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Data Article

Data and experimental setup for a comprehensive study of ketamine's effect on neuronal plasticity following social isolation rearing in male and female rats

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ABSTRACT

In this study, we collected electrophysiological data from acute hippocampal slices of male and female Sprague Dawley rats. Rats were exposed to social isolation rearing and then acutely treated with various doses of ketamine in order to rescue hippocampal plasticity deficits induced by isolation stress. We used two different approaches to study neuronal plasticity: Long-Term Potentiation (LTP) which is a well-established cellular model for memory and Paired-Pulse Facilitation (PPF) which is short-term of presynaptic plasticity. The aim of this article is to offer more experimental details about out LTP and PPF procedures.

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Specifications Table

Subject	Neuroscience: Neurophysiology
Specific subject area	Experiments and analysis of ketamineś effect on neuronal plasticity
Type of data	Table Image
How data were acquired	Local Field Potential recordings in Acute Hippocampal Slices ClampEx 10.7
Data format	Raw and processed
Parameters for data collection	Fiber Volley-Input/Output Curve: Local Field Potential recordings (LFPs) in response to different stimulus intensity (0.2mA-0.65mA). These were used to determine the stimulus for Long-Term Potentiation (LTP) and Paired Pulse facilitation (PPF). For LFP recordings, we used stimuli inducing 50-60% of maximum response. LTP: A time series of LFPs pre- and post- high frequency stimulation (Two trains of 50 pulses at 100Hz 30s apart) PPF: Local Field Potential recordings following two monophasic pulses at 3 different intervals: 20ms,50ms and 100ms.
Description of data collection	The LFP data acquisition was performed on acute hippocampal slices of rat brain in a custom electrophysiology rig. All data was obtained at Florida State College of Medicine between 9am and 9pm. Rats were exposed to two different housing conditions (Paired and Isolated) for 5-7 weeks. Beginning on the fourth week of housing, female rats were vaginally lavaged daily during the light cycle to assess estrous cycle stage. The latter was assessed by cell cytology under a light microscope (Nikon DS-Qi1Mc). After the fifth week of isolation, whenever females were in Diestrus 1 or Proestrus, they were weighed and injected intraperitoneally with 1.0 ml/kg body mass of either VEH (0.9% Saline), 2.5 mg/kg ketamine (KET), or 5.0 mg/kg KET. They were then transported in their home to the electrophysiology recording space to rest for exactly 3 hours. Then, rats were rapidly decapitated and their brains rapidly dissected and placed into ice-cold oxygenated (95% O2, 5% CO2) cutting solution. Parasagittal brain slices containing dorsal hippocampus were obtained (400µm) using a vibrating blade microtome (Leica VT1200S). Hippocampal slices were then incubated in carbogenated artificial cerebrospinal fluid (ACSF) at 37°C for 1 hour, then incubation temperature was restored to room temperature (22 ± 1 °C). Hippocampal slices were then individually transferred to the recording chamber. Oxygenated ACSF warmed to physiological temperature (35°C ± 2 °C) (Warner Instruments TC-344B) was continuously perfused onto the stage using a gravity siphon, and waste was cleared using a vacuum. A slice anchor (Warner Instruments, SHD-26H/2) held the tissue in place. Slices were visualized using a Nikon Eclipse FN1 at 40x with the image projected to a digital screen using a Nikon DS-Qi1Mc digital camera and NIS-Elements AR 3.2 64-bit software. Field potentials were evoked using a concentric bipolar stimulated electrode (FHC CBAPC75) placed in the Schaeffer collaterals of CA3, and stimuli were issued by a Master-8 stimulus generator coupled to an AMPI Iso-Flex power box. Field potentials were recorded with a silver electrode in a glass pipette (World Precision Instruments, 4IN Thinwall GL 1.5 OD/1.12ID) made using a Narshige PC-10 pipette puller and backfilled with 4M NaCl. The recording electrode was coupled to an Axon Multiclamp 700B (Molecular Devices) and placed in the CA1 stratum radiatum. Synaptic transmission strength was measured by assessing the initial slope of fEPSPs using stimuli of monophasic 100 µs pulses at 0.033Hz. Stimuli was adjusted to produce 50-60% of maximum response. LTP was then induced with two trains of 50 square pulses (100Hz) delivered 30 seconds apart. PPF and LTP were never assessed on the same slice. Synaptic transmission strength was measured in the same manner as previously described, with the stimuli adjusted to 50-60% maximum response before paired pulses were initiated. Two monophasic pulses of 100µs were applied in a single sweep, with the pulses being delivered at intervals of 20ms, 50ms, and 100ms. Sweeps were separated by 30 seconds.
Data source location	Institution: Florida State University, College of Medicine City/Town/Region: Tallahassee, Florida Country: United States of America

(*continued on next page*)

Data accessibility	Mendeley Data. DOI: https://dx.doi.org/10.17632/j47wcv5gk3.2 Link: https://data.mendeley.com/datasets/j47wcv5gk3/2
Related research article	J. Logue, K. Schoepfer, A.B. Guerrero, Y. Zhou, M. Kabbaj, Sex-specific effects of social isolation stress and ketamine on hippocampal plasticity, Neuroscience Letters. 766 (2022): 136301. DOI:https://dx.doi.org/10.1016/j.neulet.2021.136301

Value of the Data

- The data can be used to describe the effects of social isolation rearing on hippocampal synaptic plasticity, as well as the rescuing effects of low-dose ketamine in male and female rats.
- Long-term potentiation is considered a cellular model for the study of memory. Paired-pulse facilitation offers insight on the pre-synaptic component of synaptic potentiation.
- Electrophysiologists using animal models can benefit from this data as there is a lack of accessible data in this field, which reduces the possibility to create large databases for pharmacological and environmental studies examining neuronal plasticity.
- Altogether, the data offers the possibility to access the individual electrophysiological recordings, thus giving the opportunity for replication in future studies.

1. Data Description

The data consist of raw and normalized voltage of field Excitatory Post-Synaptic Potentials (fEPSP) in the Cornu Ammonis 1 (CA1) of the hippocampus in response to Schaeffer collateral stimulation in CA3 (Fig. 1). The raw (mV) and normalized data for the Long-Term Potentiation recordings (LTP) are available in two data tables (Male and Female). Both data sets are available for each subject along with their experimental information, the subjects are organized by row. Each time bin LFP is located in a different column for each subject (140 columns). We normalized the data with the following formula:

$$X' = X/\mu_{Baseline} * 100$$

The Paired-Pulse Facilitation (PPF) data is available in two data tables (Male and Female). The field excitatory post-synaptic potential (fEPSP) recordings (mV) in response to the paired stimuli at three different intervals are organized in three columns for each subject, including their experimental condition. A similar organization was used for the synaptic strength data. Each column represents a different intensity for the stimulus in each subject row.

The location of the stimulatory and recording electrodes within the regions of interest were not identical across all trials, therefore using normalized data was in order.

2. Experimental Design, Materials and Methods

2.1. Animals

Male and female Sprague-Dawley rats (Strain Code:001) aged twenty-two days (P22) were received immediately post weaning from Charles River Laboratories (Raleigh, NC). Rats were housed in rooms maintained at a temperature of 22°C and humidity of 30%-70%. They had *ad libitum* access to standard rat chow and water and were maintained on a 12-hour light/dark cycles (with lights on at 0900). All procedures were carried out according to the National Institute of Health Guide for the Care and Use of Laboratory Animals and the protocol was approved by the Florida State University Institutional Animal Care and Use Committee.

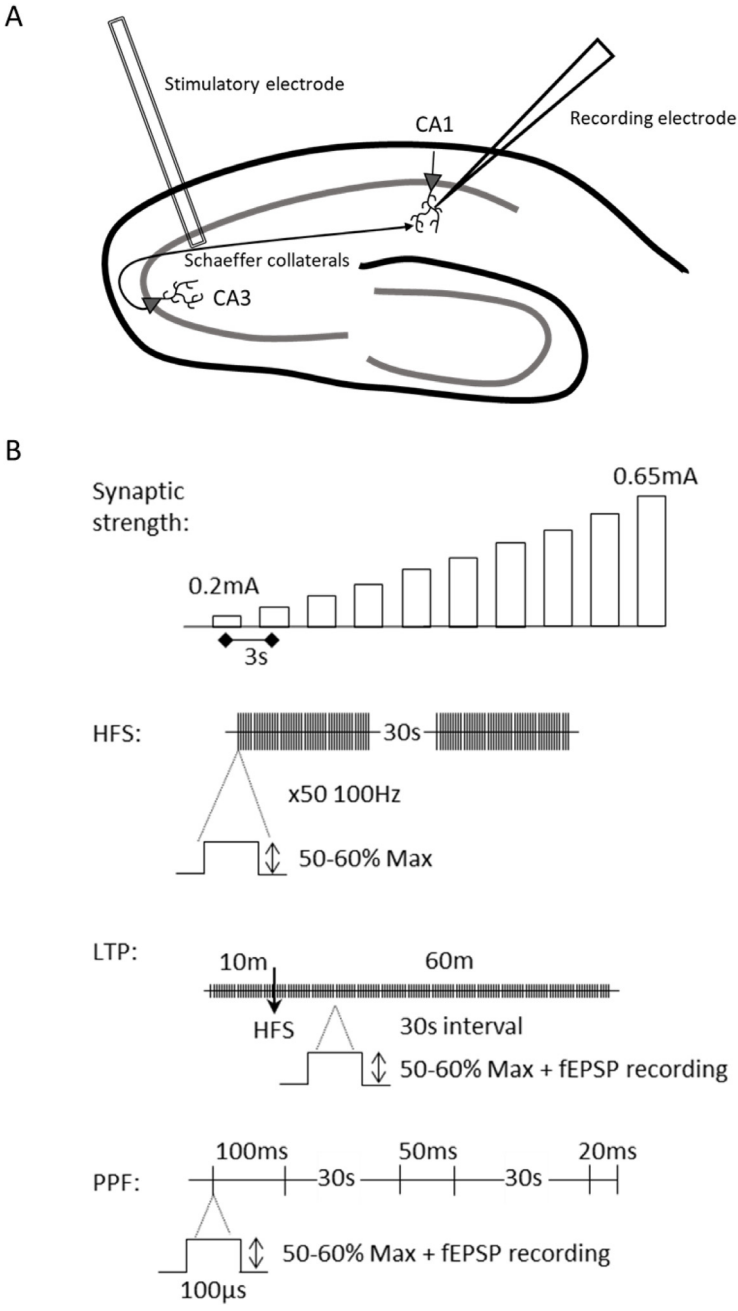

Fig. 1. A) Hippocampal slice diagram for stimulating and recording electrodes' location. B) Stimulation protocols. Synaptic transmission strength was measured by assessing the initial slope of fEPSPs using stimuli of monophasic 100 µs pulses at 0.033 Hz. The responses were tested over a range of stimulus intensities from 0.2 to 0.65 mA. LTP was induced with high frequency stimulation, including two trains of 50 square pulses (100 Hz) delivered 30 seconds apart. Baseline recordings were also obtained as reference before HFS. For PPF Two monophasic pulses of 100 µs were delivered in trials with intervals of 100ms, 50ms, and 20ms.

Table 1
Composition of solutions. Solutions were prepared daily and kept at the noted temperature for each experimental procedure.

Cutting Solution	95% O_2	5% CO_2	230mM Sucrose	2.5mM KCl	10mM $MgSO_4$	1.25mM Na_2HPO_4	26mM $NaHCO_3$	0.5mM $CaCl_2$	10mM D-Glucose
ACSF	95% O_2	5% CO_2	124mM NaCl	5Mm KCl	2.5mM $CaCl_2$	1.3 mM $MgSO_4$	1.1mM KH_2PO_4	1mM $NaHCO_3$	10mM Glucose
Recording electrode solution	4M NaCl								

Upon arrival to our facilities, rats were randomly assigned to either isolation rearing or group housing conditions with a same sex peer. Opaque barriers were used between cages to restrict visual contact in rats raised in isolation. These housing conditions were kept constant for five to seven weeks, and rats were disturbed only when their body weights were measured, cages were changed, or when estrus cycles in females were checked. To control for the female's estrus cycle, vaginal cell cytology was performed daily from the beginning of the fourth week of housing. The study of the vaginal epithelial cell structure in spontaneously ovulating rodents is a non-invasive method to determine the cyclicity of ovarian hormones [1,2]. Females were selected for recording during diestrus 1 or proestrus phases. Diestrus 1 is characterized by low levels of estrogen and progesterone, while proestrus is characterized by increased levels of both hormones.

2.2. Drug administration

Ketamine hydrochloride 100 mg/mL (KET) (Ketathesia, racemic, Henry Schein Animal Health Inc.) was diluted in 0.9% Sodium Chloride solution (VEH) (Intermountain Life Sciences) to 2.5 mg/mL and 5 mg/mL. The animals were injected intraperitoneally at a 1 mL/Kg of body mass with VEH, KET 2.5mg/Kg or KET 5mg/Kg. Immediately following the injection, the animals were transported to the recording area and left undisturbed for 3 hours.

2.3. Solution preparation

2.3.1. Cutting Solution

The solid solutes are first dissolved into distilled (DI) water, sucrose (230mM), D-Glucose (10mM) and NaHCO3 (26mM). The beaker, containing a magnetic stir bar used to mix the solution, is placed on a Nuova II stir plate from Sybron Thermolyne. Then, the liquid solutes are pipetted into the solution, KCl (2.5mM), NaH2PO4 (1.25mM), and MgSO4 (10mM). Lastly, CaCl2 (0.5mM) is pipetted in drops to prevent precipitation (Table 1). After all the components are dissolved, the container is placed in the refrigerator at 4°C until the following morning. On the morning of the recording, the bottle is placed into the freezer at -20°C until ice cold. The ice-cold solution is kept in a 500mL pyrex bottle which is partially submerged in an ice bucket while the solution is oxygenated (95% O2, 5% CO2) for 10 minutes before the cutting process can begin [3].

2.3.2. Artificial cerebrospinal fluid (ACSF)

NaCl (124mM), D-Glucose (10mM) and NaHCO3 (1mM) are mixed in DI water and placed on the stir plate. Then, KCl (5mM), NaHCO3 (1mM) and MgSO4 (1.3 mM) are pipetted into the solution. Finally, CaCl2 (2.5mM) is slowly pipetted in dropwise as before (Table 1). The solution is placed in the refrigerator at 4°C overnight. The morning of the recording, 300mL of the ACSF is poured into the recovery and incubation chamber that holds the brain slices and heated to 37°C and oxygenated for at least 10 minutes before the slicing procedure begins. The remaining

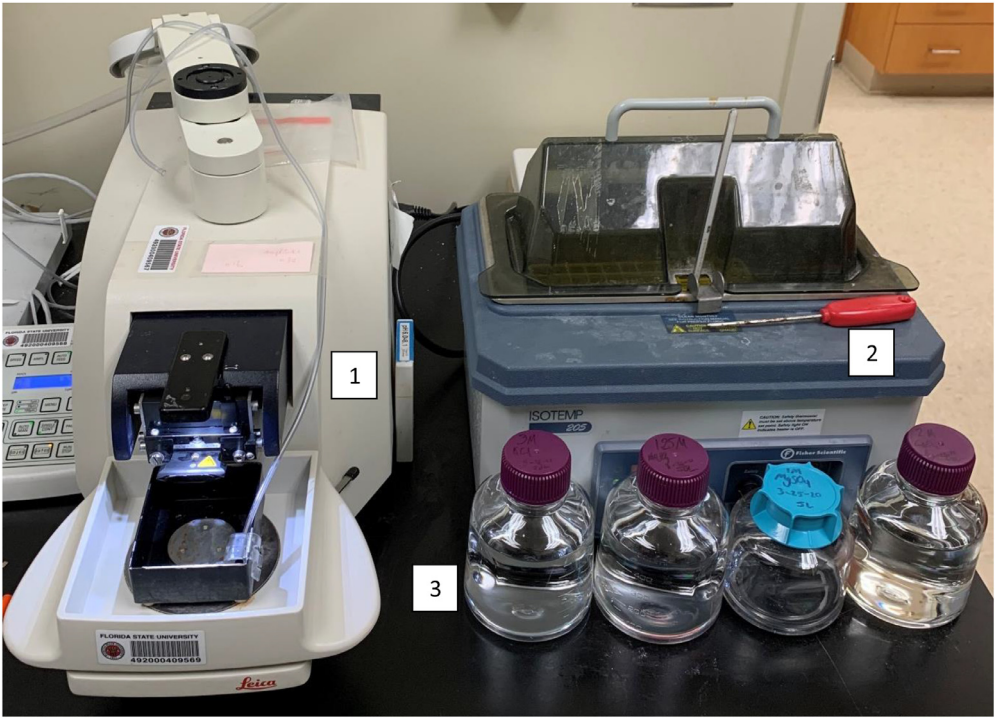

Fig. 2. Tissue preparation station. 1) Leica VT1200S blade vibratome. Slices containing dorsal hippocampus were cut at 400µm thickness. Cutting chamber was kept cold by filling the surrounding space with ice. 2) (Fisher Scientific Isotemp 205 Digital Water Bath. The hippocampal slices were incubated in ACSF at 37°C for 1 hour. 3) Solutions (left to right) 3M KCl, 125M NaH2PO4, 1M MgSO4, 2M CaCl.

700mL sits at room temperature. Once the slices have recovered from the cutting process, it is oxygenated for at least 15 minutes before being used to perform the recordings. The solution is continuously oxygenated in both the incubation chamber and the recording rig throughout the course of the experiment and is only stopped once all recordings are completed for that day [3].

2.4. Tissue preparation

Three hours after ketamine injections, rats were rapidly decapitated. The brains were dissected immediately following decapitation and placed in ice-cold oxygenated cutting solution [3]. They were then mounted on the stage of the Leica VT1200S blade vibratome using instant adhesive gel (Loctite® 454™) (Fig. 2.1). The dorsal hippocampus slices were cut at 400µm thickness. The hippocampal slices were incubated in ACSF at 37°C for 1 hour (Fisher Scientific Isotemp 205 Digital Water Bath) (Fig. 2.2), then incubation temperature was restored to room temperature (22 ± 1 °C), after which slices were individually transferred to the recording chamber and held in place using a slice anchor (Warner Instruments, SHD-26H/2) (Fig. 3.1). The recording equipment was placed on a vibration isolation workstation (Burleigh Gibraltar®) surrounded by a Faraday Cage (Vibraplane platform from Kinetic Systems) to reduce artifacts. Slices were visualized using a Nikon Eclipse FN1 at 40x with the image projected to a digital screen using a Nikon DS-Qi1Mc digital camera and NIS-Elements AR 3.2 64-bit software (Fig 3.2). The tissue was continuously perfused with ACSF warmed to physiological temperature (35 ± 2°C)

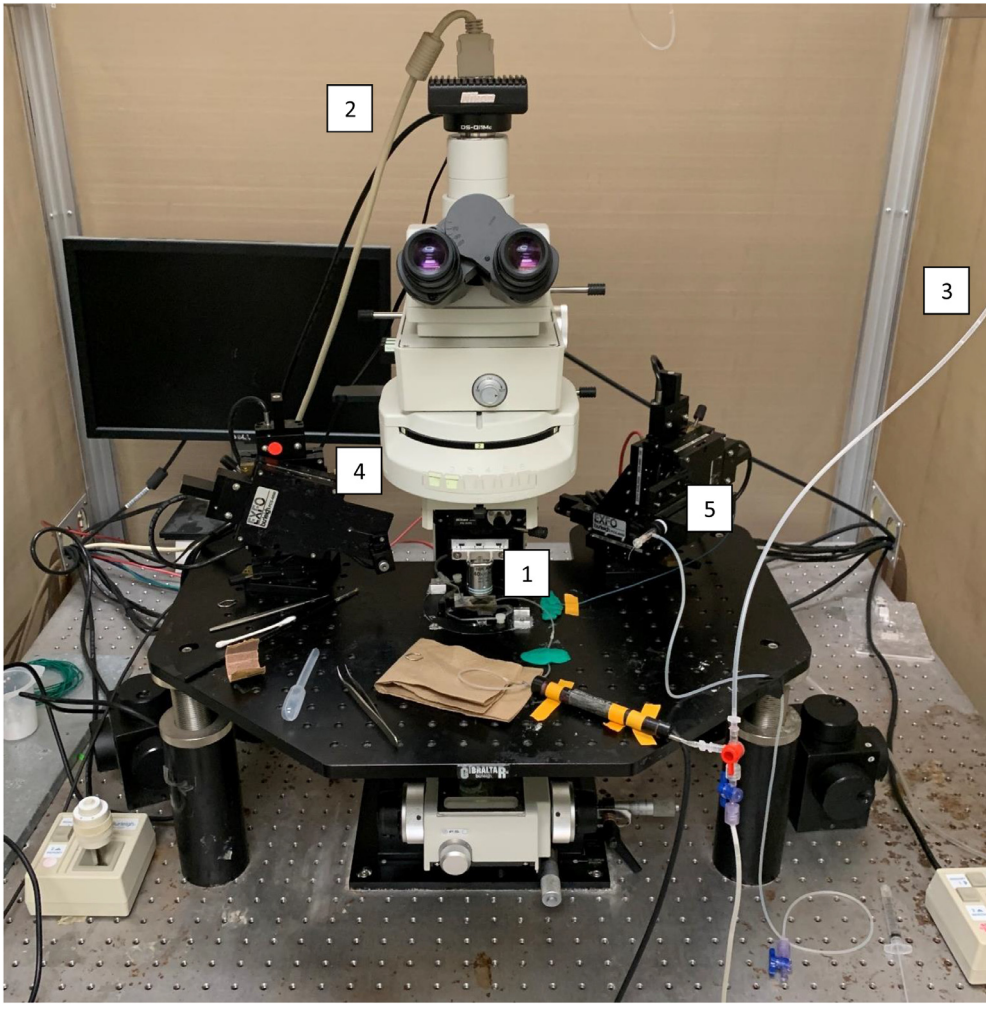

Fig. 3. Recording equipment. Placed on a vibration isolation workstation (Burleigh Gibraltar®) surrounded by a Faraday Cage (Vibraplane platform from Kinetic Systems. 1) Tissue mount slice anchor (Warner Instruments, SHD-26H/2). 2) Nikon DS-Qi1Mc camera connected to Nikon Eclipse FN1 microscope. 3) Gravity syphon used to perfuse with ACSF (35 ± 2°C). 4) Concentric bipolar stimulating electrode (FHC CBAPC75). 5) Chlorided silver electrode (Ag/AgCl) mounted inside a pulled glass pipette.

(Warner Instruments TC-344B) using a gravity siphon (Fig 3.3), and waste was cleared using a vacuum.

2.5. Synaptic strength measurement

The excitatory electrode used was a concentric bipolar stimulating electrode (FHC CBAPC75) placed in the Schaeffer collaterals (Fig. 1). The silver recording electrode was inside a glass pipette (World Precision Instruments, 4IN Thinwall GL 1.5 OD/1.12ID). The silver electrode was chlorided (Ag/AgCl) using bleach to maintain stability throughout recording sessions. In order to obtain the desired resistance (4.5 ± 0.5MΩ) the glass pipette was pulled with a Narshige

Fig. 4. Narshige PC-10 pipette puller. The pipette pulling protocols were adjusted seasonally according to temperature and humidity, with ramp tests of the glass being done regularly to assure consistency. "The pipette cookbook" (Sutter Instrument Company, CA) was used as reference.

PC-10 pipette puller (Fig. 4) and backfilled with 4M NaCl (Table 1). The recording electrode was connected to an Axon Multiclamp 700B amplifier (Molecular Devices) (Fig. 5.2) and placed in the CA1 stratum radiatum (Fig. 1). A Master-8 stimulus generator coupled to an AMPI Iso-Flex power box generated the stimuli (Fig 5.1). The generator was controlled using Master-8 Control software. Multiclamp 700B Commander software was used to control the hardware. Synaptic transmission strength was measured by assessing the initial slope of fEPSPs using stimuli of monophasic 100 µs pulses at 0.033 Hz. The responses were tested over a range of stimulus intensities from 0.2 to 0.65 mA (Fig. 1). This procedure determined the stimulus strength used in the LTP and PPF assays. The stimuli were adjusted to produce 50-60% of maximum response. This procedure allowed for control of the stimuli strength delivered to the area of interest, as the location of the electrode within the Schaeffer collaterals of CA3 was not identical across all trials.

2.6. Long-term potentiation recordings

LTP was induced with two trains of 50 square pulses (100 Hz) delivered 30 seconds apart (Fig. 1). The viability of the tissue was determined based on the presence of an increase in the intensity of the population spikes in response to the stimuli following the high frequency stimulation (HFS) protocol. Thus, the slices that did not exhibit an initial increase in slope of the

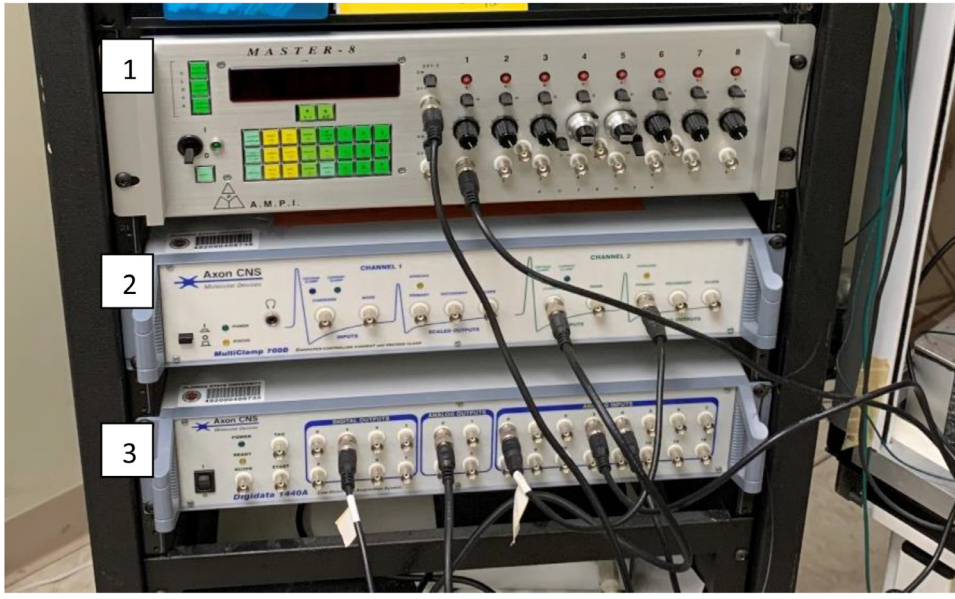

Fig. 5. 1) Master-8 stimulus generator coupled to an AMPI Iso-Flex power box. 2 & 3. Axon Multiclamp 700B amplifier (Molecular Devices).

downward deflection of the fEPSP following HFS were considered unhealthy and not included for analysis.

2.7. Paired-pulse facilitation

Paired-pulse facilitation was measured on different slices than LTP. Two monophasic pulses of 100 µs, with adjusted intensity for 50-60% maximum response, were applied in a single sweep, with the pulses being delivered in trials with intervals of 100ms, 50ms, and 20ms. The trials were separated by 30 seconds (Fig. 1).

Ethics Statement

The authors declare no conflict of interest.

CRediT Author Statement

Mohamed Kabbaj and **Yi Zhou:** conceptualize the experiments and edited the manuscript; **Jordan Logue** and **Kristin Schoepfer:** performed the resaerch investigation; **Alfonso Brea Guerrero:** curated the data and wrote original draft of the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data for a comprehensive study of ketamine's effect on neuronal plasticity following social isolation rearing in male and female rats (Original data) (Mendeley Data).

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