executive apathy	Emotional apathy
DAS executive	<16	Trait [16; 20] Symptom [21; 24]	<16
DAS emotional	<12	<12	Trait [12; 16] Symptom [17; 24]
DAS initiative	<14	<14	<14
BDI-II	<16	<16	<16

The DPX is a dot-pattern cue-probe detection task in which dots combinations are presented one by one on the screen: black dots combinations (A or B dot cues) alternated with blue dots combinations (X or Y dot probes) (Fig. 1). The subjects had to respond after the blue probes by pressing the right button in cases presenting the target sequence (“A cue – X probe” dots combination trials). In all other cases, they had to press the left button. Thus, four types of trials were differentiated: AX, AY (where Y is any other blue dot combination apart from X), BX (where B is any other black dot combination apart from A), and BY trials. The target sequence (AX) was more frequent (70% of trials) than the other sequences (12% for AY, 12% for BX and 6% for BY), leading participants to develop a strong expectation of making a “match” in response to probes following ‘A’ cues, and to ‘X’ probes generally.

For each type of trial, reaction times (RT) and the rate of false alarms (FA) (i.e., pressing on the wrong button) were calculated. The total number of omissions (absence of response) and the Behavioral Shift Index (for RT and for rates of FA, $BSI = (AY-BX)/(AY + BX)$) were also calculated. Another comparison was made to evaluate more specifically the goal maintenance; the z-transform of the FA in AX and BX trials, $Z(FA AX) + Z(FA BX)$, was compared to the z-transform of FA in AY trials, $Z(FA AY)$. Subjects with a good goal maintenance should have few FA on AX and BX trials and more on AY trials, because they will use the information provided by the cue to prepare their response. In contrast, subjects with poor goal maintenance should have the opposite profile (i.e., few FA on AY trials and more on AX and BX trials) because they will not take into account the cue and thus will tend to respond target to the X.

The MID is a visual detection task in which subjects are required to respond as quickly as possible by pressing a response button at the presentation of the probe (a blue cross) (Fig. 2). An incentive (win or loss of 15 cents) or neutral cue (no win and no loss) is presented before the probe. In each block, the three types of cues (win, loss, neutral) are presented in a random order and in similar proportions (33%, 33% and 34%, respectively). Either positive (a green disc) or negative (a red disc) feedback is given after the response. It informs the subject if his or her response was completed with enough speed. This performance feedback also informs the participant about the obtained reward in case of incentive cues. After a win cue, positive feedback indicates an actual monetary win, whereas negative feedback indicates the absence of a monetary win. After a loss cue, positive feedback indicates the absence of monetary loss, whereas negative feedback indicates an actual monetary loss. After a neutral cue, positive and negative feedback indicates no monetary variation. The feedback judgment criterion is adjusted to the individual average detection speed throughout the task, allowing approximately 60% of positive feedback (mean success rate: 61.44%).

RT, rate of anticipations (response before the presentation of the probe) and number of omissions (absence of response) were calculated for the three types of cues.

2.3. Electrophysiology

2.3.1. Electrophysiological preprocessing

Electroencephalograms (EEGs) were recorded using 64 Ag/AgCl BioSemi ActiveTwo System (Amsterdam, Netherlands) electrodes mounted on an elastic cap according to the standard 10-10 system and with a 0.01–500 Hz band-pass filter. BrainVision Analyzer 2.1 software was used to analyze the data offline at 2048 Hz with a 0.05 Hz off-line high-pass filter, a 30 Hz off-line low-pass filter and a 50 Hz notch filter. EEGs were re-referenced to the average monopolar reference (Offner, 1950). Blinks and horizontal eye movements were removed using a regression algorithm (Gratton et al., 1983). The noisy scalp channel was defined as an amplitude exceeding $\pm 100 \mu\text{V}$ throughout the recording and was interpolated by the average of the four nearest spatial electrodes.

2.3.2. Event-Related Potential analysis (ERP)

For the DPX, cue- and probe-locked ERP were analyzed. The cue-locked EEG was segmented from -250 to 5000 msec relative to cue onset, while the probe-locked EEG was segmented from -3000 to 3000 msec relative to probe onset. For the MID task, cue- and feedback-locked ERP were analyzed. The cue-locked EEG was segmented from -250 to 4500 msec relative to cue onset and from -200 to 1500 msec relative to feedback onset.

All EEG data were visually inspected for artifacts using a semi-automatic procedure. The EEG segments were rejected based on the following criteria: a maximum voltage difference of less than $0.5 \mu\text{V}$ within 100 msec intervals; a voltage step of more than $50 \mu\text{V}$ between sample points; a maximum of $100 \mu\text{V}$; a minimum of $-100 \mu\text{V}$; and a voltage difference of $100 \mu\text{V}$ within a given trial. Additional artifacts were identified visually. The EEG data was then transformed using current-source density (CSD) analysis. In both tasks, the ERP were averaged separately for each trial and were baselined to a pre-stimulus interval of -200 to 0 msec.

The ERP parameters chosen for analysis were determined by the literature and our own data. All ERP were extracted at the electrode where the maximum amplitude was observed. In the DPX task, the cue-locked ERP were the difference P2/N2, the P3b and the CNV. The difference P2/N2, interpreted as reflecting proactive task goal reconfiguration, was computed at FCz, where the minimum (trough) of the N2 was subtracted from the maximum (peak) of the P2. The P2 was defined within a 20 msec latency window centered on the peak latency, between 145 and 205 msec after the cue, whereas the N2 was defined within a 40 msec latency window centered on the peak latency, between 210 and 340 msec after the cue. The P3b, assumed to reflect attentional stimulus processing, was computed at Pz, in the time range between 400 and 600 msec after the cue. The CNV, which reflected response motor preparation, was computed at CPz, in the time range between 1750 and 2000 msec after the cue. The probe-locked ERP were the N2 and the P3a, both of which were extracted at electrode FCz. The N2, interpreted as reflecting conflict detection, was defined within a 35 msec latency window centered on the peak latency, between 140 and 270 msec after

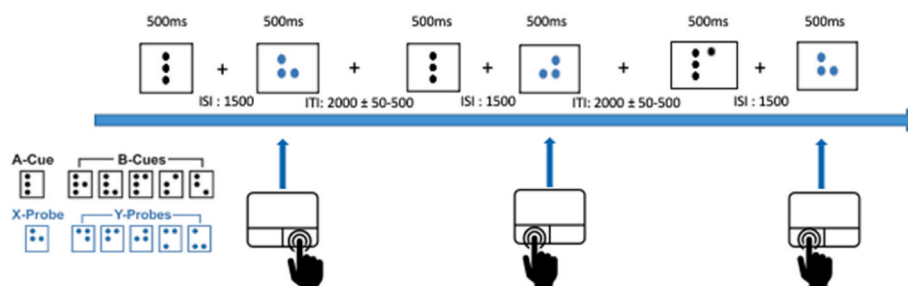


Fig. 1. The DPX task.

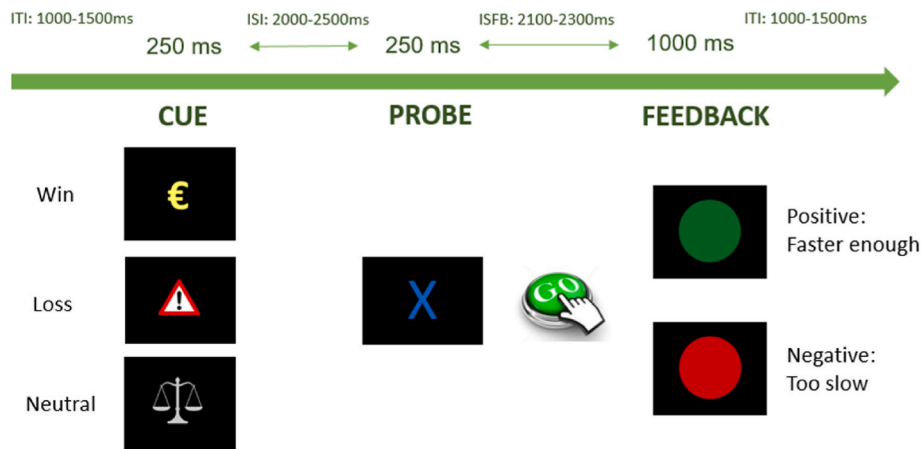


Fig. 2. The MID task.

the probe. The P3a, which reflected attentional processing for conflict resolution, was defined within a 40 msec latency window centered on the peak latency, between 220 and 320 msec after the probe. For the MID task, the ERP were all scored using time-window averages. The cue-locked ERP were the P3b and the CNV. The P3b was computed at Pz, in the time range between 300 and 600 msec after the cue. The CNV was computed at CPz, in the time range between 2100 and 2300 msec after the cue. The feedback-locked ERP were the RewP, the P3a and the LPP. The RewP, assumed to reflect reward sensitivity, was computed at Fz, in the time range between 170 and 220 msec after the feedback. The P3a, which reflected attentional processing to surprising or unfavorable outcomes as well as response inhibition, was computed at Cz, in the time range between 330 and 360 msec after the feedback. The LPP, which reflected affective processing, was computed at CPz, in the time range between 500 and 700 msec after the feedback.

2.4. Statistical analysis

A two-tailed significance level of 0.05 and a trend level of 0.10 were used for all tests. Effect sizes were calculated using a partial eta square (η_p^2).

Assumption tests were realized on behavioral and electrophysiological data. ANOVA's. See Supplementary Data Table S1 for the detailed results. ANOVAs were used when data were normally distributed (Shapiro–Wilk $p > .05$). Analysis of Variance of Aligned Rank Transformed Data (ART-ANOVA) were performed when data were not normally distributed (Shapiro–Wilk $p < .05$) (Elkin et al., 2021; Wobbrock et al., 2011).

In the DPX task, behavioral data were subjected to ART-ANOVAs, including the within-subject factor Trial (AX, AY, BX) and the between-subject factor Group (control, executive apathy, emotional apathy). For cue-locked ERP, ART-ANOVAs or ANOVAs were performed, including the within-subject factor Cue (A, B) and the between-subject factor Group. For probe-locked ERP, ANOVAs were performed, including the within-subject factor Trial and the between-subject factor Group.

In the MID task, behavioral data and cue-locked ERP were subjected to ART-ANOVAs or ANOVAs, including the within-subject factor Cue (win, loss, neutral) and the between-subject factor Group. Regarding feedback-locked ERP, the ANOVAs performed included the between-subject factor Group and the within-subject factor Feedback. According to the process being evaluated, the modalities compared were as follows:

- actual win *versus* actual loss, in order to assess reward positivity (RewP);

- actual win (or loss) *versus* neutral trial, in order to assess potential modulation of attention by rewards (or punishments) (P3a);
- actual win (or loss) *versus* absence of win (or loss), in order to assess affective treatment of rewards (or punishments) (LPP)
- neutral trials with positive *versus* negative feedback, in order to assess affective treatment of performances (LPP).

Pearson correlational analyses were performed between the three apathy subscores and the behavioral and ERP measures in each group, because of an extreme group design. Only significant correlational analyses were reported in the result section.

ANCOVA with sex was calculated due to the difference between the three groups. It showed that differences in sex did not explain any of the results ($p > .05$). See Supplementary Data Table S2 for the detailed results.

3. Results

3.1. Descriptive statistics

Table 2 summarizes the demographic and neuropsychological characteristics of the three groups. The executive group was constituted by 63% of subclinical apathy trait and 37% of clinical apathy symptom. In the emotional group, 54% had a subclinical apathy and 46% a clinical apathy.

In addition to a higher DAS executive score, the executive group presents a higher DAS initiative score, higher BDI score and higher TEPS consummatory score (all $p < .05$). However, these three higher scores are not (sub)clinically significant (Beck et al., 1996; Lafond-Brina and Bonnefond, 2022; Leaine et al., 2022).

In addition to a higher DAS emotional score, the emotional group presents a higher prevalence of male. In the general young adult population, emotional apathy is also more prevalent in men than in women (Lafond-Brina and Bonnefond, 2022).

3.2. DPX task

3.2.1. Behavioral results

The ART-ANOVA performed on RT revealed a main effect of trial ($F(2,128) = 120.17, p < .001; \eta^2 = 0.68$), with RT slower for AY than AX and BX ($p < .001$), and slower for AX than BX ($p < .005$). No effect of group ($p > .91$) nor trial \times group interaction ($p > .46$) existed.

Regarding the FA rate, the ART-ANOVA revealed a main effect of trial ($F(2,128) = 27.95, p < .001; \eta^2 = 0.28$), with higher FA rate for AX and AY than for BX ($p < .001$). No effect of group ($p > .78$) nor trial \times group interaction ($p > .41$) existed.

The ART-ANOVA performed on the BSI for RT and FA revealed no

Table 2

Demographic and neuropsychological characteristics of the three groups. Values are given as the mean (standard deviation) [the DAS, the Dimensional Apathy Scale; the BDI-II, the Beck Depression Inventory II; the TEPS, the Temporal Experience of Pleasure Scale (Gard et al., 2006); the digit span task from the WAIS-III (Wechsler, 1997)].

	Control	Executive	Emotional	Differences
Age (years)	22 (1.73)	21.4 (1.71)	21.4 (2.13)	n.s
Sex (% of males)	41.66	27.27	63.63 *	$X^2(2) = 5.99$, $p < .05$ Cramer's V = .297
Level of education	Freshman: 20.83% Junior: 50% Senior: 29.17%	Freshman: 40.90% Junior: 50% Senior: 9.10%	Freshman: 45.45% Junior: 36.37% Senior: 18.18%	n.s
DAS executive	8.63 (3.79)	19.1 (1.87) *	7.23 (4.89)	$F(2,65) = 67.04$, $p < .001$; $\eta^2 = .67$
DAS emotional	6.25 (2.59)	6,64 (2.87)	16,3 (3.40) *	$F(2,65) = 82.93$, $p < .001$; $\eta^2 = .72$
DAS initiative	7.54 (2.95)	9.45 (2,26) *	7.09 (2.91)	$F(2,65) = 4.67$, $p < .02$; $\eta^2 = .13$
BDI-II	4.21 (4.27)	10.4 (4.31) *	5.68 (5.54)	$F(2,65) = 10.60$, $p < .001$; $\eta^2 = .25$
TEPS Anticipatory pleasure	45.1 (6.61)	44.9 (4.26)	45.2 (11.9)	n.s
TEPS Consummatory pleasure	37.4 (5.33)	39.6 (4.51) *	35.5 (6.38)	$F(2,65) = 3.17$, $p < .05$; $\eta^2 = .09$
Digit span task forward	6.25 (1.15)	6.32 (1.04)	6.18 (0.85)	n.s
Digit span task backward	4.96 (1.12)	4.45 (1.10)	5.23 (1.38)	n.s

effect of group (respectively, $p > .83$ and $p > .42$).

The ANOVA performed on the goal-maintenance comparison revealed a trial \times group interaction ($F(2,64) = 3.25$, $p < .04$; $\eta^2 = 0.09$). Executive group had higher FA z-transforms for AX and BX trials compared to those for AY trials ($p < .05$), while the control and emotional groups showed no difference between the two conditions ($p > .12$) (Fig. 3).

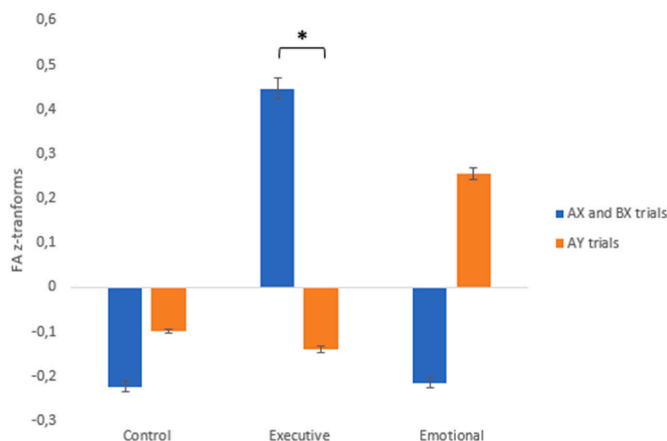


Fig. 3. Goal-maintenance comparison.

The FA z-transform in AX and BX trials was compared to the FA z-transform in AY trials in the three groups. The executive group was the only one to have higher FA z-transforms for AX and BX trials than for AY trials ($p < .05$). This finding reflected a poor goal maintenance for the executive group.

The ART-ANOVA performed on the total number of omissions revealed a main effect of group ($F(2,64) = 4.52$, $p < .05$; $\eta^2 = 0.12$). Executive group made more omissions than the control and emotional groups (respectively, $p < .02$ and $p < .06$), while the control and emotional groups showed a similar profile ($p > .99$).

3.2.2. Electrophysiological results

Table 3 summarizes the significant electrophysiological results for each group.

3.2.2.1. Cue-locked ERP. The ART-ANOVA performed on the P2–N2 difference revealed the classic main effect of cue ($F(1,65) = 3.97$, $p < .05$; $\eta^2 = 0.07$); with larger P2–N2 difference after the B cue than the A cue. No effect of group ($p > .47$) nor cue \times group interaction ($p > .66$) existed.

The ANOVA performed on the P3b revealed the classic main effect of cue ($F(1,65) = 184.19$, $p < .001$; $\eta^2 = 0.74$), with a larger P3b after the B cue than the A cue. No effect of group ($p > .90$) nor cue \times group interaction ($p > .68$) existed.

The ANOVA performed on the CNV revealed the classic main effect of cue ($F(1,65) = 123.26$, $p < .05$; $\eta^2 = 0.06$), with larger CNV after the A cue than the B cue. No effect of group ($p > .95$) nor cue \times group interaction ($p > .79$) exist.

3.2.2.2. Probe-locked ERP. The ANOVA performed on the N2 revealed a significant trial \times group interaction ($F(4,130) = 2.69$, $p < .03$; $\eta^2 = 0.11$). The executive group was the only one to present similar N2 amplitudes for AX and AY trials ($p > .47$), whereas N2 was larger in AY trials than in AX trials for the control and emotional groups ($p < .02$) (Fig. 4).

The ANOVA performed on the P3a revealed a main effect of trial ($F(2,130) = 42.66$, $p < .001$; $\eta^2 = 0.40$), with larger P3a in AY trials than in AX and BX trials ($p < .001$). No effect of group ($p > .22$) nor trial \times group interaction ($p > .46$) existed.

3.3. MID task

3.3.1. Behavioral results

The ART-ANOVA performed on RT revealed the classic main effect of cue ($F(2,130) = 65.27$, $p < .001$; $\eta^2 = 0.38$), with RT faster for win than loss and neutral cues, and for loss than neutral cues (all $p < .001$). No

Table 3

Synthesis of the significant electrophysiological results at the DPX and the MID. Values of ERP amplitudes are given as the mean (standard deviation). The group in bold is significantly different than the two other groups.

	Control	Executive	Emotional	Differences
DPX				
Probe-N2 (AY trials)	-22.3 (2.1)	-12.4 (4.3)	-20.3 (3.6)	$p < .03$; $\eta^2 = .11$
MID				
CNV (all trials)	-3.02 (3.69)	-6.66 (2.55)	-5.37 (2.85)	$p < .02$; $\eta^2 = .11$
P3a (actual loss trials)	5.9 (2.79)	17.42 (3.33)	7.41 (3.67)	$p < .03$; $\eta^2 = .10$
P3a (neutral trials with negative feedback)	2.01 (2.71)	9.76 (2.82)	-0.73 (3.11)	
LPP (actual loss trials)	4.24 (2.76)	6.35 (2.5)	-2.35 (3.37)	$p < .04$; $\eta^2 = .10$
LPP (absence of loss trials)	2.27 (1.63)	1.06 (1.51)	0.86 (1.46)	
LPP (neutral trials with positive feedback)	2.36 (1.60)	-0.26 (1.66)	-0.87 (1.18)	$p < .04$; $\eta^2 = .09$
LPP (neutral trials with negative feedback)	1.89 (1.22)	4.34 (2.51)	-1.77 (1.92)	

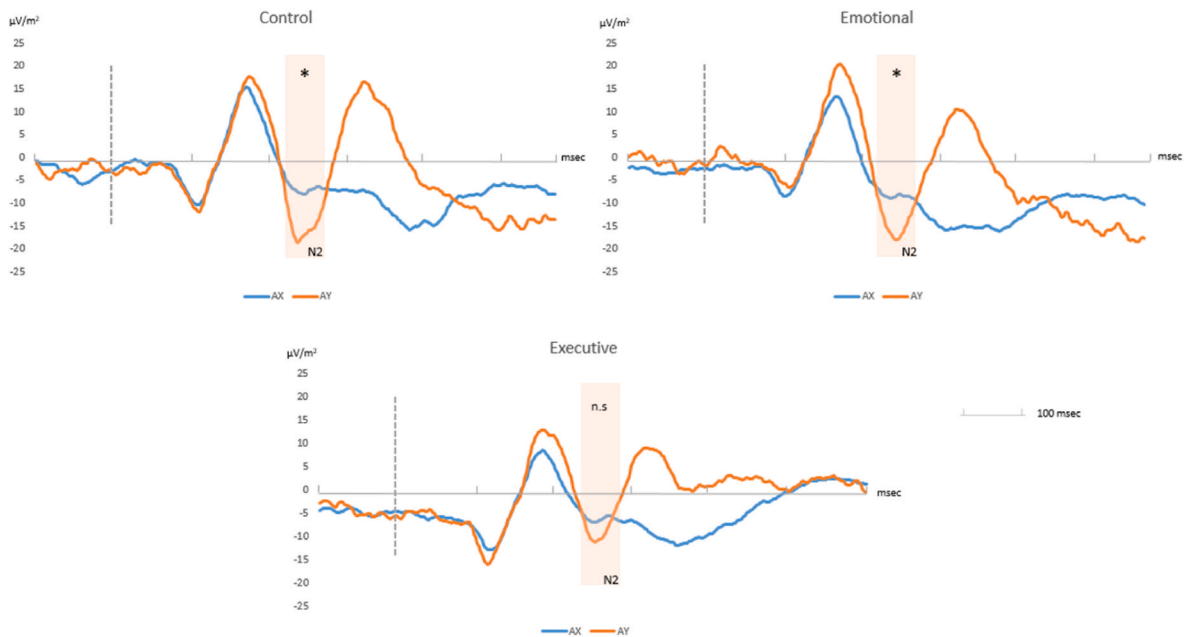


Fig. 4. N2 amplitude at FCz in the three groups: * $p < .05$; n.s: non-significant. The analyzed time window is represented in orange. The probe appears at 0msec (represented by a vertical dotted line).

effect of group ($p > .75$) nor cue \times group interaction ($p > .44$) existed.

The ART-ANOVA performed on the rate of anticipations revealed a main effect of cue ($F(2,130) = 17.55, p < .001; \eta^2 = 0.22$), with more anticipations after a win than loss and neutral cues ($p < .001$) and more anticipations after loss than neutral cues ($p < .04$). No effect of group ($p > .37$) nor cue \times group interaction ($p > .92$) was found.

The ART-ANOVA performed on omissions revealed there was no effect of cue ($p > .14$), group ($p > .12$), nor cue \times group interaction ($p > .41$).

3.3.2. Electrophysiological results

3.3.2.1. Cue-locked ERP. The ART-ANOVA performed on the P3b revealed a main effect of cue ($F(2,130) = 3.84, p < .03; \eta^2 = 0.05$), with larger P3b after a win than a loss cue ($p < .01$). No effect of group ($p > .93$) nor cue \times group interaction ($p > .33$) existed.

The ANOVA performed on the CNV revealed a main effect of group ($F(2,65) = 4.30, p < .02; \eta^2 = 0.11$), with less negative CNV amplitude for the control group compared to the executive group ($p < .02$). No effect of cue ($p > .63$) nor cue \times group interaction ($p > .22$) was found.

3.3.2.2. Feedback-locked ERP. Regarding the RewP, the sensitivity for rewards was examined for actual win and loss, so ANOVA was performed including the within-subject factor Feedback (actual win, actual loss) and the between-subject factor Group. The ANOVA performed on the RewP revealed a trend for a main effect of cue ($F(1,64) = 3.65, p < .06; \eta^2 = 0.05$), with larger RewP after an actual win than an actual loss feedback ($p < .05$). No effect of group ($p > .14$) nor cue \times group interaction ($p > .77$) existed.

The P3a was examined to shed light on how rewards may modulate attention. The effects of incentive and neutral cues on one feedback were examined to do this. Therefore, two ANOVAs were performed, including the within-subject factor Feedback (for positive feedback: actual win, neutral trial; for negative feedback: actual loss, neutral trial) and the between-subject factor Group.

The ANOVA performed on the P3a between actual win trials and neutral trials with positive feedback revealed a main effect of trial ($F(1,65) = 12.53, p < .001; \eta^2 = 0.16$), with larger P3a after an actual win than a positive neutral feedback ($p < .001$). No effect of group ($p > .58$)

nor trial \times group interaction ($p > .17$) existed.

The ANOVA performed on the P3a between actual loss trials and neutral trials with negative feedback revealed a main effect of trial ($F(1,64) = 20.64, p < .001; \eta^2 = 0.21$), with larger P3a after an actual win than a positive neutral feedback ($p < .001$), as well as a main effect of group ($F(2,64) = 3.72, p < .03; \eta^2 = 0.10$), with larger P3a for the executive group than the control and emotional group ($p < .05$). No trial \times group interaction ($p > .41$) existed.

For the LPP, the affective treatment of a reward was analyzed by examining the emotional effect of receiving or not receiving a potential incentive. Three ANOVAs were performed, including the within-subject factor Feedback (after a win cue: actual win, absence of win; after a loss cue: actual loss, absence of loss; after a neutral cue: positive neutral, negative neutral) and the between-subject factor Group.

The ANOVA performed on the LPP between actual win trials and the absence of win trials revealed there was no effect of trial ($p > .47$), group ($p > .28$), nor trial \times group interaction ($p > .16$).

The ANOVA performed on the LPP amplitude between actual loss trials and the absence of loss trials revealed a trial \times group interaction ($F(2,64) = 3.43, p < .04; \eta^2 = 0.10$). The emotional group had a reduced LPP amplitude for actual loss than the control and the executive groups (respectively, $p < .04$ and $p < .01$). The executive group was the only one to have a larger LPP for actual loss than for the absence of loss ($p < .02$) (Fig. 5).

The ANOVA performed on the LPP amplitude between neutral trials with positive and negative feedback revealed a trial \times group interaction ($F(2,65) = 3.32, p < .04; \eta^2 = 0.09$). The executive group was the only one to have a larger LPP for neutral trials with negative feedback than for neutral trials with positive feedback ($p < .01$). The executive group presents a larger LPP for neutral trials with negative feedback than the emotional group ($p < .01$).

3.4. Feedback-locked ERP Correlational analyses

In the DPX, Pearson correlational analyses revealed a negative correlation between the N2 amplitude after the AX, AY and BX trials and DAS executive score in the emotional group (respectively, $r = -0.62, r = 0.57, r = 0.60$, all $p < .05$). In people with emotional apathy, the more severe the executive apathy trait, the smaller the N2 amplitude for all

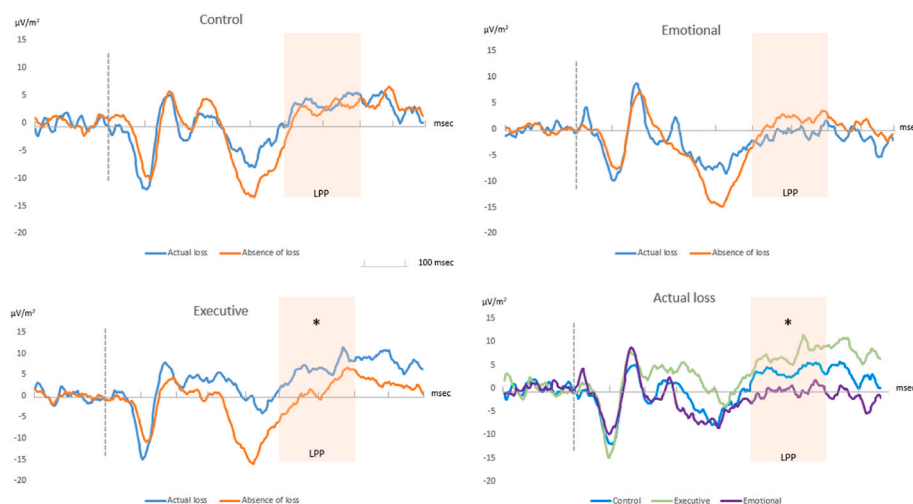


Fig. 5. LPP amplitude at CPz in each group for actual loss and absence of loss, and LPP amplitude at CPz for actual loss in the three groups: * $p < .05$. The analyzed time window is represented in orange. The feedback appears at 0 msec (represented by the vertical dotted line).

the trials.

In the MID, Pearson correlational analyses revealed a positive correlation between LPP amplitude after an actual win and TEPS consummatory score in the control group ($r = .42, p < .05$). In the control group, the better individuals' capacity for consummatory pleasure, the larger the LPP amplitude for trials with an actual win.

4. Discussion

This study's main aim was to investigate the cognitive and neuronal mechanisms of multidimensional apathy, specifically executive and emotional apathy. It relied on an EEG study conducted in two groups of healthy young people with executive or emotional phenotypes of sub-clinical and clinical apathy, as well as one group with no apathy. Our results, which were consistent with neuropsychological and fMRI data, showed that distinct mechanisms underlie each form of apathy. In the DPX, the executive group was the only group to present higher errors for AX and BX trials than for AY trials, as well as a reduced probe-N2 amplitude after AY trials. At the MID, only the executive group presented higher amplitudes for P3a and LPP after negative feedback than positive feedback, whatever the cue. On the contrary, in the MID, the emotional group was the only group to present a reduced LPP amplitude for actual loss, compared to the two other groups. These findings allow us to specify these types of apathy for the first time. There is a cognitive control deficit (specifically of the proactive control mode) in the executive form, whereas there is a particular motivational profile in the emotional form, specifically concerning the hedonic impact of reward, that is the liking motivation. Improved knowledge of these mechanisms should help the development of more targeted therapeutic interventions necessary for reducing the debilitating consequences of apathy.

4.1. Executive apathy

In accordance with our hypothesis, our behavioral and electrophysiological results found that the executive form of apathy - and solely this form - is underpinned by a deficit of proactive control. Proactive control, which strongly relies on the dorsolateral prefrontal cortex (DLPFC), is conceptualized as the maintenance of goal-relevant information to bias attention, perception, and response preparation in a top-down fashion (Braver, 2012; Braver et al., 2007). In the DPX, this poor goal maintenance corresponded to a deficit in using contextual cue information to guide behavior, as demonstrated in the greater proportion of errors for AX and BX trials compared to AY trials. This behavioral profile, which was observed only in the executive group, was

accompanied by a deficit of proactive task goal reconfiguration. Indeed, subjects with executive apathy were not prepared to give a response target to the X probe after an A cue and, therefore, could not detect conflict if the A cue was followed by a Y. This was revealed by the absence of a higher probe-locked N2 in AY trials. This failure of healthy subjects with an executive apathy to recruit proactive control is consistent with impairments in DLPFC and cognitive territory of the basal ganglia, previously revealed in fMRI studies conducted on executive apathy patients (Levy and Dubois, 2006; Pagonabarraga et al., 2015; Radakovic and Abrahams, 2018). The use of a paradigm designed to explore the engagement of two modes of cognitive control, each with a specific temporal dynamic, allowed us to specify the executive processes impaired in executive apathy and thus go even further than the neuropsychological approach classically used to explore apathy (Perri et al., 2018; Raffard et al., 2016). The impairment of the proactive control mode highlighted in executive apathy aligns with clinical observations of the daily functioning of executive apathy patients. These patients are described as having strong difficulties planning and organizing actions and maintaining goals. In the executive group, the deficit to actively maintain, in a sustained manner, the task-relevant information, may also be at the origin of their attentional failures, as revealed by a higher number of omissions in the DPX task (Sagaspe et al., 2012). Finally, our results shed light on the link between the severity of executive apathy and the lack of proactive control (in people with emotional apathy, the higher the associated executive apathy trait, the lower the N2 amplitude for AY trials). Therefore, we could hypothesize that whatever the main form of apathy presented by a subject, people with high executive apathy trait do not anticipate their goal-relevant information according to a context. This result could explain the results of several studies, which have found a correlation between executive deficits and executive apathy as well as unidimensional apathy in patients suffering from psychiatric (Faerden et al., 2009; Konstantakopoulos et al., 2011; Raffard et al., 2016) or neurological disorders (Lohner et al., 2017; Meyer et al., 2014).

Interestingly, our results also revealed that, even in the case of an incentive cue, subjects with executive apathy showed a deficit of proactive control. Indeed, in the MID task, subjects with executive apathy do not consider the context (the reward information given by the cue in the MID task). Exclusively for the executive group, the amplitude of the LPP, a component reflecting affective processing, was larger for neutral trials with negative feedback than for neutral trials with positive feedback. Thus, unlike the other groups, the executive apathy group did not actively maintain the relevant information given by the cue. The deficit of proactive control underlying executive apathy is not modulated by

motivation since, in these subjects, the affective processing (liking component) was only modulated by the performance feedback information, regardless of the cue.

Therefore, our results suggest that motivational therapies, based on the activation of efficient motivational strategies, could be useless for treating executive apathy. Instead, cognitive remediation based on executive functions seems to be the most appropriate therapy for reducing the negative impact of executive apathy. Conforming to this, a recent fMRI study on depressive patients showed the benefits of a video game intervention designed to improve cognitive control on activation and functional connectivity of the cognitive control network as well as on self-reported apathy (Gunning et al., 2021). Furthermore, when considering pharmacological treatments, dopaminergic treatments had already been tested for unidimensional apathy, with very heterogeneous effects along the subjects and the pathologies (Herrmann et al., 2008; Mintzer et al., 2021; Padala et al., 2017; Rosenberg et al., 2013; Ruthirakuhan et al., 2018). However, results from some studies in which participants' profile of multidimensional apathy has been assessed a posteriori, showed that participants with executive apathy benefited the most from the dopaminergic treatments (Herrmann et al., 2008; Padala et al., 2017). Our results are in accordance with these studies, since only executive apathy is underlied by a deficit of proactive control supported by the dopaminergic system. On the contrary, dopaminergic drugs could not be useful in emotional apathy, since the liking deficits are underlied by the opioid and cannabinoid systems. Therefore, for the next pharmacological studies, wisely choose the participants with a profile of apathy could change the effect response of a treatment in a pathological population.

4.2. Emotional apathy

Regarding the emotional form of apathy, our results, in line with our hypothesis, reveal that this form of apathy is underpinned by a specific motivational profile. This result agree with previous fMRI studies, performed on patients suffering from emotional apathy, which showed these patients had dysfunctions of the orbital and ventromedial prefrontal cortex and the limbic territories of the basal ganglia, especially the ventral striatum (Casey et al., 2018; Knutson et al., 2005). However, the structures highlighted in the fMRI studies could not distinguish between wanting and/or liking deficits in emotional apathy. Our electrophysiological results specified an impaired liking process but a preserved wanting process in healthy subjects with emotional apathy. Indeed, the emotional group could anticipate based on motivational cues to the same extent as the control group: they did not show any alteration of wanting components, as revealed by the P3b and CNV components (Demidenko et al., 2021; Novak et al., 2016; Novak and Foti, 2015). Concerning the liking motivation, the first step of reward responsiveness was preserved in emotional apathy. Indeed, like the control group, people with emotional apathy modulated their RewP, with a larger RewP for gain than loss of rewards, which is assumed to reflect early processes that will lead to positive affects (Gable et al., 2021). However, the last stage process of the liking component was impaired in emotional apathy, as revealed by the absence of modulation by incentive punishments of the ERP component (LPP), assumed to reflect the affective processing of feedback information (Broyd et al., 2012). The LPP could reflect a lack of sensitivity to punishment, that could prevent subsequent behavioral adjustments (Glazer et al., 2018). This lack of sensitivity to punishment has already been linked to emotional apathy as a one-year predictor in patients with schizophrenia, through self-reported questionnaires (Raffard et al., 2019). This specific motivational pattern could explain the emotional indifference and lack of emotional responsiveness in daily life that patients with emotional apathy are often described as having. Reduced sensitivity to punishments and danger could result in lower behavioral responsiveness to negative or stressful events. Indeed, a recent review on clinical and rodents studies confirms that the negative valence system allows to

differentiate depression and apathy: the punishments induced exaggerated emotional responses in depression, but blunted responses in apathy (Jackson and Robinson, 2022). This blunt anxiety and stress response generates a lack of reaction to the environment, producing a reduction of goal-directed behavior. Moreover, the hedonic interface theory posits that positive and negative affective experiences act as motivation for goal-directed behaviors by adding value to voluntary actions (Dickinson and Balleine, 2010). However, this theory also states that once values or desires are assigned to goal-directed behaviors, the cognitive processes converting these values in pursuit of the goals can function in the absence of affect. As we hypothesized, subjects with emotional apathy present preserved cognitive control processes as seen in the fact that their behavioral and electrophysiological patterns are similar to the control group in the DPX task.

Moreover, despite an anatomical overlap between emotional apathy and anhedonia, our electrophysiological results at the MID could help to clarify the distinction between these two symptoms. Indeed, anhedonia, clinically defined as the inability to experience and/or anticipate pleasure, is underpinned by the same structures as emotional apathy (Gard et al., 2006; Husain and Roiser, 2018; Pagonabarraga et al., 2015; Treadway and Zald, 2011). However, while our results shed the light on emotional blunting for loss in emotional apathy, anhedonia had been linked to an emotional blunting for gain, reflecting by a reduced LPP when obtaining a positive reward (Dell'Acqua et al., 2022; Garland et al., 2023; Klawohn et al., 2021). Moreover, depressed patients present an emotional blunting for positive events (i.e., anhedonia) but an attentional bias to negative events (i.e., hypersensitivity to loss, the contrary to the deficit we highlighted in emotional apathy) (Epstein et al., 2006; Leppänen, 2006; Ma, 2015; Xie et al., 2021). Therefore, depression could be linked only to anhedonia, but not to emotional apathy. A first but tenuous argument in favor of this hypothesis could be that emotional apathy is the only form of apathy that is never correlated with depression, in healthy population for different cultures (Kawagoe et al., 2020; Lafond-Brina and Bonnefond, 2022; Santangelo et al., 2017a), as well as in various neurodegenerative and psychiatric pathologies (Barek et al., 2021; Radakovic et al., 2017, 2018; Raimo et al., 2020; Santangelo et al., 2017b). This hypothesis needs to be explored because it could help to improve the understanding of emotional apathy and anhedonia, in order to help creating new therapies in depression.

Moreover, the representation of genre could be a specific pattern of emotional apathy linked to the specific liking motivational impairment. Indeed, in our epidemiological study, we show that the masculine gender was specifically associated with emotional apathy, whereas the feminine gender was more prevalent in executive and initiative apathy (Lafond-Brina and Bonnefond, 2022). Several studies in young adults showed that adherence to masculine norms is associated with less fear of failure and punishment, a lack of emotional expression, reduced motivation, and a lack of perseverance and engagements in actions (Streck et al., 2022; Yu et al., 2021). These associations are coherent with our results and the clinical descriptions of emotional apathy. Thus, we wonder if social masculinity norm favors the emotional apathy trait, and thus the trait being a product of gender stereotypes, and/or if the emotional apathy trait is biologically more prevalent in the male sex, underlying the emergence of traditional masculinity in society. Our data do not allow us to answer these questions. Nevertheless, several studies in the Orsini lab with rodents could tend not to dismiss the biological hypothesis over the normative one by showing that sexual hormones could be linked to motivation and goal-directed behaviors. For example, estrogen may play a major role in increasing the sensitivity to rewards and punishments and goal-directed behaviors, inducing less apathy in female rats with higher estrogen rates compared to females not in estrus and males (Orsini et al., 2022). Further studies at the intersection of biology, psychology, and sociology could answer this timely question.

Finally, by highlighting the hedonic mechanism underlying emotional apathy, our results should inform more targeted treatments. Indeed, contrary to executive apathy, motivational therapies seem quite

suitable to address emotional apathy by relying on their excellent proactive capacities. Moreover, one study already showed that emotional cognitive behavioral therapy could modulate neural structures underlying emotional processing in depressive patients; however, the study did not test the impact of the therapy on apathy (Ritchey et al., 2011). For pharmacological treatments, our results, in accordance with the literature, could suggest the importance of testing opioids or cannabinoids treatments specifically for people with emotional apathy. Indeed, the liking, specifically impaired in emotional apathy, is modulated by opioid or endocannabinoid neurotransmitters in the limbic prefrontal cortex, the orbitofrontal, the insula regions, and the ventral pallidum, but not by dopaminergic neurotransmitters (Berridge and Robinson, 2016; Smith and Berridge, 2007). One study showed that endocannabinoid lipids and opioid peptides enhance socioemotional behaviors in rodents (Manduca et al., 2016). Thus, enhancing cannabinoid and opioid signaling could help facilitate incentive motivational goal-directed behavior. However, future studies will need to be cautious about the dosage to ensure emotionally apathetic people do not go from emotional indifference and apathy to addiction and compulsive drug seeking (Mitchell et al., 2018).

4.3. Limitations

Despite some subclinical and clinical symptoms of apathy, all participants in the current study were free of any lifetime neurological, metabolic, or psychiatric diagnoses and were all university students with high education. This could have resulted in a high functioning sample. In addition, in a previous study with university students, about 20% presented a specific executive or emotional apathy, whereas 7% had an initiative form, 14% more than one form of apathy and 70% no apathetic trait (Lafond-Brina and Bonnefond, 2022). Thus, our apathetic samples were chosen for having a specific form of apathy, whereas in the general population and in neurodegenerative pathologies, people often present several forms of apathy at once (Radakovic and Abrahams, 2018). Therefore, the choice of our specific sample may reduce generalizability to the general population. Replication of our results in more general, neurological, and psychiatric samples could build on these results toward a more general cognitive and neural substrate of multidimensional apathy. Moreover, following the RDoC perspective, investigating the substrate of apathy in different healthy and patient samples could reveal similarities and dissimilarities between different groups, and increase the understanding of apathy as a transdiagnostic symptom (Klaasen et al., 2017; Nusslock and Alloy, 2017).

4.4. Conclusion and perspectives

Our study provides a more thorough understanding of the mechanisms underlying multidimensional apathy, which can inform novel non-pharmacological or pharmacological treatment strategies in the treatment of apathy. Indeed, by using a phenotyping (or extreme groups) approach, which is more powerful than correlations in the case of a reduced sample size, we specified, for the first time, the specific mechanisms underlying executive and emotional apathy. Only in neurodegenerative disorders, several studies shed the light on dominant form of apathy, like executive apathy in Parkinson disease (Radakovic et al., 2018). However, in psychiatric, even if almost all the disorders are associated with apathy (Strauss and Cohen, 2017), a multidimensional approach of apathy is rarely used, and the difference between each form of apathy and anhedonia or avolition are still unknown. Further research should focus on multidimensional apathy in psychiatry and explore the dominant form of apathy in distinct psychiatric disorders, to help developing new, personalized efficient treatments for reducing the debilitating consequences of this symptom.

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Authors contributions

G. L-B: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Visualization; Writing - original draft; Writing - review & editing.

A. B: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing.

B. P: Data curation; Investigation; Writing - review & editing.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation (Research ethics committee of the University of Strasbourg - UNISTRA/CER/2020-13) and with the Helsinki Declaration of 1975, as revised in 2008.

Research data

Research data is available on request to G.L-B.

Authors contributions

G. L-B: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Visualization; Writing - original draft; Writing - review & editing.

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B. P: Data curation; Investigation; Writing - review & editing.

Declaration of competing interest

The authors declare no competing interests to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2024.02.022>.

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