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Altered Short-Term Plasticity in the Prefrontal Cortex After Early Life Seizures

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Abstract

Seizures during development are a relatively common occurrence and are often associated with poor cognitive outcomes. Recent studies show that early life seizures alter the function of various brain structures and have long-term consequences on seizure susceptibility and behavioral regulation. While many neocortical functions could be disrupted by epileptic seizures we have concentrated on studying the prefrontal cortex (PFC) as disturbance of PFC functions is involved in numerous co-morbid disorders associated with epilepsy. In the present work we report an alteration of short-term plasticity in the PFC in rats that have experienced early life seizures. The most robust alteration occurs in the layer II/III to layer V network of neurons. However short-term plasticity of layer V to layer V network was also affected, indicating that the PFC function is broadly influenced by early life seizures. These data strongly suggest that repetitive seizures early in development cause substantial alteration in PFC function, which may be an important component underlying cognitive deficits in individuals with a history of seizures during development.

Keywords

Early life seizures; short-term synaptic plasticity; prefrontal cortex; epilepsy

Introduction

The first year of life is associated with a high incidence of seizures (Garfinkle and Shevell 2011, Hauser 1992, Hauser 1994, Heide, et al. 2011), and seizures during this crucial time in neurodevelopment are often associated with serious adverse neurological consequences that persist into adulthood (Brunquell, et al. 2002, Holmes 2009). Children who have

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experienced early life seizures (ELS) are at increased risk for cognitive impairments and behavioral disorders (Holmes 2009). Depression, anxiety, hyperactivity and deficits in attention are common psychiatric problems in children with epilepsy. The level of alteration of behavior and cognitive performance depends on the age of seizure onset, type, number and severity of epileptic episodes (Hoare 1984, Seidenberg, et al. 1986). An earlier age of onset and longer seizure duration correlate with poor learning ability and memory function (Hermann, et al. 2002, Kaaden and Helmstaedter 2009, Kent, et al. 2006).

The hippocampo-prefrontal cortex circuit plays an important role in various aspects of learning and memory, such as consolidation of information and working memory (Laroche, et al. 2000). Anatomical and electrophysiological studies have shown direct connections between hippocampus and medial PFC and the importance of proper functioning of both regions for memory processing (Jay, et al. 1992, Tierney, et al. 2004, Wall and Messier 2001). Clinical and experimental studies have demonstrated alterations in working memory function due to epileptic seizures (Abrahams, et al. 1999, Grippo, et al. 1996, Kleen, et al. 2011b). Studies show that in animals that have experienced recurrent seizures in early development, there are pathological alterations in synaptic organization (Holmes, et al. 1998, Huang, et al. 1999) and synaptic transmission (Isaeva, et al. 2006) in the hippocampal network that parallel deficits in spatial learning and memory (Huang, et al. 1999, Karnam, et al. 2009, Liu, et al. 1999). Even a single episode of neonatal seizures can permanently alter glutamate receptor expression in the CA1 region of hippocampus and impair working memory (Cornejo, et al. 2007, Cornejo, et al. 2008). As the CA1 region of hippocampus has direct projections to mPFC, one could expect that alterations in the hippocampus due to ELS by itself or through modification of information flowing to the mPFC may explain an impairment of working memory in rats that have experienced seizures in early development. On the other hand several studies show that modulation of mPFC activity and lesions in restricted areas of PFC can exert a major influence on memory and cognitive processes (Delatour and Gisquet-Verrier 1996, Delatour and Gisquet-Verrier 2000, Dias and Aggleton 2000, Granon, et al. 1994, Granon and Poucet 1995, Lacroix, et al. 2002, Ragozzino, et al. 1999a, Ragozzino, et al. 1999b).

The preponderance of clinical and animal data strongly indicates that neonatal seizures lead to substantial deficits that are associated with frontal cortical dysfunction. We have recently shown that animals experienced ELS have a deficit in behavioral flexibility associated with changes in prefrontal cortical (PFC) architecture (Kleen, et al. 2011a), but the mechanisms underpinning this behavioral finding remain uncertain. Like many regions in the CNS, the PFC exhibits plasticity on both long and short timescales (Hempel, et al. 2000). Short-term plasticity (STP) in particular is thought to be critically important for many of the functions of the PFC including short-term working memory (Mongillo, et al. 2008), information processing (Abbott and Regehr 2004) and more recently it has been implicated in decision-making processes (Curtis and Lee 2010, Deco, et al. 2010, Rotman, et al. 2011). Numerous computer-modeling studies of STP in neuronal circuits predict that alterations in STP could lead to cognitive deficits, and further evidence for the importance of STP comes from various disease models in which alterations in STP coincide with cognitive deficits (Deng, et al. 2011, Ishizaki, et al. 2000, Sakane, et al. 2006, Schoch, et al. 2002).

In the present study we used the flurothyl model of ELS to investigate the influence of neonatal seizures on excitatory signaling in LV pyramidal cells, the major output neurons of the PFC, and possible alteration in STP by ELS. The apical dendrites of LV neurons receive feedback information from thalamic inputs as well as information from cortico-cortical connections in layer II/III (LII/III) (Kuroda, et al. 1996, Kuroda, et al. 1998, Szentagothai 1978). Their basal dendrites are heavily innervated by the hippocampus and form an interconnected network of deep pyramidal neurons whose continued firing during the delay

phase of a working memory task is thought to underlie short-term working memory (Goldman-Rakic 1995). Since both networks contribute to cognitive processes that are impaired in patients with a history of ELS and there is evidence that STP in LII/III-to-LV and LV-to-LV networks is modulated differently (Young and Yang 2005), we chose to study STP in these two networks individually. Our data show that recurrent seizures early in development affect STP in LII/III-to-LV and LV-to-LV networks in LV PFC neurons.

Materials and Methods

Animals

All experiments were performed in accordance with the guidelines set down by the National Institute of Health and Dartmouth Medical School for the humane treatment of animals. The animal protocol was approved by the Institutional Animal Care and Use Committee of Dartmouth College. Sprague-Dawley rats (N = 9) were subjected to a total of 62-65 flurothyl-induced seizures from postnatal day (P) 6 to P16 using previously described methods (Karnam, et al. 2009, Kleen, et al. 2011b, Lucas, et al. 2011). Each rat received 5-6 seizures per day with 1 hour between seizures. The age range we chose for this experiment roughly corresponds to the first year of life in humans (Avishai-Eliner, et al. 2002) given the accelerated development of the rat compared to the human, therefore this number of seizures is clinically relevant and would be consistent with moderate childhood epilepsy. Flurothyl, an inhaled convulsive agent, was delivered to the pups, which were in a plastic container located in an airflow hood. Liquid flurothyl (0.1 mL) was injected slowly onto filter paper placed on the inside of the container where it evaporated. Pups were removed from the flurothyl after approximately 2 mins when tonic extension of both forelimbs and hindlimbs was observed. Littermate control pups (N = 16) were handled and removed from the dam during the time of the seizure to control for the effects of maternal separation stress. As has been previously reported with this model, flurothyl animals are initially smaller than control animals during the time of seizures but show normal subsequent phenotypic development into adulthood without any spontaneous seizures (Holmes et al., 1998, Karnam, et al. 2009, Kleen, et al. 2011b, Lucas, et al. 2011).

Slice Preparation

Brain slices were prepared from P27-P60 rats. The rats were deeply anesthetized with isoflurane and decapitated. Brains were removed and quickly placed into ice-cold aCSF of the following composition (in mM): 126 NaCl, 3.5 KCl, 2.0 CaCl₂, 1.3 MgCl₂, 25 NaHCO₃, 1.2 NaH₂PO₄, 11 glucose pH = 7.27-7.30. Brains were transferred to the chamber of a Leica 1000S vibroslicer (Leica Microsystems Nussloch GmbH, Germany) and submerged in ice-cold cutting solution containing (in mM): 2 KCl, 0.5 CaCl₂, 7 MgCl₂, 26 NaHCO₃, 1.2 NaH₂PO₄, 250 sucrose, and 11 glucose. Slices (400 µm) were cut and transferred to an incubation chamber where they rested in oxygenated aCSF for at least 2 hours before recordings.

Extracellular Recordings

Following incubation, slices were transferred to a recording chamber (Warner Instruments, Hamden, CT) held at 32°C and perfused with oxygenated aCSF warmed to 32°C at a rate of 1.5mL per min. Visualization of individual layers of the prelimbic region of the PFC was achieved using a 4X objective attached to an Olympus BX51WI microscope (Tokyo, Japan). Recording electrodes were made of borosilicate glass capillaries, which were pulled to a resistance of 2-4 mΩ and filled with aCSF containing 50 µM gabazine. Stimulation of LII/III and LV was achieved using a concentric bipolar stimulating electrode (FHC Inc., Bowdoin ME) connected to a flexible stimulus isolator (ISO-Flex, A.M.P. Instruments, Jerusalem, Israel). Stimulus amplitudes were set at a level that produced 50% of the maximal field

excitatory postsynaptic potential (fEPSP) amplitude for each slice and were not statistically different between groups (LII-to-LV networks, 0.09 ± 0.01 mA for control and 0.09 ± 0.01 mA for ELS; and LV-to-LV networks, 0.11 ± 0.01 mA for control and 0.10 ± 0.01 mA for ELS). For post-tetanic plasticity data, baseline response amplitude was collected for 10 mins prior to tetanic stimulation. Baseline stimulation was done at two different frequencies: 1 pulse delivered every 10s for a “low baseline stimulation” paradigm and 1 pulse delivered every 2 s for a “high baseline stimulation” paradigm. Recordings were monitored for stability online, and experiments exhibiting large fluctuations in fEPSP amplitude were discontinued. After the 10 min baseline period, a tetanic stimulation (15 pulses at 50 Hz) was delivered and a post-tetanic response was collected at the same frequency as for baseline recordings. Stimulation was done in either LII/III or LV of the mPFC for each low baseline and high baseline paradigm. For paired pulse experiments, 2 pulses were delivered to either LII/III or LV at varying interstimulus intervals. Activity-dependent plasticity was assessed through administration of 15 pulses delivered at 50Hz to either LII/III or LV. The amplitude of the stimulation was kept constant throughout the experiment. Recordings were made using an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). 2-4 slices (n) were used per animal (N) and data was compared to age-matched littermate controls.

Drugs

Gabazine (SR-95531) and TTX were obtained from Tocris (Ellisville, MO). All other chemicals were purchased from Sigma (St. Louis, MO).

Data Acquisition and Statistical Analysis

All data for the short-term plasticity recordings was collected using WinWCP software (Strathclyde Electrophysiology Glasgow Scotland, UK). Recordings were digitized online with an analog-to-digital converter Digidata1322A (Axon Instruments, Foster City, CA). Statistics were done using Prism 5 (GraphPad, La Jolla, CA), Origin 7.5 (Microcal Software, Northampton, MA), and SPSS (IBM Armonk, NY). fEPSP amplitude values (50% of maximal response on stimulation) were collected at an average of 10 responses per slice and the per-slice averages were then averaged and compared using a Mann-Whitney test. Paired-pulse ratio was calculated as a ratio of the amplitude of the second fEPSP and first fEPSP and a two-sample t-test was used to investigate differences in the paired-pulse ratio between the control and ELS groups. Alteration of post-tetanic plasticity and activity dependent plasticity was analyzed using a repeated measures ANOVA. All data shown were averaged by slice.

Results

ELS does not alter basal evoked excitatory synaptic transmission

In the first set of experiments we estimated the effect of ELS on basal evoked excitatory synaptic transmission in both, LII/III-to-LV and LV-to-LV networks separately (Fig. 1A,B). Stimulation of LII/III or LV of mPFC evoked fEPSPs in LV in all slices from flurothyl treated and littermate control animals. fEPSP amplitude was not different between control (172.6 ± 14.2 μ V in LII/III-to-LV; 159.2 ± 14.2 μ V in LV-to-LV) and ELS (163.1 ± 10.6 μ V in LII/III-to-LV; 167.6 ± 14.2 μ V in LV-to-LV) groups indicating that basal evoked excitatory synaptic transmission at both LII/III-to-LV and LV-to-LV networks was unchanged by ELS ($p = 1$, $n = 40$ control, $n = 36$ ELS in LII/III-to-LV; $p = 0.6$, $n = 32$ control, $n = 30$ ELS in LV-to-LV, Fig. 1C).

ELS does not affect paired pulse plasticity

To test the hypothesis that synaptic efficacy in the LV of the PFC may be altered by seizures in the neonatal period, we examined the effect of ELS on paired pulse plasticity at different inter-stimulus intervals in control and ELS slices. Paired pulse plasticity can take the form of facilitation or depression depending on presynaptic release probability (Abbott, et al. 1997, Manabe, et al. 1993, Markram and Tsodyks 1996, Ramoa and Sur 1996, Thomson and Deuchars 1994). In each group, only 1-2 slices respond to paired-pulse stimulation with a consistent depression in all interstimulus intervals. These slices were removed from the further analysis. In the rest of the slices in both ELS and controls, paired-pulse stimulation of LII/III or LV produced significant facilitation of the second fEPSP response in LV at interstimulus intervals between 15 and 100ms, with a peak effect at 50ms (Fig. 2A). The magnitude of facilitation was similar in LII/III-to-LV and LV-to-LV networks in the control group ($n = 53$ LII/III-to-LV, $n = 40$ LV-to-LV) and the ELS group ($n = 31$ LII/III-to-LV, $n = 24$ LV-to-LV) with no significant alteration of facilitation in ELS slices versus controls, regardless of the stimulation layer and inter-stimulus interval (at interstimulus interval 50 ms $p = 0.4$ for LII/III-to-LV, $p = 0.2$ for LV-to-LV control vs ELS).

Frequency dependent alteration of short-term post-tetanic plasticity in the mPFC after ELS

Synapses in LV of the PFC also prominently express short-term post-tetanic plasticity (Hempel, et al. 2000). We next tested if this type of STP is affected in ELS animals. mPFC neurons typically receive trains of input from neighboring neurons during the delay phase of a working memory task in the 20-60Hz range. To induce post-tetanic plasticity (PTP) we used a brief tetanic stimulation (50 Hz, 1 train of 15 pulses) that mimics this physiological condition (Fenelon, et al. 2011). Test stimuli were delivered once every 10s (0.1 Hz) to obtain fEPSP responses for a baseline period and the post-tetanic response was recorded for LII/III-to-LV and LV-to-LV networks for 10 mins ($n = 42$ control, $n = 32$ ELS, LII/III-to-LV; $n = 31$ control, $n = 26$ ELS LV-to-LV). On average the PTP induced by this brief stimulation lasted 4-6 mins. In LII/III-to-LV, average maximal potentiation of post-tetanic responses was $140.3 \pm 3.0\%$ of baseline in the control group and $174.7 \pm 6.6\%$ of baseline in the ELS group. The average level of post-tetanic enhancement in ELS group was significantly increased compared to the control group ($p < 0.001$, Fig. 3A, left column). In LV-to-LV the maximal post-tetanic response in the controls was $140.8 \pm 3.3\%$. In ELS group the maximal post-tetanic response was significantly increased compared to controls ($159.1 \pm 7.8\%$ of baseline, $p < 0.001$, Fig. 3A, right column).

Since there is evidence that the post-tetanic enhancement in the mPFC may be modulated in a frequency-specific manner (Young and Yang 2005), we also tested PTP with a high frequency stimulation paradigm. In these experiments, test stimuli were delivered once every 2 s (0.5 Hz; high frequency baseline) to obtain fEPSP for a baseline period. Baseline fEPSP amplitudes recorded at a frequency of 0.1 Hz were not different from fEPSP amplitudes recorded at 0.5 Hz (control: $179.1 \pm 15.16 \mu V$ in LII/III-to-LV ($n = 36$); $161.1 \pm 14.38 \mu V$ in LV-to-LV ($n = 32$) and ELS: $176.7 \pm 12.67 \mu V$ in LII/III-to-LV ($n = 30$); $172.6 \pm 15.62 \mu V$ in LV-to-LV ($n = 23$)). A brief tetanic stimulus (50 Hz, 1 train of 15 pulses) was delivered to the slice as in the lower frequency stimulation paradigm above, and the test stimuli were resumed once every 2 s for a 5 min post-tetanic period. In control slices using the high frequency stimulation, maximal post-tetanic response was $127.3 \pm 3.3\%$ of baseline in LII/III-to-LV ($n = 31$) and $127.6 \pm 4.5\%$ of baseline in LV-to-LV ($n = 22$). In ELS slices maximal post-tetanic response was $139.27 \pm 3.67\%$ in LII/III-to-LV ($n = 29$) and $136.7 \pm 4.7\%$ in LV-to-LV ($n = 23$). Under the high frequency baseline conditions, ELS slices show a small but significant increase of fEPSP amplitude during the first 6s of post-tetanic period in ELS slices in LII/III-to-LV ($p = 0.02$, Fig. 3B, left column) but not in LV-to-LV ($p = 0.45$, Fig. 3B, right column) as compared to controls.

Activity-dependent plasticity after ELS

Next we examined whether ELS affects the response to repetitive stimulation, often referred to activity-dependent plasticity (Ishizaki, et al. 2000, Sakane, et al. 2006, Schoch, et al. 2002). In both groups, repetitive stimuli (15 pulses delivered at 50 Hz) elicited an initial facilitation followed by a gradual decrease of fEPSP that eventually brings the response near baseline. There was a significant group by time effect in activity-dependent plasticity in LII/III-to-LV ($p < 0.001$). The significant difference was attributable to a decrease between ELS and control fEPSP amplitudes after pulse four in the train. The relative fEPSP amplitudes at the end of the train were $115.2 \pm 7.9\%$ in controls ($n = 49$) and $99.4 \pm 4.3\%$ after ELS ($n = 29$) in LII/III-to-LV. In LV-to-LV there were no significant differences in response to repetitive stimulation between ELS and control group in ($p = 0.37$). The relative fEPSP amplitudes at the end of the train were $120.5 \pm 7.2\%$ in controls ($n = 38$) and $111.8 \pm 13.4\%$ after ELS ($n = 25$). These data revealed a layer specific decrease in the level of the depolarization in ELS group during repetitive stimulation.

Discussion

The main finding of the current study is that early life generalized seizures alter STP in the prefrontal cortex. The alterations in STP suggest changes in processing of information and “on-line” modulation of neural circuits, which may play a contributing role in the behavioral and cognitive comorbidities (Brooks-Kayal 2010, Dunn, et al. 2003, Kaufmann, et al. 2009, Cabaleiro 1969, Duchowny 1991) that occur after ELS in children, and may also relate to the deficits in behavioral flexibility (Kleen, et al. 2011a) and short-term working memory (Kleen, et al. 2011b) reported in rats with a history of ELS.

We found selective alterations in both stimulus number dependent plasticity and PTP (Fig. 3-5), without any changes in paired-pulse facilitation (Fig. 2). Basal evoked synaptic transmission at both LII/III-to-LV and LV-to-LV networks was unchanged by ELS suggesting that changes in STP we identified are not simply reflective of altered connectivity in these networks. Selective alterations in STP have different implications for information processing in the PFC. To assess PTP and stimulus-number dependent plasticity, we have stimulated the PFC at gamma frequency to mimic a physiologically relevant firing frequency seen in LV neurons during the delay period of a working memory task. It is widely believed that sustained firing at this frequency between the presentation of a transient cue and a behavioral response is required for the retention of information that leads to the selection of an appropriate response after the delay period (Goldman-Rakic et al. 1995). In this regard, the finding that ELS animals show a decreased response *during* the 50 Hz stimulation in LII/III-to-LV and show an increased response in LII/III-to-LV and LV-to-LV *after* the 50 Hz stimulation suggests that these changes may also happen *in vivo* in response to endogenous gamma-frequency range activity. It may seem counterintuitive that an increase in plasticity could be deleterious, but such alterations would be predicted to interfere with the induction and maintenance of sustained activity and therefore cause network-level alterations in information processing (Deco et al., 2010, Rotman et al., 2011).

Activation of fibers in LII/III carries thalamic and sensory input information. In the LII/III-to-LV network, we found a robust increase in PTP, which occurs in parallel to a decrease in fEPSC amplitude during high frequency stimulation in ELS animals. An alteration in this network would likely lead to alterations in behavioral flexibility and the ability to use top-down processing to select the most appropriate behavioral response. We also evaluated STP in LV-to-LV networks. The reverberatory connections between pyramidal neurons in LV form intrinsic horizontal neural circuits that are modified by afferent hippocampal fibers. These networks also show an increase in post-tetanic response, albeit this change is less robust than in LII/III-to-LV. Since the hippocampus most densely innervates LV, this

network is thought to be largely involved in working memory among other PFC functions (Kritzer and Goldman-Rakic 1995, Melchitzky, et al. 1998, Pucak, et al. 1996). Taken together, these data may represent a systems-level neural alteration underpinning behavioral data that show working memory and behavioral flexibility deficits after early life generalized seizures (Kleen, et al. 2011a, Kleen, et al. 2011b).

The PFC receives a number of inputs from various brain regions that fire at distinctive frequencies and encode different types of information. Interestingly, the increase in PTP shown in ELS animals seems to have some frequency specificity because it is greater under low frequency baseline input than it is under high frequency baseline input. High frequency inputs have been shown to result in a lower level of post-tetanic enhancement than lower frequency baseline inputs using the same tetanic stimulation (Young and Yang 2005). Neurotrophins as well as a variety of neuromodulators can modulate synaptic responses and plasticity with frequency specificity (DeFrance, et al. 1985, Gil and Connors 1997, Mansvelder, et al. 2009, Zhong, et al. 2008). Given the broad and generalized nature of the ELS insult, and the sheer number of potential modulators, it is extremely unlikely that only one of these candidate modulators is contributing to the increase in post-tetanic plasticity and in fact it may be some combination of these modulators working in concert that leads to the alterations in post-tetanic plasticity.

Future studies are ongoing to understand whether this STP change occurs as a result of altered input to the PFC (e.g. from the hippocampus) or whether abnormal network activity within the developing PFC alone can cause alterations in STP. Focal epileptiform activity is noted not only in childhood epilepsies, but also in many other developmental neurological disorders; investigation of the role this aberrant network activity during neurodevelopment plays in cognitive impairment is crucial to understanding how best to approach the treatment of these impairments.

Conclusions

We used a flurothyl animal model of early life seizures to show alteration of STP in the PFC. This model shows cognitive deficits in both a hippocampal-dependent task (Huang, et al. 1999) as well as PFC-dependent tasks (Kleen, et al. 2011a, Kleen, et al. 2011b), but thus far there was no direct study elucidating the outcomes of ELS on PFC function. Given the importance of STP for information processing (Klyachko 2011, Rotman, et al. 2011), the findings shown here suggest that ELS may alter the PFC by itself as well to produce behavioral deficits on a network level, thereby bridging the gap between cellular alterations and abnormal cognition.

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Abbreviations

ELS	early life seizures
STP	short-term plasticity
PFC	prefrontal cortex
LV	layer 5

LII/III layer 2/3
fEPSP field excitatory post-synaptic potential

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Highlights

65 early life seizures administered to rat pups in the second postnatal week.

3 forms of short-term plasticity are assessed in 2 networks in the prefrontal cortex.

Post-tetanic potentiation increases in both prefrontal networks.

Activity dependent plasticity decreases in only LII-LV networks.

This suggests a network disruption that may account for cognitive deficits after ELS.

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Figure 1.

ELS does not affect baseline fEPSP amplitude. (A) Focusing on the prelimbic region of the mPFC. (B) EPSPs were evoked by stimulation of LII/III or LV (black stimulating electrodes) and recorded in LV (white recording electrode). (C) Cumulative histogram shows no difference in fEPSP amplitude in ELS group (blue) compare to littermate controls (red). Bars represent the averages of 10 responses per slice, 30-40 slices per group $\pm$ SEM.

Figure 2.

ELS does not alter paired-pulse facilitation regardless of stimulation layer or interstimulus interval. (A) Overlay of four recordings of fEPSP in response to paired-pulse stimulation of LII/III at 15-100 ms interstimulus intervals. (B,C) Change in paired-pulse ratio of fEPSP amplitudes depending on interstimulus interval in control (red) and ELS (blue) groups in LII/III-to-LV (B) and LV-to-LV (C) networks. Bar graph values are means $\pm$ SEM.

Figure 3.

The post-tetanic response is increased after ELS. (A) Under low baseline paradigm (0.1 Hz) the post-tetanic response in both LII/III-to-LV (left column) and LV-to-LV (right column) networks was significantly increased in ELS (blue) group compared to control (red) ($p < 0.001$, repeated measures ANOVA). (B). Under a high baseline stimulation paradigm (0.5 Hz) the post-tetanic response in LII/III-to-LV (left column) was increased for 6s post-tetanus in ELS (blue) group compared to control (red) (*, $p < 0.05$ repeated measures ANOVA, group effect first 3 data points after time 0s), but was not altered in LV-to-LV network (right column). Inset traces within each graph represent the baseline fEPSP (red or blue), and corresponding the post-tetanic fEPSP (black). Graph values are means $\pm$ SEM.

Figure 4.

Layer specific alteration of activity-dependent plasticity after ELS. Individual points represent mean values of fEPSP amplitudes normalized to the first fEPSP amplitude during train of 15 stimuli delivered at 50 Hz to LII/III (top) or LV (bottom) and recorded in LV at ELS (blue) and control (red) groups. Activity-dependent plasticity was altered from pulse 5 to 15 in the 15-pulse train in LII/III-to-LV (**, $p < 0.001$ group by time effect, repeated measures ANOVA). No significant differences were noted in the LV-to-LV network. Graph values are means $\pm$ SEM.