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Interneurons Are Necessary for Coordinated Activity During Reversal Learning in Orbitofrontal Cortex

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ABSTRACT

BACKGROUND: Cerebral cortical gamma-aminobutyric acidergic interneuron dysfunction is hypothesized to lead to cognitive deficits comorbid with human neuropsychiatric disorders, including schizophrenia, autism, and epilepsy. We have previously shown that mice that harbor mutations in the *Plaur* gene, which is associated with schizophrenia, have deficits in frontal cortical parvalbumin-expressing interneurons. *Plaur* mice have impaired reversal learning, similar to deficits observed in patients with schizophrenia.

METHODS: We examined the role of parvalbumin interneurons in orbitofrontal cortex during reversal learning by recording single unit activity from 180 control and 224 *Plaur* mouse neurons during a serial reversal task. Neural activity was analyzed during correct and incorrect decision choices and reward receipt.

RESULTS: Neurons in control mice exhibited strong phasic responses both during discrimination and reversal learning to decisions and rewards, and the strength of the response was correlated with behavioral performance. Although baseline firing was significantly enhanced in *Plaur* mice, neural selectivity for correct or erroneous decisions was diminished and not correlated with behavior, and reward encoding was downscaled. In addition, *Plaur* mice showed a significant reduction in the number of neurons that encoded expected outcomes across task phases during the decision period.

CONCLUSIONS: These data indicate that parvalbumin interneurons are necessary for the representation of outcomes in orbitofrontal cortex. Deficits in inhibition blunt selective neural firing during key decisions, contributing to behavioral inflexibility. These data provide a potential explanation for disorders of cognitive control that accompany the loss of these gamma-aminobutyric acidergic interneurons in human neuropsychiatric disorders, such as autism, epilepsy, and schizophrenia.

Keywords: Autism, Interneuron, OFC, Parvalbumin, *Plaur*, Reversal learning, Schizophrenia

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Gamma-aminobutyric acid (GABA)ergic cortical interneurons are critical for network function, and loss of interneurons may figure prominently in the etiology of neuropsychiatric diseases, such as autism, epilepsy, and schizophrenia (1–6). Altered development of forebrain GABAergic interneurons may compromise the assembly of local cortical networks (7–9). This developmental progression was modeled using mice with mutations in the urokinase plasminogen activator receptor (*Plaur*) (10–13). During embryonic development, the *Plaur* null mouse has decreased numbers of inhibitory cortical interneurons due to abnormal neuronal migration (14). As a result, the adult *Plaur* null mouse has decreased fast-spiking parvalbumin-expressing (PV^+) interneurons in prefrontal regions (15–17), similar to observations in postmortem studies of humans with cognitive disorders. *Plaur* mice exhibit reversal and other behavioral impairments, much like impairments in adaptive behavioral control observed in patients with schizophrenia (18–20). However, it is important with animal models to show how gene mutations associated with human disorders may lead to the phenotypes observed in human patients (21).

Here, we addressed this question directly by examining single unit activity in control and *Plaur* mouse orbitofrontal cortex (OFC) during performance of a cue-guided reversal task. The mouse must first learn to associate one stimulus with a rewarding outcome and another stimulus with no reward. Subsequently, the cue-outcome associations are reversed, and the mouse must switch its responding. We have previously shown that reversal performance in this setting depends upon mouse OFC, consistent with numerous prior reports of reversal deficits after OFC lesions in various species (3,22–25). Furthermore, reversal performance is also selectively impaired in *Plaur* mice. Here, we examine how an interneuron deficit affects associative encoding in the OFC, to address the hypothesis that fast-spiking interneurons are critical for proper OFC function during a task requiring flexible behavior.

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METHODS AND MATERIALS

Subjects

B6.129-*Plaur*$^{tm1/Mlg}$/*Plaur*$^{tm1/Mlg}$ mice that have a null mutation in the gene that encodes the urokinase plasminogen activator receptor protein were genotyped as described previously (26). Behavioral and anatomical analyses were performed on adult (3- to 6-month-old) male littermates from at least six separate pedigrees bred on the C57BL/6J background for >20 generations. B6.129 male wild-type littermate mice were used as control animals. Experiments were conducted in accordance with University of Maryland School of Medicine Institutional Animal Care and Use Committee approved protocols and the Policies on the Use of Animals and Humans in Neuroscience Research. Under sterile conditions, an electrode with a drivable microarray of nine, 25-μm diameter FeNiCr wires (A-M Systems, Sequim, Washington) in 27-gauge thin wall cannula (Small Parts, Miami Lakes, Florida) consisting of eight recording wires and one reference wire, was implanted in OFC (anterior-posterior: 2.6; medial-lateral: −1.2; ventral: 2.1 mm) (27). Before implantation, the wires were freshly cut and electroplated with platinum (H_2PtCl_6; Sigma-Aldrich, St. Louis, Missouri) to an impedance of approximately 300 kΩ. After testing, mice were transcardially perfused and tissue was processed using routine laboratory protocols (15,28).

Serial Reversal Learning Task

Control ($n = 8$) and *Plaur* ($n = 8$) mice were tested on a modified naturalistic foraging reversal task (17,29,30). A reversal discrimination task was performed using five sets of discriminations and reversals (Figure 1A; see Tables S1 and S2 in Supplement 1 for experimental details). Food-deprived mice were trained for 1 day to dig in bowls of scented media to retrieve cereal rewards until they completed eight consecutive correct trials. Placement of the baited bowl and assignment of relevant and irrelevant exemplars were randomized. At each trial start, the mice explored two identical bowls that contained combinations of odors and digging media. The bowls remained in the testing arena until the mouse dug in one bowl, signifying a choice. The bait was a piece of Honey Nut Cheerio cereal (~5 mg; General Mills, Golden Valley, Minnesota), and the cues, either olfactory (odor) or somatosensory and visual (texture of the digging medium hiding the bait), were relevant and irrelevant stimuli. Digging media were mixed with the odor (.01% by volume) and Honey Nut Cheerio powder (.1% by volume). No differences in approach or latency to dig were observed (see Supplemental Data in Supplement 1). Each discrimination/reversal pairing occurred on a new day.

We collected the number of correct and error trials for all mice. Values are reported as the mean ± standard error of the mean. For trials to criteria and errors (any dig in a nonbaited bowl), a two-way analysis of variance (ANOVA) was used to determine statistical significance between treatment groups and discriminations with Student-Newman-Keuls post hoc testing. We categorized errors into perseverative (errors from the start of reversal until the first correct response) or regressive (responding to the previously rewarded cue after committing at least one correct response). Behavioral analysis was performed with MATLAB (MathWorks, Natick, Massachusetts).

Data Acquisition and Analysis

Experiments were performed in a behavioral chamber (31). Active wires were screened daily, and the electrode assembly was advanced by ~60 μm per day at the end of the recording session. Neural activity was recorded using Plexon Multichannel Acquisition Processor systems (Plexon, Dallas, Texas). Signals from the electrode wires were amplified 20 times by an operational-amplifier headstage (HST/8o50-G20-GR; Plexon). Immediately outside the training chamber, the signals were passed through a differential preamplifier (PBX2/16sp-r-G50/16fp-G50; Plexon), where the single unit (SU) signals were amplified 50 times and filtered at 150 to 9000 Hz. The SU signals were then sent to the Multichannel Acquisition Processor box, where they were filtered at 250 to 8000 Hz, digitized at 40 kHz, and amplified at 1 to 32 times. Waveforms >2.5:1 signal-to-noise were extracted from active channels and recorded to disk. For unit quantification, units were separated into putative populations by action potential half-width and peak:trough ratio. All units were graphed and determined to belong to the putative fast-spiking (FS) or regular spiking populations, based upon peak: trough ratio and spike half-width. Units with a peak:trough ratio ratio <.5, a half-width less than 100 μs, and a baseline firing rate greater than 5 Hz were deemed likely to be FS interneurons. The few FS cells observed were removed from analysis. Behavior specific timestamps were recorded by an observer simultaneous to performance. Units were identified and sorted using Offline Sorter (Plexon). Data were exported and analyzed using statistical and graphing routines in MATLAB to examine firing activity to decision and reward epochs.

SU analysis epochs were computed as the total number of spikes divided by time. The particular epoch (decision, defined as the moment a dig was initiated, or reward, defined as the moment the mouse received the reward) was taken with a 500-msec window around the desired epoch and compared with baseline firing (average activity from trial start to 800 msec before a decision epoch). A *t* test was used to determine neurons that significantly increased firing to an epoch ($p < .05$), and a multifactor ANOVA was used to determine neurons that fired preferentially for reward or decision epochs ($p < .05$). Neural activity was normalized by Z-transform, and ANOVA and post hoc comparisons were used to measure differences in transformed firing rates within and across genotypes ($p < .05$) related to activity during behavioral epochs. Pearson chi-square tests ($p < .05$) were used to compare proportions of neurons. Line graphs centered on behavioral epochs (correct/error decisions, reward) show average activity around behavioral epochs with shaded standard error of the mean. Line graphs represent average trial activity by genotypes and differences reported through ANOVA and post hoc comparisons ($p < .05$). Pearson linear correlation was used to determine correlation of neural activity (decision epoch) with behavioral performance ($p < .05$) and linear regression *r* value was calculated to provide direction of correlation. Analysis of covariance was performed by computing the covariance for both genotypes between the number of trials to criteria on reversals or discriminations, with Z-transformed firing rates during decision epoch for all neurons.

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