The neural basis of effort valuation:

A meta-analysis of functional magnetic resonance imaging studies

Paula Lopez-Gamundi[a,b,1,*], Yuan-Wei Yao[c,d,e,1,*], Trevor T-J. Chong[f,2], Hauke R. Heekeren[c,d,e,2], Ernest Mas Herrero[,b,2] , Josep Marco Pallares[a,b,2]

[a] Department of Cognition, Development and Educational Psychology, Institute of Neurosciences, University of Barcelona, Spain; Passeig de la Vall d'Hebron, 171, 08035 Barcelona

[b] Cognition and Brain Plasticity Unit, Bellvitge Biomedical Research Institute, Spain; Hospital Duran i Reynals, 3a planta / Gran Via de l'Hospitalet, 199, 08908 Hospitalet de Llobregat

[c] Department of Education and Psychology, Freie Universität Berlin, Berlin, 14159, Germany

[d] Einstein Center for Neurosciences Berlin, Charité-Universitätsmedizin Berlin, 10117, Germany

[e] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, 10117, Germany

[f] Turner Institute for Brain and Mental Health, Monash University, Victoria, 3800, Australia

* Corresponding Author: Paula Lopez-Gamundi (plopezgamundi@ub.edu) or Yuan-Wei Yao (yywyao@gmail.com)

1 Equal contribution

2 Equal contribution

Abstract

Choosing how much effort to expend is a critical for everyday decisions. While effort-based decision-making is altered in common psychopathologies and many neuroimaging studies have been conducted to examine how effort is valued, it remains unclear where the brain processes effort-related costs and integrates them with rewards. Using meta-analyses of combined maps and coordinates of functional magnetic resonance imaging (fMRI) studies (total N = 22), we showed that raw effort demands consistently activated the pre-supplementary motor area (pre-SMA). In contrast, the net value of effortful reward consistently activated regions, such as the ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS), that have been previously implicated in value integration in other cost domains. The opposite activation patterns of the pre-SMA and vmPFC imply a double dissociation of these two regions, in which the pre-SMA is involved in pure effort cost representation and the vmPFC in net value integration. These findings advance our understanding of the neural basis of effort-related valuation and reveal potential brain targets to treat motivation-related disorders.

Key words: Effort; subjective value; effort based decision making; value integration; fMRI; ventromedial prefrontal cortex; supplementary motor area, meta-analysis

1. Introduction

Every day, we are faced with choices about whether to invest effort to attain certain goals (Bailey et al., 2016; Salamone et al., 2009). These effort demands are often regarded as costly, such that individuals tend to avoid one action if it requires too much effort (Kool et al., 2010; Kurniawan et al., 2010, 2011). The ability to accurately weigh energy requirements against potential benefits (e.g., "effort-based decision-making"), is therefore crucial for optimal goal-directed action, and alterations in this function are believed to be a core component of motivational disorders, such as apathy (Chong and Husain, 2016; Hartmann et al., 2015; Husain and Roiser, 2018), and have been found across a variety of psychopathologies, including depression (Treadway et al., 2012; Yang et al., 2014), schizophrenia (Barch et al., 2014; Park et al., 2017), Parkinson's disease (Chong, 2018; den Brok et al., 2015; Le Heron et al., 2018), and substance dependence (Grodin et al., 2016). Due to its clear clinical importance, there has been a recent surge of interest in how effort devalues prospective rewards, and such studies have demonstrated that effort might be a unique cost, distinct from other more investigated cost domains, such as risk and delay. However, work on the neural mechanisms underlying effort-based valuation have yielded heterogeneous results, and the question of how humans integrate effort and reward remains a subject of contention.

Most behavioral economic theories of reward-related behavior rely on the assumption that an organism weighs a reward and its associated costs to generate a net value of an option (Kahneman and Tversky, 1979; Sutton and Barto, 1998; Von Neumann and Morgenstern, 1990). A popular hypothesis proposes that, to effectively compare different options, the net value of each must be represented in a 'common currency' (Padoa-Schioppa, 2011; Rangel et al., 2008; Westbrook and Braver, 2015). A network of regions, including the ventromedial prefrontal cortex (vmPFC; and adjacent orbitofrontal cortex) and ventral striatum (VS), have been repeatedly implicated in the encoding of the net value of rewards discounted by the costs associated with obtaining them (Bartra et al., 2013; Levy and Glimcher, 2012). Based on these data, this valuation network is posited to be 'domain-general', as it tracks net value representations regardless of the nature of the reward (e.g., primary vs secondary) (Bartra et al., 2013; Sescousse et al., 2013) or of the type of cost (e.g., risk vs delay) (Kable and Glimcher, 2007; Peters and Büchel, 2009; Prévost et al., 2010).

However, much of these data have focused on outcome-related costs such as risk or delay. Notably, research on effort-based valuation suggests a limited role for the vmPFC and VS for value integration. Instead, other frontal regions beyond this core valuation network, including the anterior cingulate cortex (ACC), supplementary motor area (SMA), and anterior insula (AI), have been shown to signal net value discounted by effort costs (Arulpragasam et al., 2018; Camille et al., 2011; Chong et al., 2017; Klein-Flugge et al., 2016; Massar et al., 2015; Skvortsova et al., 2014; Walton et al., 2003). These findings are consistent with animal studies showing that lesions to the ACC, but not the nucleus accumbens, prelimbic/infralimbic cortex (homologous to the vmPFC), or orbitofrontal cortex, reduce the amount of effort rats invested for rewards (Rudebeck et al., 2006; Walton et al., 2009, 2003). Furthermore, neural activity in the ACC, as measured by single unit recordings, varies with cost-benefit weighting (Hillman and Bilkey, 2012, 2010) and effort-related choice (Cowen et al., 2012). This body of work thus raises the possibility that a distinct frontal network is specifically recruited to integrate effort-related value.

On the other hand, these frontal regions (i.e. ACC, pre-SMA, AI, etc.) are also commonly implicated in cognitive control processes (Wu et al., 2020), which may overlap or obscure value signals. For example, value-based decision-making may trigger cognitive control functions such as conflict detection and response inhibition (Botvinick and Braver, 2015; Botvinick et al., 2001), surprise and/or prediction error signaling (Vassena et al., 2020, 2017), and invigoration of goal-directed behavior (Kouneiher et al., 2009; Kurniawan et al., 2013; Mulert et al., 2005).Therefore, it is plausible that these regions are recruited to prepare and invigorate behaviors necessary for realizing a prospective reward instead of for computing prepotent net values per se. Another situation that requires cognitive control is difficult decision-making when two simultaneously presented options have similar net value (Chong et al., 2017; Hunt et al., 2012; Klein-Flugge et al., 2016; Massar et al., 2015; Shenhav et al., 2013). Indeed, studies that have independently manipulated net value and decision difficulty showed that these frontal regions, particularly the dorsal ACC, specifically tracked decision difficulty (Hogan et al., 2017; Westbrook et al., 2019) while, in contrast, the vmPFC uniquely tracked net value (Westbrook et al., 2019). Taken together, these findings suggest that this distinct frontal network is recruited more specifically for cognitive control, such as response planning and option comparison, and that effort-related value integration is still processed in the core valuation network (e.g., vmPFC and VS) that have been identified in other cost domains.

The inconsistencies in previous studies may be related to several issues. For example, some may have been statistically underpowered due to small sample sizes, which may have reduced the probability of detecting significant effects, and/or reduce the reliability of their findings (Müller et al., 2018; Poldrack et al., 2017). Furthermore, the specific effort requirements of each task may have induced different patterns of brain activity, making it difficult to judge whether findings from individual studies can be generalized to the cognitive process of interest. A promising approach to address these issues is to quantitatively synthesize fMRI data across multiple studies using an image-based meta-analysis (Muller et al., 2018). Relative to traditional meta-analyses based only on peak coordinates of significant activity, an image-based meta-analytic approach uses the full information of the statistical maps from each study, and has greater power to detect small effect sizes (Luijten et al., 2017; Salimi-Khorshidi et al., 2009). A previous study showed that even the inclusion of 20% of statistical maps for included studies could significantly improve the precision of a meta-analysis (Radua et al., 2012).

Here, we conducted a hybrid coordinate- and image-based fMRI meta-analysis to identify the neural correlates of effort-related cost processing and value integration. Considering their critical roles in response planning, we hypothesized that frontal regions like the ACC, SMA, and AI would be consistently involved in representing prospective effort, independent of the reward offer. We also aimed to test whether effort-related value integration (i.e., the integration of reward value with the effort required to obtain it) relied on the core valuation areas such as the vmPFC and VS or broader frontal regions.

2. Materials and Methods

2.1. Literature Screen, Data Collection, and Preparation

2.1.1 Exhaustive Literature Search.

We conducted a systematic literature search to identify neuroimaging studies on prospective effort and the integration of reward value and effort costs in healthy adults. Candidates for inclusion were initially identified by searching PubMed, ProQuest, and Web of Science on June 29, 2020 using the grouped terms (“fMRI” OR “functional magnetic resonance imaging”) AND (“effort discounting” OR “effort-based decision-making” OR “effort valuation” OR “effort anticipation” OR “cost-benefit valuation” OR “cognitive effort” OR “physical effort” OR “effort expenditure” OR “effort allocation” OR “effortful goal directed action” OR “reward related motivation” OR “reward related effort”). Searches were limited to human studies where databases would allow. 121, 787, and 127 studies were identified on PubMed, ProQuest, and Web of Science, respectively. We also searched existing in-house reference libraries and names of prominent authors in the field, resulting in the addition of candidate studies. 934 candidate studies remained after search results were pooled and duplicates removed. Two researchers

(PL-G, Y-WY) then independently reviewed the title and abstract of candidate papers to determine relevance, resulting in a pool of 72 studies that underwent a full-text review (Figure 1).

2.1.2 Inclusion/Exclusion Criteria.

Studies were included if they: 1) had a healthy adult human sample in the non-elderly age range (ages 18 to 65, with one exception detailed below); 2) used functional MRI; 3) either reported or referenced a whole-brain analysis; and 4) utilized a task with an effort component with clear effort (or combined effort and reward) cues during an 'anticipation' phase. Please note that 'anticipation' in this case refers to the evaluation of prospective effortful rewards before or during decision-making, and does not include anticipatory responses to reward post-effort exertion (e.g., the 'evaluation' phase described in Assadi et al., (2009)).

To ensure that the selected studies could be meaningfully compared, we limited the final corpus to those that used experimental paradigms with certain characteristics. First, because studies have found that loss and gain are asymmetric and partially dissociable (Chen et al., 2020; Porat et al., 2014; Tanaka et al., 2014), we excluded studies that used paradigms with only loss conditions, or that only conducted gain vs loss comparisons. Second, we excluded studies that only used a single speeded response as its effort component (e.g. classical Monetary Incentive Delay task (Knutson et al., 2000)), as this was not deemed as a significant effort demand, and other reviews and meta-analyses focusing on reward anticipation with these paradigms can be found elsewhere (Diekhof et al., 2012; Knutson and Greer, 2008; Wilson et al., 2018). Finally, we only included those studies which measured activity during the *prospective* valuation of an action and its rewards, rather than only at the time of reward outcome, as estimates of previously expended effort can be biased by reward receipt (Pooresmaeili et al., 2015).

We contacted the corresponding authors of 28 candidate studies to request whole-brain statistical maps for the analyses of interest, and received whole-brain statistical maps or peak coordinates from 25 studies. In cases where only between-group (e.g. clinical studies) and/or ROI results were reported, we contacted corresponding authors to inquire about the availability of whole-brain results for relevant contrasts in healthy adult subjects. If images were not available, we requested they provide us with peak activation foci in stereotactic spatial coordinates (i.e., Talairach or MNI space), together with the direction of the effect (positive or negative).

2.1.3 Data collection and preparation.

We performed two analyses of interest. The first examined activity related to the raw effort involved in the option itself. We included analyses that examined high vs. low effort demands (i.e., categorical contrasts) and those that examined continuous changes in effort (i.e., parametric modulation). The second analysis examined activity related to the prospective net value of an effortful reward. Whenever possible, we used the contrast related to the net value of a single option (i.e., the subjective value of the chosen option discounted by the effort required to obtain it). When this contrast was unavailable, we used the contrast related to the differences between options instead. Studies that only investigated BOLD activity associated with interactions between reward and effort were excluded, as they did not rely on the same discounting assumptions as other measures of net value. It should be noted that one study (Nagase et al., 2018) included two experiments with six common participants, so we selected the experiment with a larger sample size for the meta-analysis. In another study (Chong et al., 2017), all participants took part in both cognitive and physical effort-based decision-making tasks. Thus, we combined the statistical maps from both tasks to avoid selection bias. Finally, one study (Seaman et al., 2018) had a sample that included participants ranging from 22 to 83 years old. However, the authors of this study provided whole-brain maps that controlled for the effect of age, and we chose to include this data in the net value meta-analysis.

2.1.4 Final Corpus.

As shown in Figure 1, 25 studies were ultimately included in the final corpus of studies, which were considered in one or both meta-analyses on raw effort evaluation and effort-reward integration. The raw effort valuation analysis included 15 maps (65%) and 7 coordinates for raw effort processing, resulting in 22 studies with a total sample of N = 549 (mean = 24.95; median = 22.5, range = [16-50]). A description of the final corpus of studies can be found in Table 1. The value integration analysis included 11 maps (73%) and 4 coordinates, resulting in 15 studies, with a total sample of N = 428 participants (mean = 28.5; median = 23, range = [16-75]).

2.2 Meta-Analytic Procedures

2.2.1 Seed-based d Mapping.

The combined image- and coordinate-based meta-analyses were performed using the software Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI, version 6.21; https://www.sdmproject.com). SDM-PSI preserves the information about the sign of the effect and the methods have been validated in previous studies (Albajes-Eizagirre et al., 2019; Radua et al., 2012). During preprocessing, SDM-PSI recreated voxel-level maps of standardized effect sizes (i.e., Hedge's g) and their variances and allowed the incorporation of both whole-brain t-maps and peak information (i.e., coordinates and t-values). The inclusion of statistical maps can substantially increase the sensitivity of meta-analyses compared with the pure coordinate-based approach (Radua et al., 2012). When *t*-maps were unavailable, SDM-PSI estimated them based on coordinates and their effect sizes using anisotropic kernels (Radua et al., 2014).

2.2.2 Meta-analysis.

Two separate whole-brain meta-analyses were conducted to examine consistent neural correlates of prospective effort and net value processing, respectively. Random-effect models were used to assess the mean effect size of each study, where the weight of a study is the inverse of the sum of its variance and the between-study variance. SDM z-maps were generated by dividing the voxel-wise effect sizes by their standard errors. As these z-values may deviate from a normal distribution, a null-distribution was estimated for each meta-analysis from 50 whole-brain permutations.

2.2.2.1 Region-of-Interest (ROI) Analysis.

To directly investigate the involvement of key brain regions in effort-related cost processing and value integration, we focused on seven *a priori* regions of interest (ROIs) derived from an independent meta-analysis (Bartra et al., 2013) that examined valuation network in general. Those ROIs included: the vmPFC, right and left VS, ACC, pre-SMA, and right and left AI, which generally covered the core valuation network and additional frontal regions of interest. A spherical mask of radius 6mm was created for each ROI centered on the respective peak coordinates. Mean effect sizes and variances of those ROIs were extracted from individual studies with statistical maps.

2.2.2.2 Whole-Brain Analysis.

We also examined the whole-brain results beyond these *a priori* ROIs. To reduce the false-positive results due to multiple comparisons, we applied a familywise error (FWE) correction with 1000 subject-based permutations (Albajes-Eizagirre et al., 2019). In accordance with SDM-PSI's recommendations, a threshold-free cluster enhancement (TFCE) corrected $p < 0.025$ was used (Albajes-Eizagirre et al., 2019).

In addition, we performed a conjunction analysis to identify regions that were associated with both raw effort demand and net value. For exploratory purposes, we created maps using a voxel-level uncorrected threshold of $p < 0.001$ and a cluster size > 20 voxels for both meta-analyses. Masks were generated from significant clusters that activated or deactivated in both processes (i.e., based on absolute values). We then used SPM12 (http://www.fil.ion.ucl.ac.uk/spm) to perform a conjunction analysis to extract overlapping areas for both processes, regardless of the direction (Culter & Campbell-Meiklejohn, 2019).

Finally, we conducted two supplementary analyses. First, because of the possible role of the dorsal ACC and other frontal regions in signaling choice difficulty, we were interested in assessing if our findings were influenced by studies that used net value differences as the parameter, rather than the net value of the chosen option. Thus, we repeated the meta-analysis with a subgroup of studies that used parameters only representing the net value of a single option (N=11). Second, because net value can also be more broadly defined as an interaction between reward and effort, we repeated the net value meta-analysis by including the coordinates of two additional studies (Kurniawan et al., 2010; Stoppel et al., 2011) that used interaction parameters (e.g. Reward X Effort) as opposed to traditional discounting parameters of net value (e.g. SV). These analyses were conducted using the same procedures described above.

2.2.3 Heterogeneity and Publication Bias.

Areas of significant activation were assessed for heterogeneity and publication bias. For each meta-analysis, peaks with heterogeneity I^2 values > 20% were flagged and inspected. In order to assess publication bias, Hedge's *g* effect size estimates were extracted at the study level for peak voxels of significant clusters. Funnel plots were created and visually inspected. Egger regression tests (Egger et al., 1997) were conducted to quantitatively test the asymmetry of each funnel plot.

2.3 Data Availability.

Unthresholded z-maps of our results are available at NeuroVault: https://neurovault.org/collections/9286/. The TFCE-corrected maps as well as publication bias and heterogeneity data are available from the corresponding authors upon request.

3. Results

3.1. ROI Analysis

To directly examine the roles of key regions in raw effort prospect and effort-reward integration, we focused on seven *a priori* ROIs. Results are summarized in Table 2. The vmPFC showed consistent activations related to net value and deactivations related to prospective effort. The bilateral VS showed a similar activity pattern, but smaller effect sizes for both analyses. In contrast, the pre-SMA showed consistent activations related to effort demand and deactivations related to net value. The ACC and bilateral AI showed similar activity pattern, but smaller effect sizes for both analyses. Figures 2 and 3 show the Hedge's g effect sizes for raw effort prospect and net value analyses in the vmPFC and pre-SMA ROIs. The forest plots for other regions were shown in Figure S1-S10.

3.2. Whole-Brain Analysis

3.2.1 Prospective Effort

We first examined brain regions that were consistently associated with the valuation of prospective effort demands. As illustrated in Figure 4a, the analysis yielded positive effects clustered in the right pre-SMA and adjacent caudal ACC (see Table 3). At a more lenient, uncorrected $p < 0.001$ threshold, other positive foci were detected in the left SMA, right precuneus, and left middle frontal gyrus, and negative foci were detected in the bilateral vmPFC/OFC and left middle temporal gyrus.

Heterogeneity I^2 statistics, funnel plots and Egger regressions did not detect excess heterogeneity or publication bias in any significant clusters in the TFCE-corrected findings. However, in the uncorrected analysis, activation in a cluster in the right precuneus was found to be associated with extreme heterogeneity (I^2=59.50%).

3.2.2.Net Value.

Next, we examined brain regions that were consistently associated with net value encoding. As illustrated in Figure 4b, the analysis yielded a large cluster connecting cortical and subcortical regions of the medial PFC, VS, dorsal striatum (bilateral putamen and left caudate), and temporal gyrus (see Table 3). Analysis also yielded consistent net value activations in a cluster consisting of the bilateral medial and posterior cingulate cortex and precuneus and a separate cluster in the left middle frontal gyrus. Deactivations were concentrated in small clusters in the left SMA, right dorsolateral PFC (dlPFC), and right superior frontal gyrus, although these deactivations were only detectable at a lenient uncorrected $p < 0.001$ threshold.

In addition, heterogeneity I^2 statistics, funnel plots and Egger regressions showed no evidence of excess heterogeneity or publication bias in any of the significant clusters for the main net value or single SV subgroup TFCE-corrected results. No evidence of publication bias was detected in the uncorrected net value analysis, however deactivations in the left SMA and right dlPFC had I^2 statistics of 64.09% and 50.05% respectively, suggesting that findings in these two regions were highly heterogenous.

3.2.3 Conjunction Analysis

Finally, we performed a conjunction analysis to identify areas that are sensitive to *both* net value and effort requirements. Due to the exploratory nature of this analysis, we used a lenient threshold of uncorrected $p < 0.001$ at voxel level and $k > 20$ at cluster level. Note that we used absolute values in the conjunction analysis because of the clearly dissociable effects found in the main prospective effort and net value meta-analyses. We found that the vmPFC and left lateral orbitofrontal cortex were significantly activated by net value but deactivated by effort requirement. The activation pattern was reversed in the pre-SMA and caudal ACC (Figure 4c). However, all of these findings were not detectable after whole-brain TFCE-correction.

3.2.4 Supplementary analyses

To ensure that the results of the net value meta-analysis were not driven by choice difficulty, we reran our analysis excluding four experiments that used the value of two options as their net value metric (e.g. difference in SV of more vs less effortful option). Importantly, the vmPFC and bilateral VS remained to be the foci with highest effect sizes, and the whole-brain activation pattern was qualitatively similar (see Table S1 and Figure S11), suggesting that our main findings were not influenced by the cognitive demands of comparing two options. Moreover, to ensure that our findings were robust when using a broader definition of net value, we also repeated our analysis including two additional studies that used reward and effort interactions as a measure of net value. Main foci and whole-brain activation patterns remained qualitatively similar to the initial net value meta-analysis (see Table S2 and Figure S12). However, deactivations associated with net value were not detected in these supplementary analyses, suggesting that the deactivations in the SMA detected in the main meta-analysis were not robust.

4. Discussion

We conducted a series of combined coordinate- and image-based meta-analyses to examine the neural substrates of effort-based valuation. We first investigated neural activity related to raw effort and net value in seven *a priori* ROIs previously implicated in value-based decision-making. We found these regions could be broadly divided into two groups that exhibited distinct activity pattern during these two processes, with the vmPFC and pre-SMA as the central node of each. Specifically, the vmPFC was consistently activated during net value integration but deactivated for raw effort representation, whereas the pre-SMA displayed the opposite pattern. The exploratory whole-brain and conjunction analyses further corroborate the ROI analyses. These findings provide strong evidence for a dissociable role of the vmPFC and pre-SMA in the valuation of effort costs, and implicate these two regions as core components of a network that drives motivated behavior.

Our findings provide comprehensive evidence that effort-related net value integration is processed in a network centered around the vmPFC and VS. Accumulating evidence implicates the vmPFC as a general hub for value integration, as it has been identified to signal net value of rewards across different cost domains, such as risk and delay (Croxson et al., 2009; Hogan et al., 2019; Kable and Glimcher, 2007; Levy et al., 2010; Peters and Büchel, 2009; Schmidt et al., 2012; Westbrook et al., 2019). Additionally, the network including the vmPFC have been implicated in tracking net values across reward domains (i.e., primary, secondary, and aesthetic rewards), reward processing phases (Bartra et al., 2013;

Clithero and Rangel, 2013; Levy and Glimcher, 2012; Sescousse et al., 2013), reward rates, and the value of current and previous offers (Mehta et al., 2019). These findings are therefore consistent with prominent neuroeconomic accounts which propose that the vmPFC represent the net value of an option in a 'common currency', in order to facilitate value comparison during decision-making (Padoa-Schioppa, 2011; Rangel et al., 2008; Westbrook and Braver, 2015).

One would hypothesize that a region involved in representing net value would also scale with effort demands. Except for the vmPFC, our study did not find that other net-value-related regions, such as the VS, meet this requirement. These findings are at odds with previous reports that the VS signals prospective effort costs in humans, both in the presence (Westbrook et al., 2019) and absence (Suzuki et al., 2020) of reward information. Moreover, dorsal parts of the striatum have also been found to track both effort costs (Burke et al., 2013; Guitart-Masip et al., 2012; Klein-Flugge et al., 2016; Kurniawan et al., 2010, 2013; Yang et al., 2016) and net value of prospective effortful rewards (Klein-Flugge et al., 2016; Seaman et al., 2018). However, our results implicate motor-related regions of the striatum, particularly the putamen, as signaling net value alone. One plausible explanation is that the striatum signals both net value and prospective effort during this time window, but that the simultaneous nature of these signals inhibits detection. Studies that have experimentally isolated prospective effort demands from net value, however, did not find that the striatum was activated by effort alone (Arulpragasam et al., 2018), leaving role of the striatum in effort anticipation as a salient question for future investigation.

Finally, both main and supplementary analyses consistently identified a variety of parietotemporal regions as scaling positively and uniquely with net value representations. While these regions (i.e. intraparietal lobule, intraparietal sulcus, temporal pole, etc.) have been previously implicated in SV encoding of effortful rewards (Chong et al., 2017; Massar et al., 2015), they also play a critical role in perceptual decision-making (Keuken et al., 2014), attention (Husain, 2019), risk weighting (Mohr et al., 2010), and decision difficulty (Westbrook et al., 2019). Their notable absence in reward processing (Keuken et al., 2014; Sescousse et al., 2013) may thus suggest that these parietotemporal regions are involved in high-level perceptual and cognitive functions associated with task demands as opposed to net value computation.

Previous studies have identified effort-related net value signals in other frontal regions, such as the pre-SMA and ACC, which suggests that these regions may be specifically relevant for effort-reward integration. In the current meta-analysis, however, we found that these regions – in particular, the pre-SMA and adjacent caudal ACC – all scaled positively with raw effort costs and, albeit less robustly, scaled negatively with net value. Such a pattern suggests that these regions are more likely to be involved in the processing of effort-related costs, rather than value integration per se. These findings align closely with a previous transcranial magnetic stimulation study, in which disruption of the SMA led to decreased effort perception (Zénon et al., 2015). The pre-SMA and dorsal ACC are also recruited to process other types of costs, such as risk (Mohr et al., 2010) and delay (Schüller et al., 2019). A plausible mechanism, therefore, is that these regions serve as a domain-general hub for cost encoding and transfer the cost information to the vmPFC for calculation of net value. Alternatively, neuroeconomic models of effort-based decision-making have posited that the ACC, in particular, is involved in good-to-action transformation (Padoa-Schioppa, 2011). Thus, another plausible mechanism is that the vmPFC computes and compares the net value of separate options and passes choice preference to action selection regions, such as the pre-SMA and ACC, for conversion to motor output.

Despite strong evidence about the involvement of the caudal ACC, which is close to the pre-SMA, in effort costs processing, it should be noted that the ACC, as a whole, is highly heterogeneous (Neubert et al., 2015; Yu et al., 2011). Indeed, the whole-brain results showed distinct activation patterns across the ACC, in which net-value-related activation was mainly observed in the ventral ACC, whereas cost-related activation in the dorsal ACC. These findings suggest that subregions of the ACC could be linked to different aspects of the effort-related valuation, which may also partly explain the fact that some studies identified net value signals in the ACC (Klein-Flugge et al., 2016; Massar et al., 2015). Moreover, net-value-related activation may emerge in the dorsal ACC if it is highly correlated with other confounding variables, such as decision difficulty (Shenhav et al., 2013). It is particularly plausible for studies that have used the SV difference between two options as the net value parameter, as it often approximates decision difficulty (Chong et al., 2017; Klein-Flugge et al., 2016). Notably, studies that have experimentally isolated net value and decision difficulty showed that the cognitive control network, including the dorsal ACC and other frontoparietal regions, tracked the latter but not the former (Hogan et al., 2019; Westbrook et al., 2019).

The current study has some limitations. First, the sample size of the net value analysis is relatively small. Although the inclusion of statistical images partly offsets this issue, the number of included studies still limited our ability to further explore the effects of potential moderators, such as effort type (i.e., physical vs. cognitive), parameter type (i.e., difference in SV vs. SV of one option), effort execution requirement (i.e., real vs. hypothetical), and reward probability (i.e., cumulative vs. random payout). Because effort-based decision-making is sensitive to reward probability (Barch et al., 2014; Soder et al., 2020; Treadway et al., 2012) and opportunity costs (Otto and Daw, 2019), future research should directly explore the interaction between effort demand and other cost domains and/or task features. Second, the majority of the included studies focused on physical effort measured by handgrip devices. These findings should be treated cautiously when generalizing to other formats of effort. Finally, the meta-analytic results reflected consistent regional activations across studies. Although our study identified critical brain regions related to effort-related value integration or cost encoding, how these regions interact with each other to achieve the dynamic valuation process remains to be elucidated by studies using task-based connectivity technique (Hauser et al., 2017) or imaging methods with higher temporal resolution (e.g., magnetoencephalography).

In conclusion, this study is the first to use combined image- and coordinate-based meta-analyses to examine neural activity related to effort-related costs and net value. The results showed the pre-SMA is involved in cost representation of prospective effort independent of rewards. In contrast, the vmPFC and VS, which have been implicated in value integration in other cost domains, are also involved in effort-reward integration. These findings further clarify the neural mechanisms underlying effort-related valuation and may provide candidate intervention targets for patients with decreased motivation to exert effort to obtain rewards.

Acknowledgement

PL-G was supported by a fellowship from "la Caixa" Foundation (LCF/BQ/DI19/11730047). Y-WY was supported by the PhD fellowship of the Einstein Center for Neurosciences Berlin. TT-JC was supported by the Australian Research Council (DP 180102383 and DE 180100389). The authors would like to thank Nadav Aridan, Amanda Arulpragasam, Javier Bernacer, Michael Chee, Vikram Chib, Claudie Gaillard, Erica Grodin, Tobias Hauser, Masud Husain, Miriam Klein-Flügge, Irma Kurniawan, Stijn Massar, Il Ho Park, Mathias Pessiglione, Ceyda Sayalı, Jacqueline Scholl, Kendra Seaman, Vasilisa Skvortsova, Michael Treadway, and Andrew Westbrook for sharing whole-brain statistical maps or peak coordinates.

Declarations of interest:

None

Table 1. Summary of Included Studies

Study	N	Task Type	Effort Type (Description)	Analysis	Data Type	Parameter
Aridan 2019	40	Choice	Physical (Handgrip)	Net Value	Map	P(yes)
				Effort	Map	Parametric effort demand
Arulpragasam 2018	28	Choice	Physical (Key press)	Net Value	Map	SV of Chosen Option
				Effort	Map	Effort demand of the variable option (at Cue 1)
Bernacer 2019	24	Choice	Physical (Running)	Net Value	Map	SV Difference
				Effort	Map	Max > no effort
Bonnelle 2016	37	Choice	Physical (Handgrip)	Net Value	Coordinates	"Expected Reward"
Chong 2017*	34	Choice	Physical (Handgrip) + Cognitive (RSVP)	Net Value	Map	SV Difference
				Effort	Map	Parametric effort demand
Croxson 2009	16	No choice	Physical (Trackball)	Net Value	Coordinates	Log (reward/effort)
				Effort	Coordinates	Increasing effort level
Hogan 2019	34	Choice	Physical (Handgrip)	Net Value	Map	SV of chosen option
Gaillard 2019	23	No Choice	Cognitive (Spatial WM)	Effort	Map	Categorial High vs Low WM Load
Grodin 2016	17	No Choice	Physical (Key press)	Effort	Map	Categorical High vs Low effort
Hauser 2017	28	Reward/effort learning	Physical (Handgrip)	Effort	Map	Parametric expected effort demand
Klein-Flügge 2016	21	Choice	Physical (Handgrip)	Net Value	Map	SV difference
				Effort	Map	Parametric Effort Difference
Kurniawan 2010	17	Choice	Physical (Handgrip)	Net Value**	Coordinates	Reward X [choice to grip > choice to hold]
				Effort	Coordinates	High > low effort of chosen option
Kurniawan 2013	19	No Choice	Physical (Handgrip)	Effort	Map	High > low effort demand
Massar 2015	23	Choice	Cognitive (Backwards typing)	Net Value	Map	SV of chosen option
				Effort	Map	Parametric effort level
Nagase 2018	33	Reward/effort learning	Cognitive (Arithmetic)	Effort	Map	Expected effort demand of chosen option
Park 2017	30	No Choice	Physical (Mouse click)	Effort	Coordinates	High vs low effort demand
Prévost 2010	16	Choice	Physical (Handgrip)	Net Value	Coordinates	SV of variable option
				Effort	Coordinates	Parametric Effort Demand

Sayalı & Badre 2019	50	Choice	Cognitive (Cued task switching)	Effort	Map	Expected effort demand of chosen option
Scholl 2015	20	Reward/effort learning	Physical (Trackball)	Net Value	Map	Decision value difference
				Effort	Map	Effort demand difference
Seaman 2018	75	Choice	Physical (Keyboard)	Net Value	Map	SV of chosen option
Skvortsova 2014	20	Reward/effort learning	Physical (Handgrip)	Net Value	Map	Expected value demand of chosen option
				Effort	Map	Effort Q
Stoppel 2011	18	No Choice	Cognitive (Line tracing)	Net Value**	Coordinates	Reward X Difficulty
				Effort	Coordinates	Hard > easy effort
Suzuki 2020	19	Choice	Physical (Keypress)	Net Value	Coordinates	SV of chosen option
	29	No Choice	Physical (Maze Navigation)	Effort	Coordinates	High > low effort
Vassena 2014	22	No Choice	Cognitive (Arithmetic)	Effort	Coordinates	High > low effort
Westbrook 2019	21	Choice	Cognitive (N-back)	Net Value	Map	SV of the more effortful option
				Effort	Map	Effort demand

*Maps from separate tasks were combined for all analyses. Abbreviation: RSVP, rapid serial visual presentation.

**Only included in supplementary Net Value analysis.

Table 2. Results of ROI analyses

ROI	MNI coordinate	Analysis	Hedge's *g*	*Z*	*p*	I^2 (in %)	Egger's *p*
vmPFC	(2, 46, -8)	**Net value**	**0.332**	**5.861**	**< 0.001**	**0.007**	**0.393**
		Raw effort	**-0.167**	**-2.482**	**0.013**	**39.381**	**0.678**
rVS	(12, 10, -6)	**Net value**	**0.167**	**2.334**	**0.020**	**35.404**	**0.420**
		Raw effort	-0.061	-1.170	0.242	< 0.001	0.286
lVS	(-12, 12, -6)	Net value	0.132	1.779	0.075	40.289	0.559
		Raw effort	-0.082	-1.565	0.118	< 0.001	0.879
Pre-SMA	(-2, 16, 46)	**Net value**	**-0.290**	**-2.255**	**0.024**	**78.669**	**0.130**
		Raw effort	**0.187**	**2.142**	**0.032**	**63.161**	**0.726**
ACC	(-2, 28, 28)	Net value	-0.088	-0.792	0.429	72.962	0.735
		Raw effort	0.083	1.163	0.245	47.311	0.764
rAI	(32, 20, -6)	Net value	-0.151	-1.474	0.141	68.130	0.131
		Raw effort	0.109	1.751	0.080	31.031	0.195
lAI	(-30, 22, -6)	Net value	-0.090	-0.787	0.431	74.025	0.107
		Raw effort	0.055	0.894	0.371	29.295	0.388

Abbreviations: vm, ventromedial; r, right; l, left; PFC, prefrontal cortex; VS, ventral striatum; ACC, anterior cingulate cortex; AI, anterior insula.

Table 3. Results of whole-brain analyses

Analysis	Cluster	Voxels	Peak MNI coordinates	BA	Regions	SDM-*Z*	I^2 (in %)	Egger's *p*
Net value	1*	23918	-4, 52, -8	10	Left vmPFC	7.052	0.208	0.702
			2, 52, -8	11	Right vmPFC	6.473		
			8, 10, -8		Right NAc	6.417		
			30, -6, -4		Right putamen	5.782		
			-32, -16, 4		Left putamen	5.546		
			-22, -6, -14	34	Left amygdala	5.398		
			24, 0, -16	34	Right amygdala	5.372		
			-50, -62, 14	37	Left temporal gyrus	5.335		
			-6, 14, -8		Left NAc	5.255		
			-6, 38,0	11	Left ACC	5.170		
			-52, -50, 2	21	Left middle temporal gyrus	5.145		
			24, 14, -16	48	Right insula	5.131		
	2*	3821	-14, -38, 40	23	Left PCC	5.592	6.332	0.444
			-12, -40, 44		Left precuneus	5.446		
			0, -8, 42	23	Dorsal ACC	5.003		
			-16, -34, 40		Left superior parietal gyrus	4.879		
	3*	337	-26, 28, 38	9	Left dlPFC	4.245	3.266	0.594
	4	156	-8, 16, 52	6	Left SMA	-3.718	64.089	0.085
	5	139	44, 38, 24	8	Right dlPFC	-4.263	50.050	0.186
	6	26	16, 20, 58	8	Right superior frontal gyrus	-3.797	24.707	0.249
Prospective effort	1*	112	8, 16, 64	6	Right SMA	3.966	1.069	0.494
	2	46	-8, 8, 52	6	Left SMA	3.922	0.161	0.684
	3	36	14, -66, 38	7	Right precuneus	3.615	59.40	0.111
	4	23	-28, -6, 50	6	Left middle frontal gyrus	3.505	0.162	0.933
	5	72	-8, 56, -8	11	Left vmPFC	-4.264	5.901	0.634
	6	67	-42, 30, -14	47	Left OFC	-4.037	0.002	0.947
	7	59	6, 54, -14	11	Right vmPFC	-3.798	15.71	0.936
	8	56	-56, -6, -18	21	Left middle temporal gyrus	-4.385	7.473	0.724

All results survived a statistical threshold of voxel-level uncorrected $p < 0.001$ and cluster size > 20.

* Regions survived a statistical threshold of TFCE-corrected $p < 0.025$.

Abbreviations: BA, Brodmann areas; vm, ventromedial; dl ,dorsolateral; d, dorsal; r, rostral; PFC, prefrontal cortex; NAc, nucleus accumbens; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; SMA, supplementary motor area; OFC, orbitofrontal cortex.

Figure legend

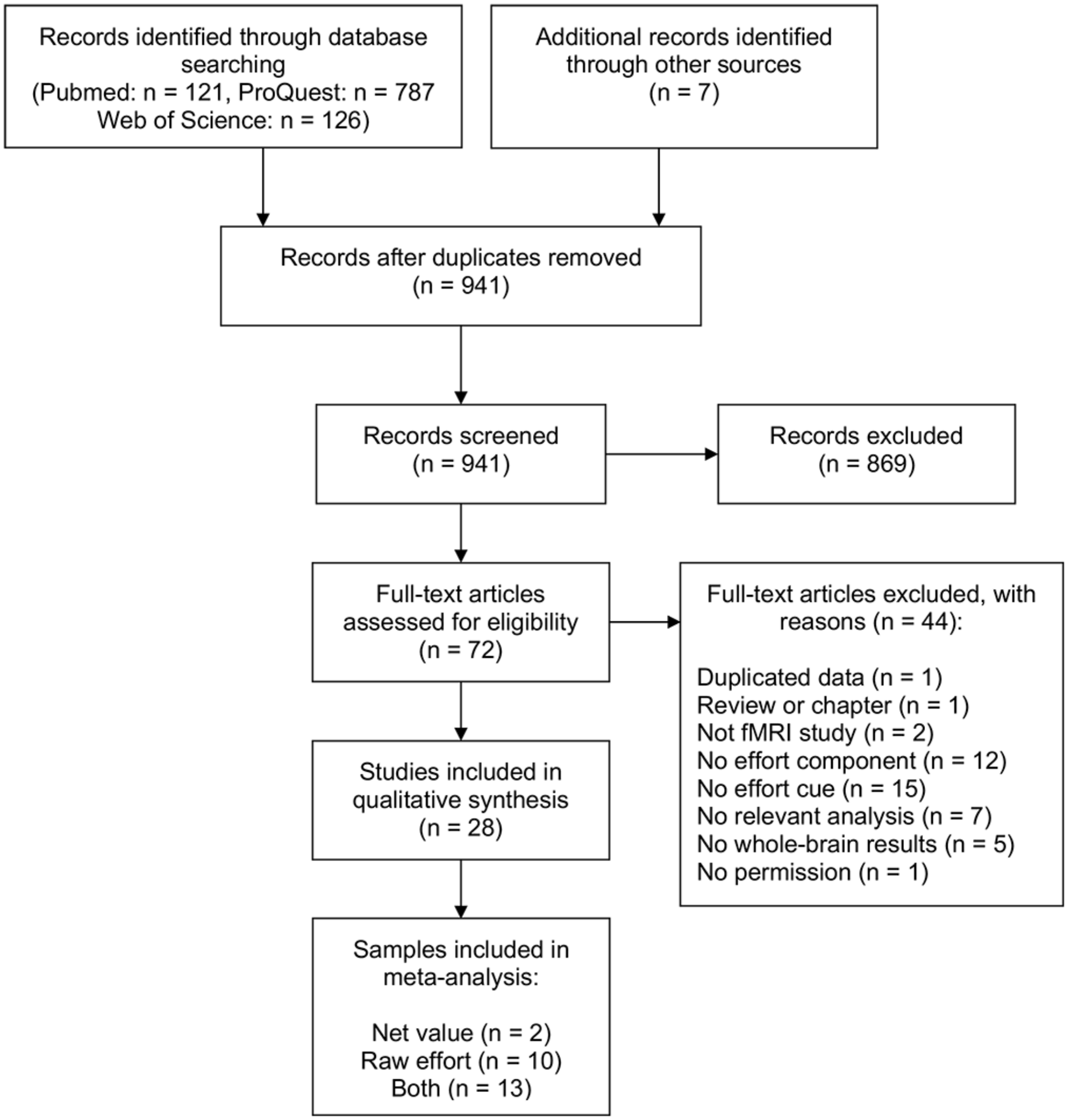

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

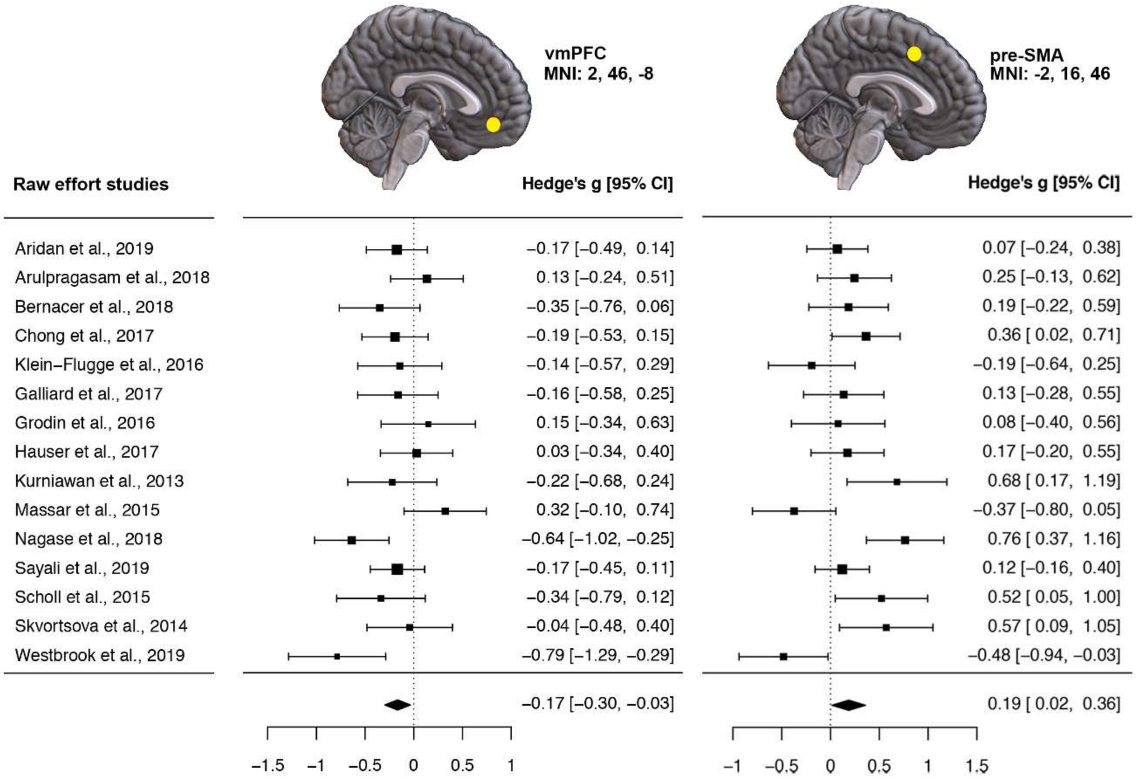

Figure 2. Forest plot illustrating activation related to effort demand in the vmPFC and pre-SMA ROIs in studies with statistical maps. Contrary to our findings for net value signaling, the pre-SMA is activated (Hedge's g= 0.20, 95% CI [0.02, 0.37]) and the vmPFC is deactivated (Hedge's g= -0.17, 95% CI [-0.30, -0.03]) when tracking pure prospective effort.

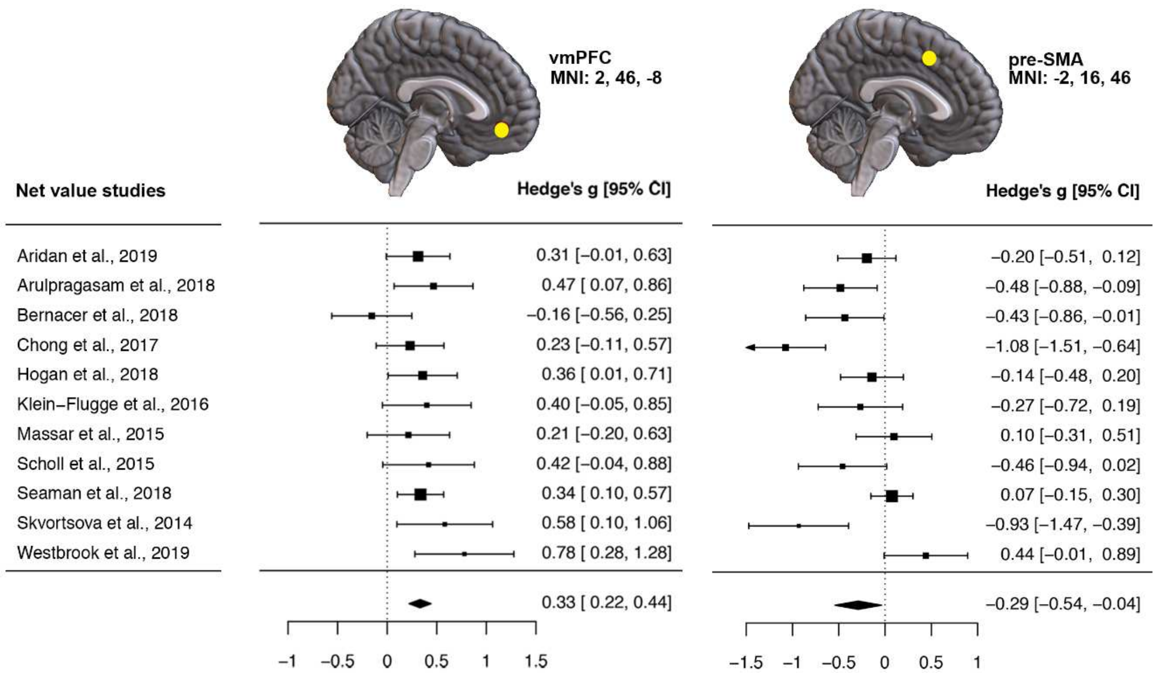

Figure 3. Forest plot illustrating activation related to net value in the vmPFC and pre-SMA ROIs in studies with statistical maps. The vmPFC is activated (Hedge's g= 0.22, 95% CI [0.22, 0.44]) and the pre-SMA is deactivated (Hedge's g= -0.28, 95% CI [-0.52, -0.03]) during effort-reward integration.

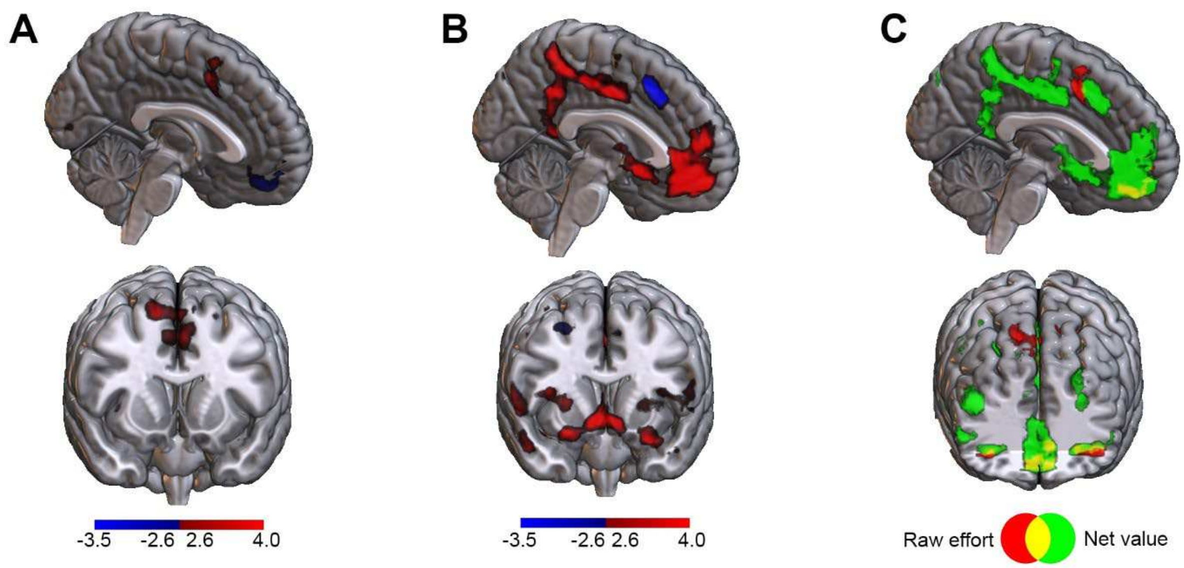

Figure 4. Whole-brain meta-analytic results. A: neural activity related to pure effort cost representation; B: neural activity related to net value; and C: their conjunction based on absolute values. Display threshold: uncorrected $p < 0.005$ at voxel level.

Reference

Albajes-Eizagirre, A., Solanes, A., Vieta, E., Radua, J., 2019. Voxel-based meta-analysis via permutation of subject images (PSI): Theory and implementation for SDM. Neuroimage 186, 174–184. https://doi.org/10.1016/j.neuroimage.2018.10.077

Aridan, N., Malecek, N.J., Poldrack, R.A., Schonberg, T., 2019. Neural correlates of effort-based valuation with prospective choices. Neuroimage 185, 446–454. https://doi.org/https://doi.org/10.1016/j.neuroimage.2018.10.051

Arulpragasam, A.R., Cooper, J.A., Nuutinen, M.R., Treadway, M.T., 2018. Corticoinsular circuits encode subjective value expectation and violation for effortful goal-directed behavior. Proc. Natl. Acad. Sci. U. S. A. 115, E5233–E5242. https://doi.org/10.1073/pnas.1800444115

Assadi, S.M., Yücel, M., Pantelis, C., 2009. Dopamine modulates neural networks involved in effort-based decision-making. Neurosci. Biobehav. Rev. 33, 383–393. https://doi.org/10.1016/j.neubiorev.2008.10.010

Bailey, M.R., Simpson, E.H., Balsam, P.D., 2016. Neural substrates underlying effort, time, and risk-based decision making in motivated behavior. Neurobiol. Learn. Mem. 133, 233–256. https://doi.org/10.1016/J.NLM.2016.07.015

Barch, D.M., Treadway, M.T., Schoen, N., 2014. Effort, anhedonia, and function in schizophrenia: Reduced effort allocation predicts amotivation and functional impairment. J. Abnorm. Psychol. 123, 387–397. https://doi.org/10.1037/a0036299

Bartra, O., McGuire, J.T., Kable, J.W., 2013. The valuation system: A coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. Neuroimage 76, 412–427. https://doi.org/https://doi.org/10.1016/j.neuroimage.2013.02.063

Bernacer, J., Martinez-Valbuena, I., Martinez, M., Pujol, N., Luis, E., Ramirez-Castillo, D., Pastor, M.A., 2019. Neural correlates of effort-based behavioral inconsistency. Cortex 113, 96–110. https://doi.org/https://doi.org/10.1016/j.cortex.2018.12.005

Bonnelle, V., Manohar, S., Behrens, T., Husain, M., 2016. Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. Cereb. Cortex 26, 807–819. https://doi.org/10.1093/cercor/bhv247

Botvinick, M., Braver, T., 2015. Motivation and cognitive control: From behavior to neural mechanism. Annu. Rev. Psychol. 66, 83–113. https://doi.org/10.1146/annurev-psych-010814-015044

Botvinick, M.M., Carter, C.S., Braver, T.S., Barch, D.M., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol. Rev. 108, 624–652. https://doi.org/10.1037/0033-295X.108.3.624

Burke, C.J., Brunger, C., Kahnt, T., Park, S.Q., Tobler, P.N., 2013. Neural Integration of Risk and Effort Costs by the Frontal Pole: Only upon Request. J. Neurosci. 33, 1706–1713. https://doi.org/10.1523/JNEUROSCI.3662-12.2013

Camille, N., Tsuchida, A., Fellows, L.K., 2011. Double dissociation of stimulus-value and action-value learning in humans with orbitofrontal or anterior cingulate cortex damage. J. Neurosci. 31, 15048–15052. https://doi.org/10.1523/JNEUROSCI.3164-11.2011

Chen, X., Voets, S., Jenkinson, N., Galea, J.M., 2020. Dopamine-Dependent Loss Aversion during Effort-Based Decision-Making. J. Neurosci. 40, 661–670. https://doi.org/10.1523/JNEUROSCI.1760-19.2019

Chong, T.T.-J., Apps, M., Giehl, K., Sillence, A., Grima, L.L., Husain, M., 2017. Neurocomputational mechanisms underlying subjective valuation of effort costs. PLOS Biol. 15, e1002598. https://doi.org/10.1371/journal.pbio.1002598

Chong, T.T.J., Husain, M., 2016. The role of dopamine in the pathophysiology and treatment of apathy, in: Progress in Brain Research. Elsevier B.V., pp. 389–426. https://doi.org/10.1016/bs.pbr.2016.05.007

Clithero, J.A., Rangel, A., 2013. Informatic parcellation of the network involved in the computation of subjective value. Soc. Cogn. Affect. Neurosci. 9, 1289–1302. https://doi.org/10.1093/scan/nst106

Cowen, S.L., Davis, G.A., Nitz, D.A., 2012. Anterior cingulate neurons in the rat map anticipated effort and reward to their associated action sequences. J. Neurophysiol. 107, 2393–2407. https://doi.org/10.1152/jn.01012.2011

Croxson, P.L., Walton, M.E., O'Reilly, J.X., Behrens, T.E.J., Rushworth, M.F.S., 2009. Effort-based cost-benefit valuation and the human brain. J. Neurosci. 29, 4531–41. https://doi.org/10.1523/JNEUROSCI.4515-08.2009

Day, J.J., Jones, J.L., Wightman, R.M., Carelli, R.M., 2010. Phasic nucleus accumbens dopamine release encodes effort- and delay-related costs. Biol. Psychiatry 68, 306–309. https://doi.org/10.1016/j.biopsych.2010.03.026

den Brok, M.G.H.E., van Dalen, J.W., van Gool, W.A., Moll van Charante, E.P., de Bie, R.M.A., Richard, E., 2015. Apathy in Parkinson's disease: A systematic review and meta-analysis. Mov. Disord. 30, 759–769. https://doi.org/10.1002/mds.26208

Diekhof, E.K., Kaps, L., Falkai, P., Gruber, O., 2012. The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude - An activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. Neuropsychologia 50, 1252–1266. https://doi.org/10.1016/j.neuropsychologia.2012.02.007

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. 315, 629–634. https://doi.org/10.1136/bmj.315.7109.629

Gaillard, C., Guillod, M., Ernst, M., Torrisi, S., Federspiel, A., Schoebi, D., Recabarren, R.E., Ouyang, X., Mueller-Pfeiffer, C., Horsch, A., Homan, P., Wiest, R., Hasler, G., Martin-Soelch, C., 2019. Striatal responsiveness to reward under threat-of-shock and working memory load: A preliminary study. Brain Behav. 9. https://doi.org/http://dx.doi.org/10.1002/brb3.1397

Grodin, E.N., Steckler, L.E., Momenan, R., 2016. Altered Striatal Response During Effort-Based Valuation and Motivation in Alcohol-Dependent Individuals. Alcohol Alcohol. Suppl. 51, 638–646. https://doi.org/10.1093/alcalc/agw003

Guitart-Masip, M., Chowdhury, R., Sharot, T., Dayan, P., Duzel, E., Dolan, R.J., 2012. Action controls dopaminergic enhancement of reward representations. Proc. Natl. Acad. Sci. U. S. A. 109.

Hartmann, M.N., Hager, O.M., Reimann, A. V, Chumbley, J.R., Kirschner, M., Seifritz, E., Tobler, P.N., Kaiser, S., 2015. Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort. Schizophr. Bull. 41, 503–512.

Hauser, T.U., Eldar, E., Dolan, R.J., 2017. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. Proc. Natl. Acad. Sci. 114, E7395–E7404. https://doi.org/10.1073/pnas.1705643114

Hillman, K.L., Bilkey, D.K., 2012. Neural encoding of competitive effort in the anterior cingulate cortex.

Nat. Neurosci. 15, 1290–1297. https://doi.org/10.1038/nn.3187

Hillman, K.L., Bilkey, D.K., 2010. Neurons in the rat anterior cingulate cortex dynamically encode cost-benefit in a spatial decision-making task. J. Neurosci. 30, 7705–7713. https://doi.org/10.1523/JNEUROSCI.1273-10.2010

Hogan, P.S., Galaro, J.K., Chib, V.S., 2019. Roles of Ventromedial Prefrontal Cortex and Anterior Cingulate in Subjective Valuation of Prospective Effort. Cereb. Cortex 29, 4277–4290. https://doi.org/10.1093/cercor/bhy310

Hogan, P.S., Galaro, J.K., Chib, V.S., 2017. Dissociable Roles of Ventromedial Prefrontal Cortex and Anterior Cingulate in Subjective Valuation of Prospective Effort. BioRxiv. https://doi.org/http://dx.doi.org/10.1101/079467

Husain, M., 2019. Visual Attention: What Inattention Reveals about the Brain. Curr. Biol. 29, R262–R264. https://doi.org/https://doi.org/10.1016/j.cub.2019.02.026

Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat. Rev. Neurosci. 19, 470–484. https://doi.org/10.1038/s41583-018-0029-9

Kable, J.W., Glimcher, P.W., 2007. The neural correlates of subjective value during intertemporal choice. Nat. Neurosci. 10, 1625–1633. https://doi.org/10.1038/nn2007

Kahneman, D., Tversky, A., 1979. Prospect Theory: An Analysis of Decision under Risk. Econometrica 47, 263–291. https://doi.org/10.2307/1914185

Keuken, M.C., Müller-Axt, C., Langner, R., Eickhoff, S.B., Forstmann, B.U., Neumann, J., 2014. Brain networks of perceptual decision-making: an fMRI ALE meta-analysis. Front. Hum. Neurosci. 8, 445. https://doi.org/10.3389/fnhum.2014.00445

Klein-Flugge, M.C., Kennerley, S.W., Friston, K., Bestmann, S., 2016. Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. J. Neurosci. 36, 10002–10015. https://doi.org/10.1523/JNEUROSCI.0292-16.2016

Knutson, B., Greer, S.M., 2008. Review. Anticipatory affect: Neural correlates and consequences for choice. Philos. Trans. R. Soc. B Biol. Sci. https://doi.org/10.1098/rstb.2008.0155

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage 12, 20–27. https://doi.org/10.1006/nimg.2000.0593

Kool, W., McGuire, J.T., Rosen, Z.B., Botvinick, M.M., 2010. Decision making and the avoidance of cognitive demand. J. Exp. Psychol. Gen. 139, 665–82. https://doi.org/10.1037/a0020198

Kouneiher, F., Charron, S., Koechlin, E., 2009. Motivation and cognitive control in the human prefrontal cortex. Nat. Neurosci. 12, 939–945. https://doi.org/10.1038/nn.2321

Kurniawan, I.T., Guitart-Masip, M., Dayan, P., Dolan, R.J., 2013. Effort and Valuation in the Brain: The Effects of Anticipation and Execution. J. Neurosci. 33, 6160.

Kurniawan, I.T., Guitart-Masip, M., Dolan, R.J., 2011. Dopamine and effort-based decision making. Front. Neurosci. 5, 81. https://doi.org/10.3389/fnins.2011.00081

Kurniawan, I.T., Seymour, B., Talmi, D., Yoshida, W., Chater, N., Dolan, R.J., 2010. Choosing to Make an Effort: The Role of Striatum in Signaling Physical Effort of a Chosen Action. J. Neurophysiol. 104, 313–321. https://doi.org/10.1152/jn.00027.2010

Le Heron, C., Plant, O., Manohar, S., Ang, Y.-S., Jackson, M., Lennox, G., Hu, M.T., Husain, M., 2018. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson’s disease. Brain 141, 1455–1469. https://doi.org/10.1093/brain/awy110

Levy, D.J., Glimcher, P.W., 2012. The root of all value: a neural common currency for choice. Curr. Opin. Neurobiol. 22, 1027–1038. https://doi.org/10.1016/j.conb.2012.06.001

Levy, I., Snell, J., Nelson, A.J., Rustichini, A., Glimcher, P.W., 2010. Neural representation of subjective value under risk and ambiguity. J. Neurophysiol. 103, 1036–1047. https://doi.org/10.1152/jn.00853.2009

Luijten, M., Schellekens, A.F., Kühn, S., Machielse, M.W.J., Sescousse, G., 2017. Disruption of Reward Processing in Addiction : An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies. JAMA psychiatry 74, 387–398. https://doi.org/10.1001/jamapsychiatry.2016.3084

Massar, S.A.A., Libedinsky, C., Weiyan, C., Huettel, S.A., Chee, M.W.L., 2015. Separate and overlapping brain areas encode subjective value during delay and effort discounting. Neuroimage 120, 104–113. https://doi.org/https://doi.org/10.1016/j.neuroimage.2015.06.080

Mehta, P.S., Tu, J.C., LoConte, G.A., Pesce, M.C., Hayden, B.Y., 2019. Ventromedial prefrontal cortex tracks multiple environmental variables during search. J. Neurosci. 39, 5336–5350. https://doi.org/10.1523/JNEUROSCI.2365-18.2019

Mohr, P.N.C., Biele, G., Heekeren, H.R., 2010. Neural processing of risk. J. Neurosci. 30, 6613–6619. https://doi.org/10.1523/JNEUROSCI.0003-10.2010

Mulert, C., Menzinger, E., Leicht, G., Pogarell, O., Hegerl, U., 2005. Evidence for a close relationship between conscious effort and anterior cingulate cortex activity. Int. J. Psychophysiol. 56, 65–80. https://doi.org/10.1016/j.ijpsycho.2004.10.002

Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., Tench, C.R., Yarkoni, T., Nichols, T.E., Turkeltaub, P.E., Wager, T.D., Eickhoff, S.B., 2018. Ten simple rules for neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 84, 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012

Nagase, A.M., Onoda, K., Foo, J.C., Haji, T., Akaishi, R., Yamaguchi, S., Sakai, K., Morita, K., 2018. Neural mechanisms for adaptive learned avoidance of mental effort. J. Neurosci. 38, 2631–2651. https://doi.org/10.1523/JNEUROSCI.1995-17.2018

Neubert, F.X., Mars, R.B., Sallet, J., Rushworth, M.F.S., 2015. Connectivity reveals relationship of brain areas for reward-guided learning and decision making in human and monkey frontal cortex. Proc. Natl. Acad. Sci. U. S. A. 112, E2695–E2704. https://doi.org/10.1073/pnas.1410767112

Otto, A., Daw, N., 2019. The opportunity cost of time modulates cognitive effort. Neuropsychologia 123. https://doi.org/10.1016/j.neuropsychologia.2018.05.006

Padoa-Schioppa, C., 2011. Neurobiology of Economic Choice: A Good-Based Model. https://doi.org/10.1146/annurev-neuro-061010-113648

Park, I.H., Lee, B.C., Kim, J.J., Kim, J. Il, Koo, M.S., 2017. Effort-Based Reinforcement Processing and Functional Connectivity Underlying Amotivation in Medicated Patients with Depression and Schizophrenia. J. Neurosci. 37, 4370–4380. https://doi.org/10.1523/JNEUROSCI.2524-16.2017

Peters, J., Büchel, C., 2009. Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. J. Neurosci. 29, 15727–15734. https://doi.org/10.1523/JNEUROSCI.3489-09.2009

Poldrack, R.A., Baker, C.I., Durnez, J., Gorgolewski, K.J., Matthews, P.M., Munafò, M.R., Nichols, T.E., Poline, J.B., Vul, E., Yarkoni, T., 2017. Scanning the horizon: Towards transparent and reproducible neuroimaging research. Nat. Rev. Neurosci. 18, 115–126. https://doi.org/10.1038/nrn.2016.167

Pooresmaeili, A., Wannig, A., Dolan, R.J., 2015. Receipt of reward leads to altered estimation of effort.

Proc. Natl. Acad. Sci. U. S. A. 112, 13407–13410. https://doi.org/10.1073/pnas.1507527112

Porat, O., Hassin-Baer, S., Cohen, O.S., Markus, A., Tomer, R., 2014. Asymmetric dopamine loss differentially affects effort to maximize gain or minimize loss. Cortex 51, 82–91. https://doi.org/10.1016/j.cortex.2013.10.004

Prévost, C., Pessiglione, M., Météreau, E., Cléry-Melin, M.-L., Dreher, J.-C., 2010. Separate valuation subsystems for delay and effort decision costs. J. Neurosci. 30, 14080–90. https://doi.org/10.1523/JNEUROSCI.2752-10.2010

Radua, J., del Pozo, N., Gomez, J., Guillen-Grima, F., Ortuno, F., 2014. Meta-analysis of functional neuroimaging studies indicates that an increase of cognitive difficulty during executive tasks engages brain regions associated with time perception. Neuropsychologia 58, 14–22. https://doi.org/10.1016/j.neuropsychologia.2014.03.016

Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S., 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur. Psychiatry 27, 605–611. https://doi.org/10.1016/j.eurpsy.2011.04.001

Rangel, A., Camerer, C., Montague, P.R., 2008. A framework for studying the neurobiology of value-based decision making. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn2357

Rudebeck, P.H., Walton, M.E., Smyth, A.N., Bannerman, D.M., Rushworth, M.F.S., 2006. Separate neural pathways process different decision costs. Nat. Neurosci. 9, 1161–1168. https://doi.org/10.1038/nn1756

Salamone, J.D., Correa, M., Farrar, A.M., Nunes, E.J., Pardo, M., 2009. Dopamine, behavioral economics, and effort. Front. Behav. Neurosci. https://doi.org/http://dx.doi.org/10.3389/neuro.08.013.2009

Salimi-Khorshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., Nichols, T.E., 2009. Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. Neuroimage 45, 810–823. https://doi.org/10.1016/j.neuroimage.2008.12.039

Sayalı, C., Badre, D., 2019. Neural systems of cognitive demand avoidance. Neuropsychologia 123, 41–54. https://doi.org/10.1016/j.neuropsychologia.2018.06.016

Schmidt, L., Lebreton, M., Cléry-Melin, M.-L., Daunizeau, J., Pessiglione, M., 2012. Neural Mechanisms

Underlying Motivation of Mental Versus Physical Effort. PLOS Biol. 10, e1001266-.

Scholl, J., Kolling, N., Nelissen, N., Wittmann, M.K., Harmer, C.J., Rushworth, M.F.S., 2015. The good, the bad, and the irrelevant: Neural mechanisms of learning real and hypothetical rewards and effort. J. Neurosci. 35, 11233–11251. https://doi.org/10.1523/JNEUROSCI.0396-15.2015

Schüller, C.B., Kuhn, J., Jessen, F., Hu, X., 2019. Neuronal correlates of delay discounting in healthy subjects and its implication for addiction: an ALE meta-analysis study. Am. J. Drug Alcohol Abuse. https://doi.org/10.1080/00952990.2018.1557675

Seaman, K.L., Brooks, N., Karrer, T.M., Castrellon, J.J., Perkins, S.F., Dang, L.C., Hsu, M., Zald, D.H., Samanez-Larkin, G.R., 2018. Subjective value representations during effort, probability and time discounting across adulthood. Soc. Cogn. Affect. Neurosci. 13, 449–459. https://doi.org/10.1093/scan/nsy021

Sescousse, G., Caldú, X., Segura, B., Dreher, J.C., 2013. Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2013.02.002

Shenhav, A., Botvinick, M.M., Cohen, J.D., 2013. The Expected Value of Control: An Integrative Theory of Anterior Cingulate Cortex Function. Neuron 79, 217–240. https://doi.org/10.1016/j.neuron.2013.07.007

Skvortsova, V., Palminteri, S., Pessiglione, M., 2014. Learning to minimize efforts versus maximizing rewards: Computational principles and neural correlates. J. Neurosci. 34, 15621–15630. https://doi.org/10.1523/JNEUROSCI.1350-14.2014

Soder, H.E., Cooper, J.A., Lopez-Gamundi, P., Hoots, J.K., Nunez, C., Lawlor, V.M., Lane, S.D., Treadway, M.T., Wardle, M.C., 2020. Dose-response effects of d-amphetamine on effort-based decision-making and reinforcement learning. Neuropsychopharmacology. https://doi.org/10.1038/s41386-020-0779-8

Stoppel, C.M., Boehler, C.N., Strumpf, H., Heinze, H.J., Hopf, J.M., Schoenfeld, M.A., 2011. Neural processing of reward magnitude under varying attentional demands. Brain Res. 1383, 218–229. https://doi.org/10.1016/j.brainres.2011.01.095

Sutton, R.S., Barto, A.G., 1998. Reinforcement learning : an introduction. MIT Press, Cambridge, Mass. :

Suzuki, S., Lawlor, V.M., Cooper, J.A., Arulpragasam, A.R., Treadway, M.T., 2020. Distinct striatal subregions and corticostriatal connectivity for effort, action and reward. bioRxiv 2020.02.12.925313. https://doi.org/10.1101/2020.02.12.925313

Syed, E.C.J., Grima, L.L., Magill, P.J., Bogacz, R., Brown, P., Walton, M.E., 2016. Action initiation shapes mesolimbic dopamine encoding of future rewards. Nat. Neurosci. 19, 34–36. https://doi.org/10.1038/nn.4187

Tanaka, S.C., Yamada, K., Yoneda, H., Ohtake, F., 2014. Neural mechanisms of gain-loss asymmetry in temporal discounting. J. Neurosci. 34, 5595–5602. https://doi.org/10.1523/JNEUROSCI.5169-12.2014

Treadway, M.T., Memmer, M., Shelton, R.C., Zald, D.H., 2012. Neural Mechanisms of Effort-Based Decision-Making in Depressed Patients. Biol. Psychiatry 71, 311S.

Vassena, E., Deraeve, J., Alexander, W.H., 2020. Surprise, value and control in anterior cingulate cortex during speeded decision-making. Nat. Hum. Behav. 4, 412–422. https://doi.org/10.1038/s41562-019-0801-5

Vassena, E., Deraeve, J., Alexander, W.H., 2017. Predicting Motivation: Computational Models of PFC Can Explain Neural Coding of Motivation and Effort-based Decision-making in Health and Disease. J. Cogn. Neurosci. 29, 1633–1645. https://doi.org/10.1162/jocn_a_01160

Vassena, E., Krebs, R.M., Silvetti, M., Fias, W., Verguts, T., 2014. Dissociating contributions of ACC and vmPFC in reward prediction, outcome, and choice. Neuropsychologia 59, 112–123. https://doi.org/10.1016/j.neuropsychologia.2014.04.019

Von Neumann, J., Morgenstern, O., 1990. Theory of games and economic behavior. Princeton University Press, New York :

Walton, M.E., Bannerman, D.M., Alterescu, K., Rushworth, M.F.S., 2003. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J. Neurosci. 23, 6475–6479. https://doi.org/10.1523/jneurosci.23-16-06475.2003

Walton, M.E., Groves, J., Jennings, K.A., Croxson, P.L., Sharp, T., Rushworth, M.F.S., Bannerman, D.M., 2009. Comparing the role of the anterior cingulate cortex and 6-hydroxydopamine nucleus accumbens lesions on operant effort-based decision making. Eur. J. Neurosci. 29, 1678–1691.

https://doi.org/10.1111/j.1460-9568.2009.06726.x

Westbrook, A., Braver, T.S., 2015. Cognitive effort: A neuroeconomic approach. Cogn. Affect. Behav. Neurosci. https://doi.org/10.3758/s13415-015-0334-y

Westbrook, A., Lamichhane, B., Braver, T., 2019. The Subjective Value of Cognitive Effort is Encoded by a Domain-General Valuation Network. J. Neurosci. 39, 3934–3947. https://doi.org/10.1523/JNEUROSCI.3071-18.2019

Wilson, R.P., Colizzi, M., Bossong, M.G., Allen, P., Kempton, M., Bhattacharyya, S., 2018. The Neural Substrate of Reward Anticipation in Health: A Meta-Analysis of fMRI Findings in the Monetary Incentive Delay Task. Neuropsychol. Rev. 28, 496–506. https://doi.org/10.1007/s11065-018-9385-5

Yang, X. hua, Huang, J., Lan, Y., Zhu, C. ying, Liu, X. qun, Wang, Y. fei, Cheung, E.F.C., Xie, G. rong, Chan, R.C.K., 2016. Diminished caudate and superior temporal gyrus responses to effort-based decision making in patients with first-episode major depressive disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 64, 52–59. https://doi.org/10.1016/j.pnpbp.2015.07.006

Yang, X. hua, Huang, J., Zhu, C. ying, Wang, Y. fei, Cheung, E.F.C., Chan, R.C.K., Xie, G. rong, 2014. Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. Psychiatry Res. 220, 874–882. https://doi.org/10.1016/j.psychres.2014.08.056

Yi, W., Mei, S., Zhang, M., Zheng, Y., 2020. Decomposing the effort paradox in reward processing: Time matters. Neuropsychologia 137, 107311. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2019.107311

Yu, C., Zhou, Y., Liu, Y., Jiang, T., Dong, H., Zhang, Y., Walter, M., 2011. Functional segregation of the human cingulate cortex is confirmed by functional connectivity based neuroanatomical parcellation. Neuroimage 54, 2571–2581. https://doi.org/10.1016/j.neuroimage.2010.11.018

Zénon, A., Sidibé, M., Olivier, E., 2015. Disrupting the supplementary motor area makes physical effort appear less effortful. J. Neurosci. 35, 8737–8744. https://doi.org/10.1523/JNEUROSCI.3789-14.2015