Brain Structure and Function (2019) 224:883–890
https://doi.org/10.1007/s00429-018-1809-8

ORIGINAL ARTICLE

A neuronal population code for resemblance between drug and nondrug reward outcomes in the orbitofrontal cortex

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Received: 3 August 2018 / Accepted: 1 December 2018 / Published online: 11 December 2018

Abstract

The orbitofrontal cortex (OFC) is implicated in choice and decision-making in both human and non-human animals. We previously identified in the rat OFC a mechanism that influences individual drug choices and preferences between a drug and a nondrug (i.e., sweet) outcome that is common across different types of drugs (cocaine and heroin). Importantly, this research also revealed some intriguing drug-specific differences. Notably, the size of non-selective OFC neurons that indiscriminately encode both the drug and the sweet outcomes varies as a function of the drug outcome available (cocaine or heroin). Here we tested the hypothesis that the relative size of the non-selective OFC population somehow represents the degree of resemblance between the drug and nondrug reward outcomes. We recorded OFC neuronal activity in vivo in the same individual rats while they were choosing between two outcomes with varying degrees of resemblance: high (two concentrations of sweet), intermediate (sweet versus heroin) and low (sweet versus cocaine). We found that the percentage of non-selective OFC neurons dramatically increased with the degree of resemblance between choice outcomes, from 26 to 62%. Overall, these findings reveal the existence of a neuronal population code for resemblance between different kinds of choice outcomes in the OFC.

Keywords Choice · Preference · Orbitofrontal cortex · Outcome resemblance · Cocaine · Heroin

Introduction

The orbitofrontal cortex (OFC) plays a crucial role in processing reward information about competing options to influence choice and preference in humans, monkeys, and rats (Bechara et al. 2000; Kepecs et al. 2008; Padoa-Schioppa 2013; Padoa-Schioppa and Assad 2006, 2008; Roesch et al. 2006; Tremblay and Schultz 1999; Wallis 2011). We previously identified in the rat OFC a neuronal population that encodes individual choices and preferences between drug use (i.e., cocaine or heroin) and an alternative action rewarded by a nondrug outcome (i.e., sweet water). In particular, we found that, regardless of the drug available (i.e., cocaine or heroin), about half of the neurons recorded in the OFC encoded, selectively or non-selectively, at least one choice outcome while the other half was nonresponsive. Importantly, among choice outcome-selective neurons, the relative size of the drug-selective population represented and predicted an individual choice and preference: the larger this relative size, the greater the rate of drug choices. There thus seems to exist in the OFC a neuronal population code for individual drug choices and preferences that is common across different drug outcomes (Guillem and Ahmed 2018; Guillem et al. 2018).

Interestingly, this research also revealed some intriguing drug-specific differences in OFC neuronal coding activity. Notably, we found that regardless of individual preferences, the size of the non-selective neurons population (i.e., neurons that encode indiscriminately both the drug- and the sweet-rewarded actions) varied as a function of the drug outcome (i.e., cocaine or heroin) available as an alternative

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to the nondrug sweet outcome (Guillem and Ahmed 2018; Guillem et al. 2018). This non-selective population was much larger when the drug outcome was heroin than when the drug outcome was cocaine. Intriguingly, when the drug outcome was heroin, the non-selective OFC neuronal population had a size comparable to that seen when the outcome of both actions was sweet water at the same or different concentrations (Guillem and Ahmed 2018; Guillem et al. 2018). Since there are more behavioral and neurobiological commonalities between sweet reward and opiate drugs, including heroin, than between sweet reward and cocaine (Avena et al. 2008; Berridge 2003; Kenny 2011; Lenoir et al. 2012; Madsen and Ahmed 2015), this led us to hypothesize that the size of the non-selective OFC population may represent some degree of qualitative resemblance between the different options (Guillem et al. 2018). As we conceive it, the resemblance in question would be mainly subjective in nature and likely concerns the interoceptive quality of the expected choice outcomes (see "Discussion").

However, this hypothesis is exclusively based on observations of OFC neuronal activity in separate groups of rats with different drug and/or training histories (Guillem and Ahmed 2018; Guillem et al. 2018). Here we sought to test this hypothesis more directly. To this end, we recorded in vivo OFC neuronal activity in the same individual rats when facing different choice outcomes with varying degrees of resemblance: low (sweet water versus cocaine), intermediate (sweet water versus heroin) and high (two concentrations of sweet water). We predicted that the relative size of the non-selective OFC population should vary according to this increasing degree of resemblance.

Materials and methods

Subjects

A total of four male Wistar rats (275–300 g) (Charles River Laboratories, L'Arbresle, France) were individually housed in cages containing enrichment materials (a nylon bone and a cardboard tunnel; Plexx BV, The Netherlands) under a 12 h light/dark cycle, with ad libitum access to food and water.

Surgeries

Animals were deeply anesthetized with ketamine (100 mg/kg, i.p., Bayer Pharma, Lyon, France) and xylazine (15 mg/kg, i.p., Merial, Lyon, France) and surgically prepared with an indwelling silastic catheter in the right jugular vein (Dow Corning Corporation, Michigan, USA). Then, under isofluorane anesthesia, rectangular arrays of 16 Teflon-coated stainless steel microwires (2 rows of 8 wires separated from each other by 0.25 mm; MicroProbes Inc., Gaithersburg, MD) were implanted unilaterally in the OFC [AP: +2.5 to +3.7 mm, ML: 1.5 to 4.5 mm, and DV: −5.0 mm relative to skull level] as previously described. A stainless steel ground wire was also implanted 4 mm into the ipsilateral side of the brain, 5 mm caudal to bregma. After surgery, catheters were flushed daily with 0.2 ml of a sterile antibiotic solution containing heparinized saline (280 IU/ml) and ampicillin (Panpharma, Fougères, France) to maintain patency. Behavioral testing began 10–14 days after surgery.

Behavioral procedures

Behavioral apparatus

Operant chambers (30 × 40 × 36 cm) used for all behavioral training and testing (Imetronic, Pessac, France) were equipped with two automatically retractable levers located on the middle of the left and right walls of the chamber. A white cue-light was mounted above each lever. The chamber was also equipped with two drinking cups, each located 6.5 cm on the left of each lever on the same wall and 6 cm above the grid floor. A lickometer circuit (Imetronic, France) allowed monitoring and recording of licking. Finally, the chamber was also equipped with two computer-controlled syringe pumps connected to different line tubings for drug delivery and/or fluid delivery into the cups, a single-channel liquid swivel (Lomir Biomedical Inc., Quebec, Canada), an electrical commutator (Crist Instrument Inc., Hagerstown, MD), and two pairs of infrared beams to measure horizontal cage crossings.

Discrete-trials choice procedure

Animals were first trained on alternate daily sessions to lever press to self-administer water sweetened with 0.2% or 0.04% saccharin during a 20-s access under a fixed-ratio 1 (FR1 time-out 20 s). One lever was associated with 0.2% saccharin, the other with 0.04% saccharin. Sessions began with extension of one single lever. If rats responded on the available lever, they were rewarded by the corresponding reward outcome. Reward delivery was signaled by a 20-s illumination of the cue-light above the lever during which time responses were not rewarded (i.e., time-out period). Sessions ended after rats had earned a maximum of 30 rewards or 3 h had elapsed. Then rats were trained under a discrete-trials choice procedure until stabilization of preference. Each daily session consisted of 44 trials spaced 10 min apart and distributed into two successive phases, first sampling (24 trials), then choice (20 trials). During sampling, the two levers were presented separately on alternate trials, thereby forcing rats to engage in only one rewarded action at a time. If rats responded within 5 min on the presented lever, they received the reward associated with that action. Reward

delivery was signaled by immediate retraction of the lever and illumination of a 40-s illumination of the cue-light above it. If rats failed to respond within 5 min, the lever retracted and no cue-light or reward was delivered. During choice, the two levers were presented simultaneously on the same trials, thereby allowing rats to choose between the two corresponding rewarded actions. If rats responded within 5 min on either lever, they received the reward outcome associated with that action. Reward delivery was signaled by immediate retraction of both levers and illumination of a 40-s illumination of the cue-light above the chosen lever. If rats failed to respond on either lever within 5 min, both levers retracted and no cue-light or reward was delivered.

Varying degree of choice outcomes resemblance

All rats were allowed to sample and choose between two outcomes with varying degrees of resemblance (Fig. 1a): high (two concentrations of sweet water, S/S), intermediate (sweet water versus heroin, S/H) and low (sweet water versus cocaine, S/C). The order of testing was counterbalanced across individuals. Half of the rats ($n = 2$) were first tested in the S/S choice situation, then in the S/C choice situation and, finally, in the S/H choice situation. The other half was tested in the following order of choice situations: S/S, S/H and S/C. In the S/S choice situation, all animals were first allowed during several daily sessions to sample and choose between two actions, one rewarded by a high (0.2%) and the other by a low (0.04%) concentration of saccharin during several daily sessions (i.e., 14.3 ± 0.8) until stabilization of preference. In the S/C or S/H choice situation, the lower concentration of saccharin was replaced by either an intravenous dose of cocaine (0.25 mg) or heroin (0.01 mg). Rats were tested during several daily sessions (24 sampling trials followed by 20 choice trials) in the S/C (13.8 ± 0.8) and S/H (13.0 ± 0.4) situation until stabilization of preference. OFC neuronal activity was recorded in vivo during the last session of each choice situation (i.e., three recording sessions per rat). OFC neuronal encoding profiles were measured during sampling trials where only one response option was available at a time in alternation with the other option (Guillem and Ahmed 2018; Guillem et al. 2018).

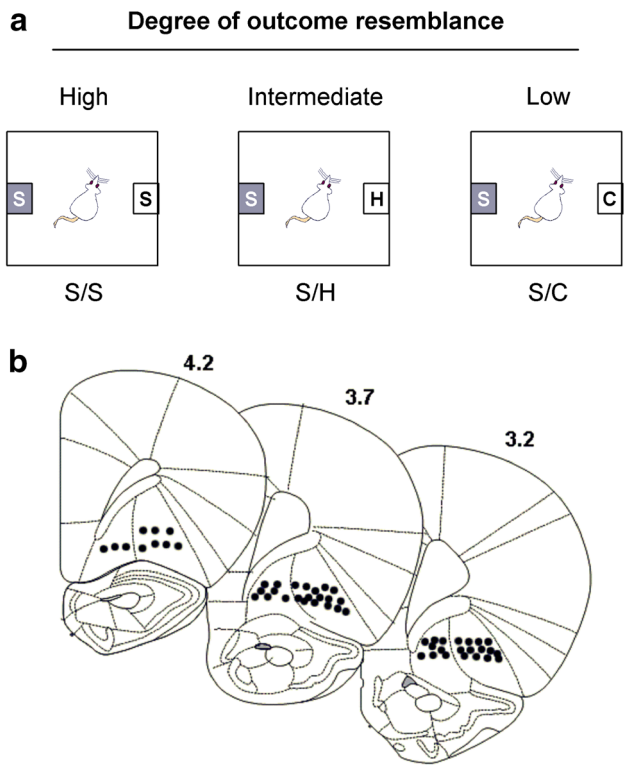

Fig. 1 Experimental design. **a** Choice between outcomes with varying degrees of resemblance: high (two concentrations of sweet water, S/S), intermediate (sweet water versus heroin, S/H), and low (sweet water versus cocaine, S/C). **b** Electrode placements within the lateral (LO) and the ventral (VO) parts of the OFC. Each black dot represents the tip of an electrode. The numbers indicate millimeters anterior to bregma

Data analysis

Neuronal recordings and single unit isolation

Voltage signals from each microwire were recorded, amplified up to 40,000×, processed, and digitally captured using commercial hardware and software (OmniPlex, Plexon, Inc., Dallas, TX). Spiking activity was digitized at 40 kHz, bandpass filtered from 250 Hz to 8 kHz and captured using commercial hardware and software (Plexon). Behavioral events in the operant task were streamed to the Plexon via TTL pulses delivered from the Imetronic system (Imetronic, Pessac, France) to allow the neuronal data to be accurately synchronized and aligned to these behavioral events. Single units spike sorting was performed off-line: principal component analysis scores were calculated and plotted in a three-dimensional principal component analysis space and clusters containing similar valid waveforms were defined (Offline Sorter, Plexon). The quality of individual-neuron recordings was ensured with the following criteria: < 3% of all interspike intervals exhibited by the unit were < 2000 µs, and the average amplitude of the unit waveform was at least three times larger than that of the noise band (> 3:1 signal-to-noise). The total data set consisted of 192 OFC single units recorded across three sessions. These units were classified into putative interneurons and pyramidal neurons according to the waveform spike width and average firing rate, as previously described (Guillem et al. 2010). In the population of recorded single units, only 9.4% were classified as narrow spiking, putative interneurons (width < 300 µs). In this report, we focus exclusively on the remaining 174 units, a population that included putative pyramidal neurons.

Electrophysiological data were analyzed using NeuroExplorer (Plexon) and Matlab (Mathworks, Natick, MA).

Neuronal data analysis

Peri-event firing rate histograms (PETHs) were used to analyze neuronal responses time-locked to each lever press during sampling trials. For each neuron, firing rate during 1 s before and 1 s after lever press action onset (signal period) was compared to average firing rate during a 3-s window period recorded 9 s before the action (baseline period) using a Wilcoxon test. A phasic change in firing was defined as a significant change in firing during the signal period compared to the baseline period using a Wilcoxon test ($p<0.05$). A neuron with a significant change of firing during one action but not during the other was defined as selective, while a neuron with a significant change of firing during both actions was defined as non-selective. Importantly, when the number of completed sampling trials differed between the preferred and non-preferred actions (e.g., 12 versus 9), we limited our analysis of neuronal selectivity between the two actions to the lowest number of sampling trials, that is, that corresponding to the non-preferred option (Guillem and Ahmed 2018). In each experiment and for each rat, the percent of responding neurons was determined for each action and compared using a two sample *Z*-test, a test that allowed to compare two independent proportions.

Histology

At the end of the study, histological procedures were used to identify the location of all wire tips used to record neurons. Under anesthesia, an anodal current (50 µA for 5 s) was passed through each microwire to create a small iron deposit. Animals were then perfused with 3.6% paraformaldehyde and 5% potassium ferricyanide solution to stain the iron deposits. The brains were cut into 50 µm coronal sections which were mounted on slides. Each slide was visualized under a microscope, and the location of each wire tip was plotted on the coronal plate (Fig. 1b). Only neurons recorded from wires that were within the lateral (LO) and ventral (VO) parts of the OFC were included in data analyses.

Drugs

Cocaine hydrochloride (Coopération Pharmaceutique Française, Melun, France) and heroin hydrochloride (Francopia Sanofi, Paris, France) were dissolved in 0.9% NaCl, filtered through a syringe filter (0.22 µm) and stored at room temperature. Drug doses were expressed as the weight of the salt. Sodium saccharin (Sigma-Aldrich, France) was dissolved in tap water at room temperature (21 ± 2 °C). Sweet solutions were renewed each day.

Results

As expected from previous research (Cantin et al. 2010; Guillem and Ahmed 2018; Lenoir et al. 2007; Madsen and Ahmed 2015), animals strongly preferred 0.2% saccharin over any alternative outcomes, including 0.04% saccharin (S/S), heroin (S/H) or cocaine (S/C) (Fig. 2a). There was no drug-preferring rat in the present study. Overall, regardless of the type of choice situations, rats' preference for 0.2% saccharin remained unchanged (i.e., % choice of the non-preferred outcome: 15 ± 7.6%, 14 ± 6.6% and 22 ± 10.7% in the S/S, S/H and S/C situations, respectively) [$F(2,6)=0.22$, NS]. In addition, they made their choice with the same decision speed across choice situations [choice latency: 2.8 ± 0.4 s, 2.7 ± 0.5 s and 2.4 ± 0.1 s in the S/S, S/H and S/C situations, respectively; $F(2,6)=0.29$, NS].

We recorded a total of 174 putative pyramidal neurons across the three choice situations in the OFC of those animals (S/S: $n=53$; S/H: $n=61$ and S/C: $n=60$). OFC neurons whose firing activity changed phasically during each rewarded outcome were identified during sampling trials preceding choice trials. Of these neurons, 48% (84/174) phasically encoded at least one of the two choice outcomes (i.e., outcome-responsive neurons), a result consistent with previous findings (Guillem and Ahmed 2018; Guillem et al. 2018). The percentage of outcome-responsive neurons remained relatively stable across the three choice situations [49.9 ± 7.5%, 50.8 ± 5.3% and 45.3 ± 3.5% in the S/S, S/H and S/C situations, respectively; $F(2,6)=0.21$; NS] (Fig. 2b). Consistent with our hypothesis, we found that outcome-responsive neurons were distributed differentially in the outcome-selective versus outcome-non-selective populations as a function of the different choice situations and, thus ex hypothesi, as a function of the degree of resemblance

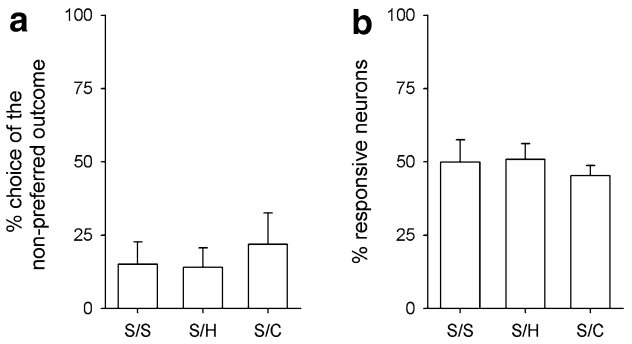

Fig. 2 Preference across different choice situations. **a** Mean (±SEM) percentage choice of the non-preferred outcome and **b** mean (±SEM) percentage of OFC responsive neurons (including both outcome-selective and non-selective neurons) during choice between two concentrations of sweet water (S/S), between sweet water and heroin (S/H), and between sweet water and cocaine (S/C)

between the choice outcomes [$F(2,12) = 15.5$; $p < 0.001$] (Fig. 3). Specifically, the percentage of non-selective neurons decreased considerably when rats were shifted from the S/S to the S/C choice situation (i.e., from 62 to 26%) while the percentage of outcome-selective neurons increased (i.e., from 38 to 74%). Post hoc comparisons revealed that the percentage of non-selective neurons in the S/C situation was significantly lower than that in the two other choice situations ($p < 0.05$) which did not differ from each other. In contrast, the percentage of selective neurons in the S/C situation was higher than that in the S/S or the S/H choice situation ($p < 0.05$) which did not differ from each other. Importantly, the decrease in the percentage of non-selective neurons across the choice situations was observed in all animals without exception (Fig. 3c).

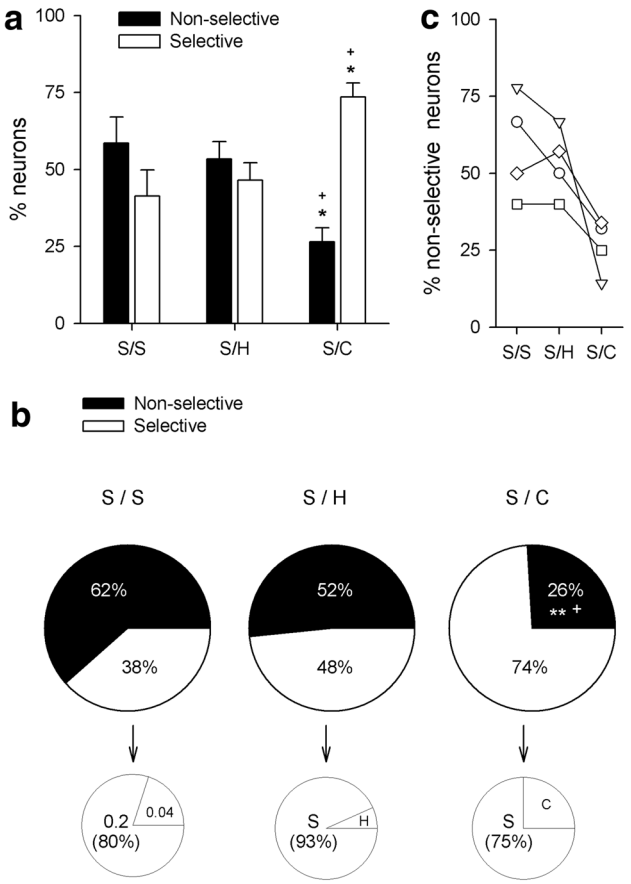

Fig. 3 Changes in OFC neuronal encoding across three different choice situations. **a** Mean (±SEM) percentage of outcome-selective (white bars) and non-selective (black bars) neurons and **b** pie chart representation of the distribution of OFC neurons into outcome-selective (white) and non-selective (black) during choice between two different concentrations of sweet water (S/S), between heroin and sweet water (S/H), and between cocaine and sweet water (S/C). $^{*}p < 0.05$ and $^{**}p < 0.01$, different from the S/S choice condition. $^{+}p < 0.05$, different from S/H choice condition. **c** Percentage of non-selective neurons across choice situations in each individual rat ($n = 4$)

Finally, confirming our previous findings (Guillem and Ahmed 2018; Guillem et al. 2018), we also found that regardless of the choice situations, rats' preference for 0.2% saccharin was associated with a larger relative size of the OFC population that selectively encodes this particular reward outcome (Fig. 3b). Specifically, among OFC selective neurons, the percentage of those that encode 0.2% was systematically greater than the percentage of those that encode the alternative outcome available (i.e., 80, 93 and 75% in the S/S, S/H and S/C choice situations, respectively). The percentage of selective neurons that encode 0.2% saccharin did not vary significantly across the choice situation, which suggests that the neuronal correlates of preference are highly stable.

Discussion

Overall and as predicted, we found that the relative size of the OFC population of non-selective neurons somehow represents the degree of resemblance between different choice outcomes. Specifically, we observed that the percentage of non-selective OFC neurons among outcome-responsive neurons increased with this degree of resemblance. It was low when the choice outcomes were sweet water and cocaine (i.e., 26%), intermediate when the choice outcomes were sweet water and heroin (52%), and high when the choice outcomes were two different concentrations of sweet water (62%). Importantly, this variation occurred with no change in preference, suggesting that the size of the non-selective OFC population cannot reflect a mere quantitative resemblance in value between the different choice outcomes. If it was the case, rats should be more indifferent or hesitant between heroin and sweet water than between cocaine and sweet water. This was clearly not the case. We speculate that the size of the non-selective OFC population somehow represents the degree of qualitative resemblance between different choice outcomes (see below).

In a previous study, we found that when choice outcomes were identical (i.e., same concentrations of sweet water), the percentage of non-selective OFC neurons was 67% (Guillem and Ahmed 2018). Since this percentage is very close to that reported here between two different concentrations of sweet water (i.e., 0.04 versus 0.2%), it probably represents the degree of qualitative resemblance between choice outcomes rather than of quantitative resemblance. In addition, the fact that this percentage is below 100% suggests that the size of the non-selective OFC population does not reflect exclusively the degree of qualitative resemblance between different choice outcomes but also some other choice task elements, such as, for instance, the spatial location of the response operandum (e.g., lever on the left wall versus on the right wall of the operant box). This conclusion is

important because it sets an upper limit to the maximum size of the non-selective OFC population in choice tasks, such as ours, which require at least two different response operandum.

Though it is difficult, at present, to define precisely what is qualitatively similar between a drug and a nondrug outcome, our findings are nevertheless largely consistent with previous research showing a greater commonality, both at the behavioral and neurobiological levels, between sweet or palatable foods and opiate drugs than between these nondrug rewards and stimulant drugs, like cocaine or amphetamine. For instance, both sweet and opiate rewards depend on nucleus accumbens mu-opioid signaling and, unlike cocaine reward, are only weakly influenced by nucleus accumbens dopamine signaling (Ettenberg et al. 1982; Koob 1992; Pecina and Berridge 1995; Zhang and Kelley 1997). Moreover, both sweet foods and opiates induce a mu-opioid-dependent hypoalgesia in both humans and rodents (Mercer and Holder 1997; Ren et al. 1997). There is also significant degree of cross-tolerance or cross-sensitization between sugar and opiates, like morphine (Colantuoni et al. 2002; Kanarek et al. 1991; Lieblich et al. 1983). In some cases, sugar can also alleviate morphine withdrawal (Jain et al. 2004). Finally, both sugar and opiate drugs induce overeating in sated animals. In contrast, cocaine, like other stimulants, suppresses eating, even in hungry rats (Cooper 1982; Parker et al. 1992; Pecina and Berridge 1995; Vandaele et al. 2016; Woolverton et al. 1978). These findings strongly suggest that a sweet outcome would be perceived and experienced by rats as more similar to a heroin outcome than to a cocaine outcome. This could be confirmed more directly using a drug-discrimination procedure (Solinas et al. 2006). In addition, since drug discriminative cues play a significant role in precipitating reinstatement of drug seeking after extinction (Mihindou et al. 2011), this hypothesis also predicts that sweet foods should be more effective in reinstating heroin seeking than cocaine seeking. This latter prediction may have important consequences for relapse prevention of opiate addiction. Addicted people may experience different degree of difficulty to quit opiates in environments with different levels of supply of sugar-sweetened foods and/or drinks. Clearly, the present study raises a number of significant questions for future research.

One intriguing, rather counterintuitive, implication of the above analysis is that there would be more commonalities between opiates and sweet foods than between opiates and stimulants, like cocaine. We thus predict that in rats trained to choose between an opiate and a stimulant, the size of the OFC population that non-selectively encodes these two drug outcomes should be smaller than the OFC population that non-selectively encodes an opiate and a sweet outcome, as measured here (i.e., about 50% in the present study). Though conducting a choice experiment between two different drugs remains a daunting endeavor, at least in rats (Caprioli et al. 2009), this prediction is nevertheless consistent with previous research showing that there exist important behavioral and neurobiological differences between heroin and cocaine (Badiani et al. 2011; Graziane et al. 2016; Koo et al. 2012; Lenoir et al. 2012). For instance, in drug-discrimination procedures, rats do not generalize or only weakly the interoceptive stimulus properties of cocaine with that of opiates, including heroin (Broadbent et al. 1995; Colpaert 1978; Lamas et al. 1998).

Finally, this study also reveals that the size of the non-selective OFC population is flexible and adapts to the actual choice situation. While the size of the overall outcome-responsive neurons remained remarkably stable (i.e., about 50%), the relative size of non-selective versus selective OFC neurons dramatically changed with available choice outcomes. For instance, in the same individual rat, the percentage of non-selective OFC neurons decreased from 77 to 14% when the lowest concentration of saccharin was replaced by an intravenous dose of cocaine. This dramatic change occurred even if the individual did not change its preference for the highest concentration of saccharin. It would be interesting in future research to measure the dynamics of these changes to determine if they occur relatively rapidly. It would also be interesting to see if the neuronal encoding profiles reported here in nondrug-preferring individuals generalize to drug-preferring individuals and to different training backgrounds. To begin to address these issues, we re-analyzed data from two previous studies and looked at the percentage of non-selective neurons in cocaine- ($n=3$) and heroin-preferring rats ($n=1$) (Guillem and Ahmed 2018; Guillem et al. 2018). Overall, we found results similar to those reported here in nondrug-preferring rats. The size of the non-selective neuronal population was larger when heroin was available for choice (i.e., 50%) than when cocaine was available for choice ($30.6 \pm 8.7\%$). Though additional research is clearly needed to better characterize non-selective OFC neuronal activity in drug-preferring individuals, this preliminary analysis nevertheless suggests that the neural encoding of reward resemblance is independent from an individual pre-existing drug preference, thereby reinforcing the generalizability of our conclusion. Finally, since the fraction of outcome-responsive neurons remained stable across the different choice situations (i.e., S/S, S/C and S/H), it is tempting to hypothesize that the same OFC neurons switch between the selective and non-selective populations as a function of the degree of resemblance of the choice outcomes. However, we cannot currently confirm this hypothesis since our electrophysiological method does not allow us to follow the identity of individual neurons across days. Nevertheless, it is consistent with recent primate research on OFC neuronal activity during choice between variable goods (Xie and Padoa-Schioppa 2016).

In conclusion, together with previous research, this study reveals the existence of two functionally distinct neuronal populations within the OFC, one composed of neurons that selectively encode each choice outcome, the other composed of neurons that non-selectively encode all choice outcomes. We previously described the role of the former population in influencing an individual choice and preference between a drug and a nondrug outcome. Here we report strong evidence that the non-selective OFC population may encode the degree of qualitative resemblance between different choice outcomes. Overall, this research suggests that a heroin outcome would be experienced qualitatively as very similar to a sweet outcome, at least by rats. Though the specific role of this novel OFC population code in decision-making is currently largely unknown, it can be used as a way to assess the degree to which different kinds of choice outcomes appear similar to an individual chooser. Further research will be needed to determine what information is being compared and contrasted by the brain to compute this degree of resemblance. Also, it would be important to determine how these findings generalize to other choice situations that involve different kinds of reward outcomes (e.g., situations that involve social rewards).

Acknowledgements We thank Christophe Bernard, Eric Wattelet, Audrey Durand and Caroline Vouillac-Mendoza for administrative and technical assistance. We also thank Etienne Gontier from the Bordeaux Imaging Center (BIC) for giving us access to his laboratory facility for brain perfusion.

Funding This work was supported by the French Research Council (CNRS), the Université de Bordeaux, and the Fondation pour la Recherche Médicale (FRM DPA20140629788).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All experiments were carried out in accordance with standard ethical guidelines (European Communities Council Directive 86/609/EEC) and approved by the committee on Animal Health and Care of Institut National de la Santé et de la Recherche (agreement A5012052).

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