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Characterization of operant social interaction in rats: effects of access duration, effort, peer familiarity, housing conditions, and choice between social interaction vs. food or remifentanil

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Abstract

Rationale and objective: Social factors play a critical role in drug addiction. We recently showed that rats will abstain from methamphetamine, cocaine, heroin, and remifentanil self-administration when given a choice between the addictive drug and operant social interaction. Here, we further characterized operant social interaction by determining the effects of access duration, effort, peer familiarity, and housing conditions. We also determined choice between social interaction vs. palatable food or remifentanil.

Methods: We first trained single-housed male and female rats to lever-press for social interaction with a sex- and age-matched peer. Next, we determined effects of access duration (3.75-to-240 s), effort (increasing fixed-ratio schedule requirements or progressive ratio schedule), peer familiarity (familiar vs. unfamiliar), and housing conditions (single- vs. paired-housing) on social self-administration. We also determined choice between social interaction vs. palatable food pellets or intravenous remifentanil (0, 1, 10 μg/kg/infusion).

Results: Increasing access duration to a peer decreased social self-administration under fixed-ratio but not progressive-ratio schedule; the rats showed similar preference for short vs. long access duration. Social self-administration under different fixed-ratio requirements was higher in single-housed than in paired-housed rats and higher for a familiar vs. unfamiliar partner in single-housed but not paired-housed rats. Response rates of food-sated rats under increasing fixed-ratio requirements was higher for palatable food than for social interaction. The rats strongly preferred palatable food over social interaction and showed dose-dependent preference for social interaction vs. remifentanil.

Conclusions: We identified parameters influencing the reinforcing effects of operant social interaction and introduce a choice procedure sensitive to remifentanil self-administration dose.

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Keywords

social reward; choice; self-administration; remifentanil; food; housing conditions

Introduction

Recent advancements in preclinical research on circuit and cellular mechanisms of the behavioral effects of addictive drugs have yet to impact clinical treatment (Ahmed 2010; Heilig et al. 2016; Negus and Banks 2021). To better bridge this preclinical-clinical gap, we turn to the reverse translation approach (Fredriksson et al. 2021; Venniro and Shaham 2020). Through reverse translation, effective clinical treatments are used as a basis for designing preclinical addiction models, thus improving the potential for discovering mechanisms that may lead to new treatments (Bossert et al. 2020; Venniro and Shaham 2020).

Recently, we applied the reverse translation approach to develop a rat model of social reward-induced voluntary abstinence (Venniro and Shaham 2020; Venniro et al. 2018). This model is designed to mimic the reinforcement-based behavioral treatment termed "community reinforcement approach" in which the availability of meaningful social rewards (employment, positive interaction with peers and family) promotes cessation or decreased drug use (Aklin et al. 2014; Hunt and Azrin 1973). Using this model, we showed that when rats are offered a mutually exclusive choice between an addictive drug (methamphetamine, cocaine, heroin, or remifentanil) or immediate social interaction with a peer, they choose social interaction over the drug and achieve "voluntary abstinence" (Venniro et al. 2021; Venniro et al. 2019; Venniro and Shaham 2020; Venniro et al. 2018).

We also found that rats reliably choose social interaction over methamphetamine or cocaine (Venniro et al. 2021; Venniro et al. 2018) even after self-administration training in preclinical models that induce addiction-like behavior in rats (escalation of drug intake (Ahmed and Koob 1998), intermittent access (Zimmer et al. 2012), and DSM-based model (Deroche-Gamonet et al. 2004)). Additionally, two weeks of social choice-induced voluntary abstinence either prevents (methamphetamine and cocaine) or decreases (heroin) the incubation of drug craving (Venniro et al. 2021; Venniro et al. 2019; Venniro et al. 2018). Incubation of drug craving refers to the time-dependent increase in drug seeking during abstinence (Fredriksson et al. 2021; Grimm et al. 2001; Pickens et al. 2011).

The reverse translation approach offers a promising means to better understand the neurobiological mechanisms of drug addiction. However, understanding how social interaction functions as a reinforcer to the species in which it is used is also important. In this regard, two early studies examined factors that influence operant responding for social interaction in rats (Angermeier 1960; Evans et al. 1994). Angermeier (1960) trained male rats to lever-press for access to a male or female peer (10-s access) at varying levels of contact. They reported that independent of the peer sex, the rats that were reared together acquired the lever-press contingency for visual contact with the peer, and both partial- and full-physical contact with it. They also reported that in rats that were reared individually, the degree to which the lever-press contingency was acquired was dependent on the level of contact with the peer; the rats acquired social self-administration at a greater degree

when the level of contact with the peer was greater. Evans et al. (1994) trained a group of single-housed female rats that had free access to food in their homecage to lever-press for 45-s social interaction with a castrated male rat, and another group of female rats that were food restricted but pair-housed to lever-press for 45-s food access. They reported no differences in rate of responding for social interaction or food, nor any differences in extinction responding when the peer or food was no longer available. These early studies provide foundations to further characterize how social interaction serves as a reinforcer in male and female rats.

In the present study, we characterized behavioral and experimental factors that modulate operant responding for social interaction (access for partial-physical contact with a sex- and age-matched peer separated via a perforated screen). The factors we examined include duration of social interaction as a proxy for reinforcer magnitude, effort to obtain social interaction under fixed-ratio (FR) and progressive- ratio reinforcement schedules, peer familiarity (familiar vs. unfamiliar), and housing conditions (single- vs. paired-housing).

Next, we assessed choice between different durations of social interaction, and social interaction vs. food or remifentanil. We also introduce a dose-sensitive remifentanil vs. social interaction choice procedure, based on the remifentanil vs. food choice procedures used in Chow et al. (2021). We assessed choice using two different procedures: ‘the controlled reinforcer frequency choice procedure’ (Beckmann et al. 2019) and the ‘discrete choice procedure’ (Chow and Beckmann 2021; Lenoir et al. 2007; Thomsen et al. 2013). In the controlled reinforcer frequency choice procedure, the choice between drug (e.g., remifentanil) vs. non-drug (e.g., food or social interaction) rewards is determined under conditions in which the rats have equal exposure to the operant rewards. An advantage of this procedure is that it requires the rats to sample the drug and non-drug rewards equally across the drug doses tested, which improves the rats’ ability to discriminate between the different drug doses vs. the non-drug reward, which promotes dose-dependent shifts (Beckmann et al. 2019; Chow and Beckmann 2021). We also assessed the rats’ choice under the ‘discrete-trials choice’ procedure (Chow and Beckmann 2021; Lenoir et al. 2007; Thomsen et al. 2013) that we used in previous studies on relapse after voluntary abstinence induced by palatable food or social choice (Caprioli et al. 2017; Fredriksson et al. 2021; Venniro et al. 2018).

Material and Methods

Subjects

For Experiments 1, 3, and 4, conducted in the Biomedical Research Center at IRP/NIDA/NIH, we used 34 male and 32 female Sprague-Dawley rats (half of them served as partner rats; estimated age at arrival: ~7-8 weeks PND; body weight at time of arrival: males, 201-225 g; females, 176-200 g; Charles River). All the rats arrived pair-housed and were given a week to acclimate together. Afterwards, we single-housed the rats for the rest of the experiments. We designated the rats into “main” rats and “partner” rats (i.e., the main rats were placed in the main operant chamber and lever-pressed for access via a perforated screen to the partner rat located in the partner chamber). We maintained the rats under a reverse 12:12 h light/dark cycle (lights off at 8 AM) with free access to food (Teklad

Rat Diet, Envigo) and water in their homecage. We kept the rats separated for at least 2 weeks before experimentation; we handled the rats daily the week prior to the start of the experiments.

For Experiment 2, conducted in the Triad Technology Center at IRP/NIDA/NIH, we used 32 female Long-Evans rats (half of them served as partner rats; body weight at time of arrival: 176-200 g; Charles River). All the rats arrived pair-housed and were given a week to acclimate. We maintained the rats under a reverse 12:12 h light/dark cycle (lights off at 8 AM) with free access to food (Teklad Rat Diet, Envigo) and water in their homecage. The details of the homecage housing conditions are provided below.

We performed all experiments in accordance with the NIH Guide for the Care and Use of Laboratory Animals (8th edition), under protocols approved by the NIDA IRP Animal Care and Use Committee.

Drugs

For Experiment 4, we obtained remifentanil hydrochloride (remifentanil) from the NIDA pharmacy and dissolved it in sterile saline. The unit doses of remifentanil used (0, 1, and 10 μg/kg/infusion) were based on previous remifentanil vs. food choice studies (Chow and Beckmann 2021).

Intravenous surgery

For Experiment 4, we anaesthetized the rats with isoflurane gas (5% induction, 2%-3% maintenance). We then inserted silastic catheters to the jugular vein as previously described (Bossert et al. 2016; Caprioli et al. 2015b). We injected the rats with the analgesic drug ketoprofen (2.5 mg/kg, s.c. Butler Schein) immediately after surgery and the following two days. We allowed the rats to recover for 6 to 7 days prior to remifentanil self-administration training during which we flushed the catheters daily using sterile saline containing gentamicin (4.25mg/ml, APP Pharmaceuticals). Before each self-administration session, we flushed catheters with 0.1 ml sterile saline and after the session, we flushed catheters with 0.2 ml gentamicin.

Apparatus

The experiments were conducted in operant chambers with an attached partner-chamber (ENV-00CT-SOCIAL; Med Associates; see (Venniro and Shaham 2020) for details). The two chambers were separated by a guillotine door (ENV-10B2-SOC) and a perforated metal gate which prevents the rats from crossing into the other chamber but allowing for full face-to-face and forepaw contact. The operant chambers were controlled by Med-PC IV. In Experiment 1 and 4, we outfitted the front panel of the operant chamber with an illuminated nosepoke (ENV-114BM) with two retractable levers (ENV-112CM) mounted on either side. Above each lever was a white cue-light (ENV-221M) and above the nosepoke port, at the top of the panel, was a red house-light (ENV-221RD). On the opposite back panel of the operant chamber, next to the gated-guillotine door, at the top corner were two Sonalert tones (2.9 kHz, ENV-223AM and 4.5 kHz, ENV-223HAM). In Experiment 3, we placed the Sonalert tones on the front panel on either side of the red house-light because we outfitted the back

panel of the operant chamber a recessed-food receptacle (ENV-200R1M-6), equipped with a head-entry detector (ENV-254-CB), which was attached to a food dispenser (ENV-203-45). In Experiment 2, we outfitted the front panel of the operant chamber with two retractable levers, above one lever was a white cue-light and above the other lever was a Sonalert tone (ENV-223AM) and a white house-light (ENV-227M). We outfitted the opposite back panel of the operant chamber with a protruding food receptacle (ENV-200R1AM-LP) next to the gated-guillotine door. In all experiments, the partner-chamber contained no manipulanda or stimuli except the guillotine door which connected the chambers.

Experiment 1: Effect of access duration on social self-administration

We first assessed the effect of access duration (i.e., time door open) on operant responding for social interaction. We used two groups of rats that we termed ‘main’ rats and ‘partner’ rats based on the sequence of the daily training. During each daily session, the main rats first lever-pressed for access to the partner rats and after the session they became the social partners for which the partner rats lever-pressed for access to social interaction. We used this design to examine if partner rats performed similar to the main rats. Similar social self-administration of the main and partner rats will allow us and other investigators to use the partner rats as experimental subjects and decrease the number of rats used in a given study.

We first trained the age- and sex-matched rats (n=8 main rats and 8 partner rats) on a door shaping procedure for one day. The door shaping procedure lasted 45 min, where we allowed the rats to habituate to the chamber for the first 5 min, followed by 30 min of a fixed-time (FT) 120-s schedule where the door opened for 60 s allowing the rats to engage in partial-physical contact (i.e., social interaction) with a same-sex peer, and, for the remaining 10 min, we allowed the rats to habituate to chamber again. Immediately after the session ended, we moved the rat from the main chamber to the partner chamber and the partner rat to the main chamber and repeated the door shaping procedure for the partner rats.

Following door shaping, we trained the rats on a fixed ratio (FR)-1 reinforcement schedule for 60-s access to a peer. The FR training consisted of the extension of a single lever (counterbalanced) where completion of the FR requirement resulted in the retraction of the lever, illumination of the cue-light above the response lever for 6 s, and the social door opening for 60 s. After the allotted time, the door closed and a 30-s intertrial interval (ITI) started. Each session lasted 1 h. We trained the rats on the FR1 schedule for 3 days, followed by FR3 schedule for 2 days, and finally FR5 schedule for 5 days. Like the door shaping, we switched the main and partner rats and repeated the FR training after each session with the partner rats.

Next, we trained rats to lever press for social interaction of different access times (3.75, 7.5, 15, 30, 60, 120, and 240 s; Latin-square design). During the duration-response sessions, completion of the FR5 response requirement resulted in the retraction of the lever, illumination of the cue-light above the response lever for $1/10^{th}$ the access time (e.g., 0.375 s for 3.75s, 0.75 s for 7.5 s, etc.), and the social door opening for the designated duration. Each trial was separated by a 30-s ITI and the sessions lasted 1 h. We trained the rats at each

access duration for 2 consecutive days, and we switched the role of the main and partner rats after each session and repeated the duration tested for the partner rats.

After the duration response assessment, we assessed the effect of different access durations on responding under a progressive ratio schedule, a measure of the relative reinforcing strength of drug and non-drug rewards (Hodos 1961; Richardson and Roberts 1996). For the progressive ratio assessment (and the subsequent choice assessment), we only tested the main rats (n=8; 4 females) because we observed a trend suggesting decreased reward efficacy in social interaction for the partner rats. We trained the rats under a progressive ratio schedule for 15, 30, and 60 s of social interaction. During the progressive ratio sessions, the completion of the required response ratio resulted in the retraction of the lever, illumination of the cue-light above the response lever ($1/10^{th}$ the time of access), and the social door opening for the allotted access time. Each session lasted a maximum of 6 h or terminated if the rat did not complete the required ratio within 1 h. The response ratio requirement increased according to the following equation: response ratio (round to nearest integer) = $5e^{(\text{reinforcer number} \times 0.2)} - 5$ (Richardson and Roberts 1996). We trained the rats on each access duration for 3 consecutive days (Latin-square design).

To further determine the reinforcing strength of different access durations, we measured the rats' choice for competing access durations. Before assessing choice for different access durations, we first trained the rats on the opposite lever, which was never encountered before, on an FR5 (30 s ITI) schedule for 30-s social interaction for five 1-h sessions. Next, we trained the rats to respond on both levers for 30-s social interaction. Each session consisted of 5 trials on each lever, random- and independent-presentations, and was separated by a 30-s ITI and ended after 1 h or completion of all 10 trials. These retraining data are not shown.

We then trained the rats on a controlled reinforcer frequency choice procedure which controls for the relative frequency of reinforcement for the available options that limits systematic biases that may develop due to repeated choices on a given option (McCarthy and Davison 1984). This choice procedure requires the rats to sample both options and provide them with the opportunity to better learn and discriminate differences in the reward options (Beckmann et al. 2019). Each controlled reinforcer frequency choice session consisted of 10 trials (5 trials/duration). During each trial, both levers were extended into the chamber. However, only one of the two options was available for reinforcement. Responding on the lever associated with the available option resulted in the levers retracting, the illumination of the cue-light ($1/10^{th}$ of access duration) above the available lever, and the door opening for the allotted time. Responding on the lever associated with unavailable option were recorded as choice responses and had no program consequences.

After training on the controlled reinforcer frequency choice procedure, we conducted a probe-test using a discrete-trials choice procedure (Chow and Beckmann 2021). In this procedure, the sessions were divided into two phases. The first phase consisted of 2 sample trials, where on a given trial, one lever was randomly presented, and responding on the extended lever resulted in the delivery of the associated reward. During the second phase (i.e., choice trials), both levers were extended and responding on either lever resulted in

retraction of both levers, illumination of the cue-light ($1/10^{th}$ of access duration) above the selected lever, and the door opening for the associated access time; sessions ended after 10 choice trials. Additionally, under the discrete-trial choice procedure, the rats had 180 s to make a response before the trial ended and the trial was defined as an omission.

Each trial, in both choice procedures, was separated by a 180 s ITI. We first split the rats (n=4/group) to compare 15 s vs. 30 s social interaction and 30 s vs. 60 s interaction. We then trained them under the controlled reinforcer frequency choice procedure for 4 days and conducted a probe discrete-trials choice test the following day. We observed no noticeable differences or changes in choice between the groups and recombined the groups to compare 3.75 s vs. 240 s social interaction. We trained rats on the controlled reinforcer frequency choice procedure for 6 days and conducted a probe discrete-trials choice test on the following day.

Experiment 2: Effect of increasing fixed ratio requirements on social interaction and food self-administration under different housing and familiarity conditions

We first assessed how effort (increasing FR response requirements over days) influenced responding for social interaction relative to responding for high-carbohydrate 45 mg palatable food (TestDiet, 5TUL - 1811155, 12.7% fat, 66.7% carbohydrate, and 20.6% protein). This pellet type was used in our previous studies on food choice-induced voluntary abstinence from methamphetamine, heroin, and fentanyl (Caprioli et al. 2015a; Caprioli et al. 2017; Reiner et al. 2020; Venniro et al. 2017b).

We first trained one group of aged-matched female rats (n=16) to lever-press for food over 5 days using an 1-h block format where one lever press produced one food pellet and the onset of a yellow cue-light for 4 s (counterbalanced light and lever to food port) with a 20-s timeout, with the lever constantly available (data not shown). The first 2 days included an initial 30-min magazine shaping session (1 pellet automatically dispensed each minute). After 5 training days, we selected the highest lever-pressing rats (n=8) to lever-press for 15-s social interaction. Each session consisted of 60 discrete trials where each trial began with the illumination of the white house-light for 4 s, followed by the extension of a single lever (counterbalanced) where rats had 60 s to complete the FR ratio response requirement. If the rat completed the FR response requirement, the lever retracted and a tone would play for 5 s while the door opened for 15 s; if the rat did not complete the FR requirement, the trial would end without presentation of the corresponding cues and food pellet delivery. Each trial was separated by a 60-s ITI and sessions lasted 2 h.

We trained the rats on different FR schedules for 19 sessions, starting on the FR1 schedule and then switching between FR1 through FR8 in the following sequence: FR1x2 sessions, FR2x2 sessions, FR1x1 session, FR3x2 sessions, FR1x1 session, FR4x2 sessions, FR1x1 session, FR5x2 sessions, FR6x2 sessions, FR7x2 sessions, FR8x2 sessions (data not shown). Next, we tested the rats for 6 sessions, starting at the FR1 schedule and doubling the response requirements daily up to FR32 until total social rewards neared 0.

Next, we trained the rats on the same procedure for the palatable food pellets. Each session consisted of discrete trials where each trial began with the illumination of the white house-

light for 4 s, followed by the extension of a single lever (opposite of the social reward) where rats had 60 s to complete the required FR. If the rat completed the required FR, the white cue-light above the lever would be illuminated for 5 s while 3 pellets were delivered over 6 s. We first trained the rats on the FR1 schedule for 3 days and then doubled the FR response requirement (FR1, 2, 4, 8, 16, 32, 64, 128) each day until total rewards reached near 0; we report the last session on the FR1 schedule and the next 7 sessions during the doubling FR requirements.

Next, we assessed the effect of housing conditions and peer familiarity on responding for social interaction. We first trained another group of aged-matched female rats (n=16) first on the same 1-h block format for food over 5 days (see above, data not shown). We then trained the highest lever-pressing rats (n=8) on an FR1 schedule for 4 days (pair-housed with unfamiliar partner; data not shown) using the same trial-based procedure described above for social self-administration. Next, we doubled the FR requirements every 2 days (FR1, 2, 4, 8, 16). We report the two-day mean during the 10 days of FR doubling. We trained the rats on the doubling FR procedure in the following order: pair-housed with an unfamiliar partner, single-housed with a familiar peer, pair-housed with a familiar partner, and single-housed with an unfamiliar peer. To manipulate the housing conditions, we either pair- or single-housed the rats. When the rats were pair-housed, the two rats that were paired together were of the same role (e.g., main rat paired with main rat). To manipulate peer familiarity, we either kept the same main rat and partner rat (i.e., familiar) pairing for the entire duration of the doubling of the FR requirements or we cycled the partner rats (i.e., unfamiliar) following each FR increase. When rats were responding for a familiar rat, the same familiar rat was used in both single-housed and pair-housed conditions. When rats were responding for an unfamiliar peer, we paired the main rats with a different rat (never the same rat used in the familiar condition). Note: we term this condition as unfamiliar since there were some re-pairings between main and partner rats as we cycled through the increasing FR requirements and the changes in the housing conditions. We trained the rats sequentially under the following conditions: pair-housed with unfamiliar partner, single-housed with familiar partner, pair-housed with familiar partner, and single-housed with unfamiliar partner.

Experiment 3: Choice between food and social interaction

To determine choice between food and social interaction, we first trained a separate group of sex- and age-matched male and female rats (n=8 (4 females) and 8 (4 females) partners) on a food magazine shaping procedure for one session (25 min). During the session, we first allowed the rats to habituate to the chamber for the first 5 min, followed by 20 min of a FT120-s schedule where the palatable food pellet (see Experiment 2) was delivered into the food receptacle, and, for the remaining 10 min, we allowed the rats to habituate to chamber again. We then trained the rats to lever-press for the food pellets in a trial-based procedure. During the food training sessions, each trial started with the extension of a single lever (counterbalanced) and completion of the FR requirement resulted in the retraction of the lever, illumination of the cue-light above the response lever for 6 s, and the delivery of a single palatable pellet. Each trial was separated by a 120 s ITI and the session ended either when 15 trials were completed or after 1 h. We trained the rats to lever-press for food on an

FR1 schedule for 2 days, followed by an FR3 schedule for 1 day, and then an FR5 schedule for 3 days.

Next, we trained the rats to lever-press for social interaction. We first train them on the social door shaping procedure, as described above (FT120-s for 60 s social interaction with a same-sex peer). Then we trained the rats on an FR schedule for 60-s social interaction (6-s cue; 120-s ITI; opposite of food lever) where the session ended after 15 trials were completed or after 1 h had elapsed. We trained the rats to lever-press for social interaction on the FR1 schedule for 2 days, followed by FR3 schedule for 1 day, and then FR5 schedule for 3 days.

Next, we trained the rats to lever-press food and social interaction lever during the same sessions. During the sessions, either the food- or social-lever was randomly extended and completion of the FR5 schedule requirement resulted in the retraction of the lever, illumination of the cue-light above the lever (6 s), and delivery of the associated reward. Each session lasted for 20 trials (10 trials/reward type), separated by a 120-s ITI, or ended after 1-h elapsed.

Finally, we trained the rats on a controlled reinforcer frequency choice procedure for social interaction vs. food. The choice procedure consisted of 2 choice blocks in the following order: 0 s social interaction vs. 1 pellet and 60 s vs. 1 pellet. Each choice block consisted of 10 trials (5 trials/reward) and was separated by a 5-min inter-block interval. To distinguish between the two blocks, a 10-s alternating tone-pattern would play before the start of each trial (alternating between 2.9 kHz and 4.5 kHz for 1.5 s and 0.3 s for the first block and 0.3 s and 1.5 s for the last block; counterbalanced). Each trial was performed as described above separated by a 180-s ITI. After 4 days of training, we increased the duration of social interaction in the first block from 0 s to 3.75 s and trained the rats for 4 days as described above.

Experiment 4: Choice between social interaction and remifentanil

To determine choice between remifentanil vs. social interaction, we trained a separate group of age-and sex-matched rats (n=16 [7 females] and 16 [7 females] partners) on a FT120 s door shaping procedure for 15-s social interaction for one session (45 min). Next, we trained the rats for 10 d to lever-press on an FR1 schedule for 15-s social interaction (5.45 s cue on reward delivery; 120-s ITI); the sessions ended after 15 trials or after 1-h had elapsed. We then catheterized the rats, as described above, and, after recovery, we trained them to lever-press for intravenous remifentanil (10 μg/kg/infusion) in a trial-based procedure. During the daily sessions, each trial stared with the extension of a single lever (opposite of social interaction training) and completion of the FR1 schedule resulted in the retraction of the lever, illumination of the cue-light above the response lever for 5.45 s, and a 0.1 ml remifentanil infusion over 5.45 s; trials were separated by a 120-s ITI. Remifentanil training sessions ended after 10 infusions or after 1 h had elapsed.

Next, we trained the rats on trial-based sessions in which remifentanil or social interaction were available. During each trial within these sessions either the remifentanil- or social-lever was randomly extended and completion of the FR1 schedule resulted in the retraction of the

lever, onset of the cue-light above the lever (5.45 s), and delivery of the associated reward. Each session lasted for 20 trials (10 trials/reward type), separated by an 18-s ITI, or ended after 1 h had elapsed.

To assess choice between remifentanil and social interaction, we first trained the rats on a controlled reinforcer frequency choice procedure. The controlled reinforcer frequency choice procedure consisted of 3 blocks in the following order: 0 μg/kg/infusion vs. 15-s social interaction, 1 μg/kg/infusion vs. 15-s social interaction, and 10 μg/kg/infusion of remifentanil vs. 15-s social interaction. The cue-light associated with social interaction was 5.45 s, while the cue-light for remifentanil infusion was 0, 0.545, or 5.45 s, as a function of increasing the dose. Each block consisted of 6 trials (3 trials/reward) and was separated by a 5-min inter-block interval. To distinguish between the three blocks, a 10-s alternating tone-pattern would play before the start of each trial (alternating between 2.9 kHz and 4.5 kHz for 1.5 s and 0.3 s for the first block, 0.9 s and 0.9 s for the middle block, and 0.3 s and 1.5 s for the last block, respectively). Each trial was operating as described above and was separated by a 180-s ITI.

After 14 days of training under controlled reinforcer frequency choice procedure, we probed the rats' choice using a discrete-trials choice procedure for 2 days. Each discrete-trials choice session consisted of 3 blocks (0, 1, or 10 μg/kg/infusion vs. 15 s social interaction) divided into a sample-phase and choice-phase. The sample-phase consisted of 2 trials, 1 for each reinforcer, and the choice-phase consisting of 6 discrete choice trials. During the sample-phase trials, only one lever and its associated reward plus reward-paired cues were available. During the discrete choice trials, both levers and their associated rewards plus reward-paired cues were available and responding on one of the levers led to the delivery of the lever-associated reward plus cues and the retraction of both levers. All trials were separated by a 180-s ITI and all blocks were separated by a 5-min inter-block interval.

Statistical analysis

We analyzed the data using repeated-measures or mixed-factorial ANOVAs in SPSS (version 25, GLM procedure; IBM Corp). We followed up on significant interaction effects ($p < 0.05$) with a Fisher's PLSD post-hoc test, a valid post-hoc procedure when the interaction from a factorial ANOVA is significant and only a limited number of post-hoc tests are performed (Saville 1990). We describe the different between- and within-subject factors for the different statistical analysis in the Results section. We only report significant effects critical for data interpretation and indicate results of post-hoc analyses in the figures. For choice data collected under the controlled reinforcer frequency choice procedure, we only analyzed choice responses (responding on the unavailable reward). We analyzed percent choice for reward A as: (choice responses for reward A / total choice responses rewards A + B)*100 under the controlled reinforcer frequency procedure and (choices for reward A / total choices made for rewards A + B)*100 for the discrete-trials choice procedure; where reward A refers to one option and reward B refers to the alternative option.

We included both male and female rats in the present study to comply with NIH mandate to include both sexes in preclinical research. However, the experiments were not intended to investigate sex differences. We provide a full reporting of the Statistical Results in Table 1.

We also provide a full reporting of the Statistical Results with sex as between-subjects factor in Supplemental Table S1.

Results

Experiment 1: Effect of access duration on social self-administration

Fixed ratio schedule: Both the main and partner rats learned to lever-press for 60-s social interaction (Fig 1A). For the statistical analysis, we first calculated the mean number of social rewards under each FR schedule (1, 3, 5) and then analyzed the data using a between-subjects factor of role (main, partner) and the within-subject factor of FR schedule. This analysis showed a significant effect of FR schedule [$F(2,28)=25.3$, $p<0.001$] but no significant effects of role [$F(1,14)=4.1$, $p=0.06$] or interaction ($p>0.05$) . The main effect of FR schedule is due to lower responding under the FR3 and FR5 schedules than the FR1 schedule. The rats showed access duration-dependent responding for social interaction with lower responding for longer social interactions (Fig 1B). The analysis, which included role as the between-subject factor of role and the within-subjects factor of access duration (3.75, 7.5, 15, 30, 60,120, 240 s), showed a significant effect of access duration [$F(6,84)=8.1$, $p<0.001$] but not role or interaction (p-values>0.05). When we converted the data to total time door open (Fig 1C), the analysis showed a significant main effect of access duration [$F(6,84)=70.3$, $p<0.001$] but not role or interaction (p-values>0.05). The main effect of access duration is due to longer door opening time and opportunity for social interaction at longer access duration times. We also applied a quadratic regression to the access duration response data. This analysis showed a significant fit [$F(2,109)=10.0$, $p<0.001$], reflecting an inverted U-pattern of the relationship between access duration and response rate.

Progressive ratio schedule: We performed the progressive ratio assessment and the subsequent choice assessment in the main rats only. Access duration had no significant effect on progressive ratio responding (Fig 1D). The analysis of the mean of the last two sessions on each access duration, which included the within-subject factor of access duration (15, 30, 60 s), showed no significant effect ($p>0.1$).

Choice: Access duration had no effect of choice with rats showing similar preference for very short (3.75 s) vs. long (240 s) access duration under either the controlled reinforcer or the discrete-trials choice procedure (Fig. 1E–G). The analysis for choice responses (i.e., responding on the lever that was unavailable for reinforcement) under the controlled reinforcer frequency choice procedure, which included the within-subjects factors of access duration (3.75 s, 240 s) and session (1-4),, showed a significant effect of session [$F(3,21)=4.5$, $p=0.01$] but not access duration or interaction ($p>0.1$). Similarly, the analysis of the discrete-trials choice procedure using the within-subjects factor of access duration, showed no significant effect ($p>0.05$).

Together, the results of Experiment 1 indicate that access duration has a minimal effect on the reinforcing effects of social interaction as assessed by fixed ratio and progressive ratio reinforcement schedules and both the controlled reinforcer and discrete-trials choice procedures. When we included sex as a factor in Experiment 1, we found no significant effects of sex on any of the measures (see Supplemental Table S1).

Experiment 2: Effect of increasing fixed ratio requirements on social interaction and food self-administration under different housing and familiarity conditions

Effect of increasing FR requirements in single-housed rats that lever-press for a familiar partner and palatable food: The rats earned a greater number of food rewards than social rewards when the FR schedule requirement was increased over days (Fig 2A). The analysis, which included within-subject factors of reward type (food, social) and FR requirement (1, 2, 4, 8, 16, 32), showed significant effects of reward type [$F(1,7)=140.8$, $p<0.001$], FR requirement [$F(5,35)=85.7$, $p<0.001$], and interaction [$F(5,35)=17.6$, $p<0.001$]. The rats also maintained higher responding for food than for social interaction. The analysis showed significant effects of reward type [$F(1,7)=130.4$, $p<0.001$], FR requirement [$F(5,35)=36.9$, $p<0.001$], and interaction [$F(5,35)=44.5$, $p<0.001$]. The significant interactions are due a steeper decrease in responding for social interaction than for food pellets when the FR requirements were increased.

Effect of housing conditions and rat's familiarity: We next examined the effect of housing conditions (single, paired house) and partner familiarity (familiar, unfamiliar) on social self-administration (Fig 2B). Independent of the partner condition (familiar, unfamiliar), when rats were single-housed, they earned more social interactions than when they were pair-housed. Single-housed rats, but not pair-housed rats, earned more social interactions when lever pressing for a familiar partner than lever pressing for an unfamiliar partner. The analysis of the mean reinforcers earned at each FR schedule, which included the within-subjects factors of housing condition (single, pair), partner type (familiar, unfamiliar), and the within-subjects factor FR requirement (1, 2, 4, 8, 16), showed significant effects of housing condition [$F(1,7)=23.8$, $p=0.02$], partner type [$F(1,7)=7.2$, $p=0.03$], FR requirement [$F(4,28)=109.2$, $p<0.001$], housing condition x FR requirement [$F(4,28)=3.5$, $p=0.02$], and partner type x FR requirement [$F(4,28)=3.2$, $p=0.03$]. The analysis of number of lever presses showed significant effects of housing condition [$F(1,7)=29.5$, $p<0.001$], FR requirement [$F(4,28)=7.5$, $p<0.001$], housing condition x partner type [$F(1,7)=8.0$, $p=0.03$], housing condition x FR requirement [$F(4,28)=8.2$, $p<0.001$], and housing condition x partner type x FR requirement [$F(4,28)=3.0$, $p=0.03$].

Together, the results of Experiment 2 indicate that, under our experimental conditions, palatable food is a stronger operant reinforcer than social interaction. Additionally, social interaction is a stronger operant reinforcer when the rats were single-housed vs. when they were pair-housed. Finally, when rats were single housed, a familiar peer serves as a stronger reinforcer than an unfamiliar peer.

Experiment 3: Choice between food and social interaction

The rats learned to respond for a palatable food pellet and 60 s social interaction (Fig 3A) and showed a strong preference for a single palatable food pellet over social interaction (Fig 3B). The choice analysis of the mean of the last 3 days of training, which included the within-subjects factor of access duration (0, 60 s), showed a significant effect of access duration [$F(1,7)=8.4$, $p=0.02$]. It should be noted that this increase in percent choice for social for 0 s to 60 s vs. 1 pellet was not meaningful given the relative proportion of responding for food. The rats also showed a strong preference for a single palatable food

pellet over social interaction when we adjusted the access duration of the first block (Fig 3C). The analysis, which included the within-subjects factor of access duration (3.75 s, 60 s) was not significant ($p>0.05$).

Together, these results extend those of Experiment 2 and indicate that, under our experimental conditions, palatable food is a relatively stronger reinforcer to rats than social interaction. When we included sex as a factor in Experiment 3, we found no significant effects of sex in the analyses described below (see Supplemental Table S1).

Experiment 4: Choice between social interaction and remifentanil

The rats learned to respond for both social interaction (Fig 4A) and remifentanil (Fig 4B). All the rats completed within-session lever training for both social interaction and remifentanil (no significant differences; data not shown) prior to the start of remifentanil vs. social interaction choice training.

The rats showed dose-dependent choice responding under the controlled reinforcer frequency procedure (Fig 4C). The analysis for choice responses (mean of the last two sessions), which included the within-subjects factors of reward type (remifentanil, social interaction) and remifentanil dose (0, 1, 10 μg/kg/infusion) showed significant effects of remifentanil dose [$F(2,28)=4$, $p=0.03$] and interaction [$F(2,28)=30.1$, $p<0.001$]. Additionally, the analysis for percent choice for remifentanil, which included the within-subjects factor of dose (0, 1, 10 μg/kg/infusion), showed a significant effect of dose [$F(2,28)=55.0$, $p<0.001$].

The rats also showed dose-dependent choice under the discrete-trials choice procedure (Fig 4D). The analysis of choices made (mean of the two test sessions), showed a significant reward type x remifentanil dose interaction [$F(2,28)=13.6$, $p<0.001$]. The analysis for the discrete-trials data as percent choice showed a main effect of dose [$F(2,28)=30.8$, $p<0.001$].

Together, the results of Experiment 4 indicate that remifentanil dose-dependently substitutes for social interaction under both the controlled reinforcer and the discrete-trials choice procedures. When we included sex as a factor in Experiment 4, we found no significant effects of sex in any of the measures (Supplemental Table S1).

Discussion

We characterized operant social interaction in male and female rats. We report five main findings. First, increasing access duration to a peer decreased social self-administration under an FR5 reinforcement schedule but not a progressive ratio schedule. Second, the rats showed similar preference for short and long access durations. Third, social self-administration under different FR response requirements was higher in single-housed than in paired-housed rats, and higher for a familiar than for an unfamiliar rat in single-housed rats. Fourth, in single-housed and food-sated rats, response rates under increasing FR requirements were significantly higher for palatable food than for social interaction. Fifth, the rats strongly preferred palatable food over social interaction, and switched preference from social interaction to remifentanil in a dose-dependent manner. Finally, when we

analyzed the data with sex as a factor of Experiments 1, 3, and 4 in which we used both sexes, the analyses showed no significant sex differences (Supplemental Table S1). However, these experiments were not powered to detect sex differences; thus, the lack of sex differences in these experiments should be interpreted with caution. Together, our results provide insights on how social interaction serves as a reinforcer and competes with other reinforcers in an operant setting (Angermeier 1960; Baldwin et al. 2021; Venniro et al. 2019; Venniro and Shaham 2020).

Effects of access duration, effort, housing conditions, and peer familiarity

One goal of our study was to determine the effect of access duration, a putative measure of social reward magnitude, on responding for social interaction. We found that responding for different access durations under an FR5 reinforcement schedule followed an inverted U-shape function: responding increased up to 30 s access and decreased for longer access durations. Thus, 30 s appears to be the ‘optimal’ access duration for maintaining high operant response rates for social interaction. However, this conclusion is tentative, because we trained the rats for acquisition of social self-administration using a single access duration (60 s). It is possible that different access durations during acquisition will shift the duration-response curve, as seen with addictive drugs where different training doses during acquisition can shift the dose-response curve (Comer et al. 1991; Stolerman et al. 2011). An additional finding in our duration-response curve assessment was a trend ($p=0.06$) towards the partner rats earning fewer social rewards during the acquisition phase. The reasons for this trend, which requires an independent replication, are unknown. We speculate that a satiety-like effect plays a role because the partner rat was exposed to the main rat immediately before its social self-administration session.

Access duration had a minimal effect on responding under a progressive ratio schedule. Unlike the FR5 schedule where we examined access durations from 3.75 s to 240 s, we only determined access durations from 15 s to 60 s under the progressive ratio schedule. Thus, the apparent difference between the FR and progressive schedule should be interpreted with caution. Our results demonstrating the lack of effect of the two extreme access durations (3.75 vs. 240 s) on choice under both the controlled reinforcer frequency and the discrete-trials choice procedures confirm the tentative conclusion from the progressive ratio schedule results: namely, access duration has a minimal effect on the reinforcing efficacy of social interaction under our experimental conditions. Notably, our progressive ratio schedule and choice results confirm and extend prior studies applying demand analyses to different access durations showing no significant differences in social self-administration for partial-physical contact (Baldwin et al. 2021) and full-physical contact (Vanderhooft et al. 2019).

Our negative access duration results are unexpected because previous studies have shown that the reinforcer magnitude reliably affects operant responding for food and drugs under different reinforcement schedules and choice procedures (Hodos and Kalman 1963; Johanson 1975; Kliner et al. 1988; Koffarnus and Woods 2008; Lynch and Carroll 2001). A question for future research is whether manipulating access type for a given access duration (observation only, partial-physical contact via a screen, and full-physical contact (Venniro et al. 2018)) serves as a more effective manipulation of social interaction reinforcer magnitude.

Another goal of our study was to determine the effect of housing conditions and peer familiarity on social self-administration. We found that single-housed female Long-Evans rats responded more for access to social interaction than paired-housed rats. These results agree with previous studies showing that social isolation promotes social interaction (Latane et al. 1972; Varlinskaya and Spear 2008). We also found that single-housed rats respond more for a previously familiar peer than for an unfamiliar peer. These results are different from previous reports showing that female Long-Evans rats prefer an unfamiliar peer over a familiar peer under conditions of full-physical contact in an operant choice procedure (Hackenberg et al. 2021), and that male Long-Evans rats prefer an unfamiliar peer over a familiar peer under limited visual- and olfactory-contact in the classical unconditioned social preference test (Templer et al. 2018). One likely reason for these different results is that we assessed familiarity using increasing FR schedules while in the studies of Hackenberg et al. (2021) and Templer et al. (2018), the peer familiarity was assessed using choice procedures. However, the different results are not due to the rat strain, because in Experiment 3 of our study and the studies of Hackenberg et al. and Templer et al. all used Long-Evans rats. Regarding the rat strain, in the present study we used Sprague-Dawley and Long-Evans rats and observed reliable social self-administration. These results extend those from previous studies using these strains (Baldwin et al. 2021; Evans et al. 1994; Hackenberg et al. 2021; Vanderhooft et al. 2019; Venniro and Shaham 2020) and the Wistar strain (Angermeier 1960), illustrating the generality of the rewarding effects of operant social interaction across rat strains. A question for future research that was not explored in our study or previous studies is whether there are strain differences in social self-administration.

The relative reinforcing efficacy of social interaction vs. food and drugs

Another main goal of our study was to compare the relative reinforcing efficacy of operant social interaction to that of high carbohydrate palatable food reinforcer used in our previous studies to induce long-term voluntary abstinence from heroin, fentanyl, and methamphetamine self-administration (Caprioli et al. 2015a; Fredriksson et al. 2021; Reiner et al. 2020; Venniro et al. 2017a; Venniro et al. 2017b). Our results indicate that, under our experimental conditions, palatable food is a stronger reinforcer than social interaction in socially deprived and food-sated rats. The palatable food maintained significantly higher responding than social interaction under different FR requirements and was strongly preferred over social interaction. These results confirm and extend results from a recent study of Baldwin et al. (2021) who concluded, based on behavioral economic demand analyses of responding under increasing FR requirements and sensitivity to noxious stimulus-induced disruption of operant responding, that food serves as a stronger reinforcer than partial-physical contact with a peer. We did not observe a shift in preference from palatable food to social interaction under the conditions tested. Such shift can be achieved by changing the type of social interaction (partial- vs. full-physical contact) or the use of other food types (e.g., sucrose or saccharin; (Beckmann et al. 2019)) where the reinforce magnitude is more easily manipulated via volume or concentration changes. Additionally, we observed some individual differences in choice for food over social interaction, but our study was not powered to detect individual differences. Future studies with a larger sample size and additional parametric manipulations of the reinforcing magnitude of food and social interaction are needed to identify individual differences in choice between these rewards.

A final goal of our study was to develop a dose-sensitive choice procedure for social interaction vs. opioid drugs for future mechanistic studies. In our procedure, the rats increased their choice for remifentanil as the drug dose increased, an effect that was observed under both the controlled reinforcer frequency and the discrete-trials choice procedures. These results are different from our previous studies using the discrete-trials procedure with methamphetamine, cocaine, heroin, and remifentanil where social interaction (either full or partial contact) was strongly preferred over the drugs (Fredriksson et al. 2021; Venniro et al. 2020b; Venniro et al. 2019; Venniro et al. 2018). However, the choice procedure in our previous studies was designed to induce 'voluntary-abstinence' rather than shifts in choice and differed in several important procedure aspects. These include the reinforcement schedule for the social and drug reinforcer during choice (FR1 in previous studies vs. FR5 in the present study), the physical location of the social door (next to the social-paired lever in previous studies vs. the opposite chamber wall in the present study), and the drug dose-response procedure (between-session in previous studies vs. within-session in the present study). It is also possible that the shorter ITIs used in the current study (180 s versus 600 s in previous studies) can account for the different results.

Our current results, however, agree with previous drug vs. food choice studies in rats that showed dose-dependent shifts in choice for both opioid and psychostimulant drugs (Beckmann et al. 2019; Chow and Beckmann 2021; Chow et al. 2020; Schwartz et al. 2017; Thomsen et al. 2013; Townsend et al. 2019; Townsend et al. 2021) or choice for the opioid drug (heroin) over food under certain experimental conditions (Heinsbroek et al. 2021).

Together, our results indicate that under our experimental conditions social interaction is a weaker reinforcer than palatable food and that parametric manipulations of the unit dose of an opioid drug (i.e., magnitude) can shift preference from social interaction to the self-administered drug. We used the two different choice procedures because choice is influenced by multiple dimensions of reinforcement such as delay, price, reinforcement frequency and probability (Beckmann et al. 2019; Canchy et al. 2021; Chow and Beckmann 2021; Chow et al. 2020; Huskinson et al. 2015; Thomsen et al. 2013; Woolverton and Anderson 2006; Woolverton and Rowlett 1998). One often overlooked methodological issue/confound in drug vs. nondrug choice procedures is differences in the reinforcement frequency of the drug vs. the non-drug reward (Beckmann et al. 2019). The controlled reinforcer frequency procedure used in our study and previous drug vs. food studies addresses this issue and allows to identify neurobiological correlates of drug vs. nondrug choice while controlling for differences in drug intake during the choice sessions (Beckmann et al. 2019; Chow and Beckmann 2021; Chow et al. 2020). We also used the discrete-trials choice procedure (Cantin et al. 2010; Lenoir et al. 2007; Thomsen et al. 2013) to verify that choice under the controlled reinforcer frequency procedure produced results comparable to those seen in this more commonly used choice procedure.

Finally, previous studies have shown that environmental factors such as deprivation states (e.g., food restriction) and the presence or absence of reward-associated cues can influence drug vs. non-drug choice (Beckmann et al. 2019; Chow and Beckmann 2021; Thomsen et al. 2013). Thus, similar factors such as social deprivation and the presence or absence of social

interaction cues (e.g., ability to hear or smell the presence of a partner rat) are potential avenues for future research.

Concluding remarks

Social factors critically influence drug addiction (Heilig et al. 2016; Venniro et al. 2020a). In recent studies, we showed that providing rats with a choice between either full-physical contact (Venniro et al. 2018) or partial-physical contact via a screen (Venniro et al. 2021; Venniro et al. 2019) strongly inhibits drug self-administration and relapse. In the present study, we parametrically characterized operant social interaction of the latter form and showed that while operant social interaction is relatively insensitive to access duration, it is highly sensitive to the effort required to gain access to a peer and the availability of an alternative palatable food reinforcer. We also showed that operant social interaction is decreased in pair-housed rats and in single-housed rats when the reinforcer is an unfamiliar peer. Finally, we introduced a choice procedure that is sensitive to the dose of the opioid drug which allows for future mechanistic studies on circuits controlling social interaction vs. opioid choice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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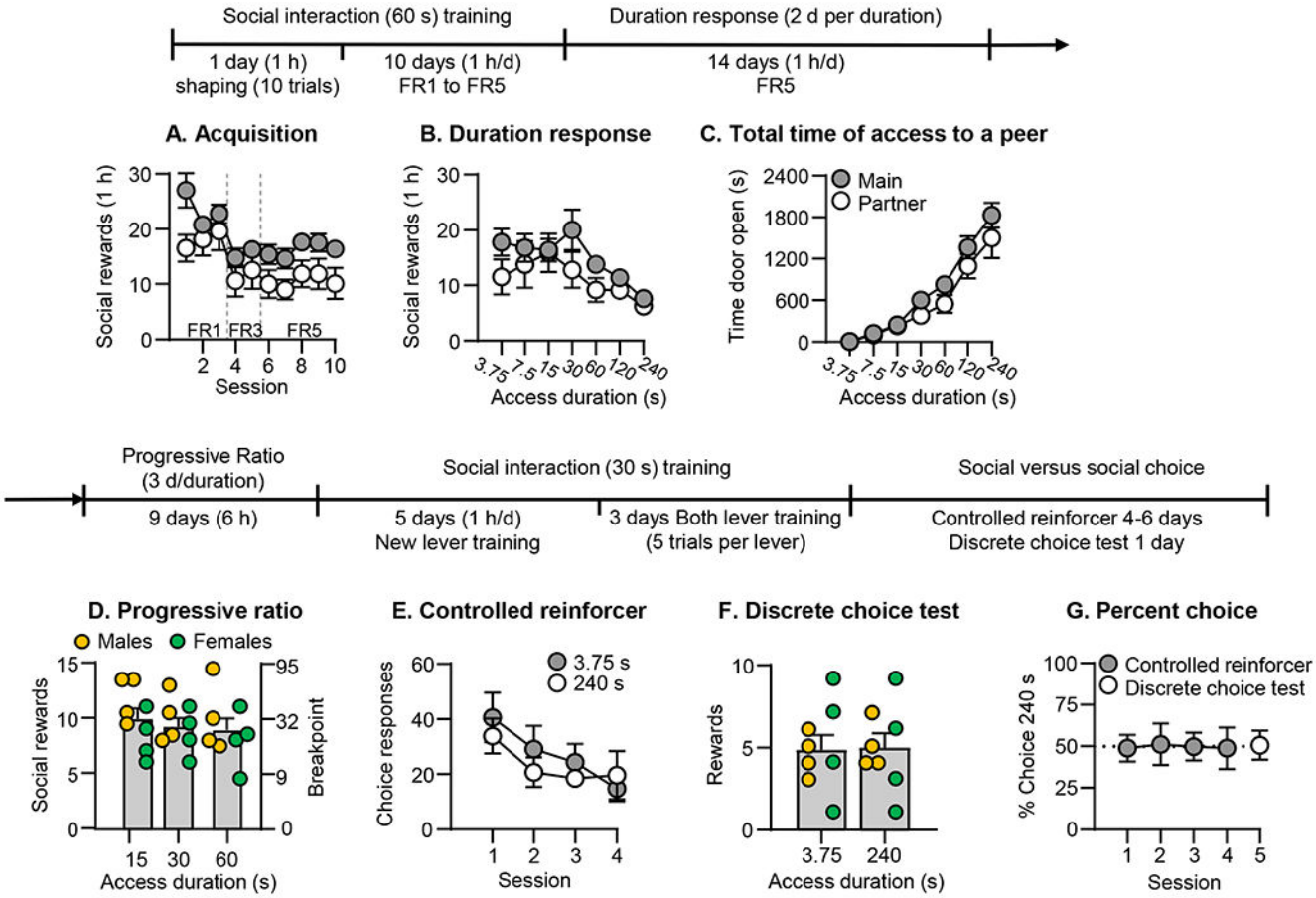

Figure 1: Effect of access duration on social interaction self-administration and choice.

(A) Acquisition. Number of social rewards (60-s social interaction) obtained during the 1-h sessions for the main (n = 8; 4 female) and partner (n = 8; 4 female) rats. **(B)** Access duration-response curve. The 2-day mean of social rewards obtained during the 1-h sessions of different access durations to a peer in main- and partner-rats. **(C)** Total time of access to a peer. The 2-day mean of the total time (in seconds) that the social door was open during the different access durations to a peer in main- and partner-rats. Data are mean±SEM. **(D)** Progressive ratio. Number of trials completed/breakpoints achieved for the different access durations during progressive ratio testing (mean of last 2-days) for social interaction with a peer (n = 8; 4 female). **(E)** Controlled reinforcer frequency test. Number of choice responses, responding on the unavailable reinforcer, during the final four sessions of the controlled reinforcer frequency choice procedure for 3.75 s and 240 s of access to a peer. **(F)** Discrete-trials choice test. Total number of rewards (out of 10 possible) obtained during the discrete-trials choice test for either 3.75 s or 240 s of peer access. **(G)** Percent choice. Percent of choice for 240 s of peer access during the last four controlled reinforcer frequency choice sessions and the discrete-trials choice session. Data are mean±SEM.

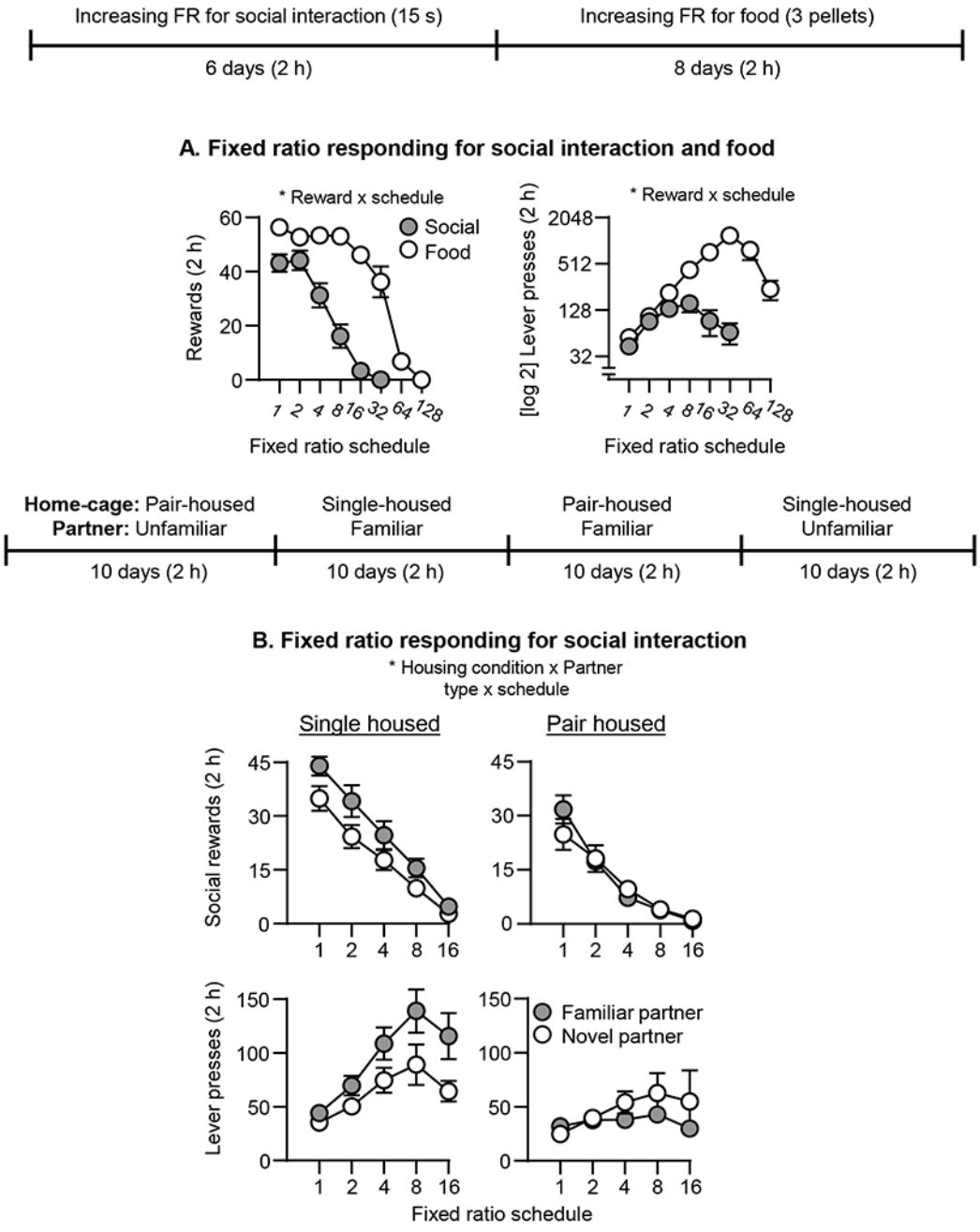

Figure 2: Effect of FR reinforcement schedule requirement, housing conditions, and partner type on responding for social interaction.

(A) Fixed ratio schedule responding for social interaction and food. Number of rewards obtained (*left*) and lever presses (*right*) for 3 food pellets and 15 s peer access in 2-h sessions at increasing fixed-ratio schedule requirements (n = 8 female). **(B)** Fixed ratio schedule responding for social interaction. Number of 15 s social rewards obtained (*top*) and lever presses (*bottom*) in single-housed (*left*) and pair-housed (*right*) rats for familiar

and unfamiliar partners in two 2-h sessions per fixed-ratio schedule (n = 8 female). Data are mean±SEM.

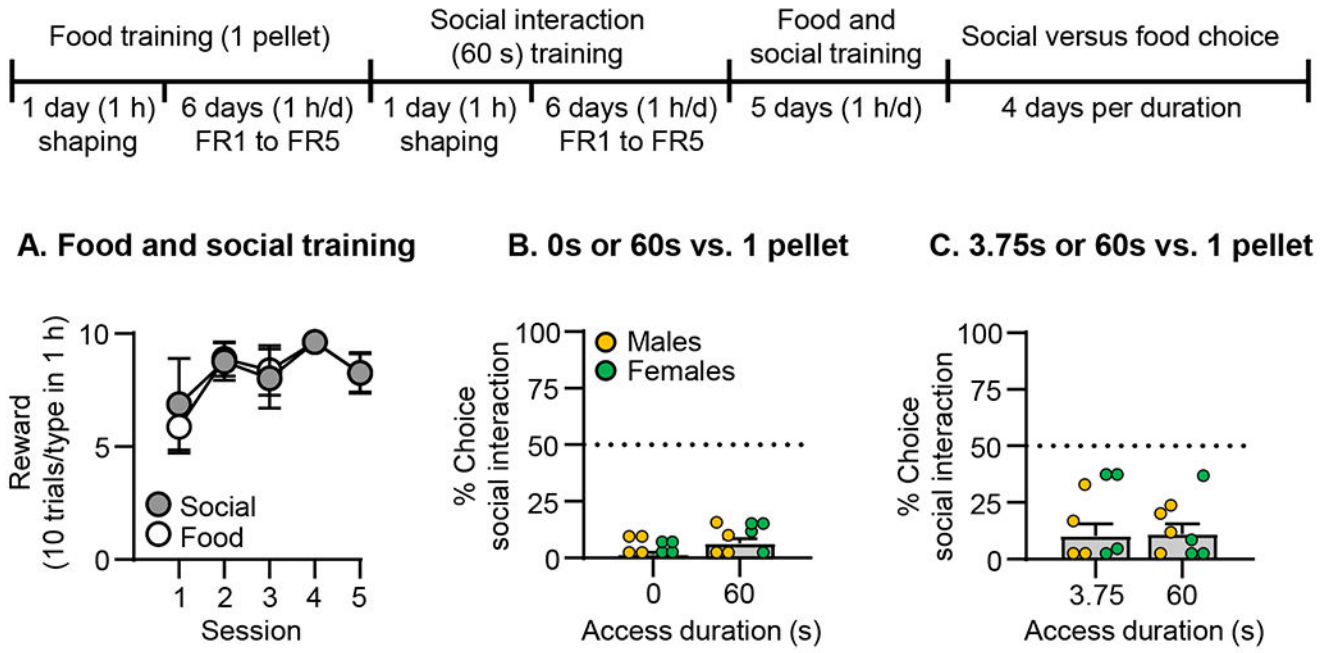

Figure 3: Social interaction vs. food choice.

(A) Food and social self-administration training. Number of food and social rewards (out of 10 possible per reward) obtained in 1-h sessions (n = 8; 4 female). **(B)** 0 s or 60 s vs. 1 pellet. Mean (last 3-days of training) percent choice for 0 s and 60 s peer access over 1 food pellet. **(C)** 3.75 s or 60 s vs. 1 pellet. Mean (last 3-days of training) percent choice for 3.75 s and 60 s peer access over 1 food pellet. Data are mean±SEM.

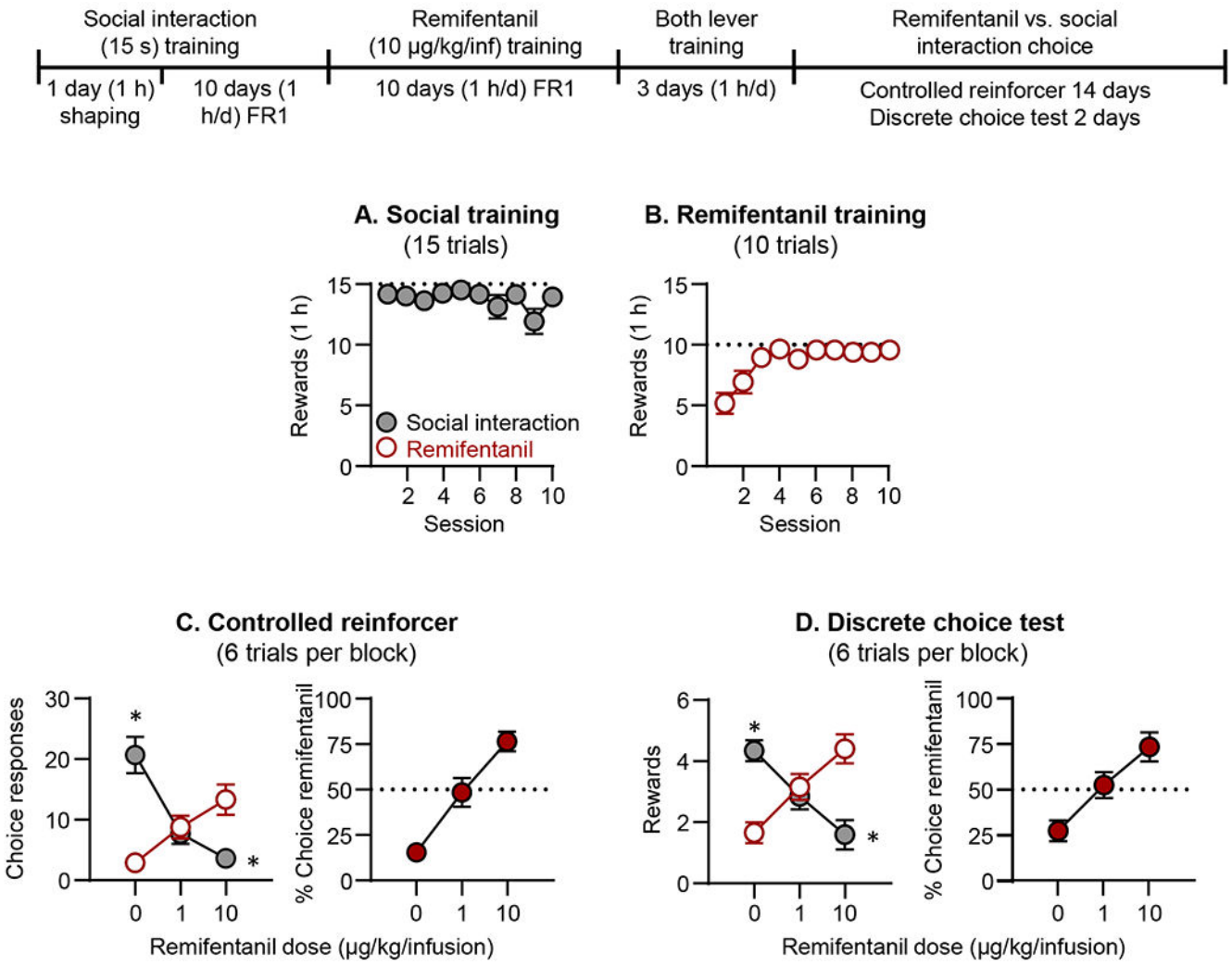

Figure 4. Remifentanil vs. social interaction choice.

(A) Social self-administration training. Number of 15-s social rewards (out of 15 possible) obtained in 1-h sessions (n = 16; 7 female). **(B)** Remifentanil self-administration training. Number of 10 µg/kg remifentanil infusions (out of 10 possible) obtained in 1 h sessions. **(C)** Controlled reinforcer frequency choice test. (*left*) Mean (last 2-days of training) number of choice responses, responding for the unavailable option, for 0, 1, and 10 µg/kg/infusion of remifentanil or 15-s peer access; (*right*) Mean (last 2-days of training) percent choice for remifentanil **(D)** Discrete choice test. (*left*) Mean (2-day) number of choices for 0, 1, and 10 µg/kg/infusion remifentanil or 15-s peer access; (*right*) Mean (2-day) percent choice for remifentanil. Data are mean±SEM. * Different from remifentanil within each dose condition, $p<0.05$.

Table 1.
Summary of statistical analysis for Experiments 1-4.

Partial Eta^2 = proportion of explained variance.

Figure Number	Factor Name	F-value	*p*-value	Partial Eta^2
Figure 1A. Acquisition	Role (main, partner), between-subjects FR schedule (FR1, FR3, FR5), within-subjects Role X FR schedule	$F_{(1,14)}$=4.1 $F_{(2,28)}$=25.3 $F_{(2,28)}$=0.32	0.062 <0.001* 0.73	0.23 0.64 0.02
Figure 1B. Duration response	Role (main, partner), between-subjects Access duration (3.75, 7.5, 15, 30, 60, 120, 240 s), within-subjects Role X Access duration interaction	$F_{(1,14)}$=1.6 $F_{(6,84)}$=8.1 $F_{(6,84)}$=1.0	0.23 <0.001* 0.42	0.10 0.37 0.07
Figure 1C. Total time of access to a peer	Role (main, partner), between-subjects Access duration (3.75, 7.5, 15, 30, 60, 120, 240 s), within-subjects Role X Access duration interaction	$F_{(1,14)}$=1.9 $F_{(6,84)}$=70.3 $F_{(6,84)}$=1.0	0.20 <0.001* 0.45	0.12 0.83 0.07
Figure 1D. Progressive ratio	Access duration (15, 30, 60 s), within-subjects	$F_{(2,14)}$=1.1	0.37	0.13
Figure 1E. Controlled reinforcer	Access duration (3.75, 240 s), within-subjects Session (1-4), within-subjects Access duration X Session interaction	$F_{(1,7)}$=0.2 $F_{(3,21)}$=4.5 $F_{(3,21)}$=1.2	0.68 0.01* 0.35	0.03 0.39 0.14
Figure 1F. Discrete choice test	Access duration (3.75, 240 s), within-subjects	$F_{(1,7)}$=0.01	0.95	0.001
Figure 1G. Percent choice	Session (1-5), within-subjects	$F_{(4,28)}$=0.04	0.997	0.01
Figure 2A. Fixed ratio responding for social interaction and food	**Rewards** Reward type (food, social), within-subjects FR (1, 2, 4, 8, 16, 32), within-subjects Reward type X FR interaction **Lever presses** Reward type (food, social), within-subjects FR (1, 2, 4, 8, 16, 32), within-subjects Reward type X FR interaction	 $F_{(1,7)}$=140.8 $F_{(5,35)}$=85.7 $F_{(5,35)}$=17.6 $F_{(1,7)}$=130.4 $F_{(5,35)}$=36.9 $F_{(5,35)}$=44.5	 <0.001* <0.001* <0.001* <0.001* <0.001* <0.001*	 0.95 0.93 0.72 0.95 0.84 0.86
Figure 2B. Fixed ratio responding for social interaction	**Rewards** Housing condition (single, pair), within-subjects Partner type (familiar, unfamiliar), within-subjects FR (1, 2, 4, 8, 16), within-subjects Housing condition X Partner type interaction Housing condition X FR interaction Partner type X FR interaction Housing condition X Partner type X FR interaction **Lever presses** Housing condition (single, pair), within-subjects Partner type (familiar, unfamiliar), within-subjects FR (1, 2, 4, 8, 16), within-subjects Housing condition X Partner type interaction Housing condition X FR interaction Partner type X FR interaction Housing condition X Partner type X FR interaction	 $F_{(1,7)}$=23.8 $F_{(1,7)}$=7.2 $F_{(4,28)}$=109.2 $F_{(1,7)}$=3.2 $F_{(4,28)}$=3.5 $F_{(4,28)}$=3.2 $F_{(4,28)}$=1.0 $F_{(1,7)}$=29.5 $F_{(1,7)}$=2.5 $F_{(4,28)}$=7.5 $F_{(1,7)}$=8.0 $F_{(4,28)}$=8.2 $F_{(4,28)}$=0.2 $F_{(4,28)}$=3.0	 0.02* 0.03* <0.001* 0.12 0.02* 0.03* 0.43 <0.001* 0.16 <0.001* 0.03* <0.001* 0.96 0.03*	 0.77 0.51 0.94 0.31 0.34 0.32 0.13 0.81 0.26 0.52 0.53 0.54 0.02 0.30
Figure 3A. Food and social training	Reward type (social, food), within-subjects Session (1-5), within-subjects Reward type X Session interaction	$F_{(1,7)}$=0.1 $F_{(4,28)}$=1.3 $F_{(4,28)}$=0.9	0.71 0.29 0.50	0.02 0.16 0.11
Figure 3B. 0s or 60s vs. 1 pellet	Access duration (0, 60 s), within-subjects	$F_{(1,7)}$=8.4	0.02*	0.55

Figure 3C. 3.75s or 60s vs. 1 pellet	Access duration (3.75, 60 s), within-subjects	$F_{(1,7)}$=0.2	0.70	0.02
Figure 4A. Social training	Session (1-10), within-subjects	$F_{(9,135)}$=1.3	0.25	0.08
Figure 4B. Remifentanil training	Session (1-10), within-subjects	$F_{(9,135)}$=8.1	<0.001*	0.35
Figure 4C. Controlled reinforcer Repeated Measures ANOVA (Rat #103 excluded)	**Choice responses** Reward type (social interaction, remifentanil), within-subjects Remifentanil dose (0, 1, 10 μg/kg/infusion), within-subjects Reward type X Remifentanil dose interaction Percent choice for remifentanil Remifentanil dose (0, 1, 10 μg/kg/infusion), within-subjects	 $F_{(1,14)}$=0.9 $F_{(2,28)}$=4.0 $F_{(2,28)}$=30.1 $F_{(2,28)}$=55.0	 0.35 0.03* <0.001* <0.001*	 0.06 0.22 0.69 0.80
Figure 4D. Discrete choice test	**Choice responses** Reward type (social interaction, remifentanil), within-subjects Remifentanil dose (0, 1, 10 μg/kg/infusion), within-subjects Reward type X Remifentanil dose interaction Percent choice for remifentanil Remifentanil dose (0, 1, 10 μg/kg/infusion), within-subjects	 $F_{(1,15)}$=0.2 $F_{(2,30)}$=1.0 $F_{(2,30)}$=14.4 $F_{(2,30)}$=32.0	 0.69 0.38 <0.001* <0.001*	 0.01 0.06 0.49 0.68