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RESEARCH ARTICLE

Higher Neural Functions and Behavior

Ketamine disrupts gaze patterns during face viewing in the common marmoset

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Abstract

Faces are stimuli of critical importance for primates. The common marmoset (*Callithrix jacchus*) is a promising model for investigations of face processing, as this species possesses oculomotor and face-processing networks resembling those of macaques and humans. Face processing is often disrupted in neuropsychiatric conditions such as schizophrenia (SZ), and thus, it is important to recapitulate underlying circuitry dysfunction preclinically. The *N*-methyl-D-aspartate (NMDA) noncompetitive antagonist ketamine has been used extensively to model the cognitive symptoms of SZ. Here, we investigated the effects of a subanesthetic dose of ketamine on oculomotor behavior in marmosets during face viewing. Four marmosets received systemic ketamine or saline injections while viewing phase-scrambled or intact videos of conspecifics' faces. To evaluate effects of ketamine on scan paths during face viewing, we identified regions of interest in each face video and classified locations of saccade onsets and landing positions within these areas. A preference for the snout over eye regions was observed following ketamine administration. In addition, regions in which saccades landed could be significantly predicted by saccade onset region in the saline but not the ketamine condition. Effects on saccade control were limited to an increase in saccade peak velocity in all conditions and a reduction in saccade amplitudes during viewing of scrambled videos. Thus, ketamine induced a significant disruption of scan paths during viewing of conspecific faces but limited effects on saccade motor control. These findings support the use of ketamine in marmosets for investigating changes in neural circuits underlying social cognition in neuropsychiatric disorders.

NEW & NOTEWORTHY Face processing, an important social cognitive ability, is impaired in neuropsychiatric conditions such as schizophrenia. The highly social common marmoset model presents an opportunity to investigate these impairments. We administered subanesthetic doses of ketamine to marmosets to model the cognitive symptoms of schizophrenia. We observed a disruption of scan paths during viewing of conspecifics' faces. These findings support the use of ketamine in marmosets as a model for investigating social cognition in neuropsychiatric disorders.

face perception; ketamine; marmoset; saccade; scan path

INTRODUCTION

The common marmoset (*Callithrix jacchus*) is a rapidly emerging nonhuman primate model for neuroscientific research. This species possesses a lissencephalic cortex that is advantageous for functional magnetic resonance imaging (fMRI) (1, 2), laminar electrophysiology (3), and optical imaging (4, 5). Marmosets have also convergently evolved a rich social behavioral repertoire that mirrors that of humans, including pair bonding and alloparental care (6). Sophisticated multimodality social communication has additionally been observed in this species and includes a library of distinct vocalizations, scent marking, tactile communication such as social grooming, and visual communication via body postures, physical gestures, and facial expressions (7–10). Together, this combination of practical experimental advantages and natural social behaviors is ideal for studies of the neural basis of social cognition, and impairments in processing of social signals often observed in neuropsychiatric conditions (11–13).

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Facial processing is of critical importance to social cognition in primates. The ability to detect, identify, and extract social information from faces is highly efficient and supported by a specialized network of cortical and subcortical areas exhibiting selectivity for faces (14, 15). Investigations in humans have shown selective activation in the fusiform gyrus, lateral occipital cortex, superior temporal sulcus, and inferotemporal cortex (16). Similarly, in macaques, distinct "face patches" can be observed along the occipito-temporal axis (17). Electrophysiological investigations of these areas reveal neurons that are not only face-selective but also sensitive to specific features of individual faces such as view direction and facial identity (18; see, for review, Refs. 14, 19, and 20). In the marmoset, recent fMRI evidence has revealed a face network comparable with that observed in macaques and humans (1, 2, 21), and previous behavioral investigations have shown that marmosets use gaze information and facial expressions for social communication in both head-free and head-restrained contexts in the laboratory (9, 22). Such cross-species similarities in face processing and face networks suggest that the marmoset has considerable potential as a model species in face-processing research.

Irregularities in face processing are a common characteristic of some human neuropsychiatric conditions. Patients with schizophrenia, for example, have been shown to exhibit impairments in configural face processing (23–25), aberrant facial emotion processing (for review, see Ref. 26), and abnormal gaze patterns during face viewing, including avoidance of the eyes (27–29). Neural correlates of these impairments have been documented, including attenuated amplitudes for event-related potential components associated with face processing (12, 30), structural and functional abnormalities in face-processing areas such as the fusiform gyrus (31–33), and emotional information processing areas such as the amygdala (34, 35; for review, see Ref. 36).

The *N*-methyl-D-aspartate (NMDA) noncompetitive antagonist ketamine has long been used to model symptoms of schizophrenia (37). Unlike dopaminergic agents, which primarily model the positive symptoms of schizophrenia (e.g., hallucinations and delusions), the ketamine model additionally produces negative symptoms including flat affect, emotional withdrawal, and cognitive symptoms (for review, see Ref. 38). These cognitive symptoms include impairments of configural and emotional face processing (39–42), suggesting that investigations of face processing using the ketamine model may provide a gateway to further understanding of cognitive and face-processing impairments in schizophrenia.

Investigations in nonhuman primate models have provided valuable insight into the neural basis of face processing, as tools like intracortical microstimulation and pharmacological manipulations have been used to disrupt the system and investigate causal relationships (43–45). For example, pharmacological manipulations have demonstrated a causal role of the posterior superior temporal sulcus in gaze-following behavior, which relies on configural face processing, in the macaque (46). Here, we evaluated the use of the common marmoset as a model for cognitive impairments affecting face processing by monitoring eye movements during a simple face-viewing task following administration of ketamine or saline. Ketamine administration altered the pattern of saccades between facial features with minimal impacts on oculomotor behavior in general. Taken together, our findings show that investigations of oculomotor behavior in marmosets can provide valuable insights into cognitive functions such as face processing and how these may be impacted in disease states.

METHODS

Subjects

Before these experiments, eight adult common marmosets underwent an aseptic surgical procedure to implant a combination recording chamber/head restraint, the purpose of which was to stabilize the head during eye-tracking experiments. The chamber implantation procedure is described in detail in Johnston et al. (47). Subsequently, each animal was acclimated to restraint in a custom-designed primate chair (47, 48).

Of these animals, four were experimentally naïve and could not be adequately calibrated. The remaining four marmosets had been trained to fixate on stimuli presented on screen and thus were amenable to our calibration protocol (see METHODS, *Data Collection*). Data from these four animals were used for all subsequent analyses (*Callithrix jacchus*; 1 female; weight 382–615 g; age 29–74 mo). All experimental procedures conducted were in accordance with the Canadian Council of Animal Care policy on the care and use of laboratory animals and a protocol approved by the Animal Care Committee of the University of Western Ontario Council on Animal Care. The animals were under the close supervision of university veterinarians.

Data Collection

Marmosets were seated in a custom primate chair (47) with the head restrained, inside a sound attenuating chamber (Crist Instruments Co., Hagerstown, MD). A spout was placed at the animal's mouth to deliver reward (acacia gum) via an infusion pump (Model NE-510, New Era Pump Systems, Inc., Farmingdale, NY). Eye position was calibrated in each session by rewarding 300–600-ms fixations on dots presented centrally or at ±5° abscissa or ordinate on the display monitor using the CORTEX real-time operating system (NIMH, Bethesda, MD). All stimuli were presented on a CRT monitor (ViewSonic Optiquest Q115, 76 Hz noninterlaced, 1,600 × 1,280 resolution). Eye positions were digitally recorded at 1 kHz via video tracking of the left pupil (EyeLink 1000, SR Research, Ottawa, ON, Canada). Animals were intermittently rewarded at random time intervals to maintain their interest.

Injections.

Following calibration, each marmoset received an intramuscular injection of either 0.5 mL/kg of saline or ketamine (dose = 1 mg/kg). Each marmoset completed two sessions on separate days, with the order of saline and ketamine injections counterbalanced. Data collection commenced 5 min following injection.

Stimuli.

The same block design and stimuli used in Schaeffer et al. (2) were used here, in which monkeys viewed short video clips

consisting of conspecifics' faces or scrambled version of these faces (12 s), interleaved with fixation blocks (18 s) where they were presented with a central, circular, black fixation stimulus (2°, see Fig. 1). Marmosets were not required to fixate during these blocks. During video blocks, the fixation stimulus was removed, and the video was presented at the center of the screen (16.5° height × 29.5° width) with face videos and their scrambled versions being presented in a pseudorandomized manner, counterbalanced across subjects. For the face videos, 12-s clips were created from videos of four marmosets seated in a marmoset chair (iMovie, Apple Incorporated, CA). Scrambled versions of the videos were created by random rotation of the phase information, preserving motion components by using the same random rotation matrix for each frame (MATLAB, The MathWorks, Natick, MA). See Supplemental data (all Supplemental material is available at https://doi.org/10.6084/m9.figshare.14447865.v1) for example stimuli. Stimuli were presented via Keynote (Version 7.1.3, Apple Incorporated, CA) with stimulus timing achieved using a photodiode. Animals were intermittently rewarded at random time intervals to maintain their interest.

Data Analysis

Analysis was performed using Python code written in-house. Eye velocity (visual deg/s) was obtained by smoothing, via a second-order 20-Hz low-pass Butterworth filter, and numerical differentiation. Saccades were defined as radial eye velocity exceeding 30 deg/s for a movement greater than 0.5 visual degrees. Saccade amplitude and peak radial velocity were obtained following smoothing by linear convolution of an 11-sample-wide hamming window. Fixations were defined as periods where radial eye velocity remained below 10 deg/s for at least 50 ms. In the Face Video clips, frames at the beginning and end of any movement were selected as "key" frames. Rectangular regions of interest (ROI) were manually labeled in the video clips at these key frames. The position of these ROIs in the intervening frames was linearly interpolated using Python code such that the ROI outlined facial features of interest (e.g., eyes and snout) as they moved in the video clip. Accuracy of the interpolation was then manually verified, adding additional key frames as necessary. See Supplemental Data for an example video of the labeling process.

Differences in saccade amplitudes and fixation durations between conditions were evaluated using 2 × 3 repeated-measures analyses of variance (ANOVA) with factors Drug Treatment (saline, ketamine) and Viewing Block (Fixation, Scrambled Video, Face Video). These were carried out in SPSS (v.25, IBM Corp, 2019). Greenhouse–Geisser corrections were applied where the assumptions of sphericity were violated. Partial eta squared (η^2_p) is reported as a measure of effect size. Post hoc tests of means were corrected using the Bonferroni method. Differences in transition probabilities between regions of interest between treatments were analyzed with multinomial logistic regressions using the multinom function (nnet package v7.3–14; Ref. 49) and custom code written in R (R v3.5.2; Ref. 50).

RESULTS

Task Engagement

To determine whether the effects reported below could be accounted for by the proportion of time the animals were engaged in the task, we measured for each animal the time their eyes were open in each Viewing Block for the ketamine and saline treatments. A repeated-measures ANOVA was conducted comparing mean proportions (N = 4) during Fixation (0.925 vs. 0.919), Scrambled Video (0.925 vs. 0.886), and Face Video Blocks (0.956 vs. 0.952) for saline and ketamine treatments, respectively. We observed a significant main effect of Viewing Block, $F(2,6) = 7.93$, $P = 0.046$, $\eta^2_p = 0.726$; no significant effect of Treatment, $F(1,3) = 0.221$, $P = 0.670$, $\eta^2_p = 0.069$; and a significant interaction of Viewing Block and Treatment, $F(2,6) = 6.724$, $P = 0.029$, $\eta^2_p = 0.691$. However, no significant pairwise differences were observed following correction for multiple comparisons.

Main Sequence

First, we investigated the main sequence relationship, i.e., the tendency of saccade amplitude and velocity to follow a linear relationship. For each animal, we conducted a linear

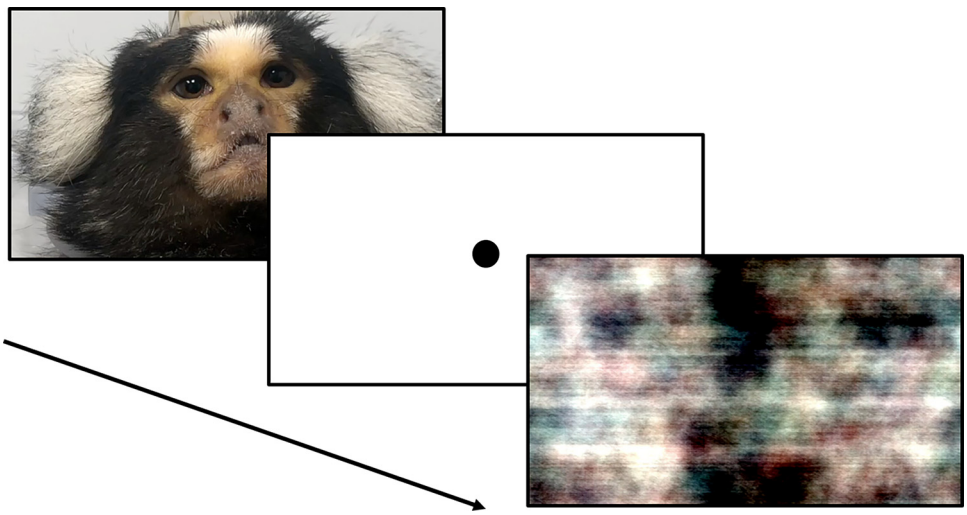

Figure 1. Task design: Face Video and Scrambled Video Blocks (12 s) were presented in a pseudorandomized order, interleaved with Fixation Blocks (18 s).

regression on saccade amplitude and peak radial velocity separately for each Viewing Block and Drug Treatment. The number of saccades for each animal (*M1–M4*) by Drug Treatment (saline and ketamine, respectively) were as follows: *M1*: 899, 513; *M2*: 894, 279; *M3*: 921, 890; and *M4*: 1,203, 172. A repeated-measures ANOVA was conducted for the Viewing Blocks (Fixation, Scrambled Video, Face Video) and Drug Treatments (saline, ketamine) on the slope values from these linear regressions (Fig. 2*A*). We observed no significant main effect of Viewing Block, $F(2,6) = 2.01$, $P = 0.215$, $\eta^2_p = 0.401$, or Treatment, $F(1,3) = 0.570$, $P = 0.505$, $\eta^2_p = 0.160$. Neither did we observe a significant Viewing Block × Treatment interaction, $F(2,6) = 3.02$, $P = 0.124$, $\eta^2_p = 0.502$. The main sequence relationship as a function of Drug Treatment is presented in Fig. 3.

Saccade Amplitude

Median saccade amplitudes were computed for each monkey (see RESULTS, *Main Sequence* for number of saccades). A repeated-measures ANOVA was conducted for the Viewing Blocks (Fixation, Scrambled Video, Face Video) and Drug Treatments (saline, ketamine) on these data (Fig. 2*B*). We observed significant main effects of Viewing Block, $F(2,6) = 27.14$, $P = 0.001$, $\eta^2_p = 0.900$, and Treatment, $F(1,3) = 17.63$, $P = 0.025$, $\eta^2_p = 0.855$. Furthermore, we observed a significant Viewing Block × Treatment interaction, $F(2,6) = 6.093$, $P = 0.036$, $\eta^2_p = 0.670$, showing a ketamine-induced reduction in saccade amplitudes in the Fixation Block ($\Delta = 2.38°$, $P = 0.018$) and Scrambled Video Block ($\Delta = 2.37°$, $P = 0.014$) but not in the Face Video Block ($\Delta = 1.92°$, $P = 0.055$).

Total Scan Path Length

Total scan path lengths were computed for each monkey using the sum of the saccade amplitudes. As the Fixation Blocks (18 s) were longer than the Video Blocks (12 s) and twice as frequent, this analysis was only conducted for Scrambled and Face Video Blocks that were matched for length. Thus, the number of saccades for each animal (*M1–M4*) by Drug Treatment (saline and ketamine, respectively) were as follows: *M1*: 247, 125; *M2*: 260, 84; *M3*: 298, 304; and *M4*: 332, 47. A repeated-measures ANOVA was conducted for the Viewing Blocks (Fixation, Scrambled Video, Face Video) and Drug Treatments (saline, ketamine) on these data (Fig. 2*C*). We observed no significant main effect of Viewing Block, $F(1,3) = 4.65$, $P = 0.120$, $\eta^2_p = 0.608$, or Treatment, $F(1,3) = 9.87$, $P = 0.052$, $\eta^2_p = 0.767$. We also observed no significant Viewing Block × Treatment interaction, $F(1,3) = 0.173$, $P = 0.706$, $\eta^2_p = 0.054$.

Fixation Duration

Median fixation durations were computed for each monkey. The number of fixations for each animal (*M1–M4*) by

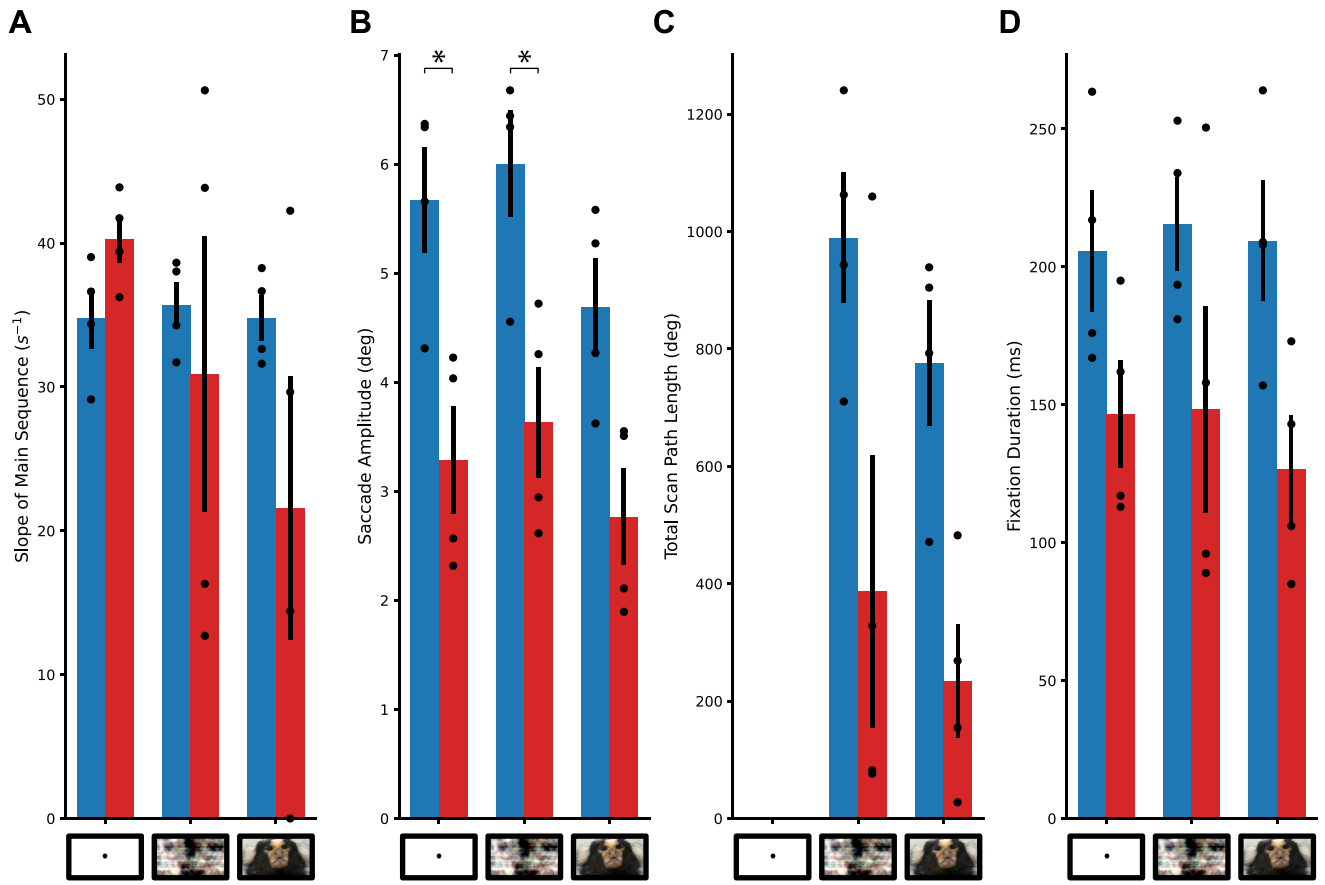

Figure 2. Ketamine effects on general oculomotor behavior during fixation and viewing of scrambled or face videos. Mean of slope of main sequence (*A*), median saccade amplitudes (*B*), total scan path length (*C*), and fixation durations (*D*) from four common marmosets following administration of saline (blue) or ketamine (red) for Fixation, Scrambled Video, and Face Video Blocks. *$P < 0.05$.

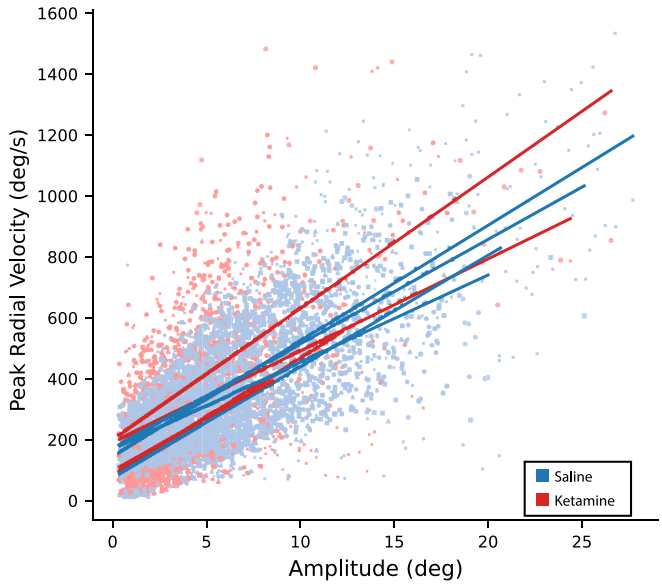

Figure 3. Main sequence relationship for saccades separately for saline and ketamine treatments collapsed across Viewing Blocks ($N = 4$).

Drug Treatment (saline and ketamine, respectively) were as follows: *M1*: 1,104, 1,289; *M2*: 1,420, 1,204; *M3*: 1,590, 1,625; and *M4*: 1,579, 1,607. A repeated-measures ANOVA was conducted for the Viewing Blocks (Fixation, Scrambled Video, Face Video) and Drug Treatments (saline, ketamine) on these data (Fig. 2*D*). We did not observe significant main effects of Viewing Block, $F(2,6) = 2.04$, $P = 0.248$, $\eta^2_p = 0.405$, $\varepsilon = 0.502$, or Treatment, $F(1,3) = 2.64$, $P = 0.203$, $\eta^2_p = 0.468$. We did observe a significant interaction of Viewing Block and Treatment, $F(2,6) = 10.75$, $P = 0.045$, $\eta^2_p = 0.782$, $\varepsilon = 0.508$. However, follow-up pairwise comparisons revealed no significant differences.

Scan Path Analyses

Regions of interest (ROIs) were labeled in Face Videos as described in METHODS, *Data Analysis*. The left and right eyes and the snout were defined as three regions and everywhere else was defined as the "outside" region. These ROIs were selected to mirror the eye and mouth ROIs used in human research (51, 52). Saccade onset locations and landing positions while viewing these videos were then classified by ROI (see RESULTS, *Total Scan Path Length* for number of saccades). We then computed multinomial logistic regression models predicting the ROI containing the landing positions of the saccade by *1*) Saccade Onset Region, *2*) Treatment, and *3*) the interaction of these terms. In addition, we used the above ROIs to model saccades while the subjects viewed the corresponding scrambled videos. Briefly, a logistic regression can be used to model a binary dependent variable by estimating the logarithm of the odds (i.e., log-odds) of one outcome over another as a linear combination of one or more independent variables. A multinomial logistic regression extends this method to a categorically distributed dependent variable with k possible outcomes (e.g., landing position ROI, $k = 4$) by separately estimating the log-odds of $k - 1$ outcomes (e.g., the Snout ROI) over a selected "pivot" outcome (i.e., the Outside ROI) as a linear combination of a set of independent variables (e.g., Saccade Onset Region, Treatment, and the interaction of these terms) (53).

Table 1. *Predicting saccade end region with treatment condition using a multinomial logistic regression while marmosets viewed face videos*

Predictors (Treatment)	DV (Saccade End)	β	SE	*P*
Saline (Intercept)	Left eye	−2.48	0.18	<0.001*
	Snout	−1.63	0.12	<0.001*
	Right eye	−2.19	0.16	<0.001*
Ketamine	Left eye	0.41	0.29	0.167
	Snout	0.41	0.20	0.047*
	Right eye	−0.44	0.34	0.193

DV, dependent variable. *$P < 0.05$.

Addition of the predictor Treatment to a model that contained only the intercept significantly improved fit, $\chi^2(2,385) = 7.98$, $P = 0.046$. Here, ketamine injection predicted a significantly greater number of saccades terminating in the snout, but not in the eye regions (Table 1 and Fig. 4*A*). A model with the predictor of Saccade Onset Region further significantly improved fit, $\chi^2(2,379) = 138.1$, $P < 0.001$. Here, saccades made within regions and between the eye regions were predicted as significantly more likely (Table 2). A model with the interaction of Treatment and Saccade Onset Region significantly improved the fit, $\chi^2(2,367) = 22.6$, $P = 0.032$. This interaction shows that the effect of Saccade Onset Region was significant in the saline treatment condition (Fig. 5*A*) but abolished when ketamine was administered (Table 3 and Fig. 5*B*).

Conversely, when this model was constructed using saccades from the Scrambled Video Block, no significant effect of Treatment was observed, $\chi^2(2,679) = 1.74$, $P = 0.627$. The model with the predictor of Saccade Onset Region significantly improved fit, $\chi^2(2,673) = 124.8$, $P < 0.001$, predicting saccades within regions as more likely (Table 4 and Fig. 4*B*). No significant interaction of Treatment and Saccade Onset Region was observed, $\chi^2(2,661) = 12.8$, $P = 0.382$ (Fig. 5, *C* and *D*).

In sum, although the subjects viewed videos of conspecific faces, ketamine administration induced a preference for viewing the snout over the eyes. Furthermore, saccades within a region or between the eyes were more likely. However, this structure was disrupted by ketamine administration. These effects are not observed when the subject viewed scrambled versions of these videos.

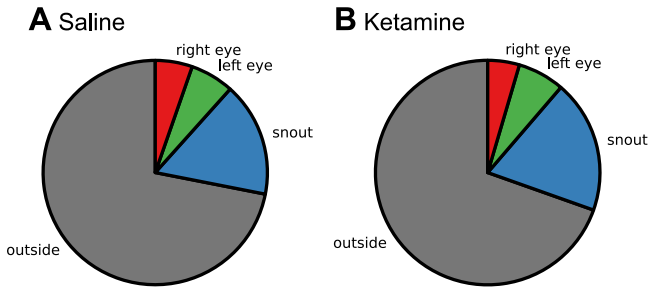

Figure 4. Proportions of total saccades by saccades with landing positions in each of the four regions of interest (right eye: red, left eye: green, snout: blue, outside: gray) while viewing Face Videos for saline (*A*) and ketamine (*B*) treatments.

Table 2. *Predicting saccade end region with saccade onset region using a multinomial logistic regression while marmosets viewed face videos*

Predictors (Onset)	DV (Saccade End)	β	SE	*P*
Outside (Intercept)	Left eye	−2.55	0.18	<0.001*
	Snout	−2.27	0.16	<0.001*
	Right eye	−2.71	0.19	<0.001*
Left eye	Left eye	1.26	0.38	0.001*
	Snout	−0.04	0.55	0.947
	Right eye	1.21	0.42	0.004*
Snout	Left eye	−0.06	0.55	0.919
	Snout	2.50	0.24	<0.001*
	Right eye	0.80	0.42	0.061
Right eye	Left eye	0.66	0.51	0.198
	Snout	0.97	0.41	0.018*
	Right eye	1.51	0.41	<0.001*

DV, dependent variable. *$P < 0.05$.

DISCUSSION

The marmoset model holds substantial promise for investigations of neural circuits underlying social behavior. These highly social animals possess oculomotor behavior and responses to face stimuli similar to those seen in macaques and humans. Recent work shows marmosets have a conserved face-processing network resembling the "face patches" observed in macaques and humans (1, 2, 21). This presents an opportunity to use these nonhuman primates for investigations of face processing and how it is disrupted in disease states. To this end, we used subanesthetic dose of ketamine injections to simulate symptoms observed in neuropsychiatric disorders such as schizophrenia and observed the oculomotor behavior of marmosets viewing videos of conspecific faces. We found that saccade peak velocities, saccade amplitudes, total scan path length, and fixation durations were not significantly altered by ketamine while viewing faces, demonstrating that the low doses of ketamine had limited effects on saccade control in general. However, significant ketamine-induced disruptions of scan paths were observed during viewing of conspecific faces but not scrambled versions of these faces. We observed a significant difference in the distribution of saccades to the snout but

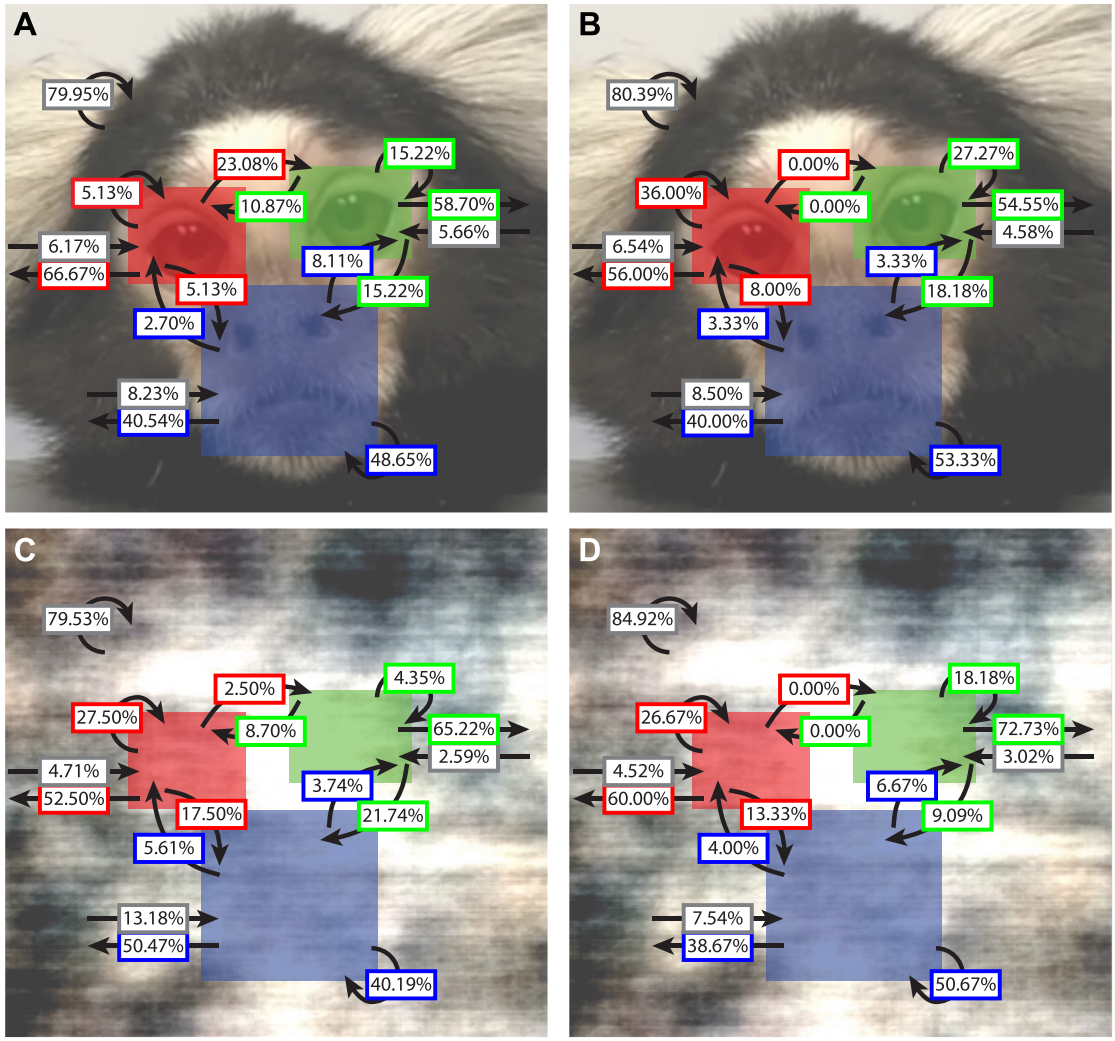

Figure 5. Transition probabilities of saccades between/within regions of interest during viewing of Face Videos. Proportions of saccades by region containing saccade landing positions for each saccade onset region separately for each combination of Viewing Block (unscrambled: *A*, *B*; scrambled: *C*, *D*) and Treatment Condition (saline: *A* and *C*, ketamine: *B* and *D*). In addition, colors indicate the saccade onset region (red: left eye, green: right eye, blue: snout, gray: outside). Values in like-colored boxes sum to 100%.

Table 3. *Predicting saccade end region with the interaction of saccade onset region and treatment condition using a multinomial logistic regression while marmosets viewed face videos*

Predictors (Onset; Drug)	DV (Saccade End)	β	SE	*P*
Outside; Saline (Intercept)	Left eye	−2.56	0.21	<0.001*
	Snout	−2.27	0.19	<0.001*
	Right eye	−2.65	0.22	<0.001*
Left eye; Saline	Left eye	0.00	0.76	0.997
	Snout	−0.29	0.76	0.701
	Right eye	1.59	0.45	<0.001*
Snout; Saline	Left eye	−0.15	0.76	0.847
	Snout	2.46	0.31	<0.001*
	Right eye	1.04	0.50	0.037*
Right eye; Saline	Left eye	0.88	0.53	0.099
	Snout	0.92	0.46	0.046*
	Right eye	1.30	0.48	0.007*
Outside; Ketamine	Left eye	0.05	0.39	0.894
	Snout	0.03	0.35	0.938
	Right eye	−0.22	0.45	0.626
Left eye; Ketamine	Left eye	2.07	0.93	0.027*
	Snout	0.59	1.11	0.593
	Right eye	−13.79	501.04	0.978
Snout; Ketamine	Left eye	0.17	1.11	0.877
	Snout	0.08	0.50	0.876
	Right eye	−0.66	0.97	0.498
Right eye; Ketamine	Left eye	−15.39	0.00	<0.001*
	Snout	0.22	0.98	0.819
	Right eye	0.87	0.94	0.351

DV, dependent variable. *$P < 0.05$.

not eye regions following ketamine as compared with saline. Furthermore, saccades within regions and between the eye regions were predicted as significantly more likely when marmosets were treated with saline, but these patterns were abolished when treated with ketamine.

Subanaesthetic doses of ketamine have been previously shown to have effects on low-level oculomotor behavior. Ketamine elicits spontaneous nystagmus in humans (54), monkeys (55), and cats (56). Furthermore, Leopold and colleagues (55) observed spontaneous eye movements following ketamine injection, and noted an impairment in gaze holding, as well as reduced saccade frequency and a disruption of the main sequence relationship. In the present work, we observed minimal nystagmus and a strong reduction of saccade amplitude when the animals were presented with the scrambled visual stimuli or central fixation stimulus, but these effects were attenuated when they were presented with a video of a conspecific's face. In addition, we investigated the main sequence relationship in the saline and ketamine conditions. We observed similar saccade velocities, e.g., 500 deg/s for a 10° saccade, as Mitchell and colleagues (22) albeit slower than the saccades in recent work by Chen and colleagues (57). Of interest, in the present study, we observed no change in the slope of main sequence relationship following administration of ketamine. In the macaque, a consistent ketamine-induced decrease in the slope of the main sequence is observed (55, 58), but Godaux and colleagues (56) did not observe such an impairment in cats. Further investigation of the effects of ketamine on saccade velocity, especially in dose-dependent manner, would be required to determine whether a species difference exists here.

Fewer investigations have been conducted with regard to the effects of ketamine on face processing. Such effects may be classified as general impairments in configural/featural processing of faces, impairments in facial emotional processing, or abnormal patterns of gaze. Here, we discuss these effects following administration of ketamine and similar observations in individuals with schizophrenia. Neill and colleagues (40) demonstrated the absence of the facial inversion effect in humans following ketamine injections as compared with placebo treatments. The facial inversion effect is an index of configural face processing, reflecting the increased processing time required for inverted as compared with upright faces, for which strong expectations exist regarding configural information (59). Similar impairments of configural processing, but not featural processing, have been observed in patients with schizophrenia. Although these impairments can be attributed in part to cognitive impairments and general deficits in early stages of visual processing in these patients (60, 61), an additional face-specific deficit is observed (Ref. 62; cf. Ref. 63). In addition to general impairments in face processing, ketamine-induced impairments in facial emotion processing have been demonstrated using behavioral (64) and electrophysiological (39) approaches. Such impairments have also been observed in patients with schizophrenia (65). A general difficulty with identifying the emotion being expressed has long been observed (for review, see Ref. 26). In addition, a specific impairment in identifying negative emotions, such as sadness or fear, has been observed (34, 66). Neural correlates of this can be observed in the amygdala, where seemingly low activation for negative faces can be seen due to abnormally high activation for neutral faces (34, 35; for review, see Ref. 36). The amygdala has an established role in fear processing and is known to modulate activity in the fusiform gyrus in relation to emotional information (67). To our knowledge, no other studies have been conducted investigating the effects of ketamine on scan paths of animals looking at conspecifics' faces. However, abnormal gaze patterns, including avoidance of the eyes, is observed in patients with schizophrenia (27–29); damage to the amygdala has been documented reducing eye contact in human's engaging in conversations with real people (68). Scan path abnormalities are also observed in individuals with autism spectrum disorder, although the effect has been shown to be restricted to reduction in eye contact (69, 70).

Table 4. *Predicting saccade end region with treatment condition using a multinomial logistic regression while marmosets viewed scrambled videos*

Predictors (Onset)	DV (Saccade End)	β	SE	*P*
Outside (Intercept)	Left eye	−2.86	0.19	<0.001*
	Snout	−1.97	0.13	<0.001*
	Right eye	−3.40	0.25	<0.001*
Left eye	Left eye	2.17	0.37	<0.001*
	Snout	0.76	0.40	0.057
	Right eye	−0.01	1.05	0.996
Snout	Left eye	0.64	0.40	0.109
	Snout	1.94	0.20	<0.001*
	Right eye	1.17	0.43	0.006*
Right eye	Left eye	0.42	0.76	0.582
	Snout	0.62	0.48	0.191
	Right eye	1.36	0.66	0.040*

DV, dependent variable. *$P < 0.05$.

The eyes are an important facial feature, and it has been demonstrated that fixations on eyes are predictive of increased face identification accuracy and a reduction of the facial inversion effect (71). Intranasal administration of oxytocin, a hormone with a role in enhancing prosocial behaviors, has been shown to increase fixations to eye regions relative to the mouth region in macaques (72) and marmosets (73), demonstrating the value of this metric in assessing primate scanning behavior of conspecific faces (see also, Ref. 51). In the present work, we observed a pattern consistent with observations in patients with neuropsychiatric disorders; probability of saccades increased to the snout region but not to eye regions following injection with ketamine, effectively reducing the ratio of time spent on eyes versus the snout. It should be noted that fewer saccades were made to nonface regions following ketamine injection, although this is likely attributable to the fact that faces were presented at the center of the screen and fewer large saccades were made by the subjects following ketamine administration. However, this central fixation bias alone cannot fully explain our observations as this effect was not present for scrambled versions of the videos. General deficits in early visual processing and specific deficits in face processing are commonly observed in individuals with schizophrenia (60–62). It should be noted that although the phase-scrambled videos preserve the motion components of the face videos and provide an adequate control in this regard, comparisons with nonface objects would be required to disentangle deficits specific to face processing from those resulting from impairments in early sensory processing stages.

Recent work has also investigated visual exploration of faces in humans by investigating the probabilities of transitions between regions of interest and observed that individuals with schizophrenia were less likely to transition from the mouth to the eye region (52). In the present work, when monkeys were injected with saline, we observed a gaze pattern in which saccades within a region on the face and between the eyes are more probable. However, this pattern was lost following ketamine administration. Investigations in patients have revealed that these abnormal gaze patterns are most pronounced in free-viewing tasks as we used here, and more closely resemble healthy controls when in a task, such as identifying the age or gender of the imaged individual (74). Future investigations using marmosets trained on a formal task, such as a match-to-sample, in which second-order features are manipulated, may prove illuminating in disentangling the role of ketamine on holistic face processing and provide a model to investigate the interaction of face processing and scan path abnormalities observed in neuropsychiatric disorders.

The specific contributions of certain brain areas to normal face scanning behavior remains an area of active interest. Recent work in macaques has demonstrated a role of the orbitofrontal cortex (OFC) in scanning of faces (75). Specifically, lesions in the OFC resulted increased overall looking at faces and increased attention to the eyes, which the authors posit may be due to the absence of top-down influences from OFC on sensory association cortices and subcortical structures like the amygdala, which play a role in allocating attention to social and nonsocial stimuli. Future pharmacological investigations targeting established nodes of the face-processing network would prove invaluable in further advancing our knowledge on this topic.

In conclusion, our findings demonstrate that ketamine induces a substantial impairment of the scanning pattern of faces in the common marmoset monkey and support its use as a model investigating face-processing networks and their impairments in neuropsychiatric disorders.

SUPPLEMENTAL DATA

Supplementary Material 1: Example Video Stimuli. An example Face Video (*A*) and corresponding Scrambled Video (*B*) and an example video of the labelling process used to track regions of interest (*C*): https://doi.org/10.6084/m9.figshare.14447865.v1.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.D.J. and S.E. conceived and designed research; J.S. and K.D.J. performed experiments; J.S. and R.K.W. analyzed data; J.S., K.D.J., and S.E. interpreted results of experiments; J.S. prepared figures; J.S. and K.D.J. drafted manuscript; J.S., K.D.J., D.S., and S.E. edited and revised manuscript; J.S., K.D.J., R.K.W., D.S., and S.E. approved final version of manuscript.

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