Ketamine reduces temporal expectation in the Rhesus monkey

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Abstract

Rationale

Ketamine, a well-known general dissociative anesthetic agent that is a non-competitive antagonist of the N-methyl-D-aspartate receptor, perturbs the perception of elapsed time and the expectation of upcoming events.

Objective

The objective of this study was to determine the influence of ketamine on temporal expectation in the Rhesus monkey.

Methods

Two Rhesus monkeys were trained to make a saccade between a central warning stimulus and an eccentric visual target that served as imperative stimulus. The delay between the warning and the imperative stimulus could take one of four different values randomly with the same probability (variable foreperiod paradigm). During experimental sessions, a subanesthetic low dose of ketamine (0.25 - 0.35 mg/kg) was injected i.m. and the influence of the drug on movement latency was measured.

Results

We found that in the control conditions, saccadic latencies strongly decreased with elapsed time before the appearance of the visual target showing that temporal expectation built up during the delay period between the warning and the imperative stimulus. However, after ketamine injection, temporal expectation was significantly reduced in both subjects. In addition, ketamine also increased average movement latency but this effect could be dissociated from the reduction of temporal expectation.

Conclusion

In conclusion, a subanesthetic dose of ketamine could have two independent effects: increasing reaction time and decreasing temporal expectation. This alteration of temporal expectation could explain cognitive deficits observed during ketamine use.

Introduction

Ketamine, a well-known general dissociative anesthetic agent that is a non-competitive antagonist of the glutamatergic N-methyl-D-aspartate receptor (NMDAr; see Dingledine et al. 1999), has been shown to induce various dose-dependent psychoactive and psychiatric effects sometimes mimicking psychosis (Krystal et al. 1994; Corlett et al. 2016; Stone and Pilowsky 2006) see review in Morgan et al. 2009). Moreover, a growing body of evidence suggests that a subanesthetic dose of ketamine could reduce depression symptoms with both short- and long-term effects (Skolnick et al. 1996; Zarate et al. 2006; Krystal 2007). This beneficiary effect on depression could be obtained with a single total dose as low as 0.5 mg/kg of ketamine (Berman et al. 2000). Given the increasing use of ketamine in psychiatry, a better understanding of its consequences on behavior and cognition is essential. Indeed, ketamine also impacts different aspects of temporal cognition (Guillermain et al. 2001; Pomarol-Clotet et al. 2006; Morgan et al. 2012; but see Lofwall et al. 2006). Ketamine perturbs the subjective experience of time and alters its 'perception' (Coull et al. 2011). Ketamine also reduces the influence of time on movement preparation (Coull et al. 2011). This influence is often referred to as 'temporal expectation'. Temporal expectation (or preparation) is usually defined as the readiness to act before a predictable event and is classically studied using a warning stimulus (S_1, e.g. a sound or a visual signal) that predicts the occurrence of an imperative stimulus in the same or a different sensory modality (S_2; Woodrow, 1914). The period between S_1 offset and S_2 onset is referred to as the foreperiod. Temporal expectation builds-up during the FP causing a shorter reaction time after S_2 appearance ('FP'; Stilitz 1972; Luce 1986; Niemi 1981; Niemi and Näätänen, 1981; see reviews in Nobre et al. 2007; Los 2010, Los et al. 2017). Foreperiod duration could either always be the same, making the timing of S_2 entirely predictable, or vary randomly between different values drawn from a given probability distribution. If FP duration is randomly drawn from a uniform probability distribution the latency of the motor response to S_2 decreases with elapsed time yielding a characteristic decreasing RT-FP function. This 'FP effect' is the behavioral measure of temporal expectation. Recently, it has been shown that the FP effect is

also present in the oculomotor domain in primates if both S_1 and S_2 are visual targets (in humans: Oswal et al. 2007; Ameqrane et al. 2014; Degos et al. 2018; Hsu et al. 2019) and using more complex FP probability distributions (in the Rhesus monkey: Janssen and Shadlen 2005). Although the influence of ketamine on the perception of the flow of time in humans has been described previously (Coull et al. 2011), there is no evidence of such an effect in the Rhesus monkey. Potential differences of ketamine effects between species are particularly important to estimate, given that animal models are used to infer pharmacological effects in humans. Therefore, the aim of the present paper was twofold. Firstly, to determine whether ketamine could alter temporal expectation in the Rhesus monkey using a simple variable foreperiod paradigm in the oculomotor domain. Secondly, to determine whether the influence of ketamine on temporal expectation could be dissociated from its effect on reaction time in general.

Methods

Animal housing and care

Data were collected from 2 captive-born Rhesus monkeys (Macaca mulatta), 1 male (subjects S, 9 years old and 7 kg) and one female (subject L, 6 years old, 6 kg). Animals were individually housed and handled in strict accordance with the recommendations of the Weatherall Report about good animal practice. Monkey housing conditions, surgical procedures, and experimental protocols were all carried out in strict accordance with the National Institutes of Health guidelines (1996) and the recommendations of the EEC (86/609) and the French National Committee (87/848) field number CE5/2011/055. The authorization for conducting our experiments in the institute was delivered by the Animal Health and Veterinary Medication Division of the Department of Public Veterinary Health, Nutrition and Food Safety of the French Ministry of Health (last renewals. no. Arrêté préfectoral N° DTPP 2010–424). Our routine laboratory procedures included an environmental enrichment program where monkeys had access to toys, mirrors, and swings. Monkeys also had visual, auditory, and olfactory contact with other animals and, when appropriate, could touch/groom each other. Any possible pain associated with surgeries was pharmacologically ameliorated by means of a daily injection of Ketofen (0.03 ml/kg) or Buprecare (0.067 ml/kg). The well-being and health conditions of the monkeys were constantly monitored by an institutional veterinary doctor. The experiments were performed while the monkey's head was fixed.

Experimental Design and Statistical Analysis

The significance threshold α for all analysis was 0.01. All analyses were realized using repeated-measures analysis of variance (ANOVA). Analyses were performed using SPSS 25 (SPSS Inc., Chicago, IL). Results will be presented as mean ± standard error of the mean unless specified.

Surgical procedures

Each animal was deeply anesthetized with ketamine hydrochloride (5 mg/kg i.m.) for initial sedation, and anesthesia was induced with 2–4 % isofluoran gas and then maintained during

surgery. Heart rate, temperature, and respiration were carefully monitored and kept within physiological range. Pain medication was given prior to the surgery and routinely given after surgery. During surgery, a head post was fixed to the head (9/32" or 7.1 mm internal diameter; part #6-FHP-X2F produced by Crist Instrument, Hagerstown, MD, USA). The head post had an "X"-shaped footplate designed for attachment to the skull with a total of 12 titanium bone screws. The vertical post had a tapered cross section, designed to mate with a headpost holder (see part #6-FHB-S2B, Crist Instrument, Hagerstown, MD, USA). The center of the head post was located adjacently caudal to the stereotaxic zero bar, aligned with the interauricular scalp line (see Valero-Cabre et al. 2012).

Apparatus

Subjects sat in darkness, facing a cathode ray tube (CRT) screen, which presented stimuli at a frequency of 120 Hz. An EyeLink 1000 infrared eye tracking system (SR Research, Mississauga, Ontario) was used to record movements of the right eye at 1 KHz. All experiments were run with a home-made stimulus generation software based on a real time Linux kernel (Xenomaï). Stimulus display and oculomotor data collection were synchronized on a frame-by-frame basis. Saccades were detected offline in MATLAB (MathWorks, Natic, MA) with a velocity threshold of 30°/s. The experimental paradigm used has been previously validated in humans and Rhesus monkeys (in humans: Ameqrane et al. 2014; in monkeys: Ameqrane et al. 2015). Each trial started with an initial fixation period (referred to as "initial fixation"), with a small cross (0.7°) appearing on the CRT screen for a random duration (850 ± 100 ms; see X on Fig. 1). At the end of this random delay, two empty square "boxes" appeared on the screen (1.4 × 1.4 °), one in the center of the screen and one 9° eccentric, randomly to the right or to the left. The empty boxes were displayed to provide upcoming target position information beforehand. Afterwards, a square target (1.4 × 1.4°) was flashed in the central box for 50 ms (warning stimulus S_1). Extinction of S_1 indicated to subjects the beginning of the foreperiod (FP). Animals were required to hold on fixation of the central box until

another target (1.4 × 1.4°) was briefly presented for 50 ms in the eccentric box. The delay period could take one of 4 different values with the same probability: 400, 900, 1400, and 1900 ms in monkey S and 50, 167, 283 and 400 ms in monkey L (variable FP paradigm). In order to receive reward, subjects had to maintain fixation of the central box and wait for the appearance of the eccentric target. Saccadic latency had to be longer than 100 ms after appearance of the eccentric target. In order to avoid long latency saccades likely initiated in a decreased state of alertness or motivation, saccade latency had to be less than 600 ms.

Ketamine administration and washout

Each experimental session started with a block of 200 trials before injection to measure the baseline saccadic latency on a day-by-day basis. In monkey S, either ketamine (0.25 mg/kg) was injected i.m. or a control saline solution of the same volume (0.3 ml NaCl 0.9%). In monkey L, either ketamine (0.25- 0.35mg/kg) was injected i.m. or nothing. On a given day, whether ketamine was tested or control data collected was determined randomly. The injection site was localized in the neck (in the region of the Splenius Capitis muscle) using fine needles causing little or no discomfort to the animal. From a previous study of our group (Condy et al. 2005), it is known that higher doses (>=0.5 mg/kg) might cause abnormal oculomotor behavior like spontaneous nystagmus, drift, and abnormal saccades. These effects were avoided in the present study by using 0.25 to 0.35 mg/kg. We performed two ketamine injections per week per monkey maximum. In our experience, this procedure avoids tolerance effects (Pouget et al. 2010).

Results

Figure 1B shows a sample of saccades collected in the control condition (*blue traces*) or after ketamine injection (*red traces*) in monkey S. As already shown in Ameqrane et al. (2015), saccades occurring before the onset of the imperative stimulus (premature saccades) were more frequent in the control case (monkey S: 6%; monkey L: 4 %) than after ketamine injection (monkey S: 2%; monkey L: 3%). This reduction of the occurrence of premature saccades was statistically significant

in monkey S (chi-square test, $X^2[1, 22547]=264.943$, $p<0.001$) but not in monkey L ($X^2[1, 4158]=1.081$, $p=0.298$). In the present paper, we will analyze saccades occurring after target onset. Visual inspection of saccades represented on Fig. 1B shows that the latency of saccades was also altered by ketamine. However, effects on saccade metrics varied between subjects. Saccade amplitude was marginally decreased in monkey S (control: 10.5±0.04, n=11011 saccades; ketamine: 10.0±0.04, n=11413; one-way ANOVA, $F[1, 22422]=121.065$; $p<0.001$) and increased in monkey L (control: 10.8±0.02, n=2472; ketamine: 11.4±0.03, n=1528; one-way ANOVA, $F[1, 3998]=218.863$; $p<0.001$). Consequently, maximum velocity was decreased in monkey S (control: 674.8±1.4, n=11011; ketamine: 641.8±1.4, n=11413; one-way ANOVA, $F[1, 22422]=293.612$; $p<0.001$) and increased in monkey L (control: 546.8±0.9, n=2472; ketamine: 523.6±1.0, n=1528; one-way ANOVA, $F[1, 3998]=286.779$; $p<0.001$). Although statistically significant due to the large sample of saccades, these differences in saccadic parameters were small in absolute terms (0.5 to 0.6 deg). It is not surprising that saccade amplitude and maximum velocity were moderately affected by the drug given the presence of NMDA receptors in the final oculomotor pathway (Mettens et al. 1994).

Ketamine alters temporal expectation

Figure 2 shows the relationship between saccadic reaction time and FP duration (RT-FP function) in monkey S in the control case (saline injection 0.3 ml; *dashed curve*) and after 0.35 mg/kg of ketamine injection (same volume as saline injection; *continuous* curve). Average saccadic latency after saline injection were shorter (253±0.4ms, n=11011 saccades) than after ketamine injection (279±0.5ms, n=11413 saccades). However, the shape of the RT/FP function was also altered by ketamine. Accordingly, we found a significant interaction between FP duration and injected product (ANOVA; $F[3, 22416]=40.273$; $p<0.001$). An ANOVA of simple effects revealed a significant influence of FP duration after both saline ($F[3, 11007]=27.597$; $p<0.001$) and ketamine injection ($F[3, 11409]=21.144$; $p<0.001$). Indeed, following saline injection latencies were different for

different FP durations and the usual downward decreasing trend was observed (*dashed curve* on Fig. 2). However, after ketamine injection latencies tended to increase with increasing FP duration. Therefore, ketamine increased average saccadic latencies but also altered the foreperiod effect.

A straightforward hypothesis would be to suggest that ketamine simply reduced the level of alertness of the animal. Therefore, movement latency could be increased on average and the influence of elapsed time on saccade preparation decreased. Decreased alertness is commonly observed when animals get satiated and stop executing the task. In order to test this hypothesis, we firstly evaluated the influence of alertness during the experimental session after saline injection (control sessions) by computing the percentage of visually-guided saccades executed per block of trials presented to the animal. After saline injection in monkey S, the total number of saccades recorded tended to decrease as time elapsed during the experimental session (block 1, n=5718 saccades; block 2: n=5484, block 3: n=2232, block 4: n=723; total number of days of data collection=22 days), suggesting a progressive decrease of alertness or progressive satiation. In order words, during most experimental session, at least two blocks of trials were generally collected but four blocks of trials per session were less frequent. However, the percentage of saccades per block of trials remained approximatively constant (block 1, 83%; block 2, 83 %; block 3, 82 %; block 4, 85 %). Reduced alertness or boredom or satiation manifested itself by a reduced number of blocks of trials performed but the animal completed a block of trials to the end once it was initiated. Most importantly, after saline injection the FP effect was still present even after 4 blocks of 200 trials in a single session and a possible decrease of alertness (see *orange curve* on Fig. 3A). Indeed, a main effect of block repetition on the RT-FP function was found ($F[3, 10995]=4.220$; $p=0.005$) but no significant interaction effect between block repetitions and FP duration was observed ($F[9, 10995]=1.923$; $p=0.044$). The FP effect was *not* suppressed by a potential reduced alertness, satiation or fatigue at the end of data collection. After ketamine injection, the total number of saccades recorded tended also to decrease as time elapsed during the experimental session (block 1, n=4780 saccades; block 2: n=4709, block 3: n=3843, block 4: n=1347; total number of days of data

collection=22 d) but the percentage of saccades per block of trials remained approximatively constant (block 1: 81%; block 2: 77 %; block 3: 80 %; block 5: 83 %).

Figure 3B suggests different effects of ketamine injection on average saccadic latency and the FP effect. Indeed, average saccadic reaction time tended to increase between block 1 and block 2 (compare *blue* and *red* curves on Fig. 3B) but tended to decrease afterwards (compare *blue*, *green* and *orange* curves on Fig. 3B). A main effect of block repetition was found ($F[3, 11397]=81.399$; $p<0.001$) but there was no significant interaction effect between block repetition and FP duration ($F[9, 11397]=0.868$; $p=0.554$). The absence of a significant interaction effect suggests that RT-FP functions were similar between blocks of trials (shifted upward or downward on Fig. 3B) and that the absence of FP effect was consistent during the whole experimental session. Even if average saccadic latency decreased in block 3 and 4, the FP effect *did not* recover, suggesting a dissociation between the influence of the drug on average movement latency (upward/downward shit of the curves) and the FP effect (slopes). The effect of ketamine on average movement latency could dissipate faster than its influence on the slope of the RT-FP function.

Figure 3C shows a direct comparison of the RT-FP function during block 4 after saline (*dashed* curve) or ketamine injection (*continuous* curve). Importantly, for a 400 ms FP duration, saccadic latencies were similar between experimental conditions i.e. the 'starting point' of the RT-FP function was similar in both conditions. However, the influence of elapsed time during the FP did not alter saccadic reaction times after ketamine injection as it did in controls and a significant ANOVA interaction effect was found ($F[3, 1654]=8.150$; $p<0.001$).

The same set of experiences was repeated on monkey L. However, in order to obtain a robust FP effect in monkey L, shorter FP durations had to be used (FP durations: 50, 167, 283 and 400 ms). Indeed, we observed idiosyncratic differences concerning the range of FP durations that evoked the typical decreasing RT-FP function. Figure 4A shows that the characteristic negative slope could be obtained only for short FP durations (FP ≤ 400 ms), suggesting that the influence of the passage of time on movement latency was different between animals. For longer FP durations (similar as those

used in monkey S, FP > 400 ms), we observed that RT were *increasing* with increasing FP duration. This 'inversion' of the FP effect has been described previously (see Discussion). In monkey L, we also compared the influence of ketamine on the decreasing RT-FP function immediately after the injection of the treatment (Early; see Fig. 4B) and after a 30 minutes delay (Late; Fig. 4B). After ketamine injection, saccadic latencies initially increased independently of FP duration (Fig. 4B; *Early* curve shifted upward) but after the 30 minutes delay saccadic latency was differently affected by FP duration. Therefore, we found a significant main effect of FP duration ($F[3, 5730]=425.247$; $p<0.001$) and treatment ($F[2, 2790]=279.750$; $p<0.001$) but also a significant interaction between factors ($F[9, 5730]=11.793$; $p<0.001$). In summary, ketamine firstly increased average saccadic latencies but then altered temporal expectation in monkey L. Figure 5 compares the normalized RT-FP functions between conditions and monkeys for late blocks of trials. Although the effect of ketamine was stronger in monkey S it was qualitatively similar in monkey L.

Discussion

We found that in two Rhesus monkeys, saccadic RT initially decreased with increasing FP duration suggesting a beneficial action of temporal expectation. However, a range of shorter FP durations was required to observe the decreasing RT-FP function in monkey L compared with monkey S. Monkey L was a very active subject with very short average saccadic latencies. Indeed, saccadic latencies were usually <160 ms in this subject, approximately 100 ms shorter than in monkey S. Metaphorically, the internal clock of monkey L could be 'ticking' faster resulting in a shift of the decreasing part of the RT-FP towards shorter durations. Given that a larger range of FP durations was tested in monkey L, we also observed an 'inversion' of the FP effect: saccadic latencies *increased* with elapsed time for FP durations longer than 400 ms. A similar effect has been observed in humans (Müller-Gethmann et al. 2003). We suggest that attention could be progressively disengaged from the task as FP duration gets longer resulting in a longer RT when the stimulus eventually appears. The transition point from the decreasing to the increasing part of the RT-FP function could vary between subjects.

In spite of the individual differences between subjects, we found that ketamine reduced temporal expectation before the appearance of the eccentric visual target. Indeed, the two subjects of the present study showed a significantly different RT-FP functions after ketamine injection. However, two qualitatively different effects were observed. Firstly, ketamine increased average reaction time independently of FP duration. Secondly, ketamine altered the shape of the RT-FP function that we interpreted as a reduction of temporal expectation. In monkey S, both effects were present from the beginning of behavioral testing. The influence of ketamine on average reaction time was maximum during the first block of trials and then decreased during the rest of the experiment. In monkey L, the influence of ketamine on average reaction time was also present from the beginning of the experimental session. In this animal, the influence of ketamine on temporal expectation appeared later during the experimental session.

Figure 6 summarizes the two different effects of the drug in the present study. Firstly, ketamine could shift the RT-FP function to higher average values without altering its shape (Fig. 6, *blue curve*). This effect is not surprising given that ketamine increases saccadic reaction time in pro- and anti-saccades in the Rhesus monkey (Condy et al. 2005) and perturbs several aspects of eye movements (Weiler et al. 2000). Secondly, ketamine could also change the shape of the RT-FP function (Fig. 6, *red curve*). This effect cannot be simply attributed to an increase in sensorimotor delays but could be attributed to a selective impairment of temporal processing for saccades. Idiosyncratic combination of these two different factors could explain differences between observed effects in the two subjects of the present study. This combination of different effects is not surprising given the large distribution of NMDAr in the nervous system and their impressive number of different functions in sensorimotor and cognitive processes (Dingledine et al. 1999). The difference of the intensity of observed effects between monkeys could be also attributed to the different range of FP durations used. Indeed, in monkey S, using the 400 – 1900 ms range produced a robust FP effect that was not observed in monkey L with the same FP durations. Moreover, difference in ketamine metabolism and/or absorption after i.m. injection in the Splenius Capitis could also play a role. Even sex difference could also contribute to the intensity of ketamine effects as observed in rats (Saland and Kabbaj 2018) and mice (Thelen et al. 2019). In humans, light ketamine infusion could cause time to subjectively slow down or even stop (Guillermain et al. 2001; Micallef et al. 2004; Pomarol-Clotet et al. 2006; Coull et al. 2011). This influence of ketamine seems to be very specific to temporal cognition and does not alter e.g. color perception at the same dosage (Coull et al. 2011). Ketamine also alters temporal expectation in humans. Our results confirm these previous observations using a larger range of FP durations.

How in the brain temporal expectation could be represented is only partially elucidated and a network of distributed areas is likely to be involved. In the oculomotor domain, it has been shown that expectation of the onset of a visual target will cause a climbing neural activity in the supplementary eye fields (SEF) during the delay before the appearance of the visual stimulus (de

Hemptinne et al. 2008) or at the time of an expected change of motion direction (Heinen and Liu 1997). Moreover, electrical stimulation in the SEF can alter the timing of anticipatory smooth pursuit eye movements (Missal and Heinen 2004). In area LIP, it has been shown that neuronal activity could encode a subjective estimate of the hazard rate of the target (see Janssen and Shadlen 2005). In the sensory domain also, expectation of stimulus appearance will be accompanied by progressively increasing neuronal activity until a response is initiated (Reutimann et al. 2004; Constantinidis and Steinmetz, 1996). Theoretically, it has been shown that climbing neuronal activity could encode time intervals (Durstewitz 2003). In general, climbing neuronal activity is associated with the active maintenance of a sensory representation in the absence of the previously presented stimulus. We suggest that ketamine could reduce the slope of climbing neuronal activity and therefore reduce temporal expectation of the upcoming target.

Ketamine could also impair temporal expectation indirectly by altering dopaminergic (in rats: Moghaddam et al. 1997) and/or serotoninergic transmission (Kapur and Seeman 2002; Rothman 1994; Nishimura et al. 1998). Dopamine is an essential neurotransmitter in explicit timing tasks like duration reproduction (see review in Buhusi and Meck 2005). Therefore, effects in temporal processing observed in the present study might the consequences of altered dopaminergic transmission. However, in non-human primates, there was no sign of increased dopamine levels in the cortex or striatal region in studies using sub-anesthetic doses of R-ketamine (Yamamoto et al. 2013, 0.5 mg/kg and 1.5 mg/kg; Hashimoto et al. 2017, 0.5 mg/kg). Ketamine is not an effective dopamine releaser in monkeys (Tsukada et al. 2000; Adams et al. 2002). Moreover, we have previously shown that the slope of the RT-FP function is not altered by transiently suspending dopaminergic medication in humans (Degos et al. 2018; see also Jones et al. 2008). Indeed, in Parkinson's disease patients, the RT-FP function has a similar shape whether tested ON or OFF L-dopa medication. However, Tomassini et al. (2016) showed that dopaminergic neurotransmission could be essential to estimate temporal precision. Indeed, these authors showed that the estimation of elapsed time before an expected event was perturbed by dopaminergic receptors antagonism. The

discrepancy between the results of Degos et al. (2018) in PD patients OFF L-dopa and Tomassini et al. (2016) results with DA antagonists could be due to persistent dopaminergic transmission in the PD patients of Degos et al. (2018). Indeed, in these patients the OFF state was functionally defined by a 12-hour withdrawal of dopaminergic medication. This withdrawal might not have the same severe consequences as dopaminergic receptors antagonism. Interestingly, Degos et al. (2018) nevertheless reported an increased variability of the influence of temporal short-term memory on current movement preparation in PD patients.

Serotoninergic transmission also plays a significant role on temporal processing (in mice: Halberstadt et al. 2016; in rats, Asgari et al. 2006) and ketamine shows affinity for the 5-HT_2 receptor (Kapur and Seeman 2002). In rats, Asgari et al. (2006) have shown that the 5-HT2A/2C receptor agonist DOI perturbs temporal discrimination via stimulation of 5-HT2A receptors. In conclusion, we suggest that the effects observed in the present study are likely to be primarily mediated by hypoglutamatergic transmission at NMDA synapses although altered serotoninergic transmission by ketamine on temporal processing cannot be ruled out.

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Figures legends

Figure 1. A. Schematic drawing of the sequence of events during the task. The trial started with the appearance of a fixation cross for a randomized duration followed by the appearance of two empty "boxes," one at the center of the screen and at a 9° eccentric position. After the appearance of the two boxes, a target was flashed in the central one for 50 ms. Extinction of the central target marked the beginning of the delay period that could last either 400, 900, 1400, or 1900 ms in monkey S and 50, 167, 283 and 400 ms in monkey L. At the end of the delay period, a target appeared for 50 ms in the eccentric box and the subject had to make a saccade to the eccentric box within a 400-ms grace period. Only visually-guided saccades (latency > 100 ms) were further analyzed. B. Example of saccades from a block of control trials (*blue traces*) and after 0.25 mg/kg ketamine i.m. (*red traces*).

Figure 2. Average saccadic latency after saline or ketamine injection in monkey S. Error bars represent the 95% confidence interval.

Figure 3. Same data as presented on Fig. 2 but saccadic latencies were grouped by block number during the experimental session. Each block contained 200 trials. Colors indicate block number after saline injection (A) or ketamine injection (B, C). For clarity, only block 4 after saline or ketamine injection are represented in (C).

Figure 4. A. Influence of FP duration in the RT-FP function in monkey L. Note that the shape of the function changes around FP = 400 ms. B. Influence of ketamine injection in monkey L. In monkey L, trials after ketamine injection were compared to control trials without saline injection. Late trials were collected 30 minutes after ketamine injection.

Figure 5. Normalized saccadic latencies in control trials (*continuous lines*) and after ketamine injection (*dashed lines*) in monkey S (top) and L (bottom). Saccadic latencies were normalized with average saccade latency after the short FP.

Figure 6. Schematic representation of the two factors that could underlie observed effects. Ketamine alters motor preparation probably by increasing transmission delays at synapses in sensorimotor pathways. This results in a shift of the RT-FP function by a constant amount (*blue curve*). Ketamine alters also temporal expectation. The slope of the RT-FP function is reduced by the drug (*red curve*).