Ketamine selectively changes outcome valuation in a biased matching pennies task

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Keywords

Abstract

Throughout our daily lives we make multitudes of decisions. Occasionally, these decisions may lead to favorable outcomes, such as gains, while at other times they may lead to unfavorable outcomes, such as losses. We generally tend to repeat those decisions that have led to favorable outcomes in the past, and we tend to refrain from repeating those decisions that previously led to unfavorable outcomes. How relevant information is integrated over time in order to form optimal decisions is likely influenced by NMDA receptor activity. Here we tested the effects of ketamine, an NMDA receptor antagonist, which has been suggested to affect a wide array of cognitive functions, on choice behavior in a biased matching pennies task in monkeys. In this task, monkeys had to collect six tokens in order to receive a reward. With every binary choice, monkeys would either gain tokens, lose tokens or the number of tokens would remain unchanged. Monkeys generally tended to switch choice targets following losses and to repeat choice targets following gains. Low doses of ketamine temporarily changed choice behavior in particular following unfavorable (loss or neutral) outcomes, but not after favorable (gain) outcomes. Specifically, monkeys were less likely to switch away from a choice target after it had led to an unfavorable outcome under ketamine conditions. Reinforcement learning models suggest that ketamine independently and to varying degrees increased the value of the three possible outcomes in this task. The strongest value increase occurred for loss outcomes. This was the case when ketamine was administered intramuscularly or intranasally, whereby intranasal ketamine induced substantially less side-effects on eye movements. Overall, we found evidence that ketamine may temporarily mitigate in particular the negative valuations of unfavorable outcomes, potentially allowing some insights into its underlying cognitive effects.

Introduction

In everyday life we make a plethora of decisions, in which we process multiple options and then choose an optimal course of action. Often, we repeat those actions that have led to a positively valued outcome and we tend to refrain from repeating those actions that have led to a negatively valued outcome. How information is integrated over time in order to arrive at an optimal decision is likely influenced by NMDA receptor activity, a concept which was originally proposed in the context of multisensory integration and perceptual decisions (Binns and Salt, 1996; Wang, 2002, 2008; Standage and Paré, 2011), but has more recently been suggested to be relevant for value-based decision processes as well (Hunt et al., 2012; Chau et al., 2014; Scholl et al., 2014). The study of the effects of perturbations of NMDA receptor activity on value-based decision making has been rare (Scholl et al., 2014). One NMDA receptor antagonist that has received much attention in recent years is ketamine. Traditionally used to induce anesthesia (Reich and Silvay, 1989), it has more recently been identified as a rapid-acting antidepressant at subanesthetic doses, causing relief in many affected individuals within 24 hours of administration (Newport et al., 2015; Gould et al., 2019). How ketamine affects cognitive processes is however still not understood.

Indeed, ketamine has been found to affect a wide range of cognitive behavior in rodents, non-human primates and humans. At subanesthetic doses it has for instance been shown to impair working memory performance (Taffe et al., 2002; Roberts et al., 2010a) and selective context processing (Umbricht et al., 2000; Blackman et al., 2013), an effect that has been likened to symptoms of schizophrenia (Krystal et al., 1994; Frohlich and Horn, 2014). Ketamine has also been suggested to increase distractibility (Condy et al., 2005), to impair transitive inference reasoning (Brunamonti et al., 2014), abstract rule acquisition (Krystal et al., 2000), and the ability to dynamically switch between task- or rule-sets (Stoet and Snyder, 2006; Nikiforuk et al., 2010; Skoblenick and Everling, 2012). Furthermore, ketamine relieves symptoms not only of depression but also of PTSD (Feder et al., 2014; Zhang et al., 2015) and OCD (Rodriguez et al., 2013), and seems to have general anxiolytic properties (Engin et al., 2009; Zhang et al., 2015; Fraga et al., 2018). In individuals with a drug abuse history, ketamine seems to increase the motivation to quit (Dakwar et al., 2014) and to reduce drug use (Krupitsky and Grinenko, 1997; Dakwar et al., 2017; Ivan Ezquerra-Romano et al., 2018; Jones et al., 2018).

In an effort to summarize, ketamine's actions on cognition may fall into several broader and potentially overlapping categories. It may exert its main effect by impairing cognitive control, for instance through a disruption of working memory and the ability to flexibly respond to different contexts or changes in the environment (Stoet and Snyder, 2006; Skoblenick and Everling, 2012; Blackman et al., 2013). Alternatively, ketamine's main influence may be on performance monitoring, by reducing a subject's ability to know when an error was made (Lewis and Bates, 2013; Skoblenick et al., 2016), which may include aberrant prediction error computations (Umbricht et al., 2000; Corlett et al., 2007; Gil-da-Costa et al., 2013) and attention focused on irrelevant stimuli (Corlett et al., 2007; Smith et al., 2011). Finally, in line with its antidepressant actions, ketamine may exert much of its influence on emotional and/or motivational processes, for instance through changing how positive and negative stimuli are valued (Scheidegger et al., 2016).

Beyond its cognitive effects, ketamine also has pronounced effects one eye movement behavior (Radant et al., 1998; Weiler et al., 2000; Pouget et al., 2010; Schmechtig et al., 2013; Steffens et al., 2016). Among others, ketamine has been shown to change saccadic frequency, latency and peak velocity, and it can induce profound nystagmus (Godaux et al., 1990; Radant et al., 1998; Pouget et al., 2010). Many of these oculomotor changes have been compared to psychotic symptoms of schizophrenia (Avila et al., 2002; Smyrnis et al., 2007; Levy et al., 2010).

In this study, we used a token-based binary choice task (Seo and Lee, 2009) to test the effects of intramuscular and intranasal ketamine on choice behavior following gains and losses. The token-based nature of this task (Figure 1A), in which tokens exchangeable with juice reward could be gained or lost, allowed us to compare gains and losses within the same currency and independent of primary juice reward. Furthermore, the comparatively large number of trials in between rewards allowed us insight into variable motivational states, while block-wise stimulus value changes allowed us to test adjustments of choice behavior to changes in the environment. Finally, we were able to assess the effects of ketamine on a wide variety of eye movement parameters.

Methods

Subjects and apparatus

Data was collected from three male rhesus monkeys (*Macaca mulatta*, age: 6-13 years, body weight: ~12-16kg). All procedures were approved by the Institutional Animal Care and Use Committee at Yale University and conformed to the Public Health Service *Policy on Humane Care and Use of Laboratory Animals* and *Guide for the Care and Use of Laboratory Animals.* Monkeys were seated in front of a monitor at a viewing distance of 57cm and eye positions were monitored at a sampling rate of 225Hz (Eye tracker ET 49, Thomas Recording). Reward was delivered as liquid drops (apple juice) from a sipper tube in front of the monkey's mouth. To ensure the monkeys' motivation, fluid intake was controlled during training and experimental sessions; unrestricted access to monkey chow was available in the home cage.

Behavioral task

Monkeys were trained to perform a token-based binary choice task (Figure 1). The task structure has been described in detail previously (Seo and Lee, 2009). Briefly, following an initial central fixation period (0.5s), two green peripheral targets were displayed to the left and right of the central fixation point. Following an additional 0.5s delay period, the central fixation point was extinguished and the animal made a saccade to either the left or right target. Once the animal had fixated its chosen target for 0.05s, the outcome of its choice was revealed via a feedback ring that appeared around the choice target for 0.5s. In addition, a series of filled or empty red disks were

displayed around the central fixation point throughout the entire trial that indicated to the animal the number of tokens it had collected until that point. The color of the feedback ring indicated whether the number of tokens would increase (grain: red), whether it would remain unchanged (neutral: blue) or whether it would decrease (loss: white) at the end of the trial. Once the animal had collected six tokens, these were replaced by six drops of juice. After juice delivery, the animal received two to four free tokens at the beginning of the next trial.

The outcome of the animals' choices in a given trial was determined by the payoff matrix of a biased matching pennies game (Figure 1B). During this game, the computer opponent simulated a rational decision maker who chooses its target so as to minimize the payoff of the animal. The animal gained tokens only when it chose the same target as the computer. When the animal's choice target differed from the computer's choice target, tokens were either lost or remained equal (neutral) depending on which target the animal chose. At all times, one of the two targets represented a 'safe' target, while the other represented a 'risky' target. The positions of the safe and risky targets were kept constant for a minimum of 40 trials, and then reversed uncued with a 0.1 probability after every following trial. The safe target had a higher probability of leading to the outcome neutral than to the outcome loss (MP: $P_{neut} = 1$, $P_{loss} = 0$; MY/MB: $P_{neut} = 0.7$, $P_{loss} = 0.3$), while the risky target had a higher probability of leading to the outcome loss than to the outcome neutral (MP: $P_{loss} = 1$, $P_{neut} = 0$; MYM/B: $P_{loss} = 0.7$, $P_{neut} = 0.3$). These parameters were adjusted individually for each animal to achieve similar choice behavior following gain, neutral and loss outcomes (Figure 1C). The equilibrium strategy with the highest payoff for the animal was set to choosing the safe target with 2/3 probability and the risky target with 1/3 probability.

Experimental Procedures

Prior to starting these experiments, all animals showed stable performance on the task. In each experimental session, monkeys performed a minimum of 300 trials and worked for a minimum of 50 minutes.

For a drug session, monkeys received an intramuscular (IM) or intranasal (IN) injection of the NMDA antagonist ketamine HCL (Ketaset®, 100mg/mL solution, Zoetis Inc.) into the right or left calf muscle (IM) or right or left nostril (IN) immediately prior to begin of the experimental session. Intranasal mucosal atomization devices (MAD Nasal™, Teleflex Medical) were used for the intranasal administrations of ketamine. On control days, sterile saline (IM, IN in monkey Y) or sterile water (IN in monkey P, B) was injected at the equivalent volume to drug days immediately prior to the experimental session. There was a minimum of a two-day washout in between ketamine administrations with most administrations being spaced one week apart (mean days in between ketamine administrations: 6.4 days). All experimental sessions were recorded at the same time of day for each animal. We tested two doses of IM ketamine, a lower dose of 0.25mg/kg (monkey P, Y) and a higher dose of 0.5mg/kg (all monkeys). These doses were chosen based on the therapeutic range of ketamine used as an antidepressant in human patients (Newport et al., 2015). We also tested two doses of IN ketamine, 0.5mg/kg (monkey P, B) and 1mg/kg (all monkeys), to match the behavioral effects we observed with IM ketamine administrations.

Plasma ketamine level analysis

To be able to effectively compare behavioral effects observed following IM and IN administration of ketamine, we tested plasma levels of ketamine following IM and IN administrations in monkey B. For this, the animal was placed in its usual primate chair and blood samples were collected prior to (~ 5 min) and at set time intervals (10, 25, 40, 60, 75 min) following ketamine administration. We collected one blood sample session with the 0.5mg/kg IM administration and two blood sample sessions with the 0.5mg/kg IN and 1mg/kg IN administration each, due to potentially higher variability in administration. After discovering a more sustained blood level concentration following 0.5mg/kg IN ketamine administration (Figure S8), we added an additional blood data point at 75min following administration of the 1mg/kg IN dose. No behavioral testing took place on blood collection days. Blood was collected into EDTA tubes to prevent clotting and placed on ice. Within 2 hours of collection, blood was centrifuged for approx. 5 min at 2000 rpm, and plasma was extracted. Plasma samples were then frozen at -80° until the HPLC protocol (modified from (Gross et al., 1999)) was applied. 100ng of the internal standard clonidine and 0.5ml of thawed plasma were added to a 15ml polypropylene tube and 15ml of diethyl ether added. Following 5 min of vortex mixing, 4 mL of the upper ether layer was transferred to a new polypropylene tube and 250 µL of 0.01 M phosphoric acid added. After vortex mixing for 5 min, the lower aqueous layer was transferred to a 1.5 mL tube and evaporated under vacuum (~ 1 hour, SpeedVac evaporator, medium heat). The dry residue was dissolved in 150 µL of 0.01 sodium monobasic dihydrogen phosphate. 50 µL of the extract was injected and separated on a 3 µm Cyano Spherisorb HPLC column (4.6 x 100 mm) eluted with 80% 0.01 sodium acetate/20% acetonitrile (0.8 mL/min, 40C). Norketamine, ketamine and clonidine were detected by UV absorption (220 nm; Hitachi L-7400) with retention times of 6.1, 8.1 and 11.0 minutes, respectively; and with absolute detection limits of 0.2, 0.5 and 0.3 ng, respectively. Extracted standards were prepared using 0.5 mL aliquots of pooled human plasma. Plasma drug concentrations of samples were calculated knowing the peak height ratios of the extracted standards, the peak height ratios in samples and the amount of internal standard added (200 ng/mL). When injecting 50 µL of the extract, norketamine and ketamine were determined with concentration detection limits of 1 and 2 ng/mL, respectively.

Data analysis

Choice behavior. We tested how an animal's choice behavior was affected by gains, losses, and neutral outcomes in the previous five trials by applying the following regression model:

$$\log\left[\frac{p_t(right)}{p_t(left)}\right] = \sum_{i=1}^{5} a_i Z_1(t-i) + \sum_{i=1}^{5} b_i Z_2(t-i) + \sum_{i=1}^{5} c_i Z_3(t-i) + \sum_{i=1}^{5} d_i Z_4(t-i)$$

Where p_t is the probability of choosing the right or left target in the current trial t. a_i, b_i, and c_i are the regression coefficients at trial t-i for loss, neutral, and gain outcomes, respectively. Z_1 becomes

1 when a loss followed a right-ward choice, -1 if a loss followed a left-ward choice, and 0 otherwise. Similarly, Z_2 becomes 1 if there was a neutral outcome following a right-ward choice, -1 if there was a neutral outcome following a left-ward choice, and 0 otherwise. Z_3 becomes 1 when a gain followed a right-ward choice, -1 if a gain followed a left-ward choice, and zero otherwise. Finally, Z4 becomes 1 if there was a reward outcome (6 tokens replaced by juice drops) following a right-ward choice, -1 if there was a reward outcome following a left-ward choice, and 0 otherwise. A positive (negative) coefficient in this logistic regression model indicates that a particular outcome resulting from the choice of a given target reinforces (punishes) that same behavior. This was evaluated for several trial lags of up to five trials in the past.

For the main analysis of choice behavior, in order to increase statistical power by retaining more trials, one trial was allowed to be aborted in between trials for them to still be considered successive choice trials with a lag of one. For a control analysis, we made this criterion more stringent, whereby choice trials were only considered successive if no other trial occurred in between them.

We quantified general differences in choice behavior following different outcomes, trial lags, drug condition, and dose, using 3-way (monkey B) and 4-way ANOVA's (monkey P, Y). In addition, we compared individual regression coefficients between ketamine and saline conditions using t-tests (α=0.05).

We computed the probability of choosing the safe target (P(safe)) relative to block transitions (Figure S5). To compare P(safe) between saline and ketamine sessions, we averaged P(safe) in non-overlapping 5-trial windows from -10 to +30 trials around block transitions and compared using t-tests in each of eight trial windows (α=0.05, Bonferroni-Holm multiple-comparison corrected).

Time-resolved choice behavior. For the time-resolved analysis, we evaluated choice behavior in 20-minute non-overlapping windows as described above, with two additional restrictions: i) a minimum of 5 trials of each trial type (gain in trial t-1, gain in trial t-2 etc.) had to be available for analysis in a given time window for the data to be included in the average across sessions, and ii) a minimum of 15 rewarded trials had to have occurred in a given time window for the fourth regression term (Z_4 above) to be included in the regression model. We then quantified differences in regression coefficients between the saline and ketamine conditions using a randomization procedure in which drug condition labels were randomly shuffled (n=1000) to compute a randomized mean distribution of regression coefficient differences. We considered any differences between the saline and ketamine conditions that fell outside of ± 2 standard deviations of the randomized mean as significant.

Eye movement analyses. We estimated nystagmus by computing the slow phase velocity (SPV, Barnes, 1982) of horizontal eye movements during the 500ms target fixation epoch (prior to feedback onset). Specifically, we computed eye velocity for the entire target fixation window and then excluded any fast phase saccadic events (velocity > 20deg/s and amplitude > 0.5deg) to

extract only slow phase events (Figure 4 A, B). These were then averaged within a fixation period (i.e. trial) to obtain the SPV for each trial. To average across trials (to the left and right target), SPV was multiplied by -1 for choices made to the left target. Average SPV was compared across saline and ketamine sessions using 3-way ANOVA (2-way ANOVA when only one dose tested) with the factors drug condition, dose and time since injection (20min time windows from 0-80min post injection). For Figure 4C/D, SPV was averaged in one-minute non-overlapping windows. Saccade latency was computed as the time between fixation offset (removal of fixation point) and saccade onset (velocity > 20deg/s). Differences in saccade latency between drug and control conditions were tested using 3-way ANOVA (2-way ANOVA when only one dose tested) with the factors drug condition, dose and time since injection (20min time windows from 0-80min post injection). Differences in saccade latency at individual time points was estimated using a t-test (α=0.05) (Figure S7 B/C). Analysis of fixation breaks (errors) is described below in the section *Error rate and motivation*. All of the following eye movement measures were estimated in the time window 0-40 minutes following administration and trials within this time window were combined across experimental sessions: mean variability in eye position and velocity of eye position during active fixations (excluding any saccadic events), saccadic peak velocity, amplitude and numbers of saccades after feedback onset. Differences between ketamine and saline conditions were estimated using t-tests (α=0.05). Variability in eye position was computed as the standard deviation across eye positions during active fixation. Post-loss slowing was identified as the difference in choice saccade latencies in trials following losses vs. gains (loss-gain). Differences in post-loss slowing between ketamine and saline sessions were estimated using t-tests (α=0.05). The Δ sign in the text refers to differences between ketamine and saline conditions (ketamine-saline) unless otherwise indicated.

Ketamine plasma levels. We compared plasma levels following 0.5 mg/kg IM, 1 mg/kg IN and 0.5 mg/kg IN ketamine with a 2-way ANOVA with factors time (0-60/75 minutes following administration) and group (0.5 IM, 1 IN, 0.5 IN). We followed this up with a Tukey's HSD test of the group factor comparison.

Comparison of administration routes. To quantify differential effects on behavior and nystagmus of ketamine following the two administration routes (IM, IN), we computed average nystagmus and average regression coefficients for choices immediately following a loss (loss behavior) in the first 40 minutes of every experimental (ketamine) session. Because IN and IM data was occasionally collected months apart, instead of comparing loss regression coefficients directly, we compared the difference in ketamine regression coefficients against the corresponding mean saline regression coefficients. We ran two linear regression models; the first treated nystagmus as the response variable, the second treated loss behavior as the response variable, with the additional factors administration route and animal. For this analysis, only the two higher doses were included (0.5 mg/kg IM, 1 mg/kg IN). Mainly for visualization purposes, we additionally computed a simple correlation analysis (Pearson correlation) between the route of administration and the magnitude of nystagmus, the magnitude of loss regression coefficient difference, as well as two other eye

movement parameters – saccade latency and error rate (also within first 40 minutes of ketamine sessions).

Error rate and motivation. We defined errors in this task as breaks in fixation, i.e. trials that the animal initiated but did not complete. We compared overall error rates (proportion fixation breaks) in drug and control sessions using 3-way ANOVA with the factors drug condition, dose, and time since injection (20min time windows from 0-80min post injection).

As a proxy for motivation we quantified error rates as a function of a) previous trial outcome, with the assumption that motivation is higher following a token gain compared with a token loss in the immediately preceding trial, and b) current number of filled tokens, with the assumption that motivation is higher the more tokens have already been filled (e.g. 2 tokens vs. 5 tokens) and therefore the less tokens are still needed to receive reward. We tested the difference in error rates between the ketamine and saline condition for the different trial types time-resolved (5-min non-overlapping windows) using an ANOVA with the factors trial type (previous trial outcome: gain, neutral, loss; current number of tokens: 1-5) and drug condition (saline, ketamine). As a control analysis, we also tested the difference in error rates resolved by the cumulative number of tokens collected (30 (monkey P)/60 (monkey Y/B) token non-overlapping windows). The window of analysis for the ANOVA was selected for each monkey so as to encompass the cumulative token window in which an increased error rate generally occurred (Figure S9). This was done individually to account for differences in task parameters (e.g. monkey P generally gained fewer tokens than monkeys Y and B, see Figure 1), and differences in performance (e.g. monkey B collected fewer tokens in a session compared with monkey Y albeit similar task parameters). As such, the token analysis windows for monkey P, Y, and B were 25-150 tokens, 50-300 tokens, and 50-200 tokens respectively.

To verify that the two proxies of motivation were indeed valid estimates, we tested how often animals took breaks from the task depending on the previous trial outcome and on the number of tokens filled on the screen. Specifically, we compared the numbers of breaks initiated a) following gain versus loss outcomes, and b) with 0-1 tokens on the screen versus 4-5 tokens on the screen, using a X^2-test. For this analysis, the last trial prior to a break was discarded if it ended in a juice reward.

As a comparison analysis, we tested whether the probability to switch after a loss was dependent on the number of tokens available to the monkey and on the drug condition using 2-way ANOVA.

Reinforcement learning models

All modeling was done with the data from IM injections of 0.5mg/kg ketamine/saline.

Saline Models. We started off with fitting behavior in saline sessions with seven different models, to identify the one that captures behavior under normal conditions best. The first model (*Saline Q*

Standard) tested represents a standard reinforcement learning model in which only the chosen action value was updated from trial to trial as follows:

$$Q_t = Q_{t-1} + \alpha_1 * (V - Q_{t-1}), \tag{1}$$

whereby Q_t is the value of the chosen action at trial t, α_1 is learning rate ($0<\alpha_1<1$), and V=1/0/-1 for gain/neutral/loss outcome, respectively. The value of the unchosen action was not updated. Action selection was updated according to a softmax function:

$$P(R)_t = \frac{1}{1+\exp\left(-\beta*(Q(R)_t - Q(L)_t)\right)}, \tag{2}$$

whereby $P(R)_t$ is the probability of choosing the right target at trial t and β is inverse temperature. The second model (*Saline DF-Q*) tested is a Q-learning model with differential forgetting (Ito and Doya, 2009; Barraclough et al. 2004), in which chosen action values were updated as follows:

$$\begin{aligned} &Gain\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{gain} \\ &Neut\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{neut} \\ &Loss\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{loss} \end{aligned} \tag{3}$$

And unchosen actions were updated according to:

$$Q_{t,unchosen} = (1-\alpha_2) * Q_{t-1,unchosen} \tag{4}$$

whereby $Q_{t,chosen}$ is the value of the chosen action in trial t and $Q_{t,unchosen}$ is the value of the unchosen action in trial t; α_1 is the learning rate for chosen action and α_2 is the forgetting rate for the unchosen action. $V_{gain}/V_{neut}/V_{loss}$ are the values associated with each of the outcomes. Trial-by-trial action selection was updated as follows:

$$P(R)_t = \frac{1}{1+\exp\left(-(Q(R)_t - Q(L)_t)\right)} \tag{5}$$

The third, fourth, fifth and sixth models are simplified variations of the second model. The third model (*Saline DF-Q neutral*) tested is equivalent to the *Saline DF-Q* model in which however $V_{neut}=0$. The fourth model (*Saline F-Q*) is equivalent to the *Saline DF-Q* model in which however $\alpha_1=\alpha_2$. In the fifth model (*Saline F-Q neutral*) then both $V_{neut}=0$ and $\alpha_1=\alpha_2$. In the sixth model (*Saline NF-Q*), the chosen actions are updated according to the *Saline DF-Q* model, while the unchosen actions are not updated.

In the seventh model (*Saline F-Q asset*), we attempted to account for potential effects of motivation, whereby action values may be affected by the current number of tokens collected by the animal. In this model, chosen and unchosen action values were updated as follows:

$$\begin{aligned} Q_{t,chosen} &= (1-\alpha_1) * Q_{t-1,chosen} + Out * asset * \lambda \\ Q_{t,unchosen} &= (1-\alpha_2) * Q_{t-1,chosen} \end{aligned} \tag{6}$$

Whereby asset represented the number of tokens filled in trial t-1 and λ a motivation factor. Out was set at 1/0/-1 if the outcome in t-1 was gain/neutral/loss, respectively. Action selection was updated according to equation (4).

All models were evaluated using log-likelihood based optimization using MATLAB's fminsearch function. To compare the performance of the different models we calculated the Bayesian Information Criterion (BIC). The BIC penalizes model performance by the number of free parameters and is lowest for the model that fits the behavioral choices best.

Ketamine models. Based on the best fitting saline model (*Saline DF-Q*), we derived a selection of ketamine models in an effort to better understand ketamine's effects on choice behavior. For these models, we fitted choice data from ketamine sessions using a selection of parameters from the best *Saline DF-Q* model as well as varying free parameters to estimate how choices under ketamine differed from those under saline conditions. In a first control model (*Ketamine Control*), we used all of the fitted parameters from the *Saline DF-Q* model to compute the log-likelihood for the ketamine data.

We then derived four value models based on the hypothesis that ketamine affects the values assigned to the different outcomes. In the first of those value models (*Ketamine Value All*), we used α_1 and α_2 as fixed values from the *Saline DF-Q* model and fitted V_{gain}, V_{neut} and V_{loss} as free parameters, hypothesizing that ketamine affects the values of all three outcomes independently. Therefore, chosen action values were updated as follows:

$$\begin{aligned} Gain\ (t-1): &\quad Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{gain} \\ Neut\ (t-1): &\quad Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{neut} \\ Loss\ (t-1): &\quad Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{loss} \end{aligned} \tag{7}$$

And unchosen action values were updated according to:

$$Q_{t,unchosen} = \left(1 - A_{2(sal)}\right) * Q_{t-1,unchosen} \tag{8}$$

whereby $A_{1(sal)}/A_{2(sal)}$ represent the best fit α_1/α_2 parameters from the *Saline DF-Q* model.

The second value model (*Ketamine Value Neut+Loss*) tested the hypothesis that ketamine only affects the values of neutral and loss outcomes and does so to the same degree. Here chosen action values were updated as follows:

$$\begin{aligned} &Gain\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{g\ (sal)} \\ &Neut\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{n\ (sal)} + \kappa_1 \\ &Loss\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{l\ (sal)} + \kappa_1 \end{aligned} \tag{9}$$

where $V_{g\ (sal)}/V_{n\ (sal)}/V_{l\ (sa)}$ represent the best fit $V_{gain}/V_{neut}/V_{loss}$ from the *Saline DF-Q* model. κ is an additional free value parameter used in the action value updating following neutral and loss outcomes. Unchosen action was updated as in eq. 8.

The third value model (*Ketamine Value Neut/Loss*) resembled the second value model with the difference that neutral and loss outcomes were hypothesized to be affected differently by ketamine. For this model chosen action values were updated as follows:

$$\begin{aligned} &Gain\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{g\ (sal)} \\ &Neut\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{n\ (sal)} + \kappa_1 \\ &Loss\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{l\ (sal)} + \kappa_2 \end{aligned} \tag{10}$$

where κ_1 and κ_2 are additional free value parameters. Again, unchosen actions were updated as in eq. 8.

The fourth and final value model (*Ketamine Value Gain vs. NoGain*) again resembled the second value model with the differences that it hypothesized that ketamine affected gain value as well. For this model chosen action values were updated as follows:

$$\begin{aligned} &Gain\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{g\ (sal)} + \kappa_1 \\ &Neut\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{n\ (sal)} + \kappa_2 \\ &Loss\ (t-1): && Q_{t,chosen} = \left(1 - A_{1(sal)}\right) * Q_{t-1,chosen} + V_{l\ (sal)} + \kappa_2 \end{aligned} \tag{11}$$

With the same conventions as above. Unchosen actions were updated as in eq. 8.

We tested a memory model (*Ketamine Memory*), which hypothesized that ketamine's actions were mainly on memory – namely on the learning rate of chosen actions and on the forgetting rate of unchosen actions. For this model unchosen actions were updated as follows:

$$\begin{aligned} &Gain\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{g\ (sal)} \\ &Neut\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{n\ (sal)} \\ &Loss\ (t-1): && Q_{t,chosen} = (1-\alpha_1) * Q_{t-1,chosen} + V_{l\ (sal)} \end{aligned} \tag{12}$$

And unchosen actions as follows:

$$Q_{t,unchosen} = (1-\alpha_2) * Q_{t-1,unchosen} \tag{13}$$

Whereby α_1 and α_2 were free parameters fit with ketamine data, while $V_{g\ (sal)}/V_{n\ (sal)}/V_{l\ (sal)}$ represented the best fit parameters $V_{gain}/V_{neut}/V_{loss}$ from the *Saline DF-Q* model.

We tested a perseveration model (*Ketamine Pers.*), which hypothesized that ketamine mainly increased perseverative behavior by increasing the likelihood of animals to repeat choices. For this model, action value updating occurred using the fit parameters from the *Saline DF-Q* model (α_1, α_2, V_{gain}, V_{neut}, V_{loss}), while the action selection occurred as follows:

$$P(R)_t = \frac{1}{1+\exp\left(-\left((1-\varepsilon)*(Q(R)_t - Q(L)_t) + P*\varepsilon\right)\right)} \tag{14}$$

where P=1 if a right choice was made in t-1 and P=-1 if a left choice was made in t-1. ε is a free perseveration parameter.

In addition to the *Ketamine Pers.* model, we tested the possibility that ketamine affects both – perseverative behavior as well as outcome valuation. In this model (*Ketamine Value Pers.*), action value updating occurred according to eq. 7 and action selection occurred according to eq. 14.

We devised three different models that tested the possibility that ketamine caused a disruption in temporal credit assignment (TCA), namely an interference of irrelevant choices or outcomes and their associations. A possibility is that this interference affects choices but is not being integrated over time and can therefore be realized in the action selection process. The first TCA model (*Ketamine TCA MIS*) hypothesized that the most recent outcome becomes associated with choices that lie further in the past, which influences the probability of choosing a particular action in the next choice. In this model, action selection is updated as follows:

$$P(R)_t = \frac{1}{1+\exp(-X)}, \qquad \text{with X=X1+X2+X3+X4} \tag{15}$$

Where:

$$X1 = Q(R) - Q(L) \tag{16}$$

$$X2 = \omega_1 * I_{R(t-2)} * V_{out\,(t-1)} \tag{17}$$

$$X3 = \omega_2 * I_{R(t-3)} * V_{out\,(t-1)} \tag{18}$$

$$X4 = \omega_3 * I_{R(t-4)} * V_{out\,(t-1)} \tag{19}$$

With $I_{R(t-i)}$ =1/-1 if choice at trial t-i is right/left, respectively. $V_{out(t-1)}$ corresponds to $V_{gain}/V_{neut}/V_{loss}$ from the *Saline DF-Q* model if the preceding choice ended in a gain/neutral/loss outcome, respectively. ω_1, ω_2 and ω_3 are free misassignment parameters that determine the strength of the association between preceding choices and the most current outcome. Action value updating is done as in equation 3 using the parameters from the *Saline DF-Q* model.

The second TCA model (*Ketamine TCA Spread*) is complementary to the first TCA model. It hypothesizes that the most recent action becomes associated with outcomes that lie further in the past, which again influences the probability of choosing a particular action in the next choice. In this model, action selection is updated according to equation 15 and X1 is defined according to eq. 16; however, the updating of X2, X3 and X4 is as follows:

$$X2 = \omega_1 * I_{R(t-1)} * V_{out\,(t-2)} \tag{20}$$

$$X3 = \omega_2 * I_{R(t-1)} * V_{out\,(t-3)} \tag{21}$$

$$X4 = \omega_3 * I_{R(t-1)} * V_{out\,(t-4)} \tag{22}$$

Whereby $I_{R(t-1)}$ =1/-1 if choice at trial t-1 is right/left, respectively, and $V_{out(t-i)}$ corresponds to $V_{gain}/V_{neut}/V_{loss}$ from the *Saline DF-Q* model if the choice in trial t-i ended in a gain/neutral/loss outcome, respectively.

The third TCA model (*Ketamine TCA SL*) hypothesizes that ketamine increases statistical learning, whereby the frequency with which a particular choice has been made in the past and average outcome received across all choices influences the probability of making that particular choice. Action selection in this model is realized as follows:

$$P(R)_t = \frac{1}{1+\exp(-X)}, \qquad \text{with X=X1+X2} \tag{23}$$

with

$$X1 = Q(R) - Q(L) \tag{24}$$

$$X2 = \omega_1 * I(|rFreq_t| > \tau) * rFreq_t * avg_out_t \tag{25}$$

whereby

$$rFreq_t = Freq_{R,t} - Freq_{L,t} \tag{26}$$

$$Freq_{A,t} = \rho * Freq_{A,t-1} + I_{chosen} \quad (27)$$

$$I(|rFreq_t| \geq \tau) = 1(0), if\ |rFreq_t| \geq (<)\tau \quad (28)$$

$$avg_out_t = \varphi * avg_out_{t-1} + V_{out,t} \quad (29)$$

whereby A denotes the current action (R/L) and I_{chosen} = 1/0 if A is chosen/unchosen in trial t. $V_{out(t-1)}$ corresponds to $V_{gain}/V_{neut}/V_{loss}$ from the *Saline DF-Q* model if the preceding choice ended in a gain/neutral/loss outcome, respectively. ω_1, τ, ρ and φ are the free parameters which the model fits with the ketamine data. ω determines how strongly statistical learning influences the next choice, τ determines at which relative frequency of choices statistical learning becomes relevant, ρ and φ $_{\text{determine}}$ the rate at which choice frequency and average outcome are updated.

Finally, we tested a motivation model (*Ketamine Motivation*) that hypothesized that ketamine's main action on behavior were driven by a change in how strongly motivation affects action valuation. For this model, we used the best fit parameters from the *Saline F-Q asset* model and updated action values according to:

$$\begin{aligned} Q_{t,chosen} &= \left(1 - A_{1\ (sal)}\right) * Q_{t-1,chosen} + V_{o\ (sal)} * asset * \ \Lambda_{sal} * \lambda_2 \\ Q_{t,unchosen} &= \left(1 - A_{2\ (sal)}\right) * Q_{t-1,chosen} \end{aligned} \quad (30)$$

whereby $A_{1(sal)}$ / $A_{2(sal)}$ correspond to α_1 / α_2 from the *Saline F-Q asset* model and $V_{o(sal)}$ represents $V_{gain}/V_{neut}/V_{loss}$ from the *Saline F-Q asset* model if the outcome at trial t was gain/neutral/loss, respectively. Similarly, Λ_{sal} represents the fitted parameter λ from the *Saline F-Q asset* model. λ_2 is a free parameter fitted with the ketamine data.

Just like the saline models, all ketamine models were evaluated using log-likelihood based optimization using MATLAB's fminsearch function. To compare the performance of the different models we calculated the Bayesian Information Criterion (BIC). The model with the lowest BIC best captures the behavioral choices of the animals.

Simulations. For all model simulations, we simulated monkey choice behavior using the same computations as in the respective model and using the optimal parameters determined by the model fitting. For each monkey, we simulated the same number of saline and ketamine sessions that were actually performed by the animal. Similarly, each simulated session contained the average amount of trials performed by a given animal.

Results

Choice behavior in biased-matching pennies task

All three animals showed robust choice behavior following gain, neutral and loss outcomes in the biased matching pennies task (Figure 1C). All animals were relatively more likely to choose the same target again following a gain outcome in the preceding trials (positive regression coefficients), and were relatively more likely to switch target stimuli following loss outcomes in the preceding trials (negative regression coefficients), with choice behavior following neutral outcomes falling in between. 2-way ANOVAs revealed significant main effects for outcome and trial lag, as well as significant interactions between the two factors in all three monkeys (all $p<.0001$). In experimental control sessions, monkeys P/Y/B on average aborted 20%/20%/26% of trials, respectively. The distance in between rewarded trials was on average 12.2/3.8/3.8 trials for monkeys P/Y/B, respectively.

Effect of ketamine on choice behavior

Neither IM nor IN administration of ketamine affected the total number of choices made, the cumulative tokens obtained in an experimental session, or the average distance in between rewards (all monkeys: t-test, $p>.05$). However, ketamine selectively affected choice behavior in all three animals with both administration routes. Specifically, all animals were on average less likely to switch choice targets following loss and neutral outcomes (less negative regression coefficients), while choice behavior following gains did not consistently change (Figure 2A, 3A). This was particularly evident following more recent outcomes, and with higher doses of ketamine (Figure 2A, 3A, S1A, S4A).

For IM ketamine administrations, 3- (monkey B) and 4-way ANOVAs, with the factors outcome (gain, neutral, loss), drug (ketamine, saline), trial lag (1-5), and dose (high, low, monkey P/Y only), revealed significant 3-way interactions between the factors outcome, drug and trial lag in all three animals (MP: $F(8, 1964)=4.05$; MY: $F(8, 1649)=4.46$; MB: $F(8, 509)=3.62$; all $p<.001$). Although we did not find significant 4-way interactions with the additional factor dose in monkey P ($F(8, 1964)=1.28$, $p=.251$) and Y ($F(8, 1649)=0.61$, $p=.772$), dose did seem to have a differential effect on choice behavior, as evidenced by a significant 3-way interaction between the factors dose, drug and outcome in monkey Y ($F(2, 1649)=6.38$, $p=.002$) and a significant 3-way interaction between the factors dose, trial lag and outcome in monkey P ($F(8, 1964)=2.33$, $p=.012$). For this main analysis, to increase statistical power by retaining more trials, one trial was allowed to be aborted in between trials for them to still be considered successive choice trials with a lag of one. As a control analysis, we increased this restriction such that no trial could be aborted in between two trials for them to be considered successive. We found qualitatively similar results (Figure S2), that further corroborate the selective effect of ketamine on loss and neutral outcomes. It is noteworthy that, particularly at trial lag 1, there is no difference between the ketamine and saline condition following gains but a consistent difference following neutral and loss outcomes. This is the case

even though regression coefficients for gains at trial lag 1 are more positive and differ less in magnitude difference from zero compared to neutral and loss outcomes.

To estimate the time-course of the IM ketamine effect on choice behavior, we tested the difference in the regression coefficients in the saline and ketamine sessions in 20-minute non-overlapping time windows for the three different outcomes in the immediately preceding trial (trial lag 1) using a randomization procedure (see Methods). We found that the selective effect of ketamine on choice behavior following a loss in the preceding trial was evident within approximately 40 minutes of administration for the high dose of IM ketamine, and within approximately 20 minutes of administration for the low dose of IM ketamine (Figure 2B, S1B). The effect of ketamine on choice behavior following a neutral outcome in the preceding trial was evident in monkey P in the first 20 minutes and in monkey Y in the 20-60 minutes following a high-dose administration, and in the first 20 minutes for both monkey P and Y following a low-dose administration. Choice behavior following a gain did not differ between ketamine and saline conditions in any animal in any of the time windows (Figure 2B, S1B).

To test whether IM ketamine had any longer lasting effects, we compared choice behavior in saline sessions the day following a ketamine session with all other saline sessions (>1 day after ketamine administration). Using 3-way ANOVAs with factors saline day, outcome and trial lag, we found no main effects of saline day or any interactions with saline day for any of the monkeys or doses (main effects saline day, 0.5mg/kg: MP: $F(1, 779)=0.14$; MY: $F(1, 734)=0.75$; MB: $F(1, 374)=2.45$, 0.25mg/kg: MP: $F(1, 749)=0.04$; MY: $F(1, 539)=0.05$, all $p>.1$) (Figure S3). Individual t-tests identified some differences between individual trial lag-outcome points, but these were sporadic and inconsistent.

Intranasal administration of ketamine led to qualitatively similar results (Figure 3A), whereby animals were selectively less likely to switch away from a target that led to a loss or neutral outcome in the preceding choices. As with the IM data, we used a 3-way ANOVA in monkey Y with the factors drug, outcome and trial lag, and 4-way ANOVAs in monkeys P/B with the additional factor dose to test the effects of ketamine. We found significant main effects of drug in all animals (MP: $F(1, 1229)=30.54$; MY: $F(1, 389)=10$; MB: $F(1, 1002)=29.06$; all $p<.01$), and interactions between the factors drug, outcome and trial lag (MP: $F(8, 1229)=4.89$, $p<.001$; MY: $F(8, 389)=1.89$, $p=.06$; MB: $F(8, 1002)=3.27$, $p=.001$). Although we found no significant 4-way interactions in monkeys P/B, they showed some effect of dose via a significant 3-way interaction of the factors drug, outcome and dose in monkey B ($F(2, 1002)=3.17$, $p=.042$), and a significant 3-way interaction of the factors outcome, dose and trial lag in monkey P ($F(8, 1229)=2.07$, $p=.036$).

The time-course of the IN ketamine effect on choice behavior following a loss in the preceding trial was similar to the time-course of the IM effect and evident within approximately 20-60 minutes of administration (Figure 3B). In monkey P, the effect of IN ketamine on choice behavior following a loss was more evident at a trial lag of 2 (i.e. two trials after a loss, insets Figure 3B), in particular for the higher dose of 1mg/kg.

With either administration route, ketamine did not have an effect on the speed with which animals adjusted their choice probabilities from the previously risky target to the currently safe target after

block transitions (t-tests in non-overlapping 5-trial windows around block transition, all p>.05) (Figure S5).

Effects of ketamine on eye movement behavior

At higher doses ketamine is routinely used to induce sedation in animals. At the lower subanesthetic doses used here, mild sedative effects of ketamine may nevertheless be observed, in particular in eye movement behavior. To gauge potential mild sedative effects of ketamine, we therefore first asked the more general questions of how likely animals were to take breaks from the task (more than 1 min without trial initiation), how long experimental sessions lasted, and whether the animals' ability to maintain eye fixation throughout trials was altered. In monkey P and B, administration of 0.5mg/kg IM ketamine was associated with greater numbers of breaks taken throughout a session (MP: Δ_{break}=4.2, MB: Δ_{break}=2.4, t-test, both p<.01) and overall longer session lengths (MP: Δ_{min}=21.9, MB: Δ_{min}=20.3, t-test, both p<.01). This was not the case for the lower dose of IM ketamine and this was not the case in monkey Y (t-tests, all other p>.3). IN administered ketamine did not affect session length or numbers of breaks taken in any monkey at any dose (t-tests, all p>.05).

Ketamine did affect the ability of animals to maintain fixation throughout a trial. We found a time- and dose-dependent increase in fixation breaks under ketamine conditions (Figure S6). 3-way ANOVAs in monkeys P/Y revealed significant 3-way interactions of the factors drug, time and dose (MP: F(3, 519)=5.75, p<.001; MY: F(3, 439)=15.4, p<.001) and 2-way ANOVA in monkey B revealed a significant 2-way interaction of the factors drug and time (F(3, 135)=26.24, p<.001). The previous indicated more errors occurring with the higher dose of ketamine, and the greatest increase occurring within 0-40 minutes of administration (Figure S6A). IN administered ketamine increased the proportion of fixation breaks committed only in monkey P (Figure S6B), for which a 3-way ANOVA revealed a significant main effect of drug (F(1, 327)=8.15, p=.005) and significant interactions between the factors drug and time (F(3, 327)=3.69, p=.012) and drug and dose (F(1, 327)=4.57, p=.033), indicating more errors occurring with the higher dose and within a narrower 20-40-minute post administration window. No such effect of IN ketamine was observed in monkeys Y or B (2/3-way ANOVAs, all p > .05)

To investigate the effects of ketamine on eye movement behavior in more detail, we evaluated several more eye movement parameters, 1) during the active fixation epochs in a trial and 2) when the animals were making saccades. These analyses were mostly restricted to the 0-40 minutes following administration to capture the window of maximum ketamine efficacy (e.g. Figures 2, 3, S6). While the animals were fixating, we evaluated the variability in eye positions and eye velocity during the initial central fixation epoch, during the sampling epoch when targets were shown, and during the feedback epoch when the animals were fixating on peripheral targets (Figure 1).

We found that in all animals during the initial fixation period, vertical eye position variability was increased with 0.5mg/kg IM ketamine (MP: Δ_{var_y}=0.38deg, MY: Δ_{var_y}=0.12deg, MB:

Δ_{var_y}=0.25deg, all p<.001), while horizontal eye position variability was increased less and only in monkeys P and Y (MP: Δ_{var_x}=0.11deg, MY: Δ_{var_x}=0.02deg, all p<.001). The same pattern of effects was seen with the lower 0.25mg/kg IM ketamine dose in monkeys P/Y (MP: Δ_{var_x}=0.44deg, Δ_{var_y}=1.02deg; MY: Δ_{var_x}=0.01deg, Δ_{var_y}=0.06deg, all p<.001). Eye position variability during the target sampling period, and eye velocity during the initial fixation and the target sampling period were not consistently affected by ketamine of either dose across monkeys. All animals showed a pronounced increase in vertical (MP: Δ_{var_y}=0.09deg, MY: Δ_{var_y}=0.05deg, MB: Δ_{var_y}=0.11deg, all p<.001) and particularly horizontal (MP: Δ_{var_x}=0.19deg, MY: Δ_{var_x}=0.19deg, MB: Δ_{var_x}=0.19deg, all p<.001) eye position variability and eye velocity (MP: Δ_{vel}=3.0deg/s, MY: Δ_{vel}=2.8deg/s, MB: Δ_{vel}=2.0deg/s, all p<.001) during peripheral fixations in the pre-feedback epoch with 0.5mg/kg of IM ketamine, as well as with 0.25mg/kg IM ketamine (MP: Δ_{var_x}=0.28deg, Δ_{var_y}=0.24deg, Δ_{vel}=10.1deg/s; MY: Δ_{var_x}=0.05deg, Δ_{var_y}=0.04deg, Δ_{vel}=2.3deg/s, all p<.001). IN administered ketamine at 1mg/kg did not lead to consistent changes in eye position variability or velocity during the initial fixation and target sampling period. However, similarly to IM ketamine it led to increased vertical and horizontal eye position variability and increased eye velocity during the pre-feedback period (MP: Δ_{var_x}=0.04deg, Δ_{var_y}=0.03deg, Δ_{vel}=0.81deg/s; MY: Δ_{var_x}=0.05deg, Δ_{var_y}=0.02deg, Δ_{vel}=2.0deg/s; MB: Δ_{var_x}=0.11deg, Δ_{var_y}=0.14deg, Δ_{vel}=2.2deg/s, all p<.001). At the lower dose, 0.5mg/kg IN administered ketamine did not consistently affect these measures.

Eye position variability and velocity were particularly affected during peripheral fixations, likely reflecting ketamine-induced nystagmus (Godaux et al., 1990; Radant et al., 1998; Pouget et al., 2010). We therefore explicitly quantified nystagmus time-resolved during fixations on peripheral targets (see Methods for details). We found that IM ketamine induced profound nystagmus in a dose- (monkey P/Y) and time-dependent manner (3-way ANOVA, 3-way interaction MP: F(3, 523)=20.69, p<.001, MY: F(3, 439)=118.33, p<.001; 2-way ANOVA, 2-way interaction MB: F(3, 124)=40.72, p<.001), with the greatest nystagmus occurring with the higher dose and within approximately 5-30 minutes following the administration (Figure 4C). Albeit to a markedly lesser degree than IM ketamine, IN administered ketamine also induced nystagmus in a time- and dose-dependent manner in monkeys B/Y (3-way ANOVA, 3-way interaction MB: F(3, 242)=6.26, p<.001; 2-way ANOVA, 2-way interaction MY: F(3, 103)=3.54, p=.018) (Figure 4D). Monkey P showed evidence of nystagmus via significant main effects of drug, time and dose (drug: F(1, 326)=20.61, p<.001, dose: F(1, 326)=6.33, p=.012, time: F(3, 326)=8.77, p<.001), but no significant interactions of these factors.

Beyond active fixations, we also evaluated ketamine's effects on saccadic behavior. Specifically, we tested ketamine's effects on saccadic latency (time to initiate a saccade), peak saccade velocities, saccade amplitudes and numbers of saccades made post feedback. Latencies to initiate a choice saccade after fixation offset were markedly increased with ketamine in the first 40 minutes following administration. This increase was dose- and time-dependent for both IM (Figure S7B, 3-way ANOVA, 3-way interaction, MP: F(3, 523)=3.05, p=.028, MY: F(3, 439)=12.2, p<.001; 2-way ANOVA, 2-way interaction MB: F(3, 139)=17.82, p<.001) and IN (Figure S7C, 3-way ANOVA, 3-way interaction, MP: F(3, 327)=3.42, p=.018, MB: F(3, 267)=3.08, p=.028; 2-way ANOVA, 2-way interaction MY: F(3, 103)=5.82, p=.001) ketamine administrations. This increase

was independent of potential post-error slowing, as saccadic latencies were consistently increased with ketamine following error (fixation breaks) and correct trials (Figure S7B,C).

Furthermore, even though peak velocity and amplitude of the choice saccade were not consistently affected across monkeys, peak velocity and amplitude of saccades made after feedback onset (these were voluntary saccades) were consistently decreased with 0.5mg/kg IM ketamine (MP: $\Delta_{peakvel}$= -97.8deg/s, Δ_{ampl}= -3.1deg; MY: $\Delta_{peakvel}$= -152.3deg/s, Δ_{ampl}= -3.3deg; MB: $\Delta_{peakvel}$= -891.3deg/s, Δ_{ampl}= -2.3deg, all p<.001). Monkeys also made consistently fewer saccades after feedback with 0.5mg/kg IM ketamine (MP: Δ_{numS}= -0.27; MY: Δ_{numS}= -0.28; MB: Δ_{numS}= -0.5, all p<.001). While the decrease in saccadic amplitude was maintained with the lower 0.25mg/kg IM dose (MP: Δ_{ampl}= -1.45deg; MY: Δ_{ampl}= -2.1deg;), saccadic peak velocity and numbers of post-feedback saccades were not consistently affected by this dose. IN administered ketamine consistently reduced saccade velocity and amplitude at the 1mg/kg dose in all monkeys (MP: $\Delta_{peakvel}$= -915deg/s, Δ_{ampl}= -2.8deg; MY: $\Delta_{peakvel}$= -82.2deg/s, Δ_{ampl}= -2.0deg; MB: $\Delta_{peakvel}$= -883deg/s, Δ_{ampl}= -2.6deg, all p<.001) and saccade amplitude at the 0.5mg/kg dose (MP: Δ_{ampl}= -1.1deg; MB: Δ_{ampl}= -0.75deg, all p<.001). Other measures were inconsistently affected.

In the past, ketamine has been suggested to exert anxiolytic-like effects in various animal models (Engin et al., 2009; Zhang et al., 2015; Fraga et al., 2018). We therefore wondered whether we could identify 1) eye movement behavior that differed based on whether the animal was just experiencing a gain outcome or a loss outcome, and 2) eye movement behavior that, independent of outcome, was predictive of whether the animal was going to stay with or switch its choice strategy for the next trial (i.e. choose the same target again or switch to the alternative target), and 3) whether ketamine affected these identified behaviors in a consistent manner. We were able to identify several eye movement behaviors in the post-feedback epoch in saline sessions that consistently differed based on the current outcome. We found i) an increase in eye position variability and eye velocity during the initial fixation on feedback when a loss feedback was seen compared to a gain feedback (MP: $\Delta_{(loss-gain)var_x}$=0.29deg, $\Delta_{(loss-gain)var_y}$=0.65deg, $\Delta_{(loss-gain)vel}$=2.51deg/s; MY: $\Delta_{(loss-gain)var_x}$=0.46deg, $\Delta_{(loss-gain)var_y}$=0.87deg, $\Delta_{(loss-gain)vel}$=1.29deg/s; MB: $\Delta_{(loss-gain)var_x}$=0.62deg, $\Delta_{(loss-gain)var_y}$=0.37deg, $\Delta_{(loss-gain)vel}$=2.25deg/s; all p<.001), ii) an increase in the latency to make a saccade away from feedback after loss compared with gain outcomes (i.e. animals were looking longer at loss feedback) (MP: $\Delta_{(loss-gain)lat}$=110.6ms; MY: $\Delta_{(loss-gain)lat}$=10ms; MB: $\Delta_{(loss-gain)lat}$=47.3ms, all p<.001), and iii) an increase in the number of saccades made post-feedback following a loss outcome (MP: $\Delta_{(loss-gain)numS}$=2.04; MY: $\Delta_{(loss-gain)numS}$=0.83; MB: $\Delta_{(loss-gain)numS}$=0.99, all p<.001). However, none of these measures were affected by ketamine in a consistent manner across monkeys. We could furthermore not identify any eye movement behavior that was consistently predictive of the animals' next choice.

It has previously been suggested that ketamine may cause a deficit in performance monitoring, whereby animals may no longer be able to efficiently differentiate errors from successes (Lewis and Bates, 2013; Skoblenick et al., 2016). One specific behavioral finding has been that post-error

slowing is no longer observed under ketamine conditions (Lewis and Bates, 2013). In the context of our task design, this could mean that animals may have a deficit in recognizing a loss outcome, which in turn may be reflected in a reduced saccadic 'post-loss slowing'. Across saline sessions, all animals did indeed show post-loss slowing, with greater choice saccade latencies in trials following a loss compared to those following a gain (MP: $\Delta_{(loss-gain)}$=11.5ms, p<.001; MY: $\Delta_{(loss-gain)}$=6.4ms, p<.001; MB: $\Delta_{(loss-gain)}$=6.7ms, p=.001). Ketamine however had a very inconsistent effect on post-loss slowing across monkeys. Monkey P showed significantly reduced post-loss slowing with both IM doses and with the higher IN dose (0.25mg/kg IM: Δ_{lat}= -11.5ms, p<.001, 0.5mg/kg IM: Δ_{lat}= -15.7ms, p<.001, 0.5mg/kg IN: Δ_{lat}= -2.3, p=.35, 1mg/kg IN: Δ_{lat}=-6.34, p=.008). Monkey Y showed increased post-loss slowing with ketamine with all doses and administrations, although this was only significant for the 0.5mg/kg IM dose (0.25mg/kg IM: Δ_{lat}= 6.45ms, p=.056, 0.5mg/kg IM: Δ_{lat}= 16.2ms, p<.001, 1mg/kg IN: Δ_{lat}= 2.7ms, p=.44). Monkey B showed inconsistent and no significant changes to post-loss slowing across doses and administrations (0.5mg/kg IM: Δ_{lat}= -6.5ms, p=.30, 0.5mg/kg IN: Δ_{lat}= 6.6ms, p=.21, 1mg/kg IN: Δ_{lat}= -9.2ms, p=.16). Therefore, based on this measure, we do not find consistent evidence that animals were unable to recognize loss outcomes under ketamine conditions.

Effect of administration route of ketamine

We tested the plasma levels of ketamine at five time points following intranasal and intramuscular administration in monkey B (Figure S8). For both intranasal doses (0.5 mg/kg and 1 mg/kg) we tested plasma levels twice to account for possible variability in this route of administration. For both IN doses, plasma levels following the two administrations differed slightly but were within similar ranges (Figure S8). In general, plasma levels of ketamine were maximal within 10-25 minutes from administration and started to decline thereafter. Peak plasma concentration was highest following 0.5 mg/kg IM administration (197 ng/mL), and lower following 1 mg/kg IN (mean 182 ng/mL) and 0.5 mg/kg IN (mean 88 ng/mL) administration. Using 2-way ANOVA, we found main effects of time and administration type (route + dose) (Time: F(4, 24)=17.38, p<.001; Admin. type: F(2, 24)=7.97, p=.003). Post-hoc comparisons revealed that plasma levels following the administration of 0.5 mg/kg IM and 1 mg/kg IN ketamine did not differ significantly (Post-hoc multiple comparison corrected p = .99), while both showed greater plasma levels than administration of 0.5 mg/kg IN ketamine (Post-hoc multiple comparison corrected both p < .05). This suggests that we accomplished similar blood plasma concentrations with the administration of 0.5 mg/kg IM and 1 mg/kg IN ketamine. The difference in dosage to achieve a similar plasma concentration was likely driven by the difference in bioavailability of ketamine with the two different administration routes (Malinovsky et al., 1996; Yanagihara et al., 2003).

We hypothesized that IN administered ketamine compared with IM administered ketamine may have similar effects on cognitive processes, such as the selective effect on choice behavior following losses, but may cause less side effects (Lapidus et al., 2014), such as nystagmus. We found evidence for this when comparing the behavioral effects (Figure 2A, 3A), as well as the nystagmus induced (Figure 4C, D) by the two higher doses of ketamine (0.5 mg/kg IM, 1 mg/kg IN). To quantify this, we computed average nystagmus and the average regression coefficient

difference (ketamine - saline) for choices immediately following a loss in the first 40 minutes following ketamine administration of the higher doses and with either administration route across all three animals. We chose to represent choice behavior as behavior in the trial immediately following a loss, as the ketamine effect we observed was generally greatest for this trial type (Figure 2A, 3A). We applied a first linear regression model to the average nystagmus across experimental sessions with the factors loss regression coefficient (loss behavior), administration route and animal. The model revealed a main effect of administration route on nystagmus ($p < .001$), with IM ketamine inducing greater nystagmus than IN ketamine. It also revealed a main effect of loss behavior ($p < .001$), whereby greater nystagmus co-occurred with a greater ketamine effect on behavior (more positive regression coefficient difference). We found no main effect of animal on nystagmus ($p = .8$). In a second linear regression model, we treated loss behavior as the response variable. This revealed no effect of administration route on loss behavior ($p = .41$), but again a main effect of nystagmus ($p < .001$), with the same relation as above, as well as a main effect of animal ($p = .02$). To visualize the effect that the administration route had on nystagmus, as well as on the other eye movement parameters, error rate and saccade latency, we added a simple correlation analysis (Figure 5) that further confirmed that IN administered ketamine had markedly reduced effects on eye-movement related parameters, while causing similar choice behavior. The previous suggests that we achieved very similar effects of ketamine on loss behavior with the two higher doses of IM and IN administrations, while inducing markedly fewer side effects such as nystagmus, increases in error rates and saccade latencies, with IN ketamine, lending support to our initial hypothesis.

High motivation allows some compensation of ketamine effect on error rate

We had found that IM ketamine led to an increase in the error rate in all animals (Figure S6A). Since we defined errors as fixation breaks, we wanted to understand whether ketamine's effect on error rate was mainly due to a global effect on eye movements, or whether there was also an effect on the motivation to perform trials. We focused this analysis on behavior following the high dose (0.5mg/kg) of IM ketamine administration, since behavioral effects in general were larger. Since error rates were not consistently increased following IN administrations (Figure S6B), this analysis was restricted to IM administrations. To test this, we used two proxies for motivation. First, we assumed that the previous trial outcome affects the level of motivation, specifically, we assumed that motivation would be higher following a gain in the preceding trial, and lower following a loss in the preceding trial. As a second proxy for motivation, we assumed that motivation would be higher the more tokens were currently filled on the screen and therefore the less tokens were needed until the next reward. For example, we assumed motivation would be higher when 5 tokens were currently filled compared with 2 tokens currently filled. We found evidence for these two proxies of motivation in the two animals (monkeys P/B) that regularly took breaks from the task (defined as no trial initiation in > 1min). In control (saline) sessions, both animals were significantly more likely to take a break from the task following a loss compared with a gain the preceding trial (χ^2-test, MP: χ=12.6, p<.001, MB: χ=21.3, p<.001). Similarly, both animals were significantly more likely to take a break from the task when 0 or 1 tokens were filled on the screen

compared with 4 or 5 (χ^2-test, MP: χ=261.0, p<.001, MB: χ=23.8, p<.001). The previous suggests that the two proxies for motivation may be valid estimates.

First, we therefore computed the time-resolved difference in error rates in saline versus ketamine sessions selectively for trials that followed a gain, a neutral, or a loss outcome. Using 2-way ANOVA we found a significant interaction between drug condition and previous trial outcome in the first 30 minutes following injection in two out of three monkeys (MP: F(2, 200)=12.11, p<.001; MY: F(2, 191)=3.57, p=.03; MB: F(2, 101)=0.85, p=.43, Figure 6A). Specifically, in monkeys P/Y the difference in error rate between the saline and ketamine condition was smaller following gains and larger following losses in the immediately preceding trial. To account for differences in the numbers of trials completed and the level of satiety of the animals over time, we additionally computed the previous analysis resolved by the cumulative number of tokens collected, rather than time-resolved, and found similar results (MP: F(2, 200)=9.18, p<.001; MY: F(2,191)=4.61, p=.01; MB: F(2, 101)=1.55, p=.22, Figure S9A).

For the second proxy of motivation, we found a significant interaction between drug condition and number of tokens filled in the first 30 minutes following injection in monkey P (F(5, 401)=32.12, p<.001), but not in monkeys Y and B (MY: F(5, 382)=1.13, p=.34; MB: F(5, 203)=0.85, p=.52, Figure 6B). However, when we computed this analysis resolved by the cumulative number of tokens rather than time, we did find a significant interaction between drug condition and number of tokens filled in a narrow token window in both monkeys Y and B (MY: F(5, 373)=3.21, p=.008; MB: F(5, 189)=3.14, p=.01, Figure S9B), as well as in monkey P (F(5,397)=21.76, p<.001, Figure S9B). In all cases, the difference in error rate between the saline and ketamine condition was smaller when more tokens were currently filled on the screen.

As a comparison, we tested whether we could find a similar interaction between ketamine and the level of motivation for choice behavior. Specifically, we compared the probability to switch choices after a loss for varying numbers of tokens on the screen between the ketamine and saline condition using 2-way ANOVA (Figure S10). Even though we found a significant interaction between drug condition and number of tokens for monkey B (MP: F(3, 215)=1.41, p=.241; MY: F(3, 248)=0.91, p=.438; MB: F(3, 127)=6.30, p<.001), there was no linear relationship between the numbers of tokens available to the monkey and the probability to switch choices after a loss outcome in any of the monkeys (Figure S10).

We therefore found evidence that the effect of IM ketamine to increase error rates could at least be partially overcome when motivation was high in all monkeys. High motivation however did not seem to affect ketamine's effect on choice behavior following loss outcomes.

Behavior under saline conditions is best fit by Q-learning model with differential forgetting

In order to infer possible mechanisms underlying the behavioral ketamine effects we observed here, we tested various computational models using reinforcement learning principles. For all modeling analyses, we used data from the 0.5mg/kg IM administration condition. In a first step, we identified a model that could capture behavior under normal (saline) conditions best, by fitting behavior from saline sessions with seven different behavioral models (see Methods section *Saline*

Models, Figure 7). These models were partially selected based on previous studies that have explored several behavioral models to explain choice behavior in similar tasks (Barraclough 2004; Ito & Doya, 2009) and partially to fit our specific task design. In all of these models, the probability of choosing the right or left target was based on the difference of the value functions of these two choices (i.e. the expected outcome of these choices). The models differed in their computation of the value functions. All of the models are adaptations of the classic Q-learning model (Watkins and Dayan 1992, Sutton and Barto, 1998). The saline model with the greatest number of free parameters (n=5) was the *Saline DF-Q* model (*DF=differential forgetting*, Figure 7, Ito and Doya, 2009), which employed a separate decay rate for the chosen and unchosen action (α_1/α_2, eq. 3-4) and a value parameter for each of the possible outcomes (V_{gain}, V_{neut}, V_{loss}) that represented how reinforcing or aversive a given outcome was. By setting $\alpha_1=\alpha_2$, this became the *Saline F-Q model*, and by additionally setting $V_{neut} = 0$, thereby making a neutral outcome neither aversive nor reinforcing, the *Saline DF-Q* model and the *Saline F-Q* model became the *Saline DF-Q Neutral* model and the *Saline F-Q Neutral* model, respectively. By setting $\alpha_2=0$, this became the *Saline NF-Q* model (*NF=no forgetting*), in which the unchosen action was not updated. We also tested a standard Q-learning model (*Saline Q Standard* model), in which the unchosen action was similarly not updated and $V_{gain}/V_{neut}/V_{loss}$ were fixed at 1/0/-1, respectively, thereby fixing how rewarding and aversive a gain and loss outcome were. Finally, we tested a *Saline Asset* model, in which the current number of tokens (assets) on the screen affected the value of the current outcome and thereby the updating of the chosen action (eq. 6), potentially reflecting an effect of motivation on value updating.

Out of the seven saline models we tested, we found that the *Saline DF-Q* model best explained behavior under saline conditions, having the lowest BIC value in all three monkeys (Figure 7). We therefore used this model to explore the possible mechanisms of ketamine's actions on behavior in the next step.

Ketamine behavioral effect is best fit by Q-learning model that alters outcome values

There are several potential mechanisms that may underlie the effects of ketamine on behavior in this biased matching-pennies task. In order to address these, we fitted twelve different models to the choice data from ketamine sessions that tested a variety of hypotheses (Figure 8, Table 1). The *Ketamine Control* model (black in Figure 8) assumed that there was no difference in value updating and action selection between saline sessions and ketamine sessions; it fitted the ketamine data using the optimal parameters identified from the *Saline DF-Q model*. Beyond the control model, we tested four value models (red in Figure 8), which all assumed that the decay rates for the chosen and unchosen actions were unaffected by ketamine, while the values associated with one or more of the outcomes changed under ketamine conditions. Specifically, the *Ketamine Value All* model assumed that the value of each of the outcomes (gain, neutral, loss) was independently affected by ketamine. The *Ketamine Value Neut+Loss* and the *Ketamine Value Neut/Loss* models in turn both assumed that the value of gain outcomes was unaffected by ketamine, while the values of neutral and loss outcomes were independently affected by ketamine in the *Ketamine Value Neut+Loss* model and equally affected by ketamine in the *Ketamine Value Neut/Loss* model. Finally, the

Ketamine Value Gain vs. No Gain model assumed that ketamine 1) changed the value of gain outcomes and 2) changed the value of neutral and loss outcomes in an equal manner.

An alternative hypothesis is that ketamine mainly affects memory, which in turn may affect the choice behavior of our monkeys. The *ketamine memory* model therefore assumes that ketamine affects the decay rates of the chosen and unchosen action values (i.e. how quickly their value is forgotten over trials), while it does not affect the values associated with the individual outcomes (green in Figure 8). In a further hypothesis, ketamine may also merely increase perseverative behavior. To test this, we devised a *Ketamine Pers.* (short for perseveration) model, in which action value updating per se was unaffected by ketamine (blue in Figure 8). Instead, the action selection was biased towards an increased likelihood to repeat choices. We also tested the possibility that ketamine affects both – outcome valuation and perseverative behavior using a model that combined action valuation from the *Ketamine Value All* model and action selection updating from the *Ketamine Pers.* model (*Ketamine Value Pers.* model, purple in Figure 8).

Ketamine may also interfere with temporal credit assignment (TCA). To test this, we devised three different Ketamine TCA models (cyan in Figure 8). The probability of choosing a particular action is usually determined by the value difference between, in our case, these two actions; however, in the *Ketamine TCA Mis* model, the current outcome additionally gets assigned to the actions that were taken in multiple preceding trials which thereby additionally contributes to the likelihood of choosing a particular action (i.e. a misassignment between the current outcome and preceding actions occurs). In the *Ketamine TCA Spread* model in turn, multiple recent outcomes get assigned to the current action which further contributes to the likelihood of choosing that particular action. In the final TCA model *Ketamine TCA SL* (short for statistical learning), the history of choices as well as the history of outcomes additionally contribute to the likelihood of choosing a particular action.

Finally, ketamine may also exert its main effect by changing levels of motivation. For this we hypothesized that motivation was directly affected by the current number of tokens collected. The *Ketamine Motivation* model then hypothesized that ketamine affected the degree to which the current number of tokens affected the current value outcome.

Out of these twelve ketamine models, we found that the *Ketamine Value All* model resulted in the lowest BIC value in all three monkeys, and thereby best explained choice behavior under ketamine conditions (Figure 8). This suggests that the effect we see with ketamine can be best explained by a dynamic change of the outcome values associated with each of the three possible trial outcomes (gain, neutral, loss).

In order to visualize the behavior that these models predicted, we simulated choice behavior of each of the monkeys using the optimal parameters found by the best saline model (*Saline DF-Q model*), as well as the respective ketamine model. Figure S11 shows the simulated choice behavior analyzed akin to the real behavior (Figure 2A) using the same regression model for each of the best performing ketamine models out of the five main model categories (value, memory, perseveration, TCA, motivation). Each of the models displayed captures some aspect of the ketamine effect we observe in the real behavior. However, only simulated data from the *Ketamine Value All* model reproduces the differential effect of ketamine on choice behavior following the three different outcomes, with a pronounced change following losses, a similar albeit reduced

change following neutral outcomes and almost no change in choice behavior following gains (Figure 2A, S11). This further corroborated the finding that ketamine's main actions on behavior may be explained by an adjustment of outcomes values in this task.

Discussion

We tested the effects of subanesthetic doses of ketamine on choice behavior in a token-based biased matching pennies task (Figure 1A) in three monkeys. We found that both intramuscularly (IM) and intranasally (IN) administered ketamine led to a selective change in choice behavior following less favorable outcomes. Specifically, all animals were less likely to switch away from a choice target that had in prior choices led to a loss or neutral outcome under ketamine conditions compared with saline conditions, while this was not the case for choices following favorable outcomes, i.e. gains. This change in choice behavior lasted for approximately forty minutes following ketamine administration. In addition, we found that IN ketamine caused considerably less side-effects on eye movement behavior compared to IM ketamine at doses that led to comparable effects on choice behavior.

Ketamine has been shown to affect a wide array of cognitive functions. Among others, previous findings suggest that ketamine impairs working memory (Taffe et al., 2002), error processing (Skoblenick and Everling, 2014; Skoblenick et al., 2016), context processing, and the ability to switch dynamically between different rules/task-sets (Stoet and Snyder, 2006; Skoblenick and Everling, 2012). Ketamine has also been routinely discussed in the context of relieving symptoms of depression in humans (Newport et al., 2015), monkeys (Chu, 2019), and rodents (Tizabi et al., 2012; Fukumoto et al., 2017), and it has shown to reduce drug-abusive behavior (Dakwar et al., 2014; Jones et al., 2018). A final noteworthy effect of ketamine is its ability to reliably induce schizophrenia-like symptoms in humans (Krystal et al., 1994; Corlett et al., 2007) and monkeys (Gil-da-Costa et al., 2013). Considering this wide range of previous findings, how can our findings be best understood?

This is the first study to show that ketamine can differentially affect choices based on the choice outcomes that preceded them in an economic decision-making environment. We found strong evidence that ketamine causes selective changes in outcome valuation, whereby unfavorable outcomes, in particular losses but also neutral outcomes, were valued less negatively under ketamine conditions. In addition to the selective changes in the monkeys' choice behavior following the three possible outcomes in this task (Figure 2A, 3A), we identified the reinforcement learning model that best explained choice behavior under ketamine conditions to be the one that independently changed the value of the three different outcomes (Figure 8, S11). Ketamine seemed to most strongly increase the value of losses, followed by the value of neutral outcomes, while the value of gains only changed minimally. These findings could be in line with early and short-lasting changes in how positive and negative stimuli are valued (Scheidegger et al., 2012), potentially akin to anti-depressant like effects.

We were unable to fully explain our findings with an array of alternative hypotheses. In the past, ketamine has been found to decrease working memory performance in monkeys (Taffe et al., 2002; Roberts et al., 2010a, 2010b) and humans (Krystal et al., 2005a, 2005b). Since the change in choice behavior we observed with ketamine was generally a shift in the values of regression coefficients closer towards zero, one could argue that the effect of ketamine we observed was merely a reflection of decreased working memory of the preceding choices that were made. This is because a regression coefficient of zero in our analysis indicates that there is no preference of the choice target linked to a previous outcome, i.e. the animal is equally likely to choose the right or left target independent of what the outcome of the previous choice was, which in turn could be explained by a lack of memory of what the previous choice was and/or what the resulting outcome was. This line of reasoning is, however, unlikely to explain our results, since the change in regression coefficients we observed was selectively occurring for choice behavior following losses and to a lesser extent following neutral outcomes, while choice behavior following gains was not consistently affected (Figure 2A, 3A). Furthermore, a reinforcement learning model that hypothesized that ketamine mainly affected memory in this task (specifically the rate at which previous chosen and unchosen stimulus values decayed), performed worse than all of the value models we tested in each of the monkeys (Figure 9, S11, Table 1). It is possible that working memory does not strongly contribute to choice behavior in this task. Either way, we believe that a working memory deficit is not sufficient to explain the changes in choice behavior we observed with ketamine.

It has also been shown that monkeys under ketamine are impaired in ignoring irrelevant stimuli (Stoet and Snyder, 2006) and to flexibly switch between different tasks rules (Stoet and Snyder, 2006; Skoblenick and Everling, 2012). Even though there was no explicitly enforced switch in contexts or rules in our biased matching pennies task, it is unlikely that the effect on choice behavior we observed with ketamine was due to a deficit in context or rule switch processing, since we found no evidence that animals under ketamine were slower to adjust their choice probabilities following block transitions between safe and risky choice options (Figure S5). Furthermore, ketamine did not seem to simply increase perseverative behavior, an inability to flexibly adapt its choices. A model that hypothesized that ketamine increased perseveration did not explain choice behavior under ketamine conditions (Figure 8, S11, Table 1), and a model that hypothesized that ketamine affected outcome valuation and also increased perseverative behavior performed worse than models that hypothesized an effect on outcome valuation only (Figure 8, Table 1).

There is evidence that ketamine also interacts with motivational aspects. Ketamine has for instance shown to increase the motivation to quit a drug of abuse in subjects not seeking treatment or abstinence (Dakwar et al., 2014) and it has been discussed for its potential to treat addiction (Ivan Ezquerra-Romano et al., 2018; Jones et al., 2018). We found that the effects of ketamine on eye movements, specifically on the propensity to commit errors (fixation breaks), could be partially overcome when motivation was high. In this case we gaged levels of motivation based on the preceding outcome and the numbers of tokens available to the monkey. Curiously, high motivation did not lead to a differential change in the probability of monkeys to switch choice targets following a loss with ketamine compared with saline (Figure S10), suggesting that the effect of ketamine on choice behavior was not affected by levels of motivation. Furthermore, the ketamine motivation model we devised that hypothesized that ketamine changed the degree to which current number of assets affected outcome value could not adequately explain choice behavior under ketamine conditions (Figure 8, S11). It therefore seems that we observed an interaction between

the level of motivation and ketamine only for its effects on eye movements, suggesting that ketamine's effects on eye movements and on choice behavior may be inherently different.

We find further evidence for this from the intranasal administrations of ketamine. While we achieved a similar effect on choice behavior (Figure 2A, 3A), as well as similar plasma concentrations (Figure S8) with a 1 mg/kg IN dose and a 0.5 mg/kg IM dose, an efficacy difference which is likely explained by a difference in bioavailability (Malinovsky et al., 1996; Yanagihara et al., 2003), we observed a marked reduction in ketamine's side effects on mayor eye movement measures (Figure 5). IN administered ketamine is thought to reach the brain via the olfactory system, through holes in the cribriform plate where the olfactory nerve enters the brain (Patel et al., 2016; Wei et al., 2016), which in turn sits directly below the prefrontal cortex. When used as an antidepressant, this may allow IN administered ketamine to directly reach brain regions where it may have its therapeutic actions. It has been suggested in the past that the fast-onset psychotomimetic and dissociative side effects of ketamine, especially when administered intravenously as in most human studies, may mask possible early antidepressant actions (Opler et al., 2016). Intranasal administration of ketamine has been shown to have similar efficacy in reducing depressive symptoms compared to intravenous ketamine, while however showing markedly less psychotomimetic and dissociative side effects (Lapidus et al., 2014; Opler et al., 2016).

It seems plausible that ketamine's effects on eye movement behavior we observed here may mirror some aspects of schizophrenia-like dissociative effects, while in tandem its effects on outcome valuation may underlie some of ketamine's therapeutic effects observed in individuals with depression. However, the selective change in outcome valuation, in particular for unfavorable outcomes, we observe with ketamine is not equivalent to the anti-depressant actions observed in patients. A major difference is that the behavioral changes we observe with ketamine occurred very soon after administration and only lasted approximately 40 minutes. This is in stark contrast to the much longer lasting antidepressant effects observed in human patients that often last days or even weeks (Newport et al., 2015). A significant difference is that our monkeys were, to the best of our knowledge, psychologically healthy. It seems possible that longer lasting behavioral changes with ketamine are only reliably observed in an unhealthy (i.e. depressed) brain. Only very few studies have investigated ketamine's antidepressant actions in healthy individuals and the results of those studies are variable. Some rodent (Garcia et al., 2009; Tizabi et al., 2012) and monkey (Xu et al., 2015) studies found no discernable effect of ketamine on healthy animals (although Xu et al., 2015 also did not find consistent effects on depressed individuals), while some found effects similar but reduced to those of depressed individuals (Réus et al., 2011; Franceschelli et al., 2015), and some with opposing effects, such as an increase in depression ratings of healthy humans with ketamine (Taylor et al., 2012; Nugent et al., 2019). Although the direction of the ketamine effect on healthy individuals seems to vary, those studies that compared effects on healthy and depressed individuals directly found substantially shorter durations of behavioral effects in the healthy compared with the depressed population (Franceschelli et al., 2015; Nugent et al., 2019). While it remains difficult to compare our results to studies examining ketamine's efficacy in treating psychiatric illnesses, it may be possible that the fast changes in outcome-specific valuation, in particular the less negatively valued loss and neutral outcomes, induced by ketamine in this study may trigger longer lasting changes in subjects with depression or other psychiatric illnesses.

Overall, we found that low doses of intramuscularly and intranasally administered ketamine led to changes in choice behavior in a biased matching pennies task that could be best described as an increase in outcome valuation that was most strongly observed for losses. These changes were temporary, and they co-occurred with several side effects on eye movement behavior, which were however mitigated by administering ketamine intranasally. We hypothesize that ketamine may have temporarily affected activity of brain circuitry involved in the valuation of choice outcomes, such that in particular unfavorable outcomes were valued as less negative than under saline conditions, potentially allowing insights into some mechanisms underlying ketamine's actions in treating psychiatric illnesses.

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Figure legends

Figure 1 | Biased matching pennies task and choice behavior. A. Monkeys fixated on a central fixation square when two green targets appeared. At the time the fixation square extinguished, monkeys could indicate a left or right choice by making a saccade to the respective target. A red ring around the choice target indicated a win of a token, a blue ring indicated a neutral trial outcome, and a white ring indicated a loss of a token. Six filled or empty red tokens around the central fixation square indicated the current number of collected tokens. When all six tokens were filled, each token was exchanged for a juice reward and the next trial began randomly with 2-4 filled tokens. **B.** The payoff matrices for all three monkeys determined the outcome of the animals' choices. P indicated probability. **C.** Average regression coefficients associated with gain, neutral and loss outcomes in the previous five trials. Color filled circles indicate significant difference from zero (t-test, $p < .05$). Numbers of sessions are indicated by n. Error bars indicate SEM. Note that many error bars are smaller than the markers.

Figure 2 | Choice behavior with 0.5mg/kg IM ketamine. A. Same conventions as in Figure 1C. Dotted lines indicate ketamine data; solid lines indicate saline data. Top and bottom rows show data for 0.5 mg/kg and for 0.25 mg/kg dose, respectively. Black asterisks indicate significant difference between saline and ketamine data points (t-test, $p < .05$). **B.** Differences in regression coefficients for behavior following outcomes in trial t-1 between the saline and ketamine condition time-resolved in non-overlapping 20-minute windows. Black dotted lines indicate the mean and +/- 2 standard deviations of the randomized difference when condition labels were shuffled (n = 1000). Black asterisks indicate significant difference between saline and ketamine regression coefficients (randomization procedure).

Figure 3 | Choice behavior with 1mg/kg IN ketamine. Same conventions as Figure 2.

Figure 4 | Ketamine induced nystagmus. A. Example eye trace from a single trial at the very beginning of a ketamine session (trial 22, 1.8 min. from session begin). Top graph displays horizontal eye position, middle graph displays aligned eye velocity, shown again zoomed in in the most bottom graph. Grey bar highlights time of saccade, green bar highlights time of fixation. Graphs are aligned to central fixation point offset, allowing the animal to initiate a saccade. In this trial, the eye movement velocity during peripheral fixation hovers around zero (bottom zoomed in graph). **B.** Conventions are the same as in A. Single trial example is shown from the same ketamine session as in A (trial 103, 11.1 min. from session begin). In this trial, the animal displays negative eye movement velocity during peripheral fixation (slow wave velocity, drift of eye position back towards the center), which we define as nystagmus (Barnes, 1982). Data in A and B were collected from monkey Y. **C.** Time-resolved (1-minute windows) average slow-phase velocity across ketamine and saline sessions for 0.5mg/kg IM administered ketamine. **D.** Time-resolved average slow-phase velocity across ketamine and saline sessions for 1mg/kg IN administered ketamine.

Figure 5 | Differential effects of ketamine administration route. Comparison of ketamine effects on behavior based on administration route of the two larger doses (A) on the magnitude of choice behavior changes following loss in the preceding trial, (B) on the magnitude of nystagmus, (C) on saccade latency, and (D) on error rate. P-values are given from Pearson correlations. Black lines reflect mean, red lines reflect median. Data is combined across all monkeys.

Figure 6 | Differential effect of IM ketamine based on level of motivation. A. Time-resolved difference in error rates between saline and ketamine condition based on whether the previous trial ended in a gain, neutral or loss outcome. **B.** Time-resolved difference in error rates between saline and ketamine condition based on the current number of filled tokens on the screen. P-values from interaction between drug condition and previous trial outcome (**A**) / numbers of filled tokens (**B**) in the first 30 minutes after administration using 2-way ANOVAs. Data is shown from 0.5 mg/kg IM ketamine administration.

Figure 7 | Behavior under saline conditions best fit by Q-learning model with differential forgetting. Z-transformed BIC values of seven models fit to behavior under saline conditions for each monkey. The left side of the figure serves as a visualization of the different parameters that were fit by a given model. Filled black circles indicate a variable parameter that was fit by this model; empty circles indicate a parameter that was not included in that model. Grey filled circles for models Saline F-Q and Saline F-Q Neutral indicate that the parameter α_2 was not independently fit, but instead in these models $\alpha_1 = \alpha_2$. The Saline DF-Q model resulted in the lowest BIC value across models for each monkey and therefore explained behavior under saline conditions best (highlighted in black box).

Figure 8 | Behavior under ketamine conditions best fit by model that alters outcome values. Z-transformed BIC values of twelve models fit to behavior under ketamine conditions for each monkey. All models were based on the initial best-fitting Saline DF-Q model. The left side of the figure serves as a visualization of the different parameters that were fit by a given model (see Methods for parameter identification). Dark filled circles indicate variable parameters that were fit by a given model. Light transparent filled circles indicate fixed parameters whose values were given by the Saline DF-Q model fit. Empty circles indicate parameters that were not part of a given model. Overall model type is highlighted by circle color. The *Ketamine Value All* model resulted in the lowest BIC value across all twelve models in each monkey and therefore explained behavior best (highlighted in black box).

Table 1 | Best-fit model parameters. Detailed are the best-fit parameters of a subset of the ketamine models, excluding the Ketamine TCA models, which did not perform well, and the Ketamine Motivation model. Values are given for each monkey (top row: Monkey P, middle row: Monkey Y, bottom row: Monkey B). Grey values indicate best-fit parameters from the Saline DF-Q model. Black values indicate best-fit parameters from the respective model. BIC values for each model are given in the right-most column.

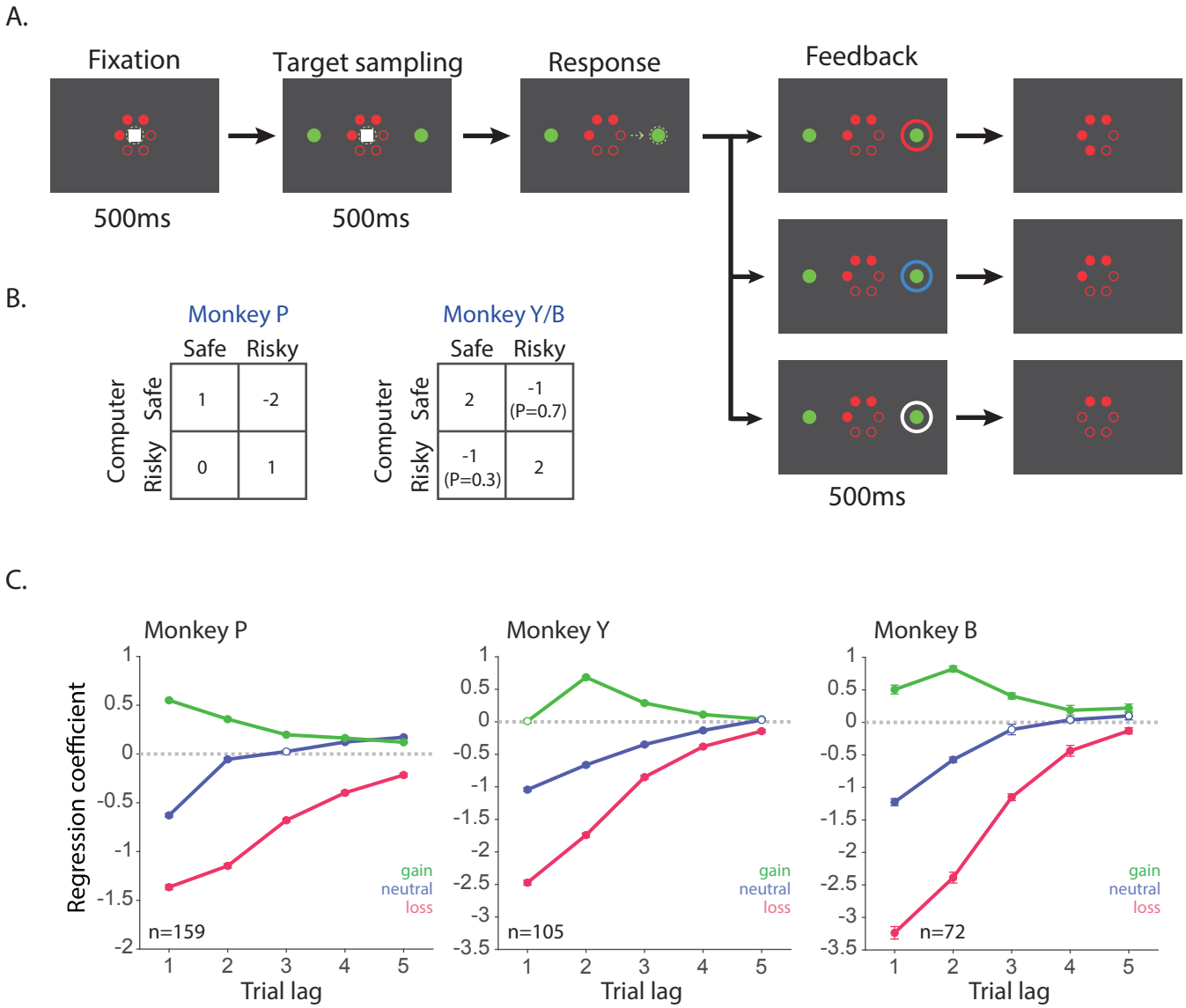
A.
Fixation
Target sampling
Response
Feedback
500ms
500ms
500ms
B.
Monkey P
Safe
Risky
Computer
Safe
Risky
1
-2
0
1
Monkey Y/B
Safe
Risky
Computer
Safe
Risky
2
-1
(P=0.7)
-1
(P=0.3)
2
C.
Monkey P
Monkey Y
Monkey B
Regression coefficient
Trial lag
gain
neutral
loss
n=159
n=105
n=72

Figure 1

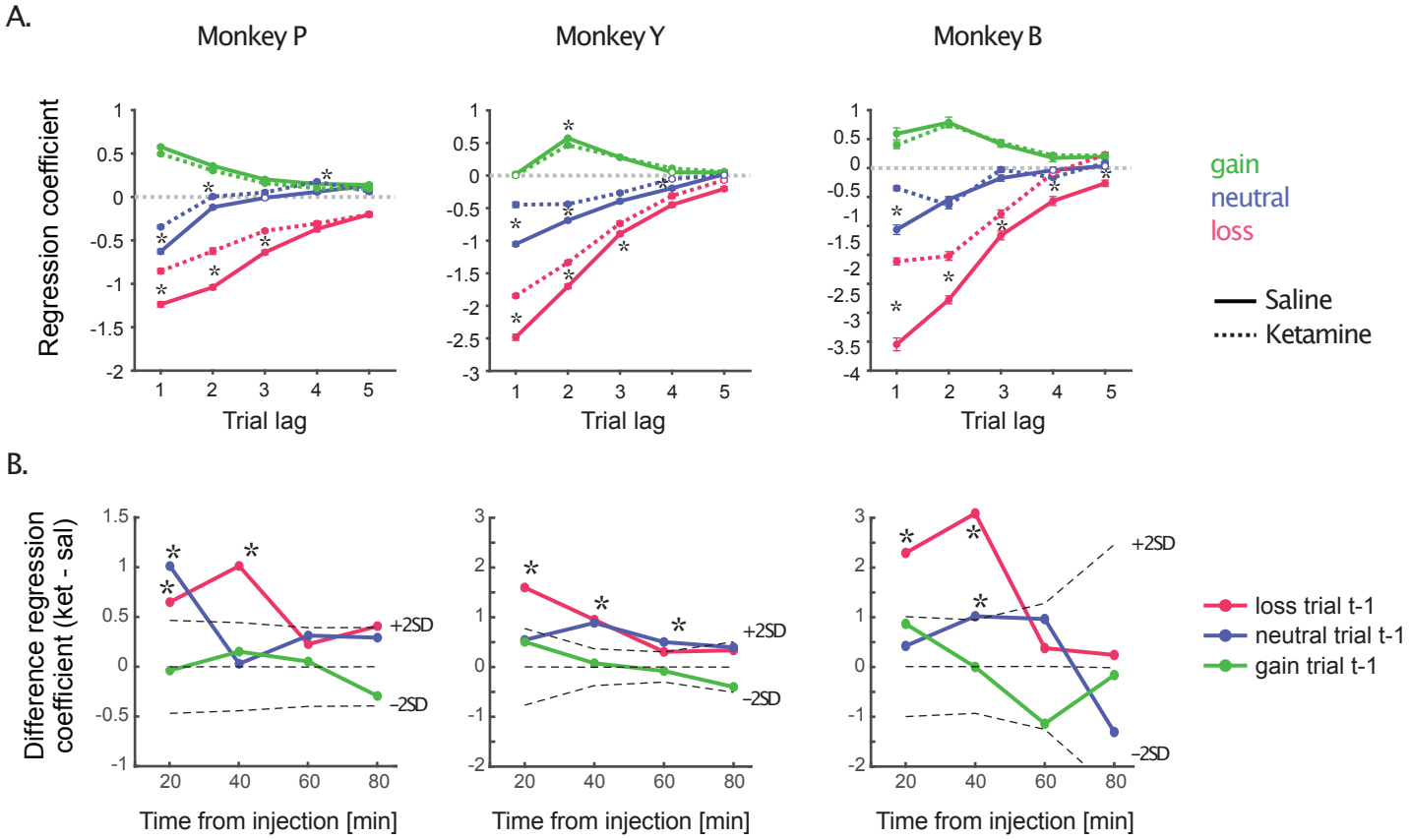
A.
Monkey P
Monkey Y
Monkey B
Regression coefficient
Trial lag
gain
neutral
loss
Saline
Ketamine
B.
Difference regression coefficient (ket - sal)
Time from injection [min]
+2SD
−2SD
loss trial t-1
neutral trial t-1
gain trial t-1

Figure 2

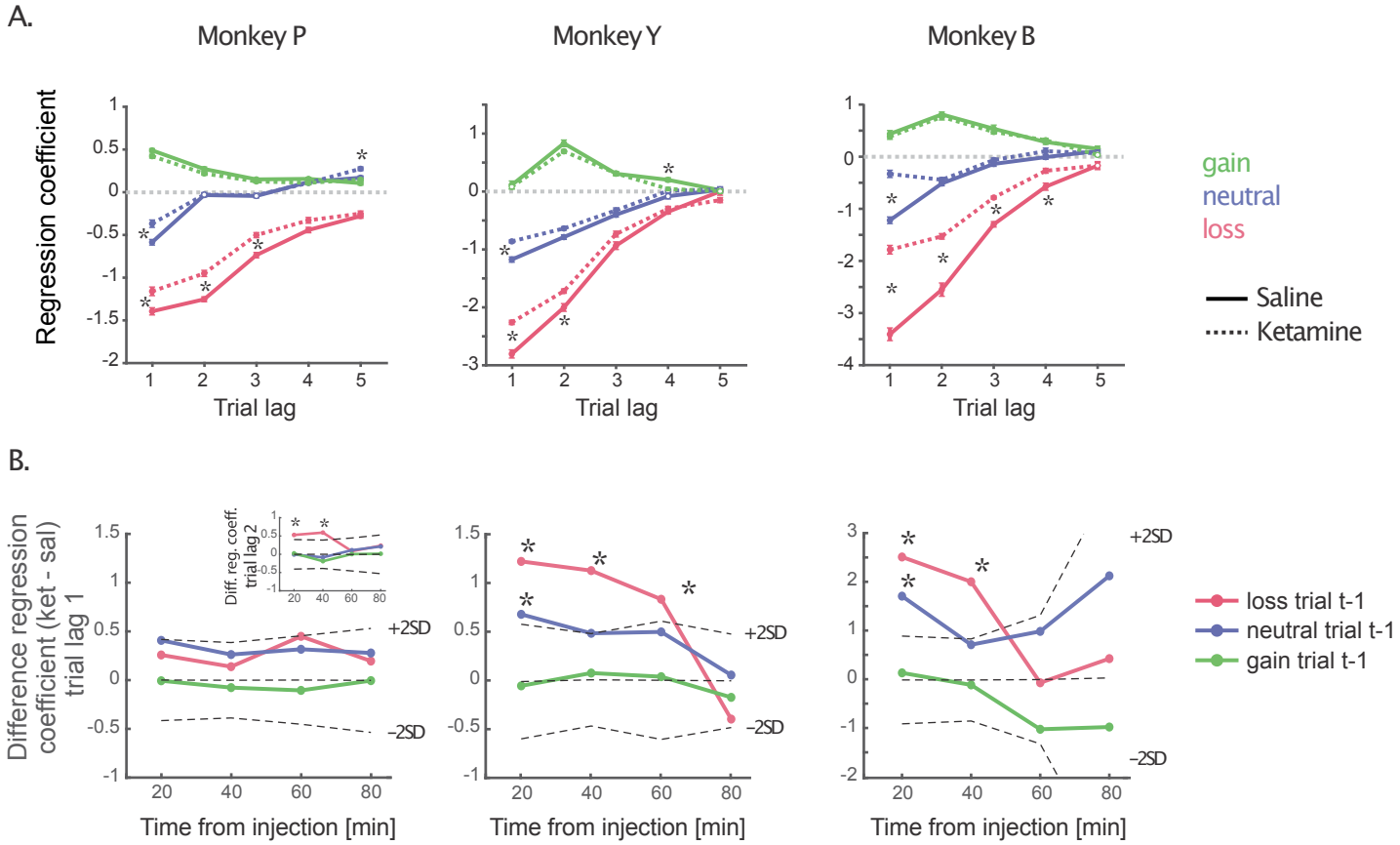
A.
Monkey P
Monkey Y
Monkey B
Regression coefficient
Trial lag
gain
neutral
loss
Saline
Ketamine
B.
Difference regression coefficient (ket - sal) trial lag 1
Diff. reg. coeff. trial lag 2
+2SD
−2SD
Time from injection [min]
loss trial t-1
neutral trial t-1
gain trial t-1

Figure 3

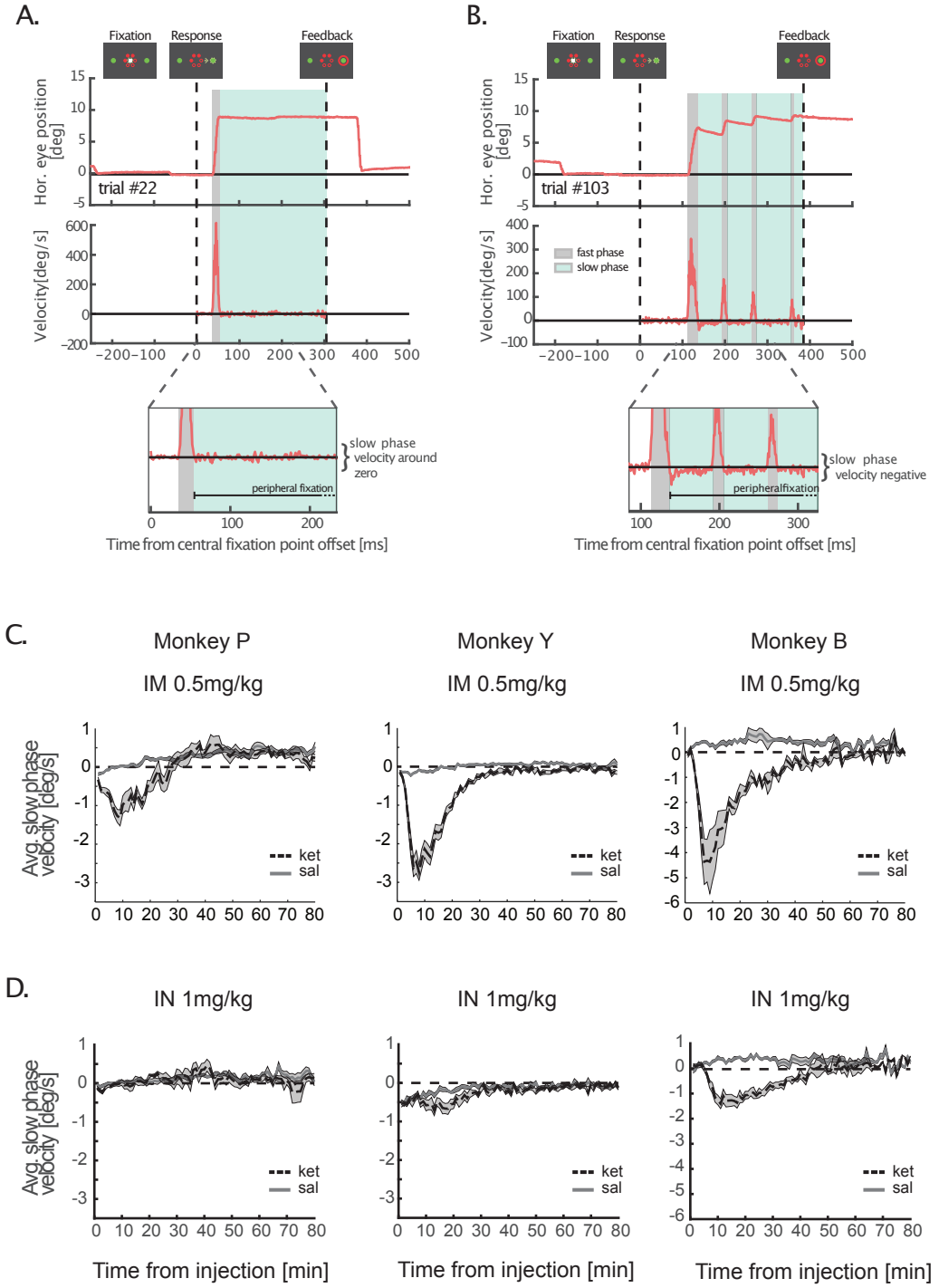
A.
Fixation
Response
Feedback
Hor. eye position [deg]
trial #22
Velocity[deg/s]
slow phase velocity around zero
peripheral fixation
Time from central fixation point offset [ms]
B.
Fixation
Response
Feedback
Hor. eye position [deg]
trial #103
Velocity[deg/s]
fast phase
slow phase
slow phase velocity negative
peripheralfixation
Time from central fixation point offset [ms]
C.
Monkey P
IM 0.5mg/kg
Monkey Y
IM 0.5mg/kg
Monkey B
IM 0.5mg/kg
Avg. slow phase velocity [deg/s]
ket
sal
D.
IN 1mg/kg
IN 1mg/kg
IN 1mg/kg
Avg. slow phase velocity [deg/s]
ket
sal
Time from injection [min]
Time from injection [min]
Time from injection [min]

Figure 4

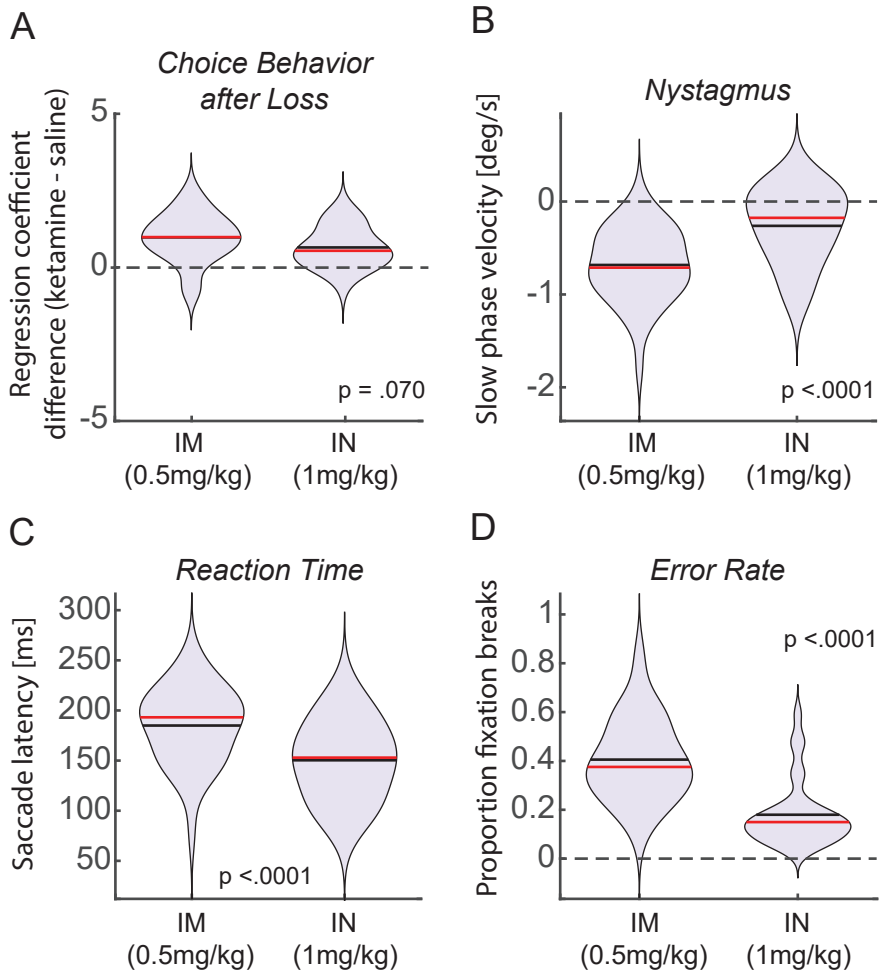
A
Choice Behavior after Loss
Regression coefficient difference (ketamine - saline)
5
0
-5
p = .070
IM (0.5mg/kg)
IN (1mg/kg)
B
Nystagmus
Slow phase velocity [deg/s]
0
-1
-2
p <.0001
IM (0.5mg/kg)
IN (1mg/kg)
C
Reaction Time
Saccade latency [ms]
300
250
200
150
100
50
p <.0001
IM (0.5mg/kg)
IN (1mg/kg)
D
Error Rate
Proportion fixation breaks
1
0.8
0.6
0.4
0.2
0
p <.0001
IM (0.5mg/kg)
IN (1mg/kg)

Figure 5

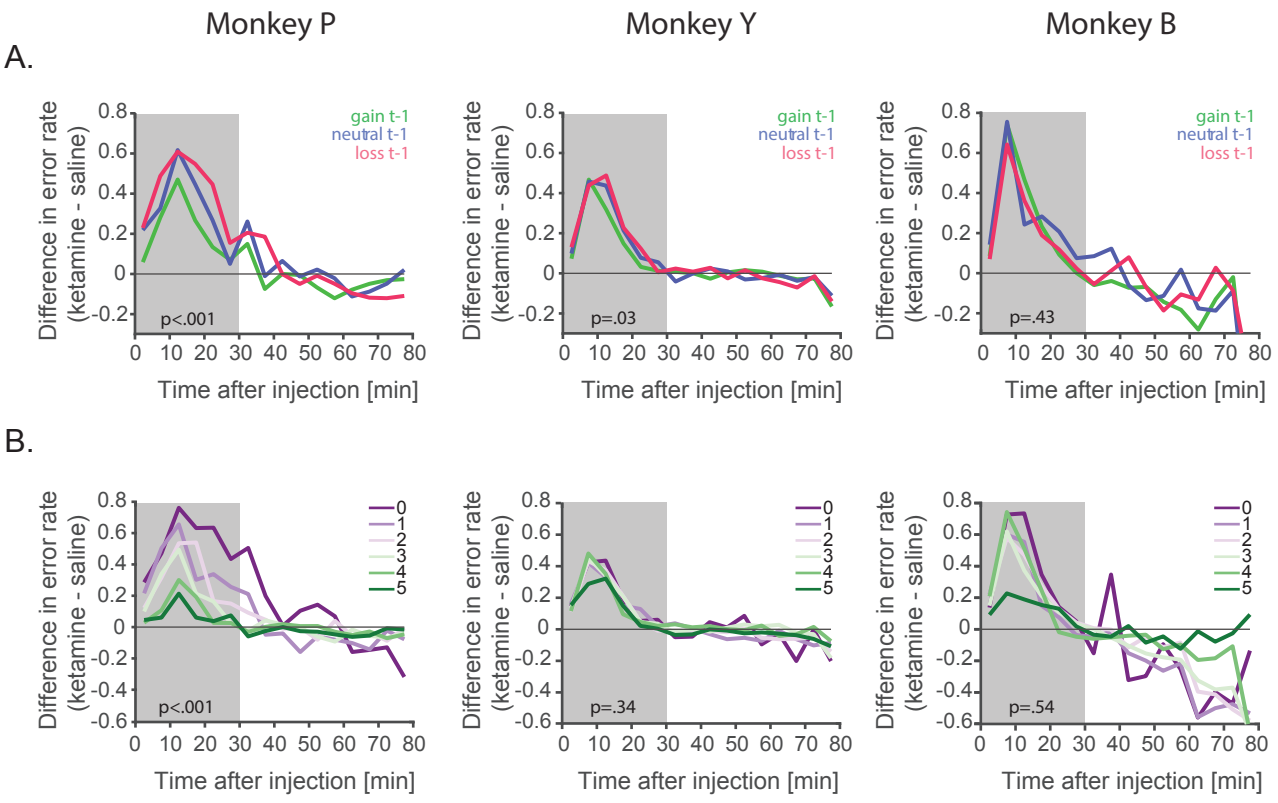
Monkey P
Monkey Y
Monkey B
A.
B.
Difference in error rate (ketamine - saline)
Time after injection [min]
gain t-1
neutral t-1
loss t-1
p<.001
p=.03
p=.43
0
1
2
3
4
5
p<.001
p=.34
p=.54

Figure 6

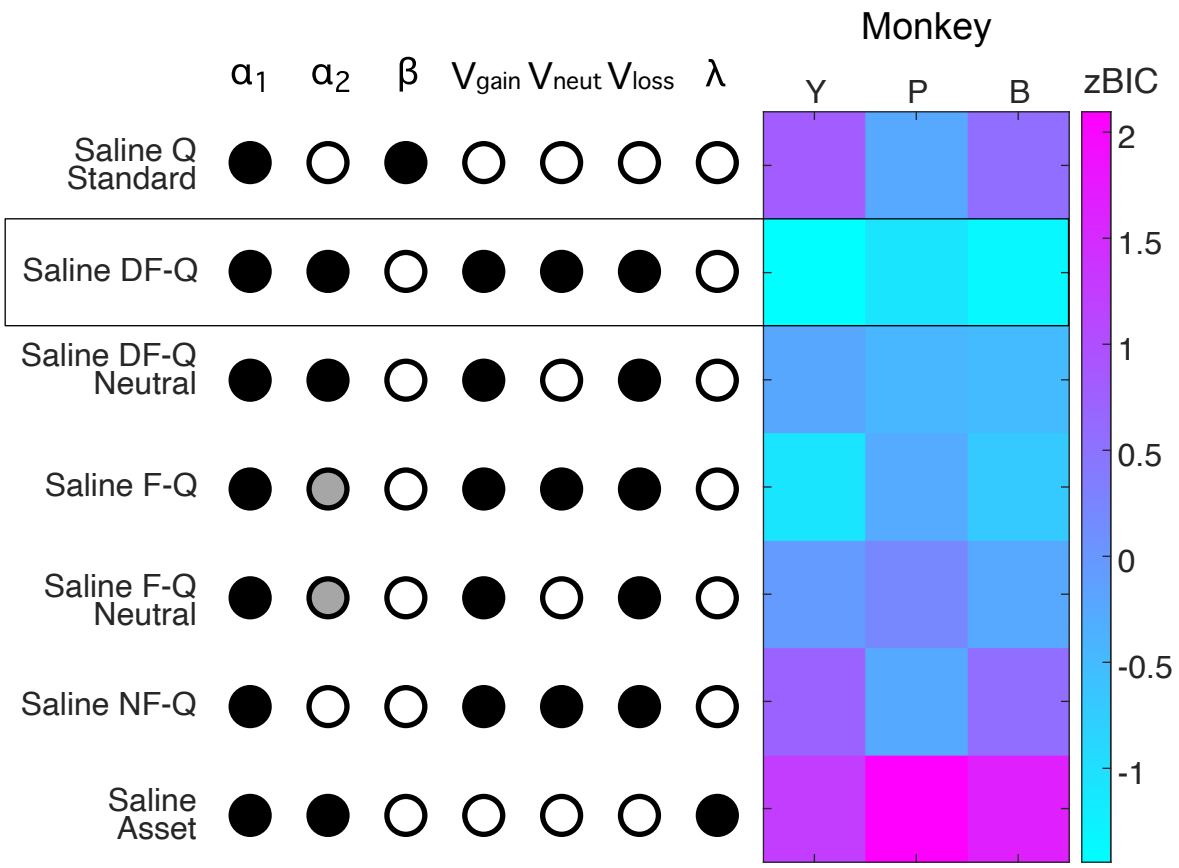
Monkey
α1
α2
β
Vgain
Vneut
Vloss
λ
Y
P
B
zBIC
Saline Q Standard
Saline DF-Q
Saline DF-Q Neutral
Saline F-Q
Saline F-Q Neutral
Saline NF-Q
Saline Asset
2
1.5
1
0.5
0
-0.5
-1

Figure 7

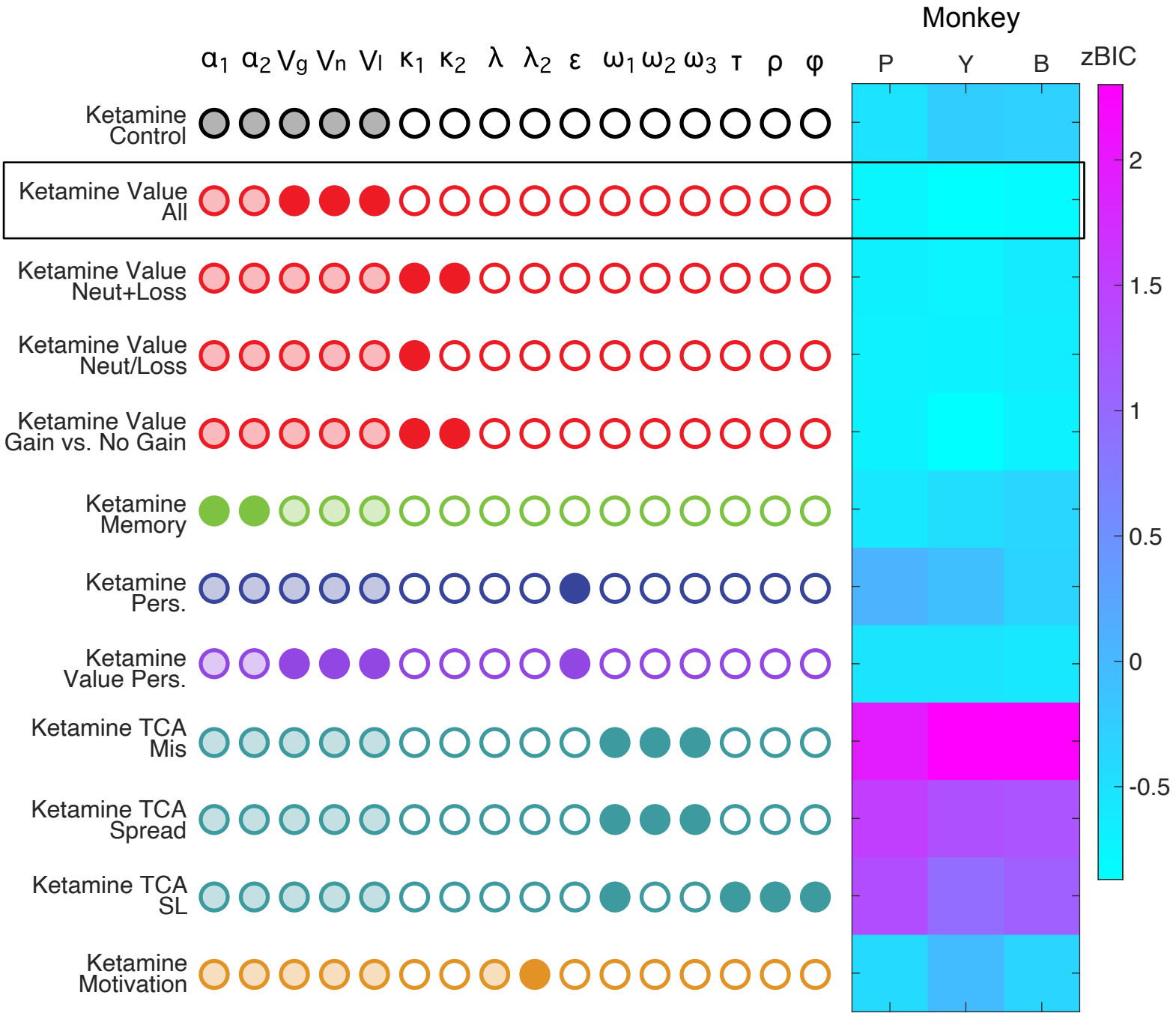
Monkey
α1 α2 Vg Vn Vl κ1 κ2 λ λ2 ε ω1 ω2 ω3 τ ρ φ
P Y B
zBIC
Ketamine Control
Ketamine Value All
Ketamine Value Neut+Loss
Ketamine Value Neut/Loss
Ketamine Value Gain vs. No Gain
Ketamine Memory
Ketamine Pers.
Ketamine Value Pers.
Ketamine TCA Mis
Ketamine TCA Spread
Ketamine TCA SL
Ketamine Motivation
2
1.5
1
0.5
0
-0.5

Figure 8

	α_1	α_2	V_{gain}	V_{neut}	V_{loss}	κ_1	κ_2	ε	BIC
Ket Control	0.74	0.09	-0.40	-1.22/	-2.13	-	-	-	19666
	0.67	0.21	-0.38	-1.78/	-2.99	-	-	-	19826
	0.84	0.18	-1.11	-2.3	-4.0	-	-	-	8119
Ket Value All	0.74	0.09	0.20	-0.29/	-0.92	-	-	-	19254
	0.67	0.21	0.09	-0.72/	-1.73	-	-	-	19020
	0.84	0.18	-0.15	-0.72	-1.72	-	-	-	7567
Ket Value Neut + Loss	0.74	0.09	-0.40	-1.22/	-2.13	0.43	0.43	-	19381
	0.67	0.21	-0.38	-1.78/	-2.99	0.73	0.73	-	19218
	0.84	0.18	-1.11	-2.3	-4.0	0.9	0.9	-	7777
Ket Value Neut/Loss	0.74	0.09	-0.40	-1.22/	-2.13	0.38	0.55	-	19350
	0.67	0.21	-0.38	-1.78/	-2.99	0.7	0.7	-	19227
	0.84	0.18	-1.11	-2.3	-4.0	0.73	1.18	-	7738
Ket Value Gain vs. No Gain	0.74	0.09	-0.40	-1.22/	-2.13	0.43	0.85	-	19332
	0.67	0.21	-0.38	-1.78/	-2.99	0.43	1.10	-	19034
	0.84	0.18	-1.11	-2.3	-4.0	0.76	1.66	-	7670
Ket Memory	0.95	0.09	-0.40	-1.22/	-2.13	-	-	-	19552
	0.87	0.18	-0.38	-1.78/	-2.99	-	-	-	19549
	1.01	0.16	-1.11	-2.3	-4.0	-	-	-	8053
Ket Pers.	0.74	0.09	-0.40	-1.22/	-2.13	-	-	0.55	20699
	0.67	0.21	-0.38	-1.78/	-2.99	-	-	0.48	20029
	0.84	0.18	-1.11	-2.3	-4.0	-	-	0.62	8082
Ket Value + Pers.	0.74	0.09	0.48	0.08	-0.5	-	-	-0.15	19612
	0.67	0.21	0.47	-0.26	-1.2	-	-	-0.09	19465
	0.84	0.18	0.31	-0.18	-1.03	-	-	-0.05	7821