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An amygdala-cingulate network underpins changes in effort-based decision making after a fitness program

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ABSTRACT

When humans make decisions, objective rewards are mainly discounted by delay, risk and effort. Whereas recent research has demonstrated that several brain areas process costs and code subjective value in effort-based decision making, it remains obscure how neural activity patterns change when effort costs are reduced due to the acquisition of healthy habits, such as moving from sedentary to active lifestyles. Here, a sample of sedentary volunteers was behaviorally assessed and fMRI-scanned before and after completing a 3-month fitness plan. The impact of effort cost on decisions, measured as the constant defining a hyperbolic decaying function, was reduced after the plan. A logistic mixed model demonstrated that the explanatory power of effort decreased with time. At a neural level, there was a marginally significant disruption of effort-cost related functional activity in the anterior cingulate after the plan. Functional connectivity between the amygdala and anterior cingulate cortex was strengthened after habit acquisition. In turn, this interaction was stronger in those participants with lower effort discounting. Thus, we show for the first time changes in value-based decision making after moving from a sedentary to an active lifestyle, which points to the relevance of the amygdala-cingulate interplay when the impact of effort on decisions fades away.

1. Introduction

Recent research has proposed how humans process effort-related costs in decision making. These studies present volunteers with one or two options, involving the possibility of performing a hand grip or repeatedly pushing a button. They are based on a solid literature in animal research, which consistently shows an engagement of the anterior cingulate cortex, amygdala and striatum in effort processing (Salamone, 2009). In human studies, a set of areas including the anterior cingulate and paracingulate cortices, putamen and ventral striatum code the net value of effortful rewards, defined as the reward magnitude divided by effort level (Croxson et al., 2009). More precisely, the putamen shows a decreased activity when choosing an effortful option (Kurniawan et al., 2010), and the anterior cingulate has an increased signal when predicting a high effort (Kurniawan et al., 2013). Within the realm of value-based decision making, different aspects of the cingulate cortex correlate with the subjective value (SV) of rewards when discounted by effort costs, either negatively (Prevost et al., 2010) (i.e., increased activity for higher efforts) or positively (Klein-Flugge et al., 2016) (i.e., increased activity for lower efforts). Remarkably, a pharmacological disconnection between the amygdala and anterior cingulate cortex precludes rats from making optimal decisions: after intervention, animals opt for a low reward/low effort arm maze instead of an effortful choice that leads to a larger reward (Floresco and Ghods-Sharifi, 2007).

In previous research, we introduced a decision-making task that included a prospective, moderate and sustained effort (running on a treadmill) instead of an immediate, intense and manual grip or button push. Our intention was to study physical effort-discounting in decision

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making with an ecological approach; in turn, we found that individual hyperbolic constants, which explain at what extent effort discounts (i.e. reduces) the SV of monetary rewards, negatively correlated with an indicator of active lifestyle (WHO's GPAQ). At a neural level, we found that SV of the pair of options correlated with activity in the dorsomedial prefrontal cortex in sedentary subjects (Bernacer et al., 2016).

To our knowledge, there is a lack of evidence about the impact of a lifestyle change on subjective valuation, both at behavioral and neural levels. In the case of effort, our goal is to test whether discounting in decision making and brain signals related with effort subjective valuation change when sedentary participants complete a fitness program. Thus, we recruited a sample of sedentary participants that received a functional magnetic resonance imaging (fMRI) scan while performing an effort- and risk-discounting decision making task; then, they were included in a 3-month mild physical activity plan that consisted on running on a treadmill 3 days a week, with the final goal of running 30 min without rest. At a behavioral level, our hypothesis is that the decaying constants explaining effort discounting will decrease after intervention, whereas risk discounting will remain unchanged. Furthermore, we predict that effort and risk will decrease and increase their explanatory power on choices, respectively, when considering the interaction with time assessment (before and after the plan). At a brain level, after the plan, we expect an attenuation of effort-related BOLD signal in the cingulate and paracingulate cortices (Croxson et al., 2009; Doya, 2008; Klein-Flugge et al., 2016; Walton et al., 2003), nucleus accumbens (Assadi et al., 2009; Botvinick et al., 2009) and/or putamen (Croxson et al., 2009; Kurniawan et al., 2010), but an strengthened risk-related signal in the insula and/or posterior parietal cortex (Miedl et al., 2012; Peters and Buchel, 2009; Preuschoff et al., 2008; Weber and Huettel, 2008). These changes are expected as a neural signature of the behavioral change mentioned above: a decreased and increased explanatory power on decisions of effort and risk, respectively. Further, since participants are expected to acquire a behavioral disposition (i.e. "habit" in classical philosophical terms: see Bernacer and Murillo, 2014) to overcome efforts without the need of 'explicitly' assigning a value to each of the prospects included in the decision, we also hypothesize an attenuated SV-related brain signal. Moreover, translating Floresco and Ghods-Sharifi (2007) results into human research, we expect an increased connectivity between the amygdala and anterior cingulate cortex after habit acquisition.

Overall, this would show for the first time a change in value-based neural patterns after a mild intervention, which behaviorally manifests as a reduction in effort discounting and a preference for optimal (i.e. less risky) prospects. This would improve our understanding of the influence of 'habit' (i.e. a behavioral disposition) acquisition on subjective valuation, and may shed light on conditions where value-based decision making is disturbed, such as apathy (Kurniawan et al., 2011), impulsivity (Pine et al., 2010), psychosis (Bernacer et al., 2013) or addiction (Park et al., 2010).

2. Materials and methods

2.1. Participants and procedure

A total of 57 participants were initially recruited for the behavioral assessment of effort discounting. From this, a subsample of 24 participants (mean age = 19.8, standard error of the mean (SEM) = 0.33, range 18–25; 14 female) were included in the longitudinal fMRI experiment reported here, meeting the following criteria: (1) absence of fMRI incompatibilities: (2) absence of regular physical activity, self-reported and assessed by the General Physical Activity Questionnaire (GPAQ, World Health Organization); (3) willingness to engage in a 3-month mild physical activity program; (4) absence of neurological or psychiatric disorders, assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), in its Spanish version; (5) normal or corrected-to-normal vision. With respect to criterion 2, we followed the recommendations by Hallal et al. (2012), which consider 3 standards to determine a physically active lifestyle: (1) 30 min of moderate physical activity at least 5 days per week; (2) 20 min of intense physical activity at least 3 days per week; (3) an equivalent combination reaching 600 metabolic equivalent (MET)-min per week. One MET-min is the energy spent when a subject sits quietly. One minute of moderate and intense physical activity corresponds to 4 and 8 METs, respectively. None of the volunteers included in the present project fulfilled standards 1 and 2 for at least 6 months prior to be assessed. Two volunteers had GPAQ scores equal or above 600 (660 and 600 METs-min) due to very occasional (one day per month) engagement in team sports. Since they did not report regular physical activity, they were included in the study. Participants were informed about the longitudinal design of the study from the beginning, and they expected two fMRI scans. Four subjects dropped out the project before completing the program, and one additional participant was excluded due to the initialization of neuroactive treatment. Therefore, 19 participants (11 female) were longitudinally evaluated. The literature on behavioral or neural changes in effort discounting is scarce. Based on longitudinal changes in temporal discounting after behavioral or neural (transcranial magnetic stimulation) interventions, we expect a moderately large effect size (Decker et al., 2015, $d = 0.55$; Kekic et al., 2017, 0.49; McClelland et al., 2016, 0.54; Yang et al., 2018, 0.59). Using G*Power 3.1.9.4, optimal sample size for an expected effect size of 0.55 is 22 participants (with standard values $\alpha = 0.05$, power $= 0.8$). With respect to neuroimaging, the final number of subjects included in our study is similar to that in previous publications (FitzGerald et al., 2009; Fleming et al., 2018; Klein-Flugge et al., 2016).

The protocol was approved by the Research Ethics Committee of the University of Navarra (protocol 038/2013).

In the first visit to the laboratory, they completed the effort- and risk-discounting tasks described below in a PC laptop, together with the GPAQ. After confirming their willingness to participate in the longitudinal study, they were assessed with the MINI and the questionnaire for fMRI compatibility, and were scheduled for the first scan, which generally took place between 7 and 10 days after the behavioral assessment. Once completed the fMRI session, one of the task pairs was randomly selected and choice by the participant was checked (for example, let us say that the task pair randomly selected was A = {30€,50%,20min} vs B = {30€,70%,30min}, and the participant chose A). Immediately, the subject entered a lottery with the selected probability (an opaque bag with 5 white and 5 black beads in this example) and, in the case of drawing a white bead, they were scheduled to perform the effort (20 min running in a treadmill) during the following week in exchange for a 30 € voucher to be spent in the University's gift shop. All participants completed the required effort and received the reward.

After this session, they started the physical activity plan in the University's gym free of charge, as an additional reward for participation in the project. The plan was designed by the trainer in charge of the facilities. They attended 2–3 days a week during 3 months, completing 20–30 min sessions of walking and running in a treadmill. Running periods were increased each week. Occasionally, participants were allowed to use static bicycle, but weightlifting was prohibited. Adherence to the program was monitored by the gym's personnel, who kept a spreadsheet to be signed by each participant every day they attended to the facilities. All volunteers attended at least 2 days a week until completion of the program. After the plan, participants were fMRI-scanned again. Before entering the scanner, they performed the behavioral effort- and risk-discounting tasks. Afterwards, random selection of a task pair and receipt of payment was done as in the first visit.

2.2. Behavioral tasks

Effort- and risk-discounting tasks have been described elsewhere (Bernacer et al., 2018, 2016). They followed the general schema of discounting tasks in neuroeconomics (see, for example, Kable and Glimcher, 2007), presenting participants with pairs of options including a fixed prospect (5 € with either no effort or no risk), and an alternative option with a larger amount discounted by effort or risk. This alternative option in both tasks included 6 amounts of money (5.25, 9, 14, 20, 30 and 50 €) and 6 effort (5, 10, 15, 20, 25 and 30 min running in a treadmill) or probability (90, 75, 50, 33, 10 and 5%; i.e. risk = 100%-probability) levels. Thus, in total, there were 36 task pairs that were presented 4 times each. The 144 trials were randomly presented and split into two sessions of 72 trials. Both sessions were consecutively run with a short break (about 1 min) between them.

Tasks were coded in Cogent 2000 (http://www.vislab.ucl.ac.uk/cogent_2000.php), developed by the Cogent 2000 team at the FIL and the ICN and Cogent Graphics developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience, which runs in Matlab (The MathWorks, Inc., Natick, MA, USA). The non-discounted and alternative options were shown randomly on the left or right part of the screen, in white text on black background. Task pairs remained on screen until selection, so there were no missing trials.

Once completed, data was analyzed following standard procedures with in-house Matlab codes. First, data was extracted from log files and organized according to effort or risk levels. Then, we fitted decisions for each participant to a sigmoid logistic curve, in order to calculate the probability of choosing the option that was actually chosen:

$$p(chosen) = \frac{1}{1 + e^{-\beta v(SVchosen - SVunchosen)}}$$

Equation 1: Sigmoid function to calculate the probability of choosing an option based on subjective valuation.

In this equation, βv is the 'exploration-exploitation' parameter or 'inverse temperature', and subjective values (SV) are estimated by a hyperbolic, exponential, double exponential or parabolic function (see below). We estimated the set of parameters that produced the best fitting to actual behavior, quantified as Schwartz's Bayesian Information Criterion (BIC):

$$BIC = -2^{*}\ln(L) + k^{*}\ln(n)$$

Equation 2: Calculation of Bayesian Information Criterion from log-likelihood.

Here, L is the log-likelihood calculated by adding up the natural logarithm of all probabilities produced by Equation 1, after assessing all individual decisions; k is the number of free parameters estimated in each function (discounting constant/s and inverse temperature: in total, 2 for hyperbolic, exponential and parabolic fittings, and 3 for double exponential), and n is the number of decisions from which the BIC was estimated (144 for individual modelling, 144 × 19 = 2736 for group estimation at one time point, and 144 × 19 × 2 = 5472 for group modelling at both time points; see below).

Concerning the estimation of SV, and following previous research, we tested whether decisions were explained by a hyperbolic, exponential, double exponential or parabolic function:

Equation 3: Hyperbolic fitting (Devaluator: effort or risk)

$$SV = Money^{*}\frac{1}{1 + K^{*}Devaluator}$$

Equation 4: Exponential

$$SV = Money^{*}e^{-c^{*}Devaluator}$$

Equation 5: Double exponential

$$SV = Money^{*}\frac{e^{-\beta^{*}Devaluator} + e^{-\delta^{*}Devaluator}}{2}$$

Equation 6: Parabolic

$$SV = Money^{*}\left(1 - H * Devaluator^{2}\right)$$

Note that the parabolic function has been modified with respect to previous reports (Hartmann et al., 2013), which included a second constant ('A') instead of 1. In our case, a free parameter produced unrealistic curves for most subjects (large discountings even in the absence of devaluator, or SV of 0 for relatively small devaluator levels), so we forced the curve to the starting point of 1.

Hyperbolic (K), exponential (c) and parabolic (H) equations are defined by one constant, whereas double exponential (β and δ) function includes two. The best combination of each constant or set of constants, including the inverse temperature (different for each function), was estimated by Matlab function 'fmincon'. We set the following initial values: K = 0.2; c = 0.1; β = 3; δ = 0.1; H = 0.000001; inverse temperature, in all cases = 1. Searching was restricted to values below 10 in the case of K, c, β and H, below 50 for δ, and below 100 for inverse temperature.

Behavioral fitting for out-of-scanner tasks was performed at three different levels: (1) at a subject level, at two time points (before and after the plan), in order to evaluate the impact of the fitness plan on individual effort discounting; (2) at group level, at two time points, in order to plot the discounting functions included in Fig. 2. In this case, decisions of all participants were treated as belonging to one 'omnibus participant'; (3) at group level, merging both time points, producing a single set of constants: this was used to create the regressors for the fMRI analysis.

2.3. fMRI task

The in-scanner task was also a decision-making paradigm where pairs of options were sequentially presented. However, in this occasion prospects included a fixed amount of money (30 €), a probability to be obtained (30, 40, 50, 60 or 70%) and an effort level (10, 15, 20, 25 or 30 min running in a treadmill). Note that the most convenient option should be the one with the highest probability, but participants should weigh the effort level required in exchange for the reward. Of all possible combinations, 20 task pairs per participant were selected, and each pair was presented 9 times. The individual selection of task pairs was intended to maximize the variability of the neuroimaging SV regressor. Thus, based on the discounting factors estimated in the out-of-scanner tasks, we selected 20 combinations that spanned from very similar to very disparate SV. Approximately one third of these pairs were 'obvious choices', where a high probability/low effort option was presented together with a low probability/high effort option. Therefore, there were a total of 180 task pairs. The complete list of task pairs for each participant is available as a spreadsheet as supplementary information. In addition, there were 45 control pairs, where participants were asked to select the option including the 'O' (Fig. 1).

Furthermore, we included two additional 'extreme' prospects to explore longitudinal changes in brain correlates when selecting a secured effortless or effortful reward. Thus, the pair {30€,100%,0 min} vs {30€,0%,0 min} was presented 45 times. We term this set of events 'No-Risk No-Effort' (NRNE) pairs. On the other hand, there were also 45 presentations of a 'No-Risk Maximum-Effort' (NRME) pair: {30€,100%,35 min} vs {30€,0%,0 min}.

In total, there were 315 pairs presented to each volunteer, split into three sessions (60 task pairs, 15 control, 15 NRNE and 15 NRME per session). Within each session, all pairs were randomly presented, and the location of the options (on either the left or right side of screen) was also randomized. All stimuli were depicted in white letters on black background. Options remained on screen for 5 s or until response, and a white cross appeared on screen for a random interval (between 2 and 6 s) between trials.

2.4. Estimation of neurocomputational parameters

Effort- and risk-discounting factors (DF), and SV were used as explanatory variables for behavioral and neural analyses. The DF is the degree at which a reward is discounted due to a devaluator (i.e. effort or risk), and it is depicted in the Y axis of the discounting curves. Thus, the DF of a particular effort or risk level is the value in the Y axis that

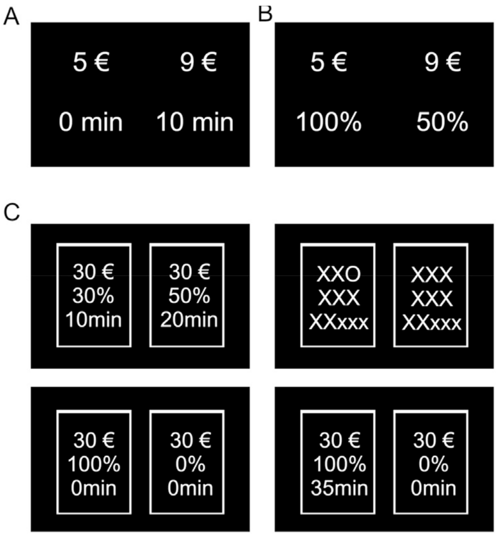

Fig. 1. Out-of-scanner and in-scanner tasks used in the experiment
A, effort-discounting task where an effortless reward (5 €), randomly located on the left or right, is presented together with a larger reward (5.25, 9, 14, 20, 30 or 50 €) that involves a hypothetical effort cost (5, 10, 15, 20, 25 or 30 min running on a treadmill). All possible 36 task pairs were randomly presented four times each, and the 144 trials were split into two consecutive sessions. B, risk-discounting task following the same schema as in the effort-discounting task. In this case, rewards included a hypothetical risk to be obtained (probability of winning, i.e. 100-risk, was displayed). C, in-scanner task was composed of four different types of trials: task pairs (top left), control (top right), no-risk no-effort (NRNE, bottom left) and no-risk maximum-effort (NRME, bottom right) pairs. Task pairs (20 different pairs, presented 9 times each, 180 trials in total) included a fixed amount of money (30 €) devalued by risk (probability of winning, i.e. 100-risk, was displayed) and effort (minutes running on a treadmill). In control trials (45 in total), participants were instructed to select the one with the 'O'. NRNE trials (45 in total) involved a secured (riskless) and effortless reward confronted with a non-rewarded option, whereas NRME trials (45 in total) involved a secured (riskless) effortful (35 min) reward confronted with a non-rewarded option.

corresponds to that particular level in the X axis. Since group analyses of the out-of-scanner tasks (pooling both time points) showed that the best fittings were the double exponential function for effort and the exponential curve for risk (see Results), we calculated SV and DF using the following parameters: $\beta = 0.1192$, $\delta = 0.0395$, $c = 0.0279$. The use of a single set of free parameters is common in longitudinal neurocomputational studies (Bernacer et al., 2013; Murray et al., 2019). Note that DF may be understood as the proportion of the reward that maintains a positive value for the subject after considering a particular level of the devaluator. Hence, higher DF values correspond to lower levels of the devaluator (i.e. lower amounts of effort or risk). SV, that is, the subject-dependent valuation of the 30 € reward once risk and effort were considered, was calculated as 30 multiplied by the DF of the effort and risk levels included in the prospect. Since a double exponential and an exponential decaying functions were assumed, SV can be formalized as follows:

Equation 7: Subjective value calculation for a given effort (E) and probability (P) level. Note that risk = 100-P.

$$SV\{30€, E, P\} = 30^{*}\ \frac{e^{-\beta^{*}Effort} + e^{-\delta^{*}Effort}}{2}{}^{*}e^{-c^{*}Risk}$$

Since each decision involved a pair of options, we computed SV, effort- and risk-DF of the pair, that is, the value of the chosen option minus the value of the unchosen option. For SV, positive values mean that the SV of the chosen option was greater than that of the unchosen option; for effort DF, positive values point to the selection of the option with the lower effort level (i.e. higher effort DF), whereas for risk DF positive values correspond to the selection of the option with the higher probability (or lower risk: higher risk DF).

2.5. *fMRI setting and analyses*

Participants were fMRI-scanned under the same procedure before and after the physical activity plan. We used a 3T fMRI scanner (Siemens TRIO, Erlangen, Germany) and a 32-channel head coil. First, a short localizing sequence ensured the correct position of the participant within the scanner. Then, the first session of the decision-making task was carried out. Between 170 and 274 vol (depending on the subjects' reaction times) were acquired in each of the 3 sessions, using an echo-planar imaging sequence to measure BOLD contrast (or "activity") (resolution = 3x3x3 mm^3; TR/TE = 3000/30 ms; FOV = 192 × 192 mm^2, Flip angle = 90°; 64, 48 and 48 vol acquired in the coronal, sagittal and axial planes respectively). The first five volumes were discarded for T1 equilibration effects. After the first session, an anatomical T1 MPRAGE image was collected (TR = 1620 ms; TE = 3.09 ms; inversion time = 950 ms; FOV = 256x192 × 160 mm^3; flip angle = 15°; image resolution = 1 mm isotropic). The remaining two sessions of the decision-making task were run with a short rest period of about 30 s, during which participants were asked not to move the upper part of their bodies.

fMRI data were analyzed with FSL (created by the Analysis Group, FMRIB, Oxford, UK, http://fmrib.ox.ac.uk/fsl) (Jenkinson et al., 2012), version 5.08. With regards to preprocessing, the skull was removed from all structural images using the BET tool included in FSL package (Smith, 2002). Individual functional images were processed with FEAT (FMRI Expert Analysis Tool) (Woolrich et al., 2001). They were realigned, motion corrected (using MCFLIRT) (Jenkinson et al., 2002) and spatially smoothed with a Gaussian kernel of 5 mm (full-width half maximum). Each time series was high-pass filtered (100 s cut off). Images were registered to the corresponding structural image and finally normalized to MNI template with non-linear methods (FNIRT). Besides, FSL's MELODIC tool was used to detect and remove structured noise due to motion or physiological signals, following the criteria described by Kelly et al. (2010).

fMRI statistical analyses were performed by using a general linear model (GLM) that included the following explanatory variables: (1) task pairs: boxcar time-locked to the presentation of the effort- and risk-discounted prospects; (2) control pairs: boxcar time-locked to the presentation of the control events; (3) NRNE: boxcar time-locked to the presentation of the No-Risk No-Effort pairs; (4) NRME: boxcar time-locked to the presentation of the No-Risk Maximum-Effort pairs; (5) SV of the pair: time-locked to the presentation of the effort- and risk-discounted prospects, modulated by the SV of the pair (SV_{chosen}-$SV_{unchosen}$), as described above; (6) effort DF of the pair: time-locked to the presentation of the effort- and risk-discounted prospects, modulated by the effort DF of the pair (EDF_{chosen}-$EDF_{unchosen}$), as described above; and (7) risk DF of the pair: time-locked to the presentation of the effort- and risk-discounted prospects, modulated by the risk DF of the pair (RDF_{chosen}-$RDF_{unchosen}$), as described above. Even though parametrically modulated regressors with the same onset (#5, #6 and #7) were obviously correlated, coefficients were within an acceptable range: Before fitness plan: SV vs EDF, average r = 0.4941 (max = 0.8666, min = 0.0340); SV vs RDF, 0.5023 (0.91,0.3419), EDF vs RDF, −0.3884 (−0.6936,0.0537); After fitness plan: SV vs EDF, 0.5959 (0.8944,0.1822); SV vs RDF, 0.4814 (0.8142,-0.0267), EDF vs RDF, −0.2890 (−0.6722,0.3047). These regressors were orthogonalized with respect to #1.

As justified in the Introduction, we were interested in assessing longitudinal changes in the neural correlates of SV, effort cost and risk processing. Hence, we focused on the following contrasts of parameter estimates: (a) SV of the pair (explanatory variable 5 against the baseline, showing the neural correlates of comparative SV); (b) minus effort DF of the pair (minus explanatory variable 6 against the baseline, which would highlight voxels with enhanced activity when the option with the higher

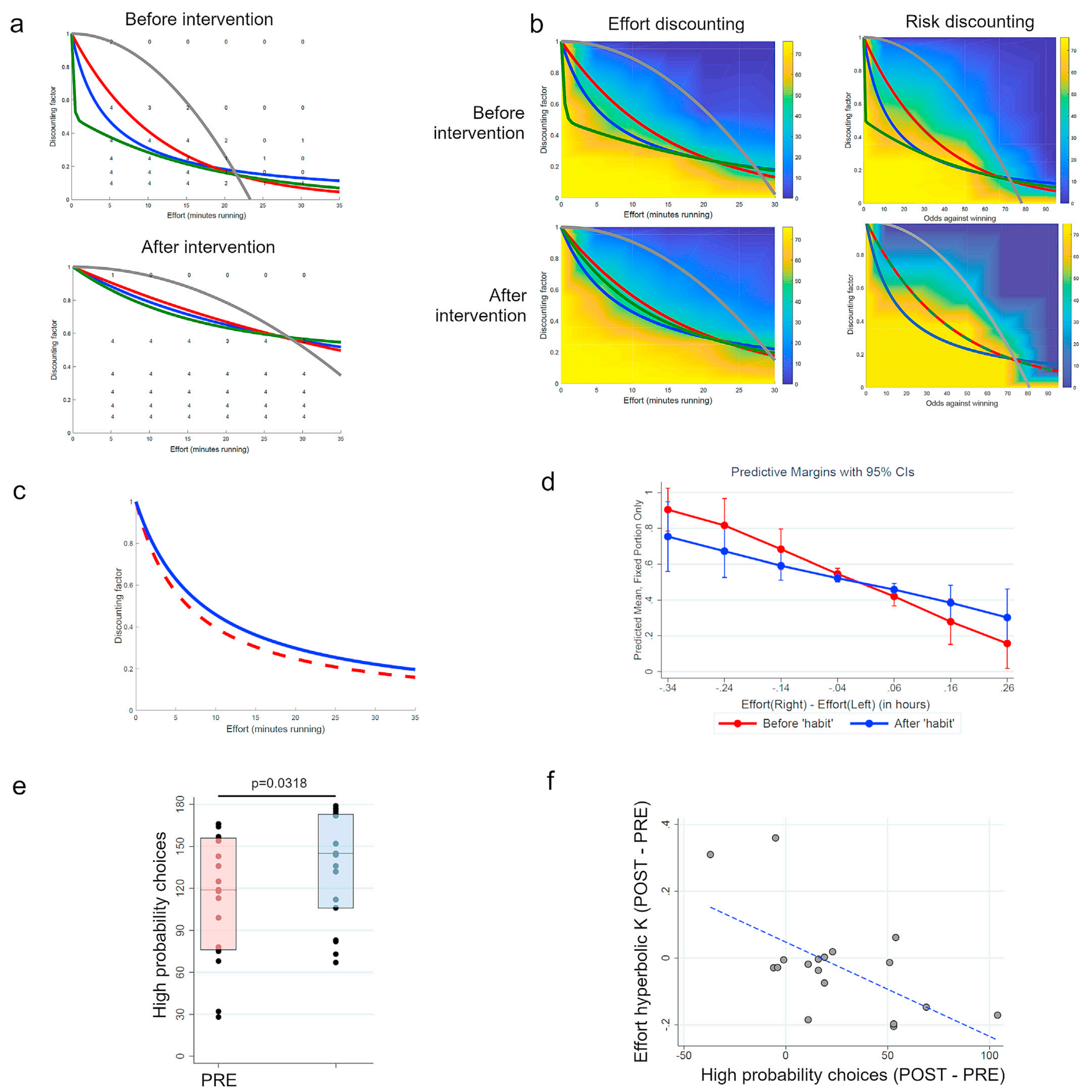

Fig. 2. Effort-discounting is attenuated after moving from a sedentary to an active lifestyle and the impact of effort on decisions decreases after the physical activity plan

Fig. 2**. Behavioral results**. A, Effort discounting curves for a representative subject, showing a behavioral impact after the fitness plan (blue = hyperbolic fitting, red = exponential, green = double exponential, grey = parabolic). Numbers represent how many times (out of 4) this participant chose the 'alternative' (effortful) option, versus the effortless (5 €, no effort) option. Y axis represent the fraction of the fixed option for each amount presented (for example, 5/5.25€). B, Group fittings for effort and risk discounting, before and after the fitness program. Color codes for the curves are the same as in A. The color map represents how many times (out of 4 × 19 = 76 presentations) the effortful or risky option was chosen). C, Hyperbolic discounting curves at a group level before (red dashed line) and after (solid blue) the fitness program. The constant defining the curves (K) were significantly different (see Results for details). D, Explanatory power of effort level of the pair before (red) and after (blue) the plan, displayed as mean predictive margins (bars are 95% confidence intervals). Note that the slope is higher before than after the plan, reflecting a loss of explanatory power of effort on decisions after habit acquisition. E, Boxplot and individual values of the number of times that the high probability option was chosen in the in-scanner task before and after the plan. This number significantly increased after the intervention, confirming a decrease in the devaluating role of effort. F, In turn, the decrease in effort discounting (hyperbolic K) estimated with the out-of-scanner task significantly correlated with the increase in the selection of the higher probability option in the in-scanner task, which confirms a generalized attenuation of effort discounting.

effort was chosen); (c) risk DF of the pair (explanatory variable 7 against baseline, showing voxels with enhanced activity when the option with the higher probability, i.e. lower risk, was chosen). Additionally, we hypothesized that the selection of the NRNE reward, when compared with the choice of the NRME option, would engage the nucleus accumbens (the main brain area involved in reward anticipation (Knutson and Cooper, 2005)) more strongly before than after the plan. Thus, we also tested the contrast between explanatory variables 3 and 4 (NRNE > NRME).

We hypothesized that the longitudinal effects on these variables would be significant in brain areas processing SV, effort and risk, respectively. For that reason, we restricted each analysis to the following regions of interest (ROI): (1) the SV mask included the bilateral ventromedial prefrontal cortex (Levy and Glimcher, 2012), anterior cingulate (Klein-Flugge et al., 2016), dorsomedial prefrontal cortex (Bartra et al., 2013) (also termed paracingulate) and nucleus accumbens (Christopoulos et al., 2009; Niv et al., 2007) (total ROI size: 5210 voxels, 41680 mm^3); (2) the effort mask contained the bilateral anterior cingulate (Croxson et al., 2009; Klein-Flugge et al., 2016; Kurniawan et al., 2013; Walton et al., 2003), nucleus accumbens (Botvinick et al., 2009), amygdala (Floresco and Ghods-Sharifi, 2007; Miller et al., 2013) and putamen (Kurniawan et al., 2010) (total ROI size: 2133 voxels, 17064 mm^3); (3) finally, the risk-processing analysis was restricted to the posterior parietal (Miedl et al., 2012; Peters and Buchel, 2009) and insular (Burke et al., 2013; Preuschoff et al., 2008) cortices, and the nucleus accumbens (Christopoulos et al., 2009) (total ROI size: 3520, 28160 mm^3). Longitudinal differences in the additional contrast of parameter estimates NRNE > NRME were tested within the bilateral nucleus accumbens (133 voxels, 1064 mm^3). All brain regions were delimited according to the Harvard-Oxford atlas included in FSL, and ROIs were smoothed with a 3 mm kernel to improve statistical inference.

This GLM was applied to each session and subject. Then, a fixed-effects within-subject second level was used to average all three sessions for each subject. Finally, group analyses were performed with non-parametric statistics, due to the relatively small sample size and the adequacy of this approach to minimize false positives (Eklund et al., 2016). Since we were interested in within-subject longitudinal changes, we performed paired *t*-test for each contrast of parameter estimates using the permutation-based FSL tool *randomise* (Nichols and Holmes, 2002). Variance smoothing (5 mm) was used to improve the sensitivity of inference, and correction for multiple comparisons was carried out with threshold-free cluster enhancement (Smith and Nichols, 2009), which is a cluster-wise inference method that does not depend on an arbitrary cluster forming threshold, but provides an stringent correction for multiple comparisons. Each contrast of interest was analyzed with 5000 permutations.

Changes in functional connectivity were assessed with another GLM, following the generalized psychophysiological interactions (gPPI) method (McLaren et al., 2012; O'Reilly et al., 2012). Preprocessing and artifact removal were done as explained above. With respect to the statistical analysis, our intention was to test the hypothesis that functional connectivity between the amygdala and anterior cingulate cortex would strengthen after the fitness plan (Floresco and Ghods-Sharifi, 2007). Thus, the selected seed region was the amygdala. In order to delimitate more adequately this seed region, we concentrated on those voxels functionally relevant in our task (task pairs > control), and sought for longitudinal differences (POST > PRE) in the bilateral amygdala (as defined by the Harvard-Oxford atlas; 203 voxels, 1624 mm^3). The permutation-based analysis with *randomise* revealed a significant cluster in the right amygdala. We selected the local maximum, drew a sphere of a 5-mm radius around it (with *fslmaths* tool), registered it to native space, and extracted the time series with *fslmeants* tool. This was done for each subject and session.

The gPPI model included the same 7 explanatory variables described in the previous GLM. In addition, the amygdala time series was the physiological factor, and we added one interaction term for each explanatory variable with the physiological regressor. In this case, we wanted to test whether changes in connectivity occurred during the task in a general (non-modulated) manner, or they were dependent on the effort level. Therefore, we focused the second level within-subject and the group analyses on the contrasts Task pairs > Control, and minus effort DF of the pair against the baseline. Paired t-tests were done as described above, with the *randomise* tool and the same settings. In this case, analyses were restricted to a ROI encompassing the anterior cingulate cortex, based on the Harvard-Oxford atlas, smoothed with a 3-mm kernel (923 voxels, 7384 mm^3).

2.6. *Statistical data analyses*

All statistical data analyses were done in Stata 12.1 (StataCorp LP). The main dependent variable of the behavioral effort-discounting task was the hyperbolic decaying constant K, which defines the individual discounting rate of rewards by effort. Hyperbolic and exponential curves had a similar goodness of fit. We focused on the hyperbolic function because it has received more solid support from the literature (Prévost et al., 2010). With respect to risk discounting, the exponential curve produced the best model fit, so we took c as the variable of interest. Once estimated before and after the plan as described above, we tested whether there was a decrease in its values after the plan. Due to the small sample size, we performed one-sided exact sign test. The exact sign test is used to compare the median of two paired samples, without further assumptions (Snedecor and Cochran, 1989) (by contrary, Wilcoxon test assumes that distributions are equal).

The behavioral features of the fMRI task were analyzed with a logistic mixed model, which is intended to determine what features of the task pairs guided decisions. Instead of running individual logistic regressions and averaging beta coefficients, the mixed model considers in one single model different slopes and intercepts between participants (random effects), as well as having several measures (in this case, trials) per participant. The outcome variable ('choice') was coded as 1 when the option on the right was chosen, and 0 when the one on the left was selected. There were 6840 data points in total (19 subjects × 180 task pairs × 2 time points), including 75 missing decisions. Several models were tested and the one that explained more accurately the data, based on BIC, was selected (Table 1). Note that lower BIC values indicate better goodness of fit. In order to consider the best model, we also took into account multicollinearity between regressors; thus, Variance Inflation Factor (VIF) was calculated for each model, although interaction terms were not considered in VIF estimation (Allison, 1997). We first asked whether attributes of the pair ($\text{Attribute}_{\text{right}} - \text{Attribute}_{\text{left}}$) were more reliable descriptors of decisions than features of each option: BIC values were lower for attributes of the pair. Then, we confirmed that objective effort and probability levels explained the data more adequately than estimated discounting factors (estimated with hyperbolic K for effort and exponential c for risk). However, the model improved by including SV, which assumes both discounting factors. Next, we added the interaction with a dichotomous variable (0 = PRE, 1 = POST) intended to test whether 'habit acquisition' (completion of the fitness program) had an impact on the explanatory power of SV, effort and probability. This improved the goodness of fit of all models. Finally, we added the corresponding random effects, in order to test whether the model improved by including individual intercepts and slopes for each regressor.

Besides, the number of optimal decisions (that is, when the prospect with the higher probability was chosen) was extracted before and after the plan, in order to test whether they were selected more often after the fitness program. This comparison was carried out, as described above, with one-sided exact sign test.

3. Results

Effect of physical activity plan on effort discounting. Participants' decisions in the out-of-scanner effort-discounting task were fitted to

Table 1

Bayesian Information Criteria (BIC) and Variance Inflation Factor (VIF) for model selection in the logistic mixed model. Best model (lower BIC with acceptable VIF) in bold typesetting. 'Partial' best models (according to Steps 1, 2 and 3) are framed.

	Fixed effects		Random effects		BIC	VIF
	Main effects	Interactions	Intercept	Slope		
Step 1: Attributes of each option (left and right), or attributes of the pair (right – left)?						
Step 2: Objective levels (minutes running, probabilities) or subjective valuation (DF, SV)?						
Objective levels	E(L), E(R), P(L), P(R)	No	Yes	No	7197	1.09
	ΔE, ΔP	**No**	**Yes**	**No**	**7182**	**1.16**
Subjective DF	ED(L), ED(R), RD(L), RD(R)	No	Yes	No	7560	3.08
	ΔED, ΔPD	No	Yes	No	7544	1.17
SV	SV(L), SV(R)	No	Yes	No	6720	2.60
	ΔSV	No	Yes	No	6714	–
Combining object. and subject.	ΔE, ΔP, ΔED, ΔPD	No	Yes	No	6950	16.39
	ΔE, ΔP, ΔSV	**No**	**Yes**	**No**	**6677**	**2.60**
Conclusion to Steps 1 and 2: Best model should include objective levels and SV of the pair						
Step 3: Adding interaction with 'habit' variable (0 = PRE, 1 = POST)						
	ΔE, ΔP	Habit	Yes	No	7014	2.32
	ΔE, ΔP, ΔSV	**Habit**	**Yes**	**No**	**6613**	**2.60**
Conclusions to Step 3: Interaction improves the model						
Step 4: Refining the model with random effects						
	ΔE, ΔP, ΔSV	Habit	Yes	ΔE	4538	2.60
	ΔE, ΔP, ΔSV	Habit	Yes	ΔP	4549	2.60
	ΔE, ΔP, ΔSV	Habit	Yes	ΔSV	5970	2.60
	ΔE, ΔP, ΔSV	Habit	Yes	ΔE, ΔP	4251	2.60
	ΔE, ΔP, ΔSV	**Habit**	**Yes**	**ΔE, ΔP, ΔSV**	**4022**	**2.60**
	ΔE, ΔP, ΔSV	No	Yes	ΔE, ΔP, ΔSV	4208	2.60

Steps 1 and 2 revealed that the best model should include effort and probability levels of the pair, and possibly SV of the pair, since BIC was lower than the models including individual attributes of each option. In Step 3, estimation was refined by including the interaction with 'habit' variable (before and after the physical activity plan). Goodness of fit improved when the model included individual random slopes for both fixed effects.

BIC, Schwartz Bayesian Information Criteria; E, objective effort level; ED, effort discounting factor; L, left; P, objective probability; R, right; RD, risk discounting factor; SV, subjective value; ΔED = ED(R)-ED(L); ΔE = Effort(R)-Effort(L); ΔPD = PD(R)-PD(L); ΔP = P(R)-P(L); ΔSV = SV(R)-SV(L); VIF, Variance Inflation Factor.

hyperbolic (Prevost et al., 2010), exponential (Green and Myerson, 1996), double-exponential (McKerchar et al., 2009) and parabolic (Hartmann et al., 2013) functions. When fitting each individual's behavior, and after averaging BIC values, hyperbolic, exponential and double exponential adjustments yielded similar values for effort discounting (before the plan: hyperbolic, 79.99; exponential, 78.47, double exponential, 79.96; parabolic, 109.09; after the plan: hyperbolic, 66.11; exponential, 65.97; double exponential, 70.96; parabolic, 95.88) (see Fig. 2A for a representative subject). With respect to risk discounting, the best model was produced by the exponential curve (before the plan: hyperbolic, 112.1; exponential, 89.42, double exponential, 111.0; parabolic, 79.53; after the plan: hyperbolic, 114.54; exponential, 88.81; double exponential, 105.49; parabolic, 80.67). Note that the parabolic fitting had the lowest BIC values, but we discarded this fitting because produced unrealistic behaviors for several subjects (negative subjective values for risks>75%, approximately). BIC values for all curves were similar between both time points (two-sided sign tests, all $p > 0.05$ except for double exponential (risk): $p = 0.0309$.

As hypothesized, the hyperbolic discounting constant (K) decreased after the physical activity plan: median $K_{PRE} = 0.1399$, $IQR = 0.1419$, median $K_{POST} = 0.1066$, $IQR = 0.1218$, one-sided exact sign test $p = 0.0318$. In other words, effort discounting after the plan was attenuated (Fig. 2B and C). This effect was not found for risk discounting: median $c_{PRE} = 0.0279$, $IQR = 0.0062$, median $K_{POST} = 0.0263$, $IQR = 0.0114$, two-sided exact sign test $p = 0.4807$.

In conclusion, we found an attenuation of effort discounting after completion of the fitness plan, whereas risk discounting remained unchanged.

Variables explaining decisions in the fMRI task. In order to assess the effect of habit acquisition on decisions, we designed a logistic mixed model with choice as dependent variable (1 = option on the right, 0 = left), and the attributes of the pairs of options as fixed effects (see Materials and Methods and Table 1 for a detailed justification of model selection). The best model included, as fixed effects, effort and risk level of each pair ($\mathrm{Effort}_{right} - \mathrm{Effort}_{left}$ and $\mathrm{Probability}_{right} - \mathrm{Probability}_{left}$), SV of the pair ($SV_{right} - SV_{left}$, calculated after the individual hyperbolic effort- and exponential risk-discounting factors) as well as the interaction of each regressor with a dichotomous variable coding for the assessment before and after the plan ('habit': 0 = PRE, 1 = POST) (Table 1). Besides, we included as random effects subject identification, SV, effort and probability of the pair, since we expected different intercepts between subjects and different individual slopes for each regressor. The model significantly explained the data (Wald $\chi^2(6) = 208.70$, $p < 0.0001$). In fact, the inclusion of the interaction term with the 'habit' dichotomous variable greatly improved the model (difference in Bayesian Information Criterion, $\Delta BIC = -186$). Due to technical reasons with original variables (Stata could not converge to a solution with efforts as minutes and probabilities as percentage), we coded efforts in hours and probabilities between 0 and 1. Effort and probability (fixed effects) were significant: effort of the pair: $B = -19.40$, $z = -4.90$, $p < 0.001$, 95% C.I. −27.16,-11.63; probability of the pair: $B = 16.16$, $z = 3.76$, $p < 0.001$, 95% C.I. 7.74,24.58. Remarkably, only the interaction between effort and habit was significant: $B = 7.56$, $z = 4.30$, $p < 0.001$, 95% C.I. 4.12,11.01; probability-by-habit: $B = 2.74$, $z = 1.48$, $p = 0.139$; SV-by-habit: $B = -0.17$, $z = -0.65$, $p = 0.516$. Random effects were also significant (χ^2 (4) = 2619.81, $p < 0.0001$). These results show that, overall, subjects tended to choose the option on the right when its effort level was lower, and also when its probability was higher (i.e. its risk was lower). After the fitness plan, the explanatory power of effort decreased (Fig. 2D). Therefore, as predicted, after becoming physically active, participants tended to minimize the impact of effort on their decisions.

Out of the 180 task pairs, subjects chose a median of 119 times (IQR = 80) the optimal (i.e. higher probability) option before the physical activity plan, and 145 times (IQR = 67) after the plan (Fig. 2E). This difference was statistically significant: one-sided exact sign test, $p = 0.0318$. Finally, we explored whether the behavioral effect of habit acquisition in the in-scanner task was associated with that of the out-of-scanner task. To do so, we assessed the correlation between the individual changes (POST minus PRE) in the selection of the high probability option and changes in the hyperbolic K: a significant negative correlation was found (Pearson's $r = -0.622$, $p = 0.0045$), showing that a decrement in K was associated with an increment in the selection of the most advantageous option after the plan (Fig. 2F).

Neural correlates of effort and risk valuation, and effect of the fitness plan. The General Linear Model (GLM) of our event-related fMRI analysis aimed to assess longitudinal changes in the neural correlates of SV (including both risk and effort), risk valuation and effort cost. Even though the best logistic mixed model explaining decisions included objective efforts and probabilities, we were interested in longitudinal changes of neural correlates in subjective valuation. We hypothesized that, after the physical activity plan, SV-related brain activity and effort-cost related signals would be attenuated, but risk-related neural correlates would be enhanced. Additionally, we predicted that the selection of an effortless compared with an effortful reward would be experienced as more rewarding (i.e. would elicit a stronger activation in the nucleus accumbens) before than after the plan. Neurocomputational parameters were estimated at a group level, considering all subjects and both time points. With this approach, BIC values were as follows: Effort: hyperbolic, 4777; exponential, 4740; double exponential, 4729; parabolic, 5472; Risk: hyperbolic, 4631; exponential, 3836; double exponential, 4562; parabolic, 4271. Therefore, we built regressors after the double exponential curve for effort ($\beta = 0.1192$, $\delta = 0.0395$), and the exponential for risk ($c = 0.0279$).

Thus, we first compared the explanatory variable modulated by SV of the pair (SV_{chosen}-$SV_{unchosen}$) before and after habit acquisition. This analysis was restricted to a large ROI including brain areas previously related to this signal: ventromedial prefrontal cortex (Levy and Glimcher, 2012), anterior cingulate (Klein-Flugge et al., 2016), dorsomedial frontal cortex (Bartra et al., 2013) (or paracingulate) and nucleus accumbens (Christopoulos et al., 2009). A non-parametric permutation-based paired *t*-test revealed a cluster in the anterior cingulate cortex ($p < 0.05$, small-volume corrected, $N = 19$). SV signal in this area was significantly decreased after the plan (Fig. 3A; Table 2). With respect to risk (or probability) valuation, we explored the explanatory variable modulated by RD of the pair (RD_{chosen}-$RD_{unchosen}$) in the posterior parietal cortex (Miedl et al., 2012; Peters and Buchel, 2009), insula (Burke et al., 2013; Preuschoff et al., 2008) and nucleus accumbens (Christopoulos et al., 2009). In this case, there were no significant differences ($p = 0.42$). With regards to effort costs, we sought for longitudinal changes in effort-related brain areas (anterior cingulate (Croxson et al., 2009; Klein-Flugge et al., 2016; Kurniawan et al., 2013; Walton et al., 2003),

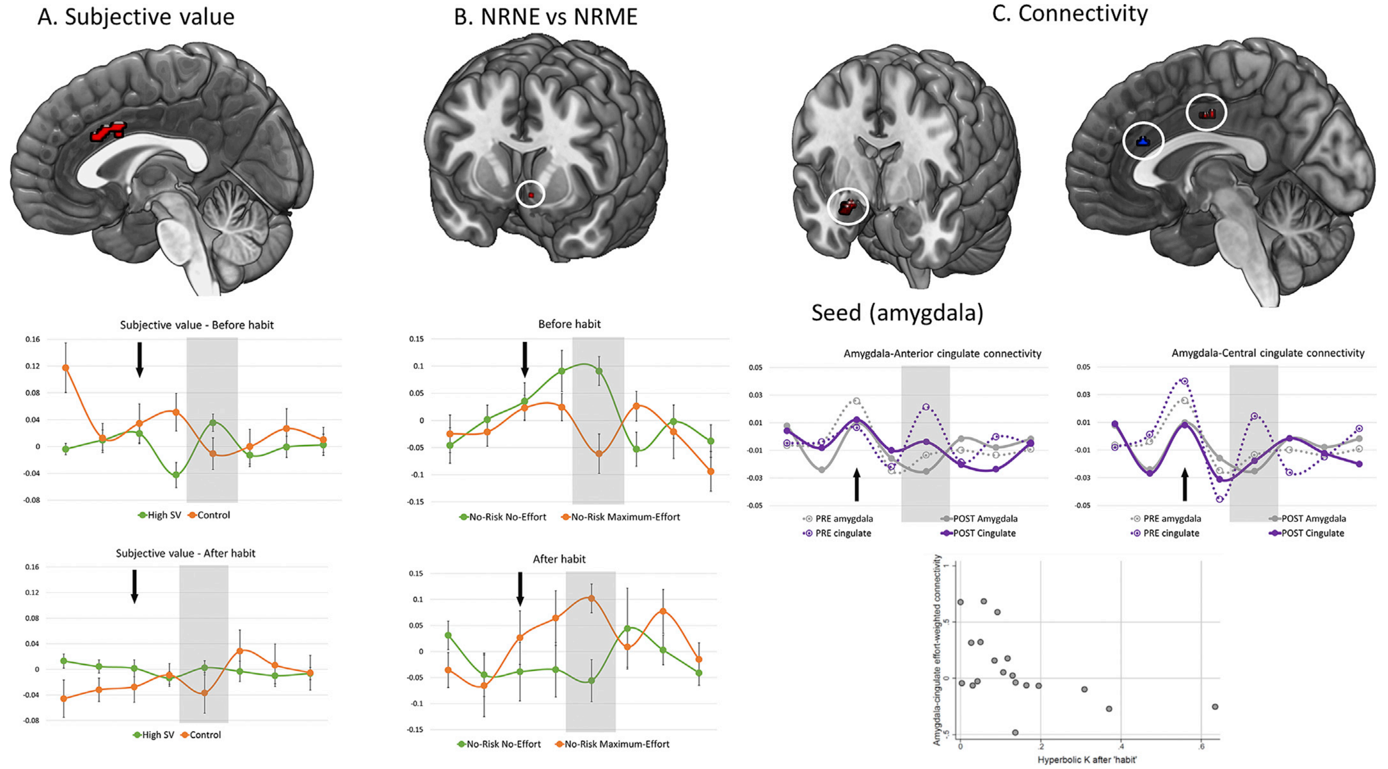

Fig. 3. Effort-based brain activity and functional connectivity are reconfigured after habit acquisition

Fig. 3**. Neuroimaging results.** A, A cluster in the anterior cingulate cortex tracked the SV of the pair before, but not after, the plan (thresholded at $p < 0.05$, small volume corrected for an ROI including the ventromedial and dorsomedial frontal cortex, anterior cingulate and nucleus accumbens, $N = 19$). Line graphs at the bottom depict peristimulus plots averaged (mean and standard error of the mean) for all subjects and events including a high SV of the pair (>median, in green), and for control events (in orange). The black arrow indicates stimulus onset, and the shaded area corresponds to approximately 5–8 s after the onset, when the peak in the BOLD signal due to the stimulus is expected. Time points are consecutive volumes (TR = 3 s). Before the plan, the cluster in the anterior cingulate discriminated high SV from control trials, but this distinction was lost after the plan. B, NRNE > NRME contrast, before and after the plan (PRE > POST), revealed a cluster in the left nucleus accumbens (thresholded at $p < 0.05$, small volume corrected for an ROI including the bilateral nucleus accumbens, $N = 19$). This suggests that, whereas the effortless option (compared with the effortful option) was perceived as rewarding before the plan, this was inverted after the plan: peristimulus plots reveal a peak in the accumbens' BOLD signal during effortful events after the plan. C, Connectivity between the amygdala and anterior cingulate was strengthened after the plan for effort-related pairs. The seed region (left) was selected from the comparison Task > Control, POST > PRE ($p < 0.05$, small volume corrected for the bilateral amygdala, $N = 19$). The gPPI model revealed two clusters: 1) one in the anterior cingulate ($p < 0.05$, small volume corrected for the anterior cingulate, $N = 19$), where interaction with amygdala strengthens in all task (effort-related) pairs vs control pairs; 2) a cluster in the central cingulate (posterior aspects of the anterior cingulate) ($p < 0.05$, small volume corrected for the anterior cingulate, $N = 19$), which was modulated by the effort cost of the pair (stronger connectivity for pairs involving a higher effort cost). Peristimulus plots reveal a synchronized activity between the amygdala and the cluster in the anterior cingulate during task pairs after (solid lines), but not before (dotted lines), the plan. Similarly, activity was synchronized between the amygdala and the cluster in the central cingulate after the plan in task pairs with a high effort cost (>75th percentile). On the bottom part, the scatterplot plot shows that those subjects with a lower hyperbolic K after the plan (i.e. lower effort discounting) had a stronger amygdala-central cingulate connectivity ($N = 19$). Note that Y-axis scaling in peristimulus plots is different for A, B and C to improve interpretability of data, but it is unchanged to compare 'before' and 'after' conditions in each section of the figure.

Table 2
Significant clusters and local maxima of the contrasts of parameter estimates.

Cluster		Voxels	p	Coordinates (X,Y,Z)	Area
SV, PRE > POST (ROI 1)					
1		37	0.032	0,20,30	Anterior cingulate
	1.1	$t = 4.43$		0,8,34	Anterior cingulate
Effort cost, PRE > POST (ROI 2)					
1		17	0.052	0,20,30	Anterior cingulate
	1.1	$t = 3.24$		0,20,30	Anterior cingulate
2		10	0.052	2,10,30	R Anterior cingulate
	2.1	$t = 3.31$		0,8,34	Anterior cingulate
NRNE vs NRME, PRE > POST (Bilateral nucleus accumbens)					
1		1	0.044	−6,8,-10	L Accumbens
	1.1	$t = 3.30$		−6,8,-10	L Accumbens
gPPI seed selection: Task vs Control, POST > PRE (bilateral amygdala)					
1		20	0.007	24,0,-18	R Amygdala
	1.1	$t = 3.50$		24,0,-18	R Amygdala
gPPI: Amygdala seed, POST > PRE, modulated by effort cost (ROI 3)					
1		7	0.049	2,-8,38	R Anterior cingulate
	1.1	$t = 3.22$		2,-8,38	Anterior cingulate
gPPI: Amygdala seed, POST > PRE, Task vs Control (ROI 3)					
1		6	0.038	0,28,22	Anterior cingulate
	1.1	$t = 3.53$		0,28,22	Anterior cingulate
2		2	0.05	2,16,30	R Anterior cingulate
	2.1	$t = 3.28$		2,16,30	R Anterior cingulate

All results are small volume corrected for the indicated bilateral regions-of-interest (ROIs; see Results and Materials and Methods for details).
ROI 1: ventromedial prefrontal cortex, anterior cingulate, dorsomedial frontal cortex, nucleus accumbens.
ROI 2: anterior cingulate, amygdala, nucleus accumbens, putamen.
ROI 3: anterior cingulate cortex.
Coordinates are in MNI standard space, and brain areas are labeled according to the Harvard-Oxford atlas included in FSL. gPPI, generalized psychophysiological interaction; L, left; NRME, no-risk maximum-effort pair; NRNE, no-risk no-effort pair; R, right; SV, subjective value of the pair ($SV_{CHOSEN} - SV_{UNCHOSEN}$).

amygdala (Floresco and Ghods-Sharifi, 2007; Miller et al., 2013), nucleus accumbens (Botvinick et al., 2009) and putamen (Kurniawan et al., 2010)) for the explanatory variable inversely modulated by ED of the pair [– (ED_{chosen}-$ED_{unchosen}$): increased BOLD signal for pairs where the higher effort was chosen]. A cluster was found in the anterior cingulate for the comparison PRE > POST at a marginal level ($p = 0.052$, small-volume corrected, $N = 19$), showing that the participation in the physical activity plan decreased effort-cost related signals in this brain region (Table 2).

Finally, we compared the NRNE vs NRME contrast before and after the plan. Since there is a solid literature about the nucleus accumbens coding for reward anticipation (Knutson and Cooper, 2005), we restricted the analysis to this brain area. As hypothesized, we found significant differences in the left accumbens, where the contrast of parameter estimates was higher before than after the plan ($p < 0.05$, small-volume corrected, $N = 19$). This confirms that, while being sedentary, the secured effortless reward is perceived as more rewarding than the secured effortful option; however, this distinction is attenuated after the plan, possibly due to the reduction in the cost of effort when an active lifestyle is adopted (Fig. 3B; Table 2).

Functional connectivity after habit acquisition. Previous animal research demonstrated that an intact connectivity between the amygdala and anterior cingulate cortex is required to overcome higher efforts in exchange for larger rewards (Floresco and Ghods-Sharifi, 2007). Hence, we hypothesized that connectivity between these two brain areas in our decision making task would be stronger after the physical activity plan. To test this, we designed a generalized psychophysiological interaction (gPPI) model (McLaren et al., 2012) that included the BOLD signal in the amygdala ('seed' region) as physiological regressor, the same explanatory variables as in the previous GLM as psychological regressors, and the interaction between the physiological and each of the psychological regressors as PPI terms. We sought for changes in connectivity in two conditions: 1) stronger connectivity in task pairs with respect to the control condition; and 2) during task pairs, modulated by the effort cost of the pair [–(ED_{chosen}-$ED_{unchosen}$): stronger connectivity when the option with the higher effort was selected. The seed area was selected from the previous GLM as those voxels within the amygdala (ROI including both amygdalin complexes) with a higher activation after the plan (POST > PRE) in the task vs control contrast ($p < 0.05$, small volume corrected, $N = 19$). This comparison revealed a local maximum at coordinates 24, 0, −16 (Fig. 3D; Table 2). A 5 mm sphere was drawn around this peak, excluding voxels outside the amygdala and registered to native space. Finally, time course from this seed region was extracted for each subject and session.

Since we had a strong hypothesis about changes in connectivity between the amygdala and anterior cingulate cortex, as reported by Floresco and Ghods-Sharifi, we restricted the analysis to an ROI including the anterior cingulate. The fMRI paired *t*-test revealed two clusters of stronger connectivity with the amygdala after the plan (POST vs PRE) for the two conditions we tested: 1) in the anterior part of the ROI ($p < 0.05$, small-volume corrected, $N = 19$), where connectivity with amygdala was stronger in effort-related decisions than in control pairs; 2) in the posterior part of the ROI (central cingulate): since this analysis used –ED of the pair as psychological regressor, the results indicate that the amygdala-central cingulate interaction after the plan is specifically stronger when the higher effort option was chosen (Fig. 3C; Table 2). In addition, we asked whether connectivity strength between these two brain areas (amygdala and central cingulate) was associated with hyperbolic K after the fitness plan. The scatterplot (Fig. 3C) revealed a possible non-linear monotonic relationship between the variables, which was confirmed by Spearman's test: $\rho = -0.6491$, $p = 0.0026$; $N = 19$.

4. Discussion

According to the theory of value-based decision making, agents subjectively assign values to the options presented, and select the one with the highest utility (Glimcher, 2013). Subjective valuation depends on the rewarding features of the object, but also on the intrinsic costs that the subject has to overcome to obtain it (Wallis and Rushworth, 2013). Whereas a plethora of research has studied the neural signatures of reward valuation, its costs and the integration of both, there was a lack of knowledge about how these neural signatures are affected when there is a naturalistic change in cost processing, for example, as a consequence of a change in lifestyle. Here, we show that the completion of a 3-month mild physical activity program attenuates effort cost in an ecological decision-making task, and this intervention is associated with a change in neural patterns when facing effort-related economic decisions: value- and effort-related signals decrease, whereas interaction between the amygdala and anterior cingulate strengthens.

Previous research has revealed which brain areas are engaged in detecting effort costs, overcoming them to obtain a larger reward, assigning values to effortful prospects and also the integration of effort with other discounting factors, such as risk. For instance, Croxson et al. revealed for the first time in humans the integration of secondary rewards and effort costs ('net value', calculated by the authors as reward divided by effort level) in the anterior cingulate cortex, ventral striatum and midbrain (Croxson et al., 2009). Prevost and colleagues reported that the anterior cingulate and insula code effort costs (increased BOLD signal for higher effort levels), rather than effort-related SV (Prevost et al., 2010). On the other hand, Kurniawan et al. found that the putamen may be involved in effort valuation, since it showed greater activity when selecting a low effort compared with an effortful option (Kurniawan et al., 2010). Later, these authors showed that the anterior cingulate, supplementary motor area (SMA) and dorsal putamen were more active in anticipation of high effort (Kurniawan et al., 2013). In a recent contribution, Klein-Flügge and colleagues found that the cingulate and nearby cortical regions (such as SMA) are involved in effort-related valuation and coding effort costs (Klein-Flugge et al., 2016). Finally, Burke et al. also found that the central cingulate and SMA processed effort costs, and that the frontal pole participates in the integration of risk and effort when both discounting factors are simultaneously presented (Burke et al., 2013). The tasks included in all these works and other contributions on the neural signature of physical effort involve an immediate manual effort, usually a hand grip or continuous button press (cancelling squares on screen). To our knowledge, the ecological validity of these tasks (i.e. their relationship with actual effort discounting in naturalistic conditions) has not been demonstrated. Since our main interest was to assess changes in effort processing after a change in lifestyle, we designed an effort-related paradigm following the general schema of discounting tasks in neuroeconomics (Green and Myerson, 2004; Kable and Glimcher, 2007; Peters and Buchel, 2010, 2009; Scheres et al., 2006), but including a prospective and sustained effort: minutes running on a treadmill. In our previous research, we showed that individual discounting constants correlate with an indicator of sedentary lifestyle (Bernacer et al., 2016). It could be argued that, since effort is presented as minutes, we could be assessing temporal instead of effort discounting. However, participants were aware that they would receive the reward during the following week, irrespective to the chosen effort level. Thus, an effect of temporal discounting can be ruled out. Also, it must be considered that rewards, efforts and risks in the out-of-scanner tasks were hypothetical, so participants could behave differently than if rewards were real. Previous research has demonstrated that discounting behavior is similar for hypothetical and real rewards (Johnson and Bickel, 2002; Madden et al., 2004). Furthermore, our results show a similar behavior between the out-of-scanner and in-scanner task, where rewards, efforts and risks were real (Fig. 2F). The behavioral results reported here confirm the ecological validity of our approach, since effort discounting (parameterized as hyperbolic K) decreased after performing habitual physical exercise. This effect was present for effort, but not for risk discounting. Apart from effort discounting, other research has proposed a relationship between temporal (Hosking et al., 2017; Manning et al., 2014; Story et al., 2014) or risk discounting (Herman et al., 2018; Scheres et al., 2006), and different personality traits or lifestyles. Hence, our research contributes to tighten the link between laboratory paradigms and naturalistic behavior.

Our neuroimaging results confirm the role of the anterior cingulate cortex in effort processing, specifically coding SV, effort costs, and acting in synchrony with the amygdala to overcome high efforts to obtain larger rewards. Since our task presented volunteers with two options, we opted to code SV, RD and ED as the difference between the chosen and unchosen option, as previous research (FitzGerald et al., 2009; Klein-Flugge et al., 2016). There is an ongoing debate about the main role of the anterior cingulate in coding either the relative value of foraging (Kolling et al., 2012; Shenhav et al., 2016) or the expected value of control (the flexible adjustment of behavior to favor goal pursuing instead of 'automatic' performance that move away from them) (Shenhav et al., 2014). In a nutshell, the former view proposes that activity in this brain area help the subject to interpret the environment's resources, and to weigh whether an alternative –other than the 'default' option– should be pursued. However, the latter argues that the primary function of the cingulate is to signal "those [situations] that require processes that are complex, deliberate, novel, and/or exploratory versus habitual and/or externally driven" (p. 1287) (Shenhav et al., 2016). Even though proposing a holistic theory for the dorsal anterior cingulate is well beyond the scope of this text, we contribute to this debate by showing that, before the plan, its activity is higher when the effort cost of the chosen option is larger than that of the unchosen one; however, after the plan this signal is attenuated. In other words, when costs are behaviorally relevant and considering efforts may compromise the agent's wellbeing, it becomes a 'complex process'; by contrary, when the subject has habituated to physical efforts and costs are reduced, the trade-off between effort and probability may be a 'habitual process', irrespective of the chosen option. The strengthened link with the amygdala after the plan, modulated by the effort cost of the decision in the central cingulate, and for all task pairs in the most anterior part, points to the consolidation of a network that promotes motivation of effortful behaviors, as previous research has suggested (Holroyd and Yeung, 2012); however, to our knowledge, this is the first time to be shown in human longitudinal studies.

As a possible neurobiological mechanism, at a merely speculative level, dopamine has been reported to underpin subjective valuation in general, effort-discounting in particular, and habitual physical exercise. More precisely, a 6-week physical activity intervention (wheel running) in rodents enhanced dopaminergic nigrostriatal facilitation of the direct pathway (Foley and Fleshner, 2008). An increase in nigroprefrontal and nigrostriatal dopaminergic transmission has also been reported in effort-related motivation in humans (Studer and Knecht, 2016). Recent research on rodents reveals that mesolimbic projections to the nucleus accumbens signal both subjective valuation and motivation (Hamid et al., 2016). The effort-related and SV decreased signals that we report after intervention are compatible with an enhanced dopaminergic release from the midbrain to the cortex, since previous research has demonstrated that an increase in tonic dopamine release may reduce the sensitivity to subtle changes in phasic release (Bernacer et al., 2013; Knutson et al., 2004), which is the most plausible source of SV-related signals in the cortex and nucleus accumbens. Finally, it has been suggested an interplay between amygdala/anterior cingulate activity, and dopamine in the nucleus accumbens as a crucial network underpinning effort-related behavior (Salamone et al., 2012).

One limitation of our study is the absence of a control group in the neuroimaging experiments. Without it, those results showing attenuation of brain signals (in particular, SV and effort cost) could be due to the well-known fMRI signal adaptation over time (Larsson et al., 2016). Considering this, SV, effort cost and reward-related (NRNE > NRME) signals would be attenuated after the fitness plan just because of the repeated exposition to the same stimuli, and not as a consequence of the plan per se. Given our results, however, not all brain signals were attenuated in the second time point. For example, task-related activity in the amygdala was enhanced, and BOLD signal in the nucleus accumbens was boosted in the NRME condition (Fig. 3B, bottom). In any case, a mixed-ANOVA design with a control group would clarify whether changes were due to repetition effects or the behavioral intervention, and remains for future investigation.

Our research attempts to tackle the study of human habits from a different perspective. In the neuroscientific literature, habits are commonly understood as rigid, automatic and unconscious behaviors that, once triggered, are inevitably completed (for example (Smith and Graybiel, 2016)). This view, based on animal research (Dickinson, 1985), solidly accounts for part of the complex diversity of human habitual performance. From a holistic point of view, human habits are also subjective dispositions that incline agents to certain behaviors or decisions (Bernacer, 2018; Bernacer et al., 2014; Bernacer and Murillo, 2014), and may end up in a more profitable performance according to the agent's current goals. For example, skills such as playing piano can be understood as technical habits, inasmuch as they are based on learned motor routines that, if correctly acquired, increase a flexible performance. In the present research, we investigate the acquisition of a behavioral habit, namely switching from a sedentary to an active lifestyle. It is important to note that this 'change in lifestyle' could not be generalizable to all effort-related behavior of the participants that took part in the study: it is unknown whether they, for example, used more frequently the stairs rather than the elevator, or walked more frequently than before the intervention. Also, we did not follow up their lifestyle after completion of the project, so we do not know whether behavioral and neural changes were long-lasting. However, we consider that they experienced a 'change in lifestyle' because, in terms of the GPAQ assessment, they moved from being sedentary to physically active. We have operationalized the impact of this 'lifestyle change' as an attenuation in effort discounting, and have demonstrated new patterns of neural activity associated to that behavioral change. Thus, we contribute to the study of 'human habits' from a holistic perspective, beyond the neural bases of automation or behavioral rigidity.

5. Conclusions

Our study shows for the first time longitudinal changes in value-based-related neural signals after a physical activity intervention. New activity patterns in the anterior cingulate cortex and its functional connectivity with the amygdala were associated with effort-based behavioral changes after the fitness program. These findings may have clinical importance in future research, since the difficulty to overcome efforts are behind pathological conditions such apathy (Bonnelle et al., 2016), avolition (Assadi et al., 2009) or akinetic mutism (Holroyd and Yeung, 2012). Further, stimulation of the anterior cingulate-amygdala network may be an interesting target to promote the acquisition of beneficial behavioral habits, such as regular physical exercise.

Conflicts of interest

None of the authors has financial or intellectual competing interests to declare.

Code and data availability

Anonymized data of the out-of-scanner and in-scanner task are available in Github (https://github.com/jbernacer/Bernacer_et_al_longitudinal_effort). Matlab codes and Stata logs are also available in Github. Unthresholded statistical maps, as well as ROIs, are available in Neurovault (https://neurovault.org/collections/4692/). Other data is available from the corresponding author upon reasonable request.

Author contributions

JB conceived the research, conducted the experiments, analyzed data and wrote the manuscript. IMV conducted the experiments. MM defined the fMRI protocol and conducted the experiments. NP, EL and DRC conducted the experiments. MAP conceived the research, conducted the experiments and wrote the manuscript. All authors revised and suggested improvements to initial drafts of the text.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116181.

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