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Behavioral and electrophysiological correlates of cognitive control in ex-obese adults

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Highlights

- Cognitive control was assessed in ex-obese individuals after bariatric surgery.
- Two Stroop tasks, a Switching task and a Go/NoGo task were administered.
- Ex-obese individuals showed higher verbal Stroop effect and switch cost.
- An attenuated switch-positivity reflected altered proactive control processes.
- More pronounced NoGo-N2 revealed higher involvement of conflict monitoring.

Abstract

Impaired cognitive control functions have been documented in obesity. It remains unclear whether these functions normalize after weight reduction. We compared ex-obese individuals, who successfully underwent substantial weight loss after bariatric surgery, to normal weight participants on measures of resistance to interference, cognitive flexibility and response inhibition, obtained from the completion of two Stroop tasks, a Switching task and a Go/NoGo task, respectively. To elucidate the underlying brain mechanisms, event-related potentials (ERPs) in the latter two tasks were examined. As compared to controls, patients were more susceptible to the predominant but task-irrelevant stimulus dimension (i.e., they showed a larger verbal Stroop effect), and were slower in responding on trials requiring a task-set change rather than a task-set repetition (i.e., they showed a larger switch cost). The ERP correlates revealed altered anticipatory control mechanisms (switch positivity) and an exaggerated conflict monitoring response (N2). The results suggest that cognitive control is critical even in ex-obese individuals and should be monitored to promote weight loss maintenance.

Keywords: Obesity; Bariatric surgery; ERP; Stroop; Switching; Inhibition.

INTRODUCTION

Obesity has been often associated with adverse neurocognitive outcomes, primarily in the form of executive function alterations (for reviews, Fitzpatrick, Gilbert, & Serpell, 2013; Prickett, Brennan, & Stolwyk, 2015; Smith, Hay, Campbell, & Trollor, 2011). Among these functions, available evidence suggests that obese adults are impaired in cognitive control, not necessarily involving food-related items.

Cognitive control abilities refer to a set of processes, such as resistance to interference, cognitive flexibility and response inhibition, which regulate, coordinate and sequence lower level processes towards adaptive goal-directed behaviors (Braver, 2012; Shallice, 1994). Resistance to interference entails processes aimed on the one hand to suppress stimulus dimensions irrelevant to the task goal but eliciting over-learned and automatic response, and, on the other hand, to selectively respond to weaker but goal-relevant stimulus dimensions. These processes have been traditionally assessed by the Stroop Color Word test, which requires to name the ink color of a word while ignoring its meaning. Obese adults have been found to exhibit higher interference effect than normal weight controls on this test because of their higher susceptibility to the predominant but task-irrelevant stimulus dimensions (i.e, the word reading; Cohen, Yates, Duong, & Convit, 2011; Fagundo et al., 2012), irrespectively of medical and psychiatric comorbidities (such as hypertension, diabetes, cardiac disease, thyroid disease, bipolar disorders, and alcohol/drug abuse; Gunstad et al., 2007).

Cognitive flexibility involves processes that allow the rapid shift from one task to another, in accordance with the change of environmental cues and/or internally formed goals (Braver, Paxton, Locke, & Barch, 2009). It has been usually examined by means of task-switching tests, such as the Wisconsin Card Sorting Test and the Trail Making Test. Compared to normal weight controls, obese individuals make more errors (especially perseverations) on the Wisconsin Card

Sorting Test (Cohen et al., 2011; Fagundo et al., 2012) and are slower in executing the Trail Making subtest, which requires to alternate between number and letter series (Cohen et al., 2011; Fergenbaum et al., 2009).

Response inhibition refers to the ability of withholding an already prepared motor action in compliance with contextual cues. Typically, it has been investigated with the Stop Signal Task or Go/NoGo paradigms. Findings on these tasks are mixed (Calvo, Galioto, Gunstad, & Spitznagel, 2014; Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006). By comparing functional magnetic resonance images of obese and lean women, Hendrick et al. (2012) observed differences in brain activations during stop as compared to go trials despite similar behavioral performance between groups.

From a neural point of view, all these control processes are mediated by multiple and distinct brain circuits, mainly involving prefrontal areas (e.g., Cole & Schneider, 2007; Vallesi, 2012). Neuroimaging findings confirmed that obesity is associated with structural and functional brain alterations of the prefrontal cortex (García-García et al., 2015; Lavagnino, Arnone, Cao, Soares, & Selvaraj, 2016; Marqués-Iturria et al., 2013; Pannacciulli et al., 2006; Walther, Birdsill, Glisky, & Ryan, 2010; Willeumier, Taylor, & Amen, 2011).

Evidence supporting that obesity is negatively associated with cognitive functioning comes from studies on patients after bariatric surgical intervention. Bariatric surgery has emerged as the most effective procedure to achieve rapid, significant and long-lasting weight reduction in individuals with moderate to extreme obesity (Maciejewski et al., 2016; O'Brien, MacDonald, Anderson, Brennan, & Brown, 2013; Padwal et al., 2011; Sjöström et al., 2004). Longitudinal studies have documented that weight loss induced by the surgery produces rapid and significant cognitive improvements (for reviews Handley, Williams, Caplin, Stephens, & Barry, 2016;

Spitznagel et al., 2015; Veronese et al., 2017). Furthermore, improvements in executive functioning persist for at least 3 years after surgery (Alosco et al., 2014). Interestingly, Marques and collaborators (2014) found no differences in brain metabolism at rest between obese women 6 months after surgery and normal weight controls, whereas there were significant differences before surgery. These findings suggest that cognitive functioning tends to go towards normalization following weight loss. Nevertheless, research on the normalization of cognitive control functions in ex-obese individuals is limited and it remains unclear whether patients who lost significant weight perform similarly to normal weight individuals. To the best of our knowledge, the functional mechanisms of cognitive control mechanisms during the execution of a task involving not food-related materials in post-bariatric patients have not been investigated yet.

To address this issue, we recruited a group of patients who successfully reached a significant weight loss after bariatric surgery and a group of age- and education-matched normal weight controls. All participants were invited to complete four computerized tasks assessing resistance to interference, cognitive flexibility, and response inhibition, namely two Stroop tasks (verbal and spatial), a cued task-switching (Switching task) and a Go/NoGo task (the Sustained Attention to Response Test, SART). The electrophysiological signal was simultaneously recorded during the execution of the two latter tasks. The analysis of event-related potentials (ERPs) allowed us to detect fast brain responses mediating cognitive processing and, importantly, to elucidate the mechanisms underlying control processes. Unlike previous ERP studies (Hume, Howells, Rauch, Kroff, & Lambert, 2015; Nijs, Franken, & Muris, 2010; Nijs, Muris, Euser, & Franken, 2010), we focused on electrophysiological correlates of cognitive control processes exclusively evoked by non food-related stimuli, with the aim to investigate

general cognitive control functions, above and beyond attentional biases towards food-related materials. If the substantial weight loss in ex-obese patients reflected and/or induced normal cognitive control processes, no significant differences should emerge between the two groups. Alternatively, we expected to find differences in behavioral and/or electrophysiological responses to stimuli demanding higher cognitive control, as detailed below.

In the case of the Stroop tasks, we predicted a larger interference effect ('Stroop effect'), which means a worsening in performance (i.e., a decrease in accuracy and/or a slowing in RTs) on incongruent compared to congruent trials in the patient group.

In the Switching task, we predicted a higher 'switch cost', in terms of accuracy and/or RTs, which means a worsening in performance on switch compared to repeat trials. Altered ERP responses to cue and target stimuli were also expected. In cued task-switching paradigms, the most robust ERP component is represented by a positive potential elicited by the onset of the cue (i.e., the signal that instructs the task to be implemented on the upcoming target), larger for switch relative to repeat trials, named 'switch-positivity' (for a review see Karayanidis & Jamadar, 2014). This potential has a parietal distribution on the scalp and emerges starting from about 150 ms after the cue onset, for a duration that varies depending on task parameters (Nicholson, Karayanidis, Poboka, Heathcote, & Michie, 2005). It reflects proactive control processes that prepare in advance the cognitive system to shift task-set on the upcoming target and includes mechanisms of goal shifting and rule activation (i.e., the loading of the relevant task goal and rules and the inhibition of the irrelevant ones; Karayanidis et al., 2010).

Another robust ERP component is represented by a positive potential time-locked to the onset of the target, smaller for switch relative to repeat trials (Barceló, Periáñez, & Nyhus, 2007; Karayanidis, Whitson, Heathcote, & Michie, 2011; Kieffaber & Hetrick, 2005; Nicholson,

Karayanidis, Davies, & Michie, 2006). This relative parietal negativity for switch trials has been sometimes referred to as ‘switch-negativity’ (Karayanidis, Coltheart, Michie, & Murphy, 2003). When preceded by a long cue-to-target interval, it emerges as early as 150 ms and reaches maximal amplitude around 400 ms after the target onset. This component has a parietal scalp distribution and reflects the recruitment of reactive control processes, which intervene to resolve the stimulus-driven interference (Kiesel et al., 2010). With this in mind, we made the following predictions: on the one hand, if ex-obese patients fail in proactive control, the amplitude of their cue-related switch-positivity would be less pronounced than that of the control group; on the other hand, if they fail in reactive control, they should show a less pronounced target-related switch-negativity.

In the SART, we expected to find more commission errors on the NoGo trials and altered ERP correlates as indexes of impaired inhibitory processes in patients. Specifically, the N2 and NoGo-P3 components, elicited by the NoGo trials, were examined (O’Connell et al., 2009; Zordan, Sarlo, & Stablum, 2008). The N2 is a negative potential occurring at about 200 ms after the onset of NoGo stimuli over fronto-central sites, whereas the NoGo-P3 is a positive potential occurring approximately at 300 ms after the onset of NoGo stimuli in a more anterior scalp position relative to the parietal Go-P3 (Eimer, 1993; M Falkenstein, Hoormann, & Hohnsbein, 1999). Although the specific functional role of these ERP components is debated (Falkenstein, 2006; Smith, Johnstone, & Barry, 2007, 2008), there is consensus that the N2 mainly reflects conflict monitoring rather than response inhibition per se, while the NoGo-P3 mainly reflects the suppression of a planned response (Donkers & Van Boxtel, 2004; Enriquez-Geppert, Konrad, Pantev, & Huster, 2010; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Randall & Smith, 2011). Conflict especially occurs when a response must be refrained in

contexts in which NoGo trials are rare and there is a prepotent tendency to make a go response, as is the case for the SART. We expected that patients exhibit altered N2 and/or in NoGo-P3 amplitude if they have problems in conflict monitoring and/or response inhibition, respectively.

METHOD

Participants

Socio-demographic characteristics of the enrolled sample are summarized in Table 1. A total of 21 patients (aged from 21 to 61 years) and 22 normal weight controls (aged from 20 to 60 years) took part in the study. Participants were included if they had a BMI < 35 kg/m², if they reported normal or corrected-to-normal visual acuity, normal color vision, normal hearing, no neurological disorders (e.g., epilepsy, dementia), no major psychiatric disorders (e.g., bipolar, schizophrenia), and no substance abuse. Patients with medical conditions that may have caused obesity (e.g., endocrine disorders, type I diabetes), taking medication that suppresses appetite, or taking psychoactive medication (e.g., anxiolytics or antidepressants) were excluded. The patient group included a person with type II diabetes and a person with hypertension, both pharmacologically treated. The two groups were matched in terms of age, years of education, female to male ratio, and handedness (scored by the Edinburgh Handedness Inventory, EHI; Oldfield, 1971) (all t s ≤ 1.45 , p s $\geq .15$). They differed in BMI measures, namely maximum reached BMI (max BMI), current BMI, and Δ BMI (max BMI - current BMI)/ max BMI (all t s ≥ 2.62 , p s $\leq .012$). All participants completed the Beck Depression Inventory (BDI; Sica & Ghisi, 2007) and the Binge Eating Scale (BES; Di Bernardo et al., 1998) to screen depression and binge eating disorder, respectively. None of patients scored above the cut-off of 16 on the BDI, therefore we could exclude the presence of clinically relevant depressive symptoms. One patient reported binge eating behaviors, i.e., scored above 17 on the BES. The Barratt Impulsiveness

Scale (BIS-11; Fossati, Di Ceglie, Acquarini, & Barratt, 2001) was also completed in order to detect impulsivity traits. The two groups did not show differences in impulsivity traits (see Table 1). Their general cognitive functioning was screened by the Mini Mental State Examination (Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996) and by a neuropsychological battery ('Esame Neuropsicologico Breve', Mondini, Mapelli, Vestri, Arcara, Bisiacchi, 2011). All participants scored more than 28 on the MMSE and above the cut-off in more than 14 out of 16 battery sub-tests, indicating a general cognitive functioning in the normal range. All patients underwent a bariatric surgical intervention for weight reduction ($n = 16$ gastric sleeve, $n = 3$ gastric bypass, $n = 1$ lapband, $n = 1$ plication) in the past (27.2 ± 23.3 months before) and, at the time of the experimental session, they were not obese anymore (all BMIs $< 30 \text{ kg/m}^2$). In terms of BMI, they lost from 30 to 53 % (mean ΔBMI : $42.2\% \pm 7$). All patients were recruited at the Unit of Plastic Surgery of the University Hospital of Padova, where they referred for seeking lipostructuring surgery after the massive weight loss. The control group was recruited from the general population. All participants signed a written consent prior to their participation and were informed of the general aim of the study (i.e., to investigate executive functions in ex-obese individuals). The procedures were approved by the Bioethical Committee of the Azienda Ospedaliera di Padova and the study was conducted according to the guidelines of the Declaration of Helsinki.

Table 1. Participant demographics

	Patients (n = 21)	Controls (n = 22)	<i>p</i>
Age	40.57 (11.05)	40.18 (12.18)	.913
Education	11.14 (3.05)	12.68 (3.82)	.153
Female	14	17	.510 ^a
EHI	79.76 (44.31)	71.36 (49.01)	.559

Maximum BMI	47.01 (7.32)	26.54 (4.95)	< .001
Current BMI	26.89 (3.04)	23.94 (4.19)	.012
Δ BMI	.42 (.07)	.09 (.07)	< .001
BDI-II	5.1 (4.6)	3.5 (4.2)	.295
BES	5.5 (6.1)	3.3 (4.3)	.213
BIS-11 (total score)	61.5 (7.5)	56.2 (9.6)	.067

Group means and standard deviation values in parentheses are reported; p-values are relative to 2-sided unpaired t-tests, unless otherwise specified; ^a Chi-square test; BMI = Body Mass Index (kg/m²); EHI = Edinburgh Handedness Inventory; Δ BMI = (Max BMI - Current BMI)/Max BMI; BDI = Beck Depression Inventory; BES = Binge Eating Scale; BIS = Barratt Impulsiveness Scale.

Experimental procedure

Participants were individually tested in an electrically isolated and sound-shielded room. They performed the two Stroop tasks at the beginning of the session, in a counterbalanced order. Afterwards, they performed the Switching task and the SART, in a counterbalanced order; during these two tasks the EEG was continuously recorded.

Tasks and stimuli

Stroop tasks

We used a verbal and a spatial version of the Stroop task (see details below). Both Stroop tasks were presented on a 15 inch LCD notebook monitor (1366 × 768 pixel), at a viewing distance of approximately 50 cm, using the Presentation software 16.3 (Neurobehavioral Systems, Inc., Berkeley, CA).

Verbal Stroop task. This was a computerized version of the Color-Word Stroop test (see Puccioni & Vallesi, 2012a, for details). Stimuli consisted of four words, namely, ‘BLU’ (Italian for ‘blue’), ‘GIALLO’ (‘yellow’), ‘ROSSO’ (‘red’), and ‘VERDE’ (‘green’). Each word was individually displayed in one of four ink colors: blue, yellow, red and green. Participants were required to identify the ink color by pressing one out of four keys of the computer keyboard (‘c’,

‘v’, ‘b’, and ‘n’, marked by colored labels) and to ignore the word meaning. Participants were asked to respond as fast and accurately as possible by using the index and the middle fingers of both hands. Each stimulus was categorized as Congruent (C) when word ink and word meaning coincided (e.g., BLU written in blue), or Incongruent (I) when they did not coincide (BLU written in red). The ink color (target) and the word meaning (distractor) on current trial n were always different from the ink and the meaning on previous trial $n-1$ (Puccioni & Vallesi, 2012c). Accordingly, sequential pairs of trials could be categorized as follows: Congruent $n-1$ and Congruent n (cC), Congruent $n-1$ and Incongruent n (cI), Incongruent $n-1$ and Congruent n (iC), Incongruent $n-1$ and Incongruent n (iI).

Spatial Stroop task. A visuo-spatial version of the Stroop task (see (Puccioni & Vallesi, 2012b, for details) was administered in order to capture possible domain specificities in the resistance to interference ability. Stimulus materials consisted of four black arrows, pointing either to north-east, north-west, south-east or south-west. Each arrow was individually displayed on a light gray background in one out of four positions on the screen (upper right, upper left, lower right, or lower left). Participants were required to identify the pointing direction of the arrows and to ignore their position on the screen as quickly and accurately as possible. To this aim, four response keys were arranged of the keyboard so that they spatially reflected the arrow directions/positions (‘r’, ‘o’, ‘v’, ‘m’). Each stimulus was categorized as Congruent when arrow direction and position coincided (e.g., north-west pointing arrow positioned in the upper right corner of the screen) or Incongruent when they did not. Similar sequences as for the verbal Stroop task were presented here.

At the beginning of both the verbal and the spatial Stroop tasks, a training block of 16 trials was performed to ensure that participants had understood the task and familiarized with it. After

the training block, two test blocks of 64 trials each were presented; Congruent and Incongruent trials were pseudo-randomly displayed and well-matched. Stimuli remained on the screen for 500 ms and were followed by a blank of 2000 ms and a random extra blank of 200-700 ms; the maximum allowable response time was 2500 ms.

Switching task

The task was developed by Tarantino and colleagues (Tarantino, Mazzonetto, & Vallesi, 2016; see for details). Stimulus materials consisted of two auditory cue stimuli (tones), two target stimuli (letters), and a fixation asterisk. A trial began with the delivery of one of two tones (a high pitched tone of 1500 Hz or a low pitched tone of 200 Hz), lasting 300 ms. The tone was followed by a 900 ms blank and by a target stimulus, which consisted of one of two letters ('A' or 'E', 36 points, Courier New bold font), lasting 1500 ms, which could appear either above or below the fixation asterisk. The experiment comprised two single-task blocks and four mixed blocks, each including 60 trials. During the single-task blocks participants were repetitively presented with a tone and, upon the onset of a target letter, had to repetitively perform one of two tasks, namely a letter identity task or a letter position task. The identity task required identifying the type of letter (the letter 'A' or 'E'), irrespective of its spatial position; the letter position task required identifying the position of the letter ('above' or 'below' the asterisk), irrespective of its identity. Participants had to decide by pressing one of two buttons of the keyboard ('f' and 'k') with the index finger of the left and right hand, respectively. The maximum allowable response time was 2000 ms from the target onset. In summary, in single-task blocks the same tone was presented across all trials and participants were required to perform the same task (Single trials). During the mixed blocks the two tones were pseudo-randomly presented and instructed participants about the specific task to be performed on each

trial. Therefore, participants were required to perform either the same task as the previous trial (Repeat trials) or the alternative task (Switch trials). The occurrence of Repeat and Switch trials in a block was equiprobable. In all blocks, a variable interval, ranging from 500 to 1000 ms, followed each trial. A four-trial practice session preceded the single-task blocks, and a 16-trial practice session preceded the mixed-task blocks. All visual stimuli were black on a white background; they were delivered on a 19 inch LCD monitor (1024×768 pixel), at a viewing distance of approximately 60 cm. The auditory stimuli were delivered by loudspeakers placed in the two sides of the monitor. The experiment was run on E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

SART

The task, based on a Go/NoGo paradigm, was conceived by Robertson and colleagues (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Here a modified version of the task was implemented. It consisted of a series of single digits, from 1 to 9, individually presented in a random order. Participants were required to press the button ‘b’ of the keyboard with the right index finger upon the appearance of each number (Go stimuli) except the number 3 (NoGo stimulus). Overall, two blocks of trials were presented, including 200 Go and 25 NoGo trials each. The digits were displayed in one of five sizes: 42, 54, 66, 78, 90 points, Times New Roman font. Each digit remained on the screen for 150 ms and was followed by a blank of 1050 ms. Therefore, the maximal duration for response was 1200 ms. The experiment began with a practice block designed to better understand the task and familiarize with it; at this phase, the examiner emphasized not to anticipate the stimulus onset. The digits were white on a grey background and were delivered on the 19 inch monitor (see Switching task for details). Stimulus presentation and response collection were controlled by E-Prime 2.0 software.

EEG recording and data preprocessing

The EEG was recorded using the BrainAmp equipment (Brain Products, Munich, Germany), with 64 Ag/AgCl ring electrodes mounted on an elastic cap according to the extended 10-20 system. The on-line reference and ground electrodes were placed at FCz and AFz, respectively. An electrode placed under the right eye (EOG) allowed the monitoring of blinks and vertical eye movements. The impedance of each electrode was kept below 5 k Ω . Raw data were band-pass filtered between 0.016-250 Hz and digitized at a sampling rate of 500 Hz. The off-line preprocessing of the EEG signal was performed in EEGLAB 12.0.2 (Delorme & Makeig, 2004), running in a Matlab environment (Version 8.2.0, MathWorks, Natick, MA, USA), and in BrainVision Analyzer 2.1 (Brain Products GmbH). The continuous EEG trace was low-pass filtered with a cut-off frequency of 40 Hz (windowed sinc FIR filter, Kaiser Window type 1, beta: 5.65, maximum passband deviation: 0.001, transition band: 10 Hz; Widmann, Schröger, & Maess, 2015). Blinks, ocular movements, and muscle artifacts were detected and removed by means of independent component analysis (ICA, Extended Infomax Algorithm). Afterwards, the EEG was segmented according to the task (see below).

Switching task

Two types of epochs were extracted: a) epochs from -200 to 1500 ms time-locked to the cue (cue-locked ERPs) and b) epochs from -50 to 800 ms relative to the target (target-locked ERPs). The resulting data were baseline-corrected using two different time windows, from -200 to 0 ms for cue-locked epochs, and from -50 to 50 ms for target-locked epochs. Practice trials, the first trial of each block, trials with errors and trials following errors were discarded. In addition, trials containing further artifacts were removed by means of a semi-automatic procedure. The automatic detection criteria included an absolute difference between two sampling points

exceeding 30 $\mu\text{V}/\text{ms}$, peak-to-peak deflections in a segment exceeding $\pm 100 \mu\text{V}$ within intervals of 200 ms, amplitudes exceeding a value of $\pm 100 \mu\text{V}$, and activity lower than 0.1 μV within intervals of 200 ms. Data were re-referenced to the average of the two mastoid channels (TP9, TP10), typically used in the ERP literature of task-switching. The averaging procedure was performed collapsing the letter identity and letter position trials. The number of included trials for each condition is reported in Table 1 of Supplementary materials.

SART

The EEG signal was segmented from -100 to 800 around the onset of Go and NoGo trials. Each epoch was baseline corrected by subtracting the average signal in the 100 ms pre-stimulus interval. In order to match Go and NoGo trials for numerosity, only the Go trials that preceded the NoGo trials were included in the analyses (Thomas, Grice, Najm-Briscoe, & Miller, 2004). Practice trials and trials containing errors were discarded. In addition, trials containing further artifacts were removed by adopting the same semi-automatic procedure used in the Switching task analyses. The number of included trials for each condition is reported in Table 2 of Supplementary materials. Data were re-referenced to the average of all channels.

Statistical analyses

All analyses were conducted with SPSS 23. The significance level for all tests was set at $\alpha = 0.05$.

Behavioral data

Stroop tasks

Mean accuracy (percentage of correct responses) and mean RTs were extracted for each trial type (Congruent and Incongruent). Analyses were conducted to verify the presence of group difference in *Stroop effect*. This effect was quantified by subtracting accuracy or RTs on

Incongruent trials from accuracy or RTs on Congruent trials (I - C), in the verbal and in the spatial task, separately. Accuracy data were analyzed by means of the non-parametric Mann-Whitney test, after excluding practice trials and the first trial of each block. For the RT data analysis, error trials, trials following an error (to avoid confounds of post-error slowing), trials with RTs below 80 ms (anticipations), and trials with RTs above 2500 ms were removed as well. A logarithmic transformation was applied to raw RTs on each trial in order to improve normality and reduce skewness (Verhaeghen & De Meersman, 1998). Afterwards, for each participant, trials with RT above or below 2.5 standard deviations (SD) from their individual mean were excluded (see Arbula, Capizzi, Lombardo, & Vallesi, 2016). On average, for each participant 1.2 % (SD = 0.9 %) outliers in the verbal task and 0.5 % (SD = 0.7) outliers in the spatial task were removed. Unpaired samples *t*-tests were used to compare the Stroop between groups. Effect size was quantified in terms of Cohen's *d*.

In order to examine the group effect by taking into account the order of trials congruency, we calculated the Stroop effect as the difference in performance between Incongruent trials preceded by Congruent ones and Congruent trials preceded by Congruent ones (cI - cC), and as the difference in performance between Incongruent trials preceded by Incongruent ones and Congruent trials preceded by Incongruent ones (iI - iC), separately. We entered these values in a 2 (Group: control vs. patients) $\times$ 2 (Trial sequence: cI - cC vs. iI - iC) repeated-measure ANOVA.

Switching task

Mean accuracy and RTs were extracted for each trial (Single, Repeat and Switch). Participants that did not success in at least 70 trials out of 120 per condition (2.7% error probability according to binomial distribution) or with noisy EEG were discharged from analyses. The final sample

comprised 18 patients and 19 controls, which did not differ in age, sex, education and handedness (all $ps > .194$). For the accuracy analysis, practice trials and the first trial of each block were excluded. In addition, for the RT analysis, trials with errors, trials following errors and trials with RTs below 80 ms (anticipations) were excluded. RT data were log-transformed and, for each participant, RTs above or below 2.5 SD from the individual mean were labeled as outliers and removed. Two behavioral indexes were then computed, namely the *mixing cost* and the *switch cost*. The mixing cost was obtained from the difference in accuracy or RTs between Repeat and Single trials and represents a worsening in performance (i.e., a decrease in accuracy and/or a slowing in response time) on Repeat compared to Single trials. It reflects control processes related to the maintenance of competing task-sets (Rubin & Meiran, 2005). The switch cost represents a worsening in performance on Switch compared to Repeat trials and reflects processes related to task-set reconfiguration (Monsell, 2003). The costs in accuracy were compared between the two groups by means of the Mann-Whitney test, whereas the group effect on RT costs was analyzed by unpaired t-test.

SART

Errors of commission (responses to NoGo stimuli) and mean RTs on Go stimuli were measured. Errors of omission (failures to press following a Go stimulus) were not analyzed since they were less than 2%. Participants that did not succeed in at least 31 trials out of 50 NoGo stimuli (3.2% error probability according to binomial distribution) or with excessive noise in EEG were discharged from analyses. The remaining sample included 14 patients and 16 controls. They did not differ in age, sex, education and handedness (all $ps > .142$). Trials with RTs shorter than 80 ms (anticipations) and longer than 1000 ms were excluded from analyses (patients: 0.8%, $SD = 1.4$; controls: 0.4%, $SD = 0.9$). RTs on each trial were then log-transformed. Group

differences in accuracy were statistically examined by the non-parametric Mann-Whitney test, whereas group differences in RTs were examined by unpaired t-test. Trials containing errors were excluded for RT analysis.

ERP data

Switching task

Cue-locked and target-locked ERPs were separately analyzed. ERP components were extracted on the basis of previous findings on the same task (Tarantino et al., 2016) and visual inspection of grand-average waveforms. In an early time window, from 200 to 400 ms after the cue onset, a positive potential, larger for Switch trials, was expected, representing the so-called *switch-positivity*. At the target onset, two positive ERP components were expected, a centro-frontal and a parietal one. The centro-frontal component should be larger for Repeat and Switch trials, whereas the parietal component should display amplitude attenuation in Switch trials compared to Repeat ones. Mean ERP amplitude over centro-frontal and parietal sites were examined in an early (160-200 ms) and later (280-380 ms) time window, respectively. The ERP amplitude in each of these time windows was averaged across electrodes where group differences appeared maximal. The resulting data were submitted to mixed 2 (Group) $\times$ 3 (Trial type) ANOVAs. For each ANOVA, the sphericity assumption was checked by the Mauchly test. When it was significant, the Greenhouse-Geisser correction was applied and corrected p-values were reported. The Bonferroni correction for multiple comparisons was applied to post-hoc tests. Effect size was expressed by partial eta squared (η_p^2).

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As in the Switching task, the ERPs evoked by the stimuli (digits) onset were extracted on the basis of the Go/NoGo literature (see Kamiyo et al., 2012 for similar analysis windows and

electrodes) and grand-average visual inspection. The N2 and Go-P3 components were measured as the mean amplitude in the 280-340 ms time window, over midline fronto-central and centro-parietal electrode sites, respectively. The NoGo-P3 appeared later, over midline centro-parietal sites, and it was measured as the mean amplitude from 400 to 500 ms. The N2 amplitude was analyzed by means of a 2 (Group) $\times$ 2 (Trial type: Go, NoGo) ANOVA. Instead, the Group effect on the P3 amplitude was analyzed separately for Go and NoGo trials by means of two separate *t*-tests, given that this component emerged in the two trial types with very different latencies (the former being the earlier).

RESULTS

Behavioral results

Stroop tasks

Mean accuracy and RTs for each trial type are reported in Table 4 of Supplementary materials. The analysis of the Stroop effect in terms of accuracy did not yield significant differences between the two groups, both in the verbal (patients: $-1.7\% \pm 4.3$, controls: $.1\% \pm 2.2$; Mann-Whitney $U = -1.76$, $p = .078$) and in the spatial task (patients: $-7.4\% \pm 8.8$, controls: $-4.6\% \pm 5.1$; Mann-Whitney $U = -.77$, $p = .439$). In terms of RTs, patients showed a significantly larger Stroop effect in the verbal task compared to the control group ($91\text{ ms} \pm 51$, controls: $51\text{ ms} \pm 46$) [$t(41) = 2.39$, $p = .021$, Cohen's $d = .73$]. The groups did not differ in the spatial version of the task (patients: $126\text{ ms} \pm 82$, controls: $147\text{ ms} \pm 102$) [$t(41) = -1.43$, $p = .160$] (see Figure 1). It is worth noting that mean RTs on Congruent trials as well as Incongruent ones per se did not differ between the two groups in either task version. This means that the larger verbal Stroop effect did not originate from an overall slowing in responding to Incongruent trials. Time from the surgery (in months) and RT verbal Stroop interference did not correlate (Spearman's $\rho = .048$, $p =$

.836). Furthermore, the group difference in the RT Stroop effect was not influenced by trial sequence. The mixed 2 (control vs. patients) $\times$ 2 (cI – cC vs. iI – iC) ANOVA on RTs showed only a main effect of Group ($F(1,41) = 4.61, p = .038, \eta_p^2 = .10$). The interaction Group $\times$ Trial sequence was not significant ($p = .909$). This null result suggested that the Stroop effect differed between the two groups irrespective of the sequential effects.

- PLEASE INSERT FIGURE 1 ABOUT HERE -

Switching task

Mean accuracy and RTs for each trial type is reported in Table 4 of Supplementary materials. As expected, a mixing and switch cost emerged in accuracy and RTs in both groups. The two groups differed only in terms of RT switch cost. Namely, patients showed a higher switch cost than controls (patients: 167 ms $\pm$ 137; controls: 92 ms $\pm$ 66) [$t(35) = 2.3, p = .028$, Cohen's $d = .70$]. Significant differences did not emerge in RT mixing cost (patients: 160 ms $\pm$ 119, controls: 146 ms $\pm$ 90) [$t(35) = .057, p = .955$], in accuracy mixing cost (patients: -4.9 % $\pm$ 8.7, controls: -4.5 % $\pm$ 7.6) [Mann-Whitney $U = -.30, p = .778$], and in accuracy switch cost (patients: -3.4 % $\pm$ 4.9, controls: -3.5 % $\pm$ 4) [Mann-Whitney $U = -.15, p = .893$]. As for the Stroop tasks, absolute RTs did not differ between the two groups in any trial type, thus excluding the presence of an overall slowing in patients. Furthermore, the time from the surgery did not correlate with the RT switch cost (Spearman's $\rho = .256, p = .320$).

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On average, the percentage of accuracy on the NoGo trials did not differ between the two groups (patients: 22.1% $\pm$ 8.7, controls: 18.9% $\pm$ 8.2) [Mann-Whitney $U = .961, p = .355$].

Similarly, the mean RTs to Go trials did not show group difference (patients: 352 ms $\pm$ 51, controls: 340 ms $\pm$ 43) [$t(28) = .699, p = .490$].

ERP results

Switching task

In the 200-400 ms time window locked to the cue onset, the control group showed a larger positivity compared to patients over centro-parietal sites, especially of the right hemisphere (i.e., over Cz, C2, C4, CPz, CP1, and CP2 electrodes). Figure 2 depicts the ERP waveforms for each group and trial type. The positivity evoked by the cue onset over centro-parietal sites, more pronounced in Switch trials, likely represents the *switch-positivity*. The ERP amplitude in this time window was collapsed across the above-listed electrodes and submitted to a 2 (Group: controls, patients) $\times$ 3 (Trial type: Single, Repeat, Switch) ANOVA. A significant effect of Trial type [$F(2,70) = 38.8, p < .001, \eta_p^2 = .714$] and a significant Group $\times$ Trial type interaction [$F(2,70) = 4.15, p = .020, \eta_p^2 = .106$] emerged. The post-hoc test of the main effect revealed that overall the ERP amplitude was progressively more positive in Repeat compared to Single trials ($p = .024$), and in Switch compared to Repeat trials ($p < .001$). The post-hoc test of the interaction confirmed that the two groups differed in the Switch trials ($p = .029$), but not in the Single ($p = .489$) and in the Repeat ($p = .074$) ones. The main effect of Group was not significant [$F(1,35) = 2.79, p = .104$].

The target-locked ERPs displayed group differences in amplitude, in all trial types, in the early (from 160 to 200 ms) as well as in the later (from 280 to 380 ms) time window. Here, positive ERPs emerged, larger in the control group compared to the patient one (see Figure 3). Group differences in the first time window were especially evident over CPz, Cz, C2, C4, and FC4 electrodes, whereas in the second time window they were evident over Pz and POz.

The 2×3 ANOVA on the mean ERP amplitude in the first time window, averaged across the above-listed centro-frontal electrodes, confirmed the presence of a significant main effect of Group [$F(1,35) = 7.45, p = .010, \eta_p^2 = .176$]. In addition, a significant main effect of Trial type was found [$F(1.5,53.2) = 20.26, p < .001, \eta_p^2 = .367$]. The post-hoc test revealed that the ERPs were more positive in Repeat and Switch trials compared to Single ones ($ps < .001$), whereas they did not differ between Repeat and Switch trials ($p = .131$), in line with the previous study (Tarantino et al., 2016). The Group $\times$ Trial type interaction term was not significant [$F(2,70) = .15, p = .859$].

Surprisingly, in this early time window the two groups also differed in midline parieto-occipital sites (Pz and POz; see Figure 3, right panel). Here, an early negative peak was detected that, based on its spatio-temporal features, likely represents a parietal N1 component. Overall (i.e., in all trial types), the amplitude of this peak was significantly more negative in the patients' group [main Group effect: $F(1,35) = 4.97, p = .032, \eta_p^2 = .124$]. In addition, it was affected by Trial type [$F(2,70) = 13.40, p < .001, \eta_p^2 = .277$], namely it was more pronounced in Single trials compared to Repeat and Switch trials ($ps < .005$). A significant Group $\times$ Trial type interaction was absent [$F(2,70) = .289, p = .750$].

The later positive ERP component, analyzed across Pz and POz electrodes, was also affected by Trial type [$F(2,70) = 23.35, p < .001, \eta_p^2 = .407$]. In contrast to the earlier centro-frontal potential, it showed less positive amplitude in Switch trials compared to Repeat and Single ones ($ps < .001$), while it did not differ between Repeat and Single-task trials. This effect reflected the relative switch-negativity described in previous literature (e.g., Karayanidis et al., 2003). Neither a significant Group effect [$F(1,35) = .961, p = .334$] nor a significant Group $\times$ Trial type interaction [$F(2,70) = 1.54, p = .221$] were observed.

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In agreement with previous studies, a negative peak corresponding to the N2 component was detected in the 280-340 ms time window, whose amplitude was enhanced (more negative) in NoGo compared to Go trials over midline fronto-central (Fz and FCz; see Figure 4, left panel). The mean amplitude of this component was entered into a 2 (Group) $\times$ 2 (Trial type: Go, NoGo) ANOVA. The analysis yielded a significant main effect of Trial type [$F(1,28) = 5.45, p = .027, \eta_p^2 = .163$]. This result confirmed that the N2 component was more negative in NoGo trials. More importantly, the ANOVA revealed a significant Group $\times$ Trial type interaction [$F(1,28) = 4.83, p = .036, \eta_p^2 = .147$]. The post-hoc test showed that the N2 amplitude was more negative in the patient group compared to the controls in NoGo trials ($p = .004$), but not in Go trials ($p = .921$).

In the same time window (i.e., from 280 to 340 ms), the Go-P3 appeared, principally over centro-parietal sites (Pz and CPz; see Figure 4, right panel). Its amplitude significantly differed between the two groups [$t(28) = 2.50, p = .018$, Cohen's $d = .91$].

The NoGo-P3 component emerged later, i.e. from 400 to 500 ms (see Figure 4, right panel, bottom). The unpaired t-test revealed no group differences in amplitude [$t(28) = .97, p = .341$].

- PLEASE INSERT FIGURE 4 ABOUT HERE -

DISCUSSION

Obesity impacts on cognitive functioning independently of its comorbidities, such as cardiovascular disorders or depression (Prickett et al., 2015; Smith et al., 2011). However, obesity-related cognitive dysfunctions can be reversed after bariatric surgery (e.g., Alosco et al., 2014). A question that remains open is whether the achievement of substantial weight loss might normalize cognitive control functions. The present study aimed at clarifying this issue by comparing a group of ex-obese patients, who successfully reached a substantial weight loss (on average the 42.2% of their maximum BMI) after bariatric surgery, to a group of normal weight individuals on a series of cognitive control tasks. Specifically, resistance to interference, task-switching and response inhibition functions were examined. In order to elucidate neural mechanisms mediating these control processes, electrophysiological responses (ERPs) during task execution were analyzed, relative to the latter two functions.

The results revealed that ex-obese patients differ from normal weight control participants in terms of both behavioral performance and neural correlates. At the behavioral level, group differences emerged on the verbal Stroop task, namely, patients showed a significantly larger Stroop effect. This finding indicates that patients were more susceptible to the interference generated by the prepotent and task-irrelevant stimulus dimension (i.e., word meaning). Consequently, they were more impaired in inhibiting the habitual response evoked by this stimulus dimension (i.e., reading the word) and in activating the alternative, more unusual, response (i.e., naming the ink color). This pattern is consistent with previous evidence on obese adults using food-related stimuli (e.g., Nijs, Franken, et al., 2010). Unlike these studies, we were able to exclude that the difficulty of our patients in exerting cognitive control to resist interference reflected the avoidance of food stimuli. Group difference on the verbal Stroop effect was not related to differential sequential effects. Furthermore, the absence of a group effect in

the spatial version of the Stroop task suggests that the performance on the two versions of the task is based on at least partially dissociable underlying mechanisms (cf., Ambrosini & Vallesi, 2017).

In the Switching task, patients were significantly slower in responding to trials that required a change in task-set relative to the task-set implemented on the preceding trial (switch trials). When the task-set to be implemented was the same (repeat trials), no group differences emerged. These findings are in line with previous investigations on obese patients, which used the Wisconsin Card Sorting Test (e.g., Fagundo et al., 2012) and the Trail Making Test (e.g., Fergenbaum et al., 2009) and revealed that also ex-obese patients might show signs of cognitive flexibility impairment. The analysis of electrophysiological correlates helped in clarifying the brain mechanisms underlying this impairment. The positive ERP component evoked 200-400 ms after the presentation of the cue to switch at centro-parietal electrode sites (i.e., the switch-positivity) showed significantly less pronounced amplitude in patients compared to controls only in Switch trials. This component has been found to be an electrophysiological marker of proactive control processes, namely the advanced preparation to a change of task-set (Capizzi, Fehér, Penolazzi, & Vallesi, 2015; Karayanidis & Jamadar, 2014; Karayanidis et al., 2010). Consequently, the attenuated amplitude of the switch-positivity in the patients' group suggests the presence of altered proactive/anticipatory control processes. These control processes refer to the endogenous mechanisms of task-reconfiguration conceptualized by Rogers and Monsell (1995), which include shifting attention between stimulus attributes or features, retrieving task goals and rules, updating (or deleting) them in working memory. An alteration of these mechanisms might explain the RT slowing in switch trials.

In contrast to the cue-evoked ERPs, group differences on target-evoked potentials were present irrespective of the specific trial type. Namely, a less pronounced positivity at an early time window after the target onset over centro-frontal sites was found in the patient group, in all trial types. Given the task structure, we might speculate that this component is likely related to exogenous stimulus-driven attention mechanisms evoked by the onset of the target. These mechanisms help to rapidly direct attention towards task-relevant stimulus features (in this case, spatial location or letter identity). Once attention had been allocated to one of the two task-relevant features, the procedural rules could be updated to implement the discrimination task, as indexed by the subsequent parietal positivity, which likely represents a P3b (Barceló et al., 2007).

Remarkably, it should be noted that the less pronounced positivity in switch trials relative to repeat trials over parietal sites (i.e., the *switch-negativity*) was equally present in both groups. This means that reactive control processes, specifically related to the switching requirements of the task, were unimpaired.

An unexpected finding was an enhanced parieto-occipital N1 component evoked by the target stimulus in patients compared to controls, in all trial types. Classically, this early posterior ERP component reflects visual processing and its amplitude is modulated by selective attention (Luck, Heinze, Mangun, & Hillyard, 1990). Therefore, we may speculate that the larger N1 component observed in the patients group reflected an enhanced engagement of selective attention at early stage of (visual) target processing, and likely compensated deficit in more frontal attention orienting mechanisms (see also Prox, Dietrich, Zhang, Emrich, & Ohlmeier, 2007). Although this effect needs to be further investigated, it suggests that goal-relevant stimuli enrolled more low-level attentional resources in the patient group.

In summary, the behavioral results on the Switching task documented that ex-obese patients are slower in flexibly adapting their responses to changing task rules and the electrophysiological correlates suggested that this difficulty might specifically derive from altered preparatory/proactive control processes, which are consequently accompanied by a more pronounced engagement of visual attention to process target stimuli.

From a behavioral point of view, no significant group differences were found in the Go/NoGo (SART) task. This finding is in line with previous investigations (Calvo et al., 2014; Hendrick et al., 2012) and, at a first glance, might be interpreted as reflecting the absence of response inhibition problems in ex-obese patients. Nonetheless, the analysis of electrophysiological correlates revealed that the two groups significantly differed in their brain responses, despite of the similar behavioral performance. Specifically, patients showed a significantly more pronounced fronto-central negative peak (N2) in response to the NoGo stimuli. This ERP component has been interpreted as an electrophysiological marker of conflict monitoring processes (Donkers & Van Boxtel, 2004; Enriquez-Geppert et al., 2010; Nieuwenhuis et al., 2003). The NoGo stimuli elicit a response conflict because their stimulus-response set (i.e., number-withholding button press) competes with the Go ones (i.e., number-button press). Therefore, the larger N2 potential might be interpreted as an exaggerated response to overcome this conflict. Interestingly, this result replicated a previous ERP study on obese children on a Go/NoGo task (Kamijo et al., 2012). Furthermore, it converges with the results on the Stroop task, where participants have also to monitor and solve a conflict generated by the habitual and the required response (Botvinick, Braver, Barch, Carter, & Cohen, 2001). In spite of the N2 difference, the NoGo-P3 amplitude was not significantly different in the two groups. Taken together, these results suggest that patients were more engaged in monitoring cognitive conflict

rather than inhibiting motor response per se. The similar number of commission errors observed in the two groups is likely due to the fact that the task taxed inhibitory control functions also in the control group and that patients implemented a compensation strategy, by relying more on reactive processes (i.e., the exaggerated N2).

Some cautions should be taken into account when interpreting the study results. The main limitation is that the pre-surgical (baseline) data are missing, therefore we could not measure possible cognitive improvements or deteriorations. Moreover, the final sample size entered in the analyses of the Switching and Go/NoGo tasks was reduced compared to the original one since some participants could not handle the requirements of the tasks. This could have reduced ERP significant results and did not allow correlations with behavioral indexes. Also, the presence of overweight in some participants could have influenced the results. To test this possibility, we ran the analyses including the factor Overweight together with the factor Group (see Supplementary materials). All significant Group effects were confirmed whereas the Overweight factor never emerged as significant, therefore we could exclude the influence of Overweight factor.

Collectively, the study reveals that even patients who successfully reached significant weight loss after bariatric surgery might show impaired cognitive control mechanisms, in their ability to resist to attentional interference, to flexibility adapt to task-set changes and to inhibit habitual responses. It is worth noting that ex-obese patients differed on some but not all measures from controls (i.e., in the verbal Stroop interference and in the switch cost), and this proves that they were impaired on specific cognitive control mechanisms, not globally. The fact that group differences only emerged at the electrophysiological level in the inhibitory task suggested that ERP measures could capture more subtle executive control dysfunctions. Furthermore, ERP results suggested that weight loss might result in some compensatory neural processes (larger N1

and N2 amplitudes). All these findings are relevant when considering that cognitive control processes, such as reduced flexibility, could undermine the adherence with diet and lifestyle recommendations (Galioto, Gunstad, Heinberg, & Spitznagel, 2013; Spitznagel et al., 2013) and that impaired cognitive abilities after surgery predict higher probability of later weight regain (Spitznagel et al., 2014).

Figure captions

Figure 1. RT Stroop effect in the two Stroop tasks (Verbal and Spatial) for each group. Error bars represent the standard error of the mean. * $p < .05$

Figure 2. Grand-average waveforms of cue-locked ERPs for each trial type (Single, Repeat, Switch) over centro-parietal sites. The waveforms represent ERPs averaged across Cz, C2, C4, CPz, CP1, and CP2 electrodes. The maps represent the topographical distribution of ERPs in the control group (left column), in the patient group (right column) and the ERP group difference (rightmost column) for the 200-400 ms time window.

Figure 3. Grand-average waveforms of target-locked ERPs for each trial type (Single, Repeat, Switch) over central (left panel) and parieto-occipital (right panel) sites. The waveforms represent ERPs averaged across FC4, Cz, C2, C4, and CPz electrodes and across Pz and POz, respectively. The maps represent the topographical distribution of ERPs in the control group (left column), in the patient group (right column) and the ERP group difference (rightmost column) for the 160-200 ms time window.

Figure 4. Grand-average waveforms of ERPs elicited in the SART. Group difference were detected over fronto-central electrodes (Fz and FCz), in the N2 component, maximally expressed in NoGo trials (bottom left panel). Additional group differences were found over centro-parietal electrodes (Pz and CPz), in the Go-P3 component, present only in Go trials. In the NoGo-P3 component, present only in NoGo trials, group differences did not reached significance. The maps represent the topographical distribution of ERPs in the control and patient groups (upper maps) and the ERP group difference (lower maps), for the 280-340 ms time window.

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Figure 1