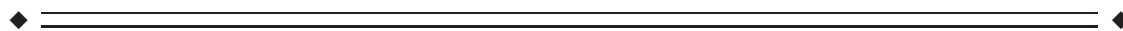


Prefrontal D2-Receptor Stimulation Mediates Flexible Adaptation of Economic Preference Hierarchies

Thilo van Eimeren,^{1,2} Ji H. Ko,^{1,2} Giovanna Pellechia,^{1,2} Sang S. Cho,^{1,2}
Sylvain Houle,¹ and Antonio P. Strafella^{1,2*}

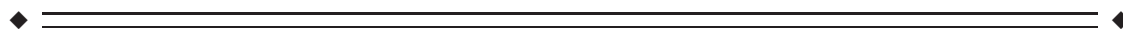
¹Department of Psychiatry, PET Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada

²Toronto Western Research Institute, Division of Brain, Imaging and Behaviour—Systems Neuroscience, BIB-SN, University Health Network, University of Toronto, Ontario, Canada



Abstract: Advantageous economic decision making requires flexible adaptation of gain-based and loss-based preference hierarchies. However, where the neuronal blueprints for economic preference hierarchies are kept and how they may be adapted remains largely unclear. Phasic cortical dopamine release likely mediates flexible adaptation of neuronal representations. In this PET study, cortical-binding potential (BP) for the D₂-dopamine receptor ligand [¹¹C]FLB 457 was examined in healthy participants during multiple sessions of a probabilistic four-choice financial decision-making task with two behavioral variants. In the *changing-gains/constant-losses* variant, the implicit gain-based preference hierarchy was unceasingly changing, whereas the implicit loss-based preference hierarchy was constant. In the *constant-gains/changing-losses* variant, it was the other way around. These variants served as paradigms, respectively, contrasting flexible adaptation versus maintenance of loss-based and gain-based preference hierarchies. We observed that in comparison with the *constant-gains/changing-losses* variant, the *changing-gains/constant-losses* variant was associated with a decreased D₂-dopamine receptor-BP in the right lateral frontopolar cortex. In other words, lateral frontopolar D₂-dopamine receptor stimulation was specifically increased during continuous adaptation of mental representations of gain-based preference hierarchies. This finding provides direct evidence for the existence of a neuronal blueprint of gain-based decision-making in the lateral frontopolar cortex and a crucial role of local dopamine in the flexible adaptation of mental concepts of future behavior. *Hum Brain Mapp* 34:226–232, 2013. © 2011 Wiley Periodicals, Inc.

Key words: dopamine; feedback-learning; frontopolar; FLB; imaging; gambling



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Thilo van Eimeren is currently at Christian-Albrechts University, Functional Imaging Team, Department of Neurology, Schleswig-Holstein University Hospital, Kiel, Germany.

*Correspondence to: Antonio P. Strafella, Toronto Western Hospital and Research Institute and CAMH-PET Centre, Toronto, ON,

Canada. E-mail: antonio.strafella@uhnres.utoronto.ca or antonio.strafella@camhpet.ca

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INTRODUCTION

Which is the lesser evil? Which grass is greener? In every day decision making, our preference is often based on differences in expected losses or gains. According to economic science [Machina, 1987], financial preference hierarchies can be formally expressed as a rank order of positive or negative expected values (+EV; -EV; e.g., $+EV_{\text{action A}} > +EV_{\text{action B}} > \dots$ or $-EV_{\text{action A}} < -EV_{\text{action B}} < \dots$). Hence, the capability to form and adapt cortical representations of gain-based and loss-based preference hierarchies critically depends on the ability to integrate and relate positive and negative expected values of multiple alternative actions. Therefore, it would appear that high-level associative areas of the prefrontal cortex—interconnected with limbic, attentional, and memory networks—are particularly apt for this task. Yet, exactly where gain- or loss-based preference hierarchies are cortically represented and how adequate adaptation of those blueprints is taking place remains largely unclear.

Prior research in this domain primarily used a four-deck card game called the Iowa Gambling Task (IGT), which was devised to mimic real-life human decision-making with uncertain financial outcomes [Bechara et al., 1994]. The specific implicit goal of this task is to overcome a preference of decks that are associated with higher gains, yet even higher losses, thus resulting in a net loss. Advantageous decision making in the IGT further demands shifting preference toward decks offering lower gains, yet even lower losses, resulting in a net gain. Functional imaging studies using the IGT frequently found that activation of the ventro-medial prefrontal (vmPFC) was predictive of good performance in this task [Christakou et al., 2009; Lawrence et al., 2009; Northoff et al., 2006]. Moreover, patients with lesions of the vmPFC tend to persevere the decks with high gains but net losses [Bechara et al., 1994]. Generally speaking, research using the IGT supports a specific role of the vmPFC in updating mental representations of loss-based preference hierarchies in decision making. However, as to which cortical area contains such a mental blueprint of gain-based preference hierarchies is much less clear and may in fact not be answered by using the IGT. Indeed, recent evidence stemming from functional imaging studies using different tasks points toward a specific role of the lateral frontopolar cortex (IFPC, lateral Brodmann area 10) in signaling choice preference in gain-based decision making [Boorman et al., 2009; Roiser et al., 2010].

It is widely accepted that prefrontal dopaminergic stimulation generally plays a crucial role in the flexible adaptation of behavior [Cools and Robbins, 2004; Durstewitz and Seamans, 2008]. Although not unanimously [Euteneuer et al., 2009; Turnbull et al., 2006], studies in patients with Parkinson's disease or Schizophrenia have found impaired performance in loss-based decision making that was unbiased by working-memory deficits, thus pointing toward an interference of dopamine with vmPFC function

[Kobayakawa et al., 2008; Mimura et al., 2006; Pagonabarraga et al., 2007; Perretta et al., 2005; Rossi et al., 2010; Sevy et al., 2007; Shurman et al., 2005]. An increasingly influential theory of prefrontal cortex dopaminergic function formulates a specific role of cortical D2 receptor stimulation in the adaption of cortical representations [Cohen et al., 2002; Durstewitz and Seamans, 2008]. A high level of D2 receptor stimulation is thought to favor flexible adaptation of cortical representations. In contrast, a low level of D2 receptor stimulation likely stabilizes cortical representations leading to robust maintenance of the status quo [Cohen et al., 2002; Durstewitz and Seamans, 2008].

In this study, our goal was to investigate prefrontal dopaminergic stimulation during gain- and loss-based decision-making using similar behavioral tasks during PET using [^{11}C]FLB 457, a chemical compound with great affinity for D2 receptors, which allows evaluation of extrastriatal dopamine release [Aalto et al., 2005]. Consequently, we felt it desirable to use a "two-way" IGT of sorts. Therefore, we derived two variants of a novel four-deck card game. In the *changing-gains/constant-losses* variant, mean gain-based differences between decks were continuously changing, whereas mean loss-based differences were kept constant. In the *constant-gains/changing-losses* variant, it was the other way around. Hence, these variants served as behavioral paradigms, which mutually contrasted a continuously high demand for flexible adaptation of mental representations (e.g., *changing-gains*) with a rapidly decreasing demand to adapt mental representations (e.g., *constant-gains*) of the gain-based and loss-based preference hierarchy.

We hypothesized that continuous adaptation of mental representations of loss-based preference hierarchies would be associated with a relatively increased level of D2 receptor stimulation (i.e., release of dopamine) in the vmPFC. In contrast, we hypothesized that continuous adaptation of mental representations of gain-based preference hierarchies is coupled with higher levels of D2 receptor stimulation (i.e., release of dopamine) in the IFPC. These hypotheses were tested using [^{11}C]FLB 457 PET in a within-subject repeated measures design across eight healthy individuals.

MATERIALS AND METHODS

Participants

Eight right-handed healthy male college students (age, 21 ± 1.3 , years of college education, 2 ± 1.2) participated in the study after being recruited by advertisement. Exclusion criteria were recent illicit substance use, known psychiatric or neurological disorder or first-degree relatives diagnosed with one, and medical disorder likely to lead to cognitive impairment. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the Research Ethics

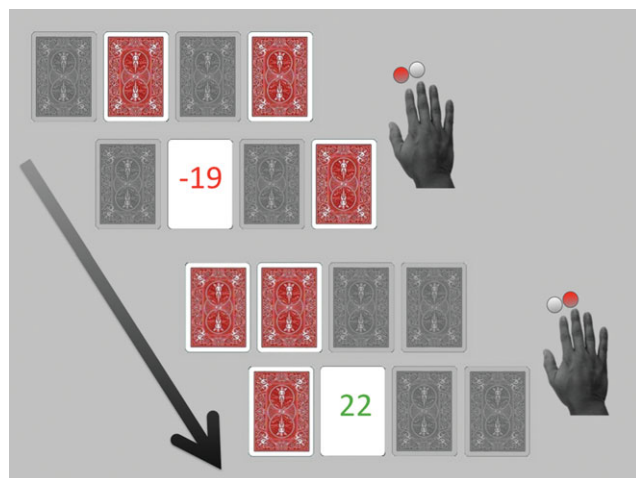


Figure 1.

Basic structure of the probabilistic financial decision-making task. Each turn, two random stacks were shaded and two remained available. Participants had to pick one stack by pressing one of two buttons. After pressing the button, the selected card flipped and revealed the return value for this trial.

Committees for the Centre for Addiction and Mental Health of the University of Toronto.

Behavioral Task

Basic task structure.

Participants performed a four-deck card game involving monetary gains and losses, which required choosing cards from a horizontal array of four stacks, so as to maximize payout. Defining a pseudo-randomized implicit hierarchy of stacks, there was a difference in average net return value between one stack and the next best in the implicit hierarchy. Each turn, two random stacks were shaded and the other two remained available (see Fig. 1). Using their right hand, participants had to pick one of the two available stacks by pressing one of two buttons. Not pressing a button within 4 s resulted in a “penalty buzz” and a penalty of 100 Canadian cents. After pressing the button, the selected card flipped and revealed the return value for this trial (ranging from -40 to $+40$ Canadian cents). To maximize payout, participants had to learn the implicit hierarchy and pick a card from the stack with the higher average net return value (correct choice). Participants were advised that each stack contained an equal number of winning and losing cards (0.5 probability of picking a winning or a losing card for every stack), but that average positive or negative return values could differ between stacks. Across the experiment, all four stacks were available in similar frequencies. We decided to gray out two stacks, so

that participants were forced to continuously explore stacks and “retest” the validity of a preliminary hierarchy.

Behavioral variants.

Two variants were performed on separate days (with 6.7 ± 7 days in between) in a counterbalanced order. In the *changing-gains/constant-losses* variant (Fig. 2, left column), the relative difference between two stacks with respect to positive return values (i.e., rank in gain-based hierarchy) was continuously changing, whereas the relative difference with respect to negative return values (i.e., rank in loss-based hierarchy) was kept constant. In the *constant-gains/changing-losses* variant, it was the other way around (Fig. 2, right column).

The resulting respective differences in average net return value—which defined the implicit hierarchy—were the same for both variants. A series of nine sessions per variant was performed on separate days, in counterbalanced order. Each session consisted of 150 trials. Between sessions, there was a fixed pause of 90 s during which the participants were told to close their eyes and wait for a warning sound announcing the imminent start of the next session.

Performance-based adaptation of task difficulty.

To minimize individual differences in learning performance, we established an algorithm to adapt task difficulty to performance (number of trials to learning criterion) during the experiment. The learning criterion was defined as 27 correct choices in 30 consecutive trials for all variants. We prepared 12 difficulty levels for each session by varying the respective differences in average net return value between one deck and the next best in the implicit hierarchy. Participants started with an intermediate level. If the learning criterion was met in the first 100 trials, difficulty level increased by 1. If the learning criterion was met in the last 50 trials, the level stayed the same for the next session. If the learning criterion was never met, difficulty level decreased by 1.

After they completed the experiment for each day, participants had to rate the following items on a visual analogue scale: liking of the experiment, performance, reliance on negative return values, reliance on positive return values, and confidence of having learned the correct hierarchy. Rating results are found in Supporting Information Figure S1.

Positron Emission Tomography

PET scans were obtained with a high resolution PET CT, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN) operating in 3D mode with an in-plane resolution of ~ 4.6 mm full width at half-maximum. To minimize participant’s head movements in the PET scanner, we used a custom-made thermoplastic facemask together with a head-fixation system (Tru-Scan Imaging,

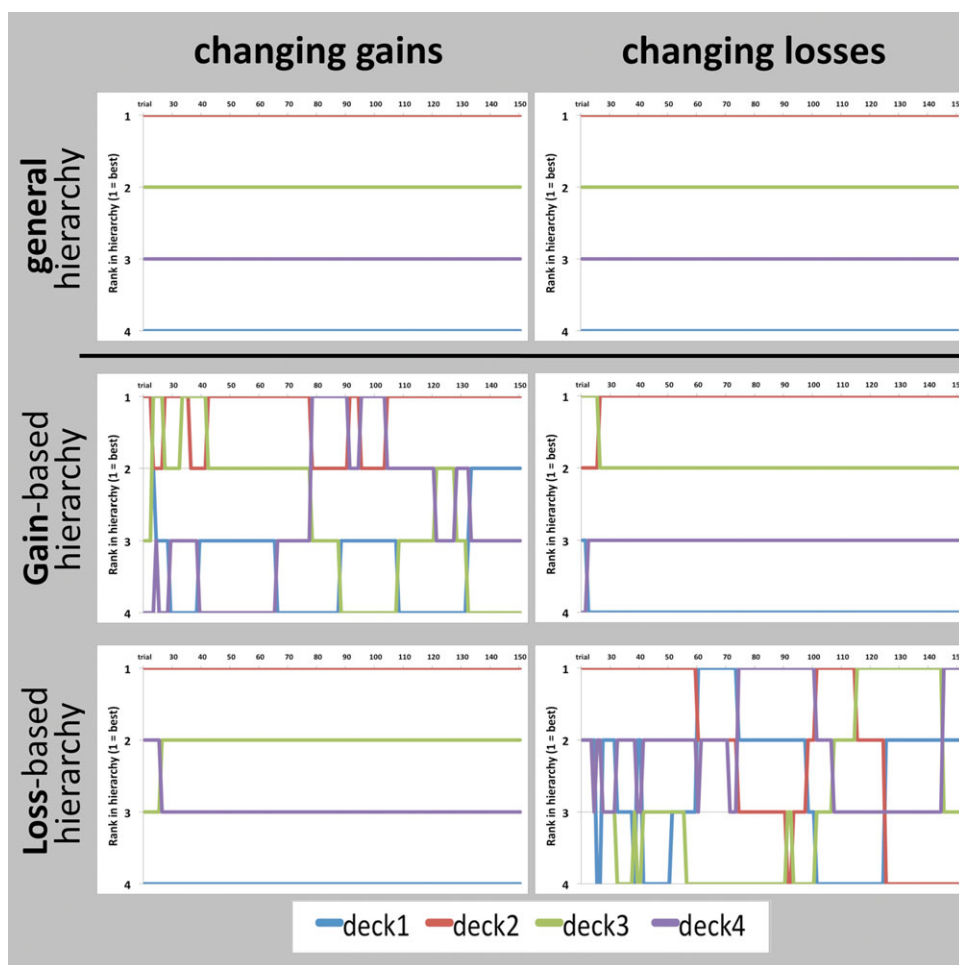


Figure 2.

Behavioral variants of the task. Exemplary data from single sessions. The general general hierarchies (top row) were constant and the same for both variants. *Left column:* In the *changing-gains* variant, the rank of a certain deck in the gain-based hierarchy (middle row) was unceasingly changing, whereas the rank in the loss-based hierarchy (bottom row) was constant. *Right column:* In the *changing-losses* variant, it was the other way around.

Annapolis). Before each emission scan, following the acquisition of a scout view for accurate positioning of the participant, a low dose (0.2 mSv) CT scan was acquired and used for attenuation correction.

[¹¹C]FLB 457 (half-life: 20.4 min) was injected into the left antecubital vein over 60 s, and emission data were then acquired over a period of 90 min in 15 one-minute frames and 15 five-minute frames [Olsson et al., 2004]. The injected amount was 10 ± 0.5 mCi for the *changing-gains/constant-losses* variant; 10 ± 0.6 mCi for the *constant-gains/changing-losses* variant.

High-resolution MRI (GE Signa 1.5 T, T1-weighted images, and 1-mm slice thickness) of each participant's brain was acquired and transformed into standardized stereotaxic space using nonlinear automated feature-matching

to the MNI template [Collins et al., 1994; Robbins et al., 2004]. PET frames were summed, registered to the corresponding MRI, and transformed into standardized stereotaxic space using the transformation parameters of the individual structural MRIs [Collins et al., 1994; Robbins et al., 2004]. Voxelwise [¹¹C]FLB 457 binding potential (BP) was calculated using a simplified reference tissue (cerebellum) method [Gunn et al., 1997; Lammertsma and Hume, 1996; Sudo et al., 2001] to generate statistical parametric images of change in BP [Aston et al., 2000]. This method uses the residuals of the least-squares fit of the compartmental model to the data at each voxel to estimate the standard deviation of the BP estimate. The individual level of feedback-learning was included in the statistical model (general linear model) as nuisance variables

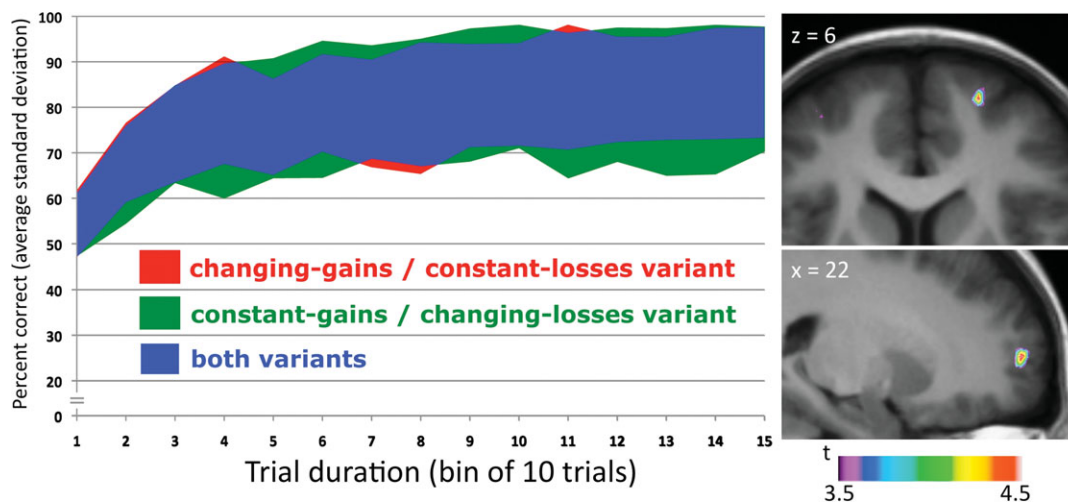


Figure 3.

Results. The graph on the left depicts the learning curves for both variants of the task, that is, average standard deviation of percent correct choices (vertical axis) per bin of 10 trials (horizontal axis). The pictures on the right show statistical parametric maps of the change in [¹¹C]FLB 456 BP overlaid upon a transverse (top) and a sagittal (bottom) section of the average

MRI of all subjects in standardized stereotaxic space. The performance of the *changing-gains/constant-losses* variant was associated with decreased [¹¹C]FLB 457 BP (i.e., increased dopamine release) in the right IFPC ($x = 22, y = 60, z = 6; t = 4.62; P < 0.05$ corr.) compared to the *constant-gains/changing-losses* variant.

[Gschwandtner et al., 2001]. Parametric images of [¹¹C]FLB 457 BP were smoothed with an isotropic Gaussian of 6-mm full width at half-maximum to accommodate for inter-subject anatomical variability. A threshold level of $t > 4.5$ was considered significant (t -test, $p < 0.05$, two-tailed) corrected for multiple comparisons [Friston et al., 1997; Worsley et al., 1996] for the regions with a priori hypothesis (i.e., frontal pole/BA 10/SFG). The volume of interest was extracted using the WFU PickAtlas and included 12,537 voxels and 100,296 mm³ [Friston et al., 1997].

RESULTS

Behavior

Average duration of the behavioral experiment (nine sessions) was 83 ± 6 min for both variants. Because of the adaptation algorithm (for individual levels per session, see Supporting Information Table S1), we observed similar respective average learning curves with relatively low variability for both variants (see Fig. 3). Average percent correct choices per bin of 10 trials increased from $58\% \pm 9\%$ to $85\% \pm 12\%$ in the *changing-gains/constant-losses* variant and from $54\% \pm 7\%$ to $85\% \pm 14\%$ in the *constant-gains/changing-losses* variant. Overall, payout was similar in both variants (*changing-gains/constant-losses*: 1999 ± 299 ; *constant-gains/changing-losses*: 1441 ± 760 Canadian cents).

PET Results

Performing the *changing-gains/constant-losses* variant was associated with decreased [¹¹C]FLB 457 BP in the right IFPC ($X = 22; Y = 60; Z = 6; 8 \text{ mm}^3; t = 4.62; p < 0.05$, corrected for multiple comparison) compared to the *constant-gains/changing-losses* variant (see Fig. 3). The mean BP of [¹¹C]FLB 457 extracted from a spherical region of interest ($r = 6$ mm) centered at the statistical peak revealed by the parametric map was 0.668 ± 0.023 and 0.582 ± 0.030 , respectively [$t(7) = 2.428, p = 0.023$, one-tailed].

When using a less conservative threshold (uncorrected for multiple comparisons), the *constant-gains/changing-losses* variant was associated with a decreased BP in the left vmPFC ($X = -6; Y = 60; Z = -22; t = 4.46$) compared to the *changing-gains/constant-losses* variant. The mean BP of [¹¹C]FLB 457 extracted from a spherical region of interest ($r = 6$ mm) centered at the statistical peak revealed by the parametric map was 0.585 ± 0.053 during the *constant-gains/changing-losses* variant and 0.640 ± 0.036 during the *changing-gains/constant-losses* variant [$t(7) = 0.488, p = 0.320$, one tailed], signifying a trend decrease in BP associated with the adaptation of loss-based preference hierarchies.

DISCUSSION

This study provides preliminary evidence that the adaptation of gain-based preference hierarchies (“Which grass

is greener?") depends on D2-receptor stimulation in the right IFPC. [¹¹C]FLB 457 BP was investigated while participants performed two behavioral variants of a probabilistic financial decision-making task resulting in similar overall payouts. In both variants, participants equally learned to make optimal decisions based on a hierarchy of positive or negative expected values, respectively. As a benefit for the reliability of the results—especially in a study with a relatively small number of observations—we observed only minor variance in individual learning curves. We ascribe this to the fact that task difficulty was adapted to performance during the experiment and that participants were relatively homogenous with respect to age and educational background.

When interpreting the decrease of BP in the *changing-gains/constant-losses*, relative to the *constant-gains/changing-losses* variant, one has to consider that behaviorally, these variants contrast a decreasing demand to adapt mental representations of a gain-based preference hierarchy with a constantly high demand for adaptation in the futile attempt to form an accurate gain-based preference hierarchy. We therefore argue that our findings reflect a continuously increased D2-receptor stimulation with continuous demand to adapt gain-based preference hierarchies in the *changing-gains/constant-losses* variant in contrast to a “decreasingly increased” D2-receptor stimulation with a decreasing demand to adapt gain-based preference hierarchies in the *constant-gains/changing-losses* variant.

This conclusion is not only based on anatomical a priori information, but also on the premise that with [¹¹C]FLB 457 PET, we are only able to describe a decrease in BP, not an increase due to a hypothetical decrease of synaptic dopamine levels below baseline [Frankle et al., 2010].

We also report a trend decrease of [¹¹C]FLB 457 BP in the vmPFC associated with the adaptation of loss-based preference hierarchies. Although not surviving the correction for multiple comparisons, this result may strengthen the assumption that the vmPFC plays an important role in loss-based decision-making coming from studies using the original IGT [Bechara et al., 1994]. Moreover, it may corroborate studies describing an influence of dopaminergic stimulation on loss-based decision-making in the IGT [Kobayakawa et al., 2008; Mimura et al., 2006; Pagonabarraga et al., 2007; Perretta et al., 2005; Rossi et al., 2010; Sevy et al., 2007; Shurman et al., 2005].

Generally, the findings underscore the notion that prefrontal D2-receptor stimulation plays an important role in decision-making by facilitating the adaptation of future behavior [Cools and Robbins, 2004].

This study generally supports the role of the IFPC in future oriented goal-directed behavior. In functional imaging studies, activation of the IFPC has been reported for many high-level tasks, such as rule learning [Strange et al., 2001], postretrieval evaluation in episodic memory retrieval [Shallice et al., 1994], and memory-based guidance of visual selection [Soto et al., 2007]. Specific sustained activation of the IFPC has also been described during stra-

tegic monitoring of the environment for intention-relevant cues in a prospective memory task [Reynolds et al., 2009]. According to Burgess et al. [2007], the IFPC is primarily engaged in contextual episodic memory associated with stimulus-independent manipulation of central representations. Of particular interest with regard to the present study is the implication of the IFPC in relational integration [Bunge et al., 2009; Christoff et al., 2001]. Our task specifically demanded to mentally rank card decks according to their expected values, in this context, the ability to make transitive relational inferences (*if “deck A is better than deck B” and “deck B is better than deck C” then “deck A is better than deck C”*) certainly constitutes a behavioral advantage.

Of note, two recent fMRI studies directly implicate the IFPC in guiding behavior according to neural representations of value hierarchy of behavioral options. One suggests that the IFPC mediates a behavioral switch in reward-based decisions [Boorman et al., 2009], when empirical evidence is in favor of doing so. The other found that adaptive reward learning was highly correlated with activity in the lateral frontal pole in a probabilistic reward-learning task [Roiser et al., 2010].

One may argue that the common theme of the suggested functions of the IFPC is that they require online comparison of ongoing events with longer-range strategies or hypotheses in goal-directed behavior. Our findings would certainly be in line with this proposition.

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