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Developmental Shift of Short-term Synaptic Plasticity in Cortical Organotypic Slices

Weixiang Chen and Dean V. Buonomano

Departments of Neurobiology and Psychology, Integrative Center for Learning and Memory, and Brain Research Institute, University of California, Los Angeles, Los Angeles, CA 90095

Abstract

Although short-term synaptic plasticity (STP) is ubiquitous in neocortical synapses its functional role in neural computations is not well understood. Critical to elucidating the function of STP will be to understand how STP itself changes with development and experience. Previous studies have reported developmental changes in STP using acute slices. It is not clear, however, to what extent the changes in STP are a function of local ontogenetic programs or the result of the many different sensory and experience-dependent changes that accompany development *in vivo*. To address this question we examined the *in vitro* development of STP in organotypic slices cultured for up to four weeks. Paired recordings were performed in L5 pyramidal neurons at different stages of *in vitro* development. We observed a shift in STP in the form of a decrease in the paired-pulse ratio (less depression) from the second to fourth week *in vitro*. This shift in STP was not accompanied by a change in initial EPSP amplitude. Fitting STP to a quantitative model indicated that the developmental shift is consistent with presynaptic changes. Importantly, despite the change in the paired-pulse ratio we did not observe changes in the time constant governing STP. Since these experiments were conducted *in vitro* our results indicate that the shift in STP does not depend on *in vivo* sensory experience. Although sensory experience may shape STP, we suggest that developmental shifts in STP are at least in part ontogenetically determined.

Keywords

short-term synaptic plasticity; organotypic; development; pyramidal neurons

Introduction

Short-term synaptic plasticity (STP) is a virtually universal form of use-dependent synaptic plasticity (Zucker and Regehr, 2002; Abbott and Regehr, 2004). Since Eccles and colleagues first described STP at the neuromuscular junction over 70 years ago (Eccles et al., 1941), hundreds of studies have revealed that the strength of a synapse can change dramatically over the course of hundreds of milliseconds as a result of recent activity (Zucker, 1989; Zucker and Regehr, 2002; Abbott and Regehr, 2004). Neocortical synapses exhibit robust short-term synaptic plasticity in the form of short-term depression or facilitation (Markram et al., 1998a; Reyes and Sakmann, 1999; Rozov et al., 2001). Despite the fact that STP is

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Dean V. Buonomano, Brain Research Institute, University of California, Los Angeles, Box 951761, Los Angeles, CA. 90095, (310) 794-5009; FAX (310) 825-2224, dbuono@ucla.edu.

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observed at essentially all neocortical synapses the contribution of short-term plasticity to cortical computations remains unknown. On theoretical grounds it has been suggested that short-term plasticity plays a role in gain control (Abbott et al., 1997; Chance et al., 1998; Galarreta and Hestrin, 1998; Rothman et al., 2009), working memory (Maass and Markram, 2002; Mongillo et al., 2008), and temporal processing (Buonomano and Merzenich, 1995; Buonomano, 2000; Fortune and Rose, 2001).

STP is primarily a presynaptic phenomenon that relies on the balance of two opposing factors: depression and facilitation (Gingrich and Byrne, 1985; Varela et al., 1997; Markram et al., 1998a; Zucker and Regehr, 2002; Abbott and Regehr, 2004). Depression is viewed as arising from the depletion of the readily releasable pool of synaptic vesicles (Schneggenburger et al., 2002), while facilitation is associated with the accumulation of residual calcium in the presynaptic terminal, which can enhance subsequent transmitter release (Katz and Miledi, 1968; Burnashev and Rozov, 2005). It is also known, however, that postsynaptic factors, such as desensitization of AMPA receptors, can also contribute to STP (Rozov and Burnashev, 1999; von Engelhardt et al., 2010).

The functional role of STP is likely to be in part determined by whether or not STP is itself plastic. Specifically, is STP carefully regulated by development and experience, or, as is often implicitly assumed, is the flavor of STP (e.g., depression versus facilitation) essentially an epiphenomenon of baseline synaptic strength. One indication that STP is not simply an epiphenomenon of initial synaptic strength is that there are differential interactions between STP and LTP at different synapses. For example, while LTP and LTD produce dramatic changes in STP in neocortical synapses, these forms of long-term plasticity produce little if any alterations in STP of CA1 synapses (Markram and Tsodyks, 1996; Buonomano, 1999; Selig et al., 1999; Bender et al., 2006; Cheetham et al., 2007; Hardingham et al., 2007). STP also varies significantly between different cortical areas (Atzori et al., 2001; Cheetham and Fox, 2010).

A number of studies have demonstrated that STP undergoes developmental changes (Reyes and Sakmann, 1999; Zhang, 2004; Cheetham and Fox, 2010; Takesian et al., 2010). Some studies have examined the role of sensory experience in the developmental changes of STP (Finnerty et al., 1999; Finnerty and Connors, 2000; Cheetham and Fox, 2011). For example, Cheetham and Fox (2011) reported that sensory deprivation in the visual cortex did not affect the developmental profile of STP. In contrast, they reported that whisker deprivation in the barrel cortex significantly affects STP, however a different study in the barrel cortex did not observe significant effects of sensory deprivation (Finnerty et al., 1999; Finnerty and Connors, 2000). A challenge inherent to examining the effects of sensory deprivation on the development of STP is that even with sensory deprivation there are numerous cross-modal developmental changes that can be altering activity in the deprived area. Indeed it is well established that cross-modal reorganization can take place in response to sensory deprivation in both juvenile and adult animals (Rauschecker, 1995; Sadato et al., 1996; Buonomano and Merzenich, 1998; Kujala et al., 2000; Bavelier and Neville, 2002; Feldman and Brecht, 2005). For example, visual deprivation induces homeostatic plasticity in both the visual and somatosensory cortex (Goel et al., 2006). To avoid potential confounding effects of cross-modal developmental changes in other brain areas, here we examine the developmental changes in STP in organotypic cultures; thus ensuring that potential changes in STP should be independent of sensory, motor, or behavioral experience.

Organotypic slices have proven to be a valuable preparation to study neuronal and synaptic function because the laminar, neuronal, and synaptic properties are relatively well conserved (for reviews see, Bolz, 1994; Gähwiler et al., 1997). Furthermore developmental changes *in vitro* seem to recapitulate aspects of *in vivo* development (Annis et al., 1993; Dantzker and

Callaway, 1998; De Simoni et al., 2003; Uesaka et al., 2005; Johnson and Buonomano, 2007). However, to date, organotypic slices have not been used to study the development of STP. Towards this goal, we used rat organotypic slices from primary auditory cortex to study the ontogenetic development of short-term synaptic plasticity *in vitro* in the absence of any form of sensory experience. Paired whole-cell recordings were performed in connected Layer 5 pyramidal neurons in slices that were cultured for 2 to 4 weeks. We found that the connection ratio and mean amplitude of unitary EPSPs are within the range previously reported in acute slices. We observed a decrease in short-term depression ratio from week 2 to week 4 *in vitro*, in the absence of a significant change in initial EPSP amplitude. There was a parallel developmental decrease in intrinsic excitability and resting membrane potential. Fitting the short-term plasticity data to a quantitative model suggests a decrease in the probability of release but no changes in the time constant of recovery from depression. We show that the developmental switch in STP profile in cortical synapses happens in organotypic slices. These results provide strong evidence that developmental shifts in STP are part of a local ontogenetic program—which does not imply that sensory experience does not influence development of STP.

Materials and Methods

Organotypic slice preparation

Organotypic slices were prepared using the interface method as previously described (Stoppini et al., 1991; Johnson and Buonomano, 2007). Briefly, 7 day old Sprague-Dawley rats were anesthetized with isoflurane and decapitated. The brain was removed and placed in chilled cutting media. Coronal slices (400 μm thick) containing primary auditory cortex were cut using a vibratome and transferred onto cell culture inserts (Millipore, 0.4 μm pore size) with 1 ml of culture media. Culture media was changed 1 and 24 hrs after cutting and every 2–3 days thereafter. Cutting media was composed of EMEM (MediaTech cat. #15-010) plus 3 mM MgCl_2 , 10 mM glucose, 25 mM Hepes, and 10 mM Trisbase. Culture media consisted of EMEM plus 1 mM glutamine, 2.6 mM CaCl_2 , 1.85 mM MgSO_4 , 30 mM glucose, 30 mM Hepes, 0.5 mM ascorbic acid, 20% horse serum, 10 units/L penicillin, and 10 $\mu\text{g/L}$ streptomycin. Slices were incubated in 5% CO_2 and 95% O_2 at 35°C for 8–28 days before recording.

Electrophysiology

Paired recordings were made from regular-spiking, infragranular pyramidal neurons (average depth 730 μm) using IR-DIC visualization. Experiments were performed at 30°C in external solution composed of: 125 mM NaCl, 5.1 mM KCl, 2.6 mM MgSO_4 , 26.1 mM NaHCO_3 , 1 mM NaH_2PO_4 , 25 mM glucose, and 2.6 mM CaCl_2 . Note that in accordance with most organotypic slice experiments the external Ca^{2+} concentration is higher than the typical ACSF of acute slices (Stoppini et al., 1991; Musleh et al., 1997)—this is standard and is in part necessary to match divalent cation concentrations between the culture media and the external recording solution (Debanne et al., 1996; Hayashi et al., 2000; Johnson and Buonomano, 2007; Tominaga-Yoshino et al., 2008). The internal solution for whole-cell recordings contained 100 mM K-gluconate, 20 mM KCl, 4 mM ATP-Mg, 10 mM phosphocreatine, 0.3 mM GTP-Na, 10 mM HEPES, and was adjusted to pH 7.3 and 300 mOsm. EPSPs were elicited by triggering spikes using current injection: trains of 5 pulses at 50, 100, or 200 ms intervals. All cell pairs were bidirectionally tested for connections. All analyses were performed using software custom written in MATLAB. The average distance between connected neurons was 19.1 μm (range: 8.1 μm to 32.8 μm), estimated using the built-in micrometer of the MP-285 micromanipulators (Sutter).

Intrinsic Excitability

To measure intrinsic excitability 250 ms current steps (0.05, 0.1, 0.15, 0.2, and 0.3 nA) were applied, and the number of spikes elicited were counted. The input-output (current-spike number) curve of each cell was fit to a sigmoid function (Marder and Buonomano, 2004). Excitability was defined as the E50 (the intensity eliciting half of the maximal number of spikes), and compared between age groups using a t-test.

Fitting data to model of STP

In order to quantitatively characterize STP we fit the short-term plasticity data to a model of STP (Tsodyks and Markram, 1997; Markram et al., 1998a; Maass and Markram, 2002). In the absence of short-term facilitation this model is characterized by two parameters: U , which defines the fraction of available transmitter that is released at each synaptic event; and τ_{rec} , the time constant that governs the recovery of synaptic efficacy from depression. This time constant is meant to capture the dynamics of the processes responsible for reversing the synaptic depression— τ_{rec} is often interpreted as relating to the replenishment of the readily releasable pool of vesicles. High values of U , which is bounded between 0 and 1, favor depression and low values facilitation. Although U is a simplified representation of the probability of release, if one were to assume the presence of many synaptic boutons U would be related to the probability of vesicle release (Markram et al., 1998b). Synaptic efficacy in response to successive action potentials is controlled by the variable R :

$$EPSP_n = A \times R_n \times U \quad (1)$$

$$R_{n+1} = 1 + (R_n - R_n \times U - 1) \times e^{\frac{-\Delta t}{\tau_{\text{rec}}}} \quad (2)$$

where n is the number of the current synaptic event, $n+1$ is the next event, and Δt is the interval between n^{th} and the $n+1^{\text{th}}$ spike. The variable $EPSP_n$ represents the strength of the n^{th} EPSP. The variable A is essentially a scaling factor directly dependent on the amplitude of the first EPSP. However, since the precise value of A does not alter in any way the STP estimates we normalized the value of $EPSP_1$ to 1 by imposing $A = 1/U$ (note that the baseline EPSP data is provided in Fig. 1). R_n represents the fraction of synaptic efficacy available for the n^{th} spike. R 's initial value is 1, it decreases with each EPSP, and recovers with the time constant τ_{rec} . The Tsodyks-Markram model of STP also incorporates a facilitation term (τ_{fac}) that accounts for short-term facilitation, however, since we did not observe facilitation at the synapses analyzed here this term was not included.

RESULTS

Paired recordings were performed in Layer 5 pyramidal neurons in organotypic slices of rat primary auditory cortex as previously described. To determine if a pair of neurons was connected, a train of 5 spikes (10 Hz) were elicited in one neuron and the averaged voltage traces of the other neuron was examined. Then the pair was tested in the opposite direction (Figure 1A and 1B). Out of 161 pairs of recorded neurons 35 were connected (connection probability of 21.7%), and out of these 35 connected pairs 4 were reciprocally connected. While the connection probability is higher than some previous reports it is within previously observed ranges, and consistent with the data that the organotypic slices have higher connection probabilities than acute slices (see Discussion; De Simoni et al., 2003). The mean amplitude of unitary EPSPs was 1.01 ± 0.12 mV, ranging from 0.16 – 3.96 mV, also comparable to acute slices (Markram et al., 1997; Debanne et al., 2008).

Developmental changes in short-term synaptic plasticity

To determine if STP in organotypic slices also undergoes developmental change *in vitro*, we analyzed STP during the second week (8–15 days) and fourth week (22–27 days) *in vitro*. STP was characterized by examining the change in EPSP amplitude in response to 5 presynaptic action potentials at 5, 10 and 20 Hz. Trains were presented every 5 sec in alternation. Synapses exhibited varying degrees of paired pulse depression, yet, from the second week to the fourth week there was a significant increase in the paired-pulse ratio (PPR = EPSP₂/EPSP₁) from 44±6% to 67±6% (10 Hz data). The mean amplitude of unitary EPSPs remained unchanged (1.07±0.24 mV compared to 0.91±0.12 mV, at 2 and 4 weeks, respectively). A two-way analysis of variance of Age versus pulse number (repeated measures factor) revealed a significant interaction between Age × Pulse Number ($F_{4,80}=3.9$, $p=0.006$), while the main effect of age was not significant. When EPSP amplitudes were normalized to EPSP₁ there was a significant main effect of age ($F_{1,20}=12$, $p=0.002$) (Figure 1C, D). Quantification of the 5 and 20 Hz data produced similar results (data not shown). Thus, while there was no significant change in mean initial EPSP amplitude, there was a significant increase in the PPR (less paired-pulse depression).

In order to examine the relationship between initial EPSP amplitude and STP we analyzed the correlation between EPSP amplitude and PPR. For Week 2 synapses there was a significant correlation between EPSP amplitude and PPR ($p=0.039$), however this correlation was not observed in Week 4 ($p=0.319$) (Figure 1E). These results suggest that over the course of maturation there may be progressively more factors involved in the regulation of STP.

Developmental changes in cellular properties

Since previous studies have also reported developmental changes in the intrinsic properties of pyramidal neurons in acute and organotypic slices (Zhang, 2004; Johnson and Buonomano, 2007) we also analyzed changes in excitability and membrane properties between Week 2 and 4 slices. To measure intrinsic excitability, 250 ms duration of current steps were injected into individual cells every 10s (with amplitudes of 0.05, 0.1, 0.15, 0.2, 0.3 nA) and the number of spikes elicited were counted (Figure 2A). There was a significant decrease in intrinsic excitability, as measured by the shift in the input-output curve (see methods, $t_{143}=3.57$, $p=0.0005$, $n=61$, 84 respectively) (Figure 2B). In addition, there was a significant decrease in the resting membrane potential during the same development period (−58.4±0.7 mV and −61.3±0.5 mV, Week 2 and 4 respectively; $t_{143}=3.3$, $p=0.001$) (Figure 2C). The input resistance was not significantly different (202.8±6.5 MΩ 189.3±6.5 MΩ) (Figure 2D).

Quantitative Modeling Analysis of STP

While a number of studies have reported developmental changes in STP, what has not yet been examined is whether these changes are mostly consistent with developmental alterations related to probability of release and/or changes in the temporal profile of STP. Quantitative models often characterize STP with a parameter U that captures initial release probability and a time constant that reflects the rate of recovery from depression (Tsodyks and Markram, 1997; Varela et al., 1997; Markram et al., 1998a). Specifically, we wanted to determine if the time constants of STP also underwent developmental changes. EPSP amplitudes in response to 5, 10 and 20 Hz stimulation were fitted to the Tsodyks-Markram STP model (see Methods). This model captured the STP data at all intervals tested (mean $R^2=0.88$, range: 0.56 – 0.99) (Figure 3A). The fits revealed a significant decrease in U from the second to fourth week *in vitro* (0.72±0.08 versus 0.39±0.05, respectively; $t_{1,17}=3.75$, $p=0.0016$) (Figure 3B). Interestingly, there was no change in the variable that captures the time constant of the recovery from depression (τ_{rec} ; 552±74 versus 559±68 ms) (Figure 3C).

DISCUSSION

The current results revealed a robust developmental increase in PPR. Since these changes were observed in culture, we can conclude that they do not rely on sensory experience, and therefore are likely to be part of an ontogenetic program. Additionally, our quantitative analysis suggests that this developmental shift seems to be best accounted for by changes in release parameters, but not by changes in the time constant governing the recovery from depression. As discussed below this has implications for the computational function of STP.

Connectivity

The connection probability between local cortical neurons relates to the influence neurons have on their neighbors and the “sparsity” of local cortical circuits (Song et al., 2005). Experimental studies have reported a wide range of connection probabilities between neocortical pyramidal neurons. In acute cortical slices, the reported connection probabilities has ranged between 9% (Mason et al., 1991; Markram et al., 1997) to more than 30% (Boudkkazi et al., 2007).

The 21.7% connection probability observed here was a bit higher than most reports in acute cortical preparations, nevertheless our results are consistent with studies suggesting that organotypic cultures exhibit increased synaptic connectivity. For example, in acute hippocampal slices, the connection probability between CA3→CA3 or CA3→CA1 is reported to be between 1% to 5% (Miles and Wong, 1986; Sayer et al., 1990; Scharfman, 1994; Bolshakov and Siegelbaum, 1995). But in organotypic hippocampal slices connections were found in 56% of CA3→CA3 pairs, and 76% of CA3→CA1 pairs (Debanne et al., 1995). To the best of our knowledge however, connection probabilities have not been reported for neocortical organotypic slices. Our observations suggest that there is only a mild, if any, increase in connection probability—in contrast to the large increase reported in hippocampal connectivity. Thus, our results further suggest that the basic circuitry architecture is fairly faithfully preserved in neocortical organotypic preparations (Gähwiler et al., 1997; De Simoni et al., 2003).

Relationship between EPSP amplitude and PPR

It is often implicitly assumed that the paired-pulse ratio is governed mostly by initial synaptic strength, this view is supported by observations indicating that PPR is inversely correlated with the probability of release or initial EPSP amplitude in both the hippocampus (Debanne et al., 1996; Dobrunz and Stevens, 1997) and neocortex (Thomson et al., 1993; Atzori et al., 2001; Boudkkazi et al., 2007). However, it is noteworthy that numerous studies have failed to observe any clear relationship between paired-pulse plasticity and the probability of release or initial EPSP amplitude (Reyes and Sakmann, 1999; Waldeck et al., 2000; Sippy et al., 2003; Frick et al., 2007; Oswald and Reyes, 2008). Furthermore, it has been shown that increased expression of the calcium binding protein NCS-1 in hippocampal cell cultures can switch paired-pulse depression to facilitation without altering basal synaptic transmission (Sippy et al., 2003). Here we observed that the correlation between EPSP amplitude and PPR was dependent on age. For week 2 synapses, there was a significant correlation between EPSP amplitude and PPR ($p=0.039$), but this correlation was not observed in week 4 ($p=0.319$) (Figure 1E). Furthermore, as shown in Figure 1 the change in PPR from developmental week 2 to 4 was not accounted for by the initial EPSP amplitude. These observations further argue that STP is not a simple epiphenomenon of basal synaptic strength.

Developmental Plasticity of STP

Numerous studies have reported an increase in PPR over the course of development. For example, observations in acute slices from somatosensory, auditory, and prefrontal cortex reveal a progressive increase in PPR, generally from strong PPD to little PPD or mild PPF (Reyes and Sakmann, 1999; Kumar and Huguenard, 2001; Zhang, 2004; Frick et al., 2007; Oswald and Reyes, 2008). Here we described for the first time that a similar change is observed in the *in vitro* development of cortical organotypic slices. Additionally, the developmental changes in intrinsic properties are also consistent with previous studies in acute slices (Kasper et al., 1994; Zhang, 2004; Oswald and Reyes, 2008).

As mentioned in the Introduction, previous studies have examined the role of sensory experience in the developmental shift in STP (Finnerty et al., 1999; Finnerty and Connors, 2000; Cheetham and Fox, 2011). However, there have been some conflicting results, perhaps due to the fact that even when one sensory area is deprived of its normal input, non-local or cross-modal experience-dependent changes can still influence the non-deprived cortical circuits (Rauschecker, 1995; Sadato et al., 1996; Buonomano and Merzenich, 1998; Kujala et al., 2000; Bavelier and Neville, 2002; Feldman and Brecht, 2005). For example, visual deprivation has been reported to increase mEPSP amplitude in the visual cortex while decreasing mEPSP amplitude in the somatosensory cortex (Goel et al., 2006)—suggesting that sensory areas are not independent of each other and that normal developmental changes in non-deprived cortex could influence deprived cortical circuits. Consequently, previous developmental studies of PPR have not been able to fully dissociate whether the observed changes in short-term plasticity reflect experience-dependent plasticity or are primarily a product of an ontogenetic program (Reyes and Sakmann, 1999; Zhang, 2004; Cheetham and Fox, 2010; Takesian et al., 2010). Because developmental changes in organotypic slices takes place in the absence of sensory input, our results suggest that this shift is at least partially a result of an ontogenetic program that is independent of experience. Nevertheless, it is also clear that experience can alter STP, but this experience-dependent effect may be accounted for by changes in baseline synaptic strength (Finnerty et al., 1999; Finnerty and Connors, 2000; Cheetham et al., 2007).

Regarding the mechanisms of the developmental STP shift our quantitative analysis suggests that the shift may be attributed to changes in the probability of release. A decrease in release probability together with increase postsynaptic responsiveness could account for the absence of a decrease in initial EPSP amplitude—which would be expected to be observed from a pure decrease in probability of release. An increase in postsynaptic responsiveness could be attributed to postsynaptic receptors or an increase in the number of synaptic contacts. Indeed, given the known developmental and activity-dependent changes in spine density it seems likely there may be an increase in the number of contacts between connected neurons (Gähwiler et al, 1997; De Simoni et al, 2003; Zuo et al, 2005, Holtmaat & Svoboda, 2009).

It should also be noted that STP can also be modulated on a time scale much faster than that observed over development as a result of network activity (Crochet et al, 2005, 2006; Reig et al, 2006). This issue is an important consideration in the current study because both organotypic and dissociated cultures exhibit development increases in network activity over time (Johnson & Buonomano, 2007; Sun et al, 2010). However, while spontaneous activity in organotypic slices does increase, such network effects are unlikely to influence our cross-age measurements for a number of reasons. First, even at 4 weeks Up state frequency remains less than 0.1 Hz (Johnson & Buonomano, 2007); second the mean recovery time constant of STP was well below 1 sec; and third, we eliminated any traces that clearly occurred during Up states.

Computational Function of STP

Although STP is observed in most types of synapses (Zucker, 1989; Zucker and Regehr, 2002) its functional role continues to be debated. Theoretical proposals regarding the function of STP include a role in gain control (Abbott et al., 1997; Chance et al., 1998; Galarreta and Hestrin, 1998; Rothman et al., 2009), working memory (Maass and Markram, 2002; Mongillo et al., 2008), and temporal processing (Buonomano and Merzenich, 1995; Buonomano, 2000; Fortune and Rose, 2001). For example, it has been postulated that STP may play an important role in temporal processing in the range of tens to hundreds of milliseconds as it provides a short-term memory of recent activity (Buonomano and Merzenich, 1995; Buonomano, 2000). Specifically, STP changes the internal state of networks of neurons in a time-dependent manner, thus allowing networks to discriminate the temporal features of sensory stimuli (Buonomano and Maass, 2009).

The issue of how STP changes with development and with synaptic plasticity is critical to understanding the computational function of STP. If it has an explicit computational role it should be possible to observe instances in which it is altered by experience. Indeed, it has been suggested that STP may undergo metaplasticity—that is, there may be specific mechanisms in place to control STP as a result of experience in a manner independent of initial synaptic strength (Waldeck et al., 2000; Sippy et al., 2003; Carvalho and Buonomano, 2011).

In addition to the developmental decrease in PPR our results demonstrated for the first time that this change in STP does not seem to be accompanied by changes in the temporal profile of STP (that is, the time constant of recovery was unaltered). This is a particularly important point in the context of the role of STP in temporal processing. Using computational models it has been recently shown that the plasticity of short-term plasticity enables circuits to solve computational problems that would be otherwise unsolvable (Carvalho and Buonomano, 2011). Specifically, by allowing synapses to “learn” to exhibit PPF or PPD simple circuits can discriminate specific spatiotemporal patterns. In this model the shifts were implemented as changes in the presynaptic release (the U parameter in the Markram-Tsodyks model). But the issue of whether the temporal profile of STP could also be regulated is also raised. This would take place by directed changes in the time constants governing recovery from depression and facilitation. The absence of a development change in recovery from depression observed here, however, would argue against this form of plasticity.

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Highlights

- We found a developmental decrease in short-term depression.
- A quantitative model suggests the observed changes are presynaptic.
- The developmental changes in STP do not alter the time constants governing STP
- The developmental shift in STP reflects is ontogenetically determined.
- The ontogenetic shift does not imply that experience does not shape STP.

Figure 1.

Paired recordings in L5 pyramidal neurons reveals a developmental increase in paired-pulse ratio from week 2 to week 4 *in vitro*. **A.** Example of a synaptically-connected pair of neurons. Spikes in the upper neuron elicit EPSPs in the lower neuron. Traces correspond to an average of 30 sweeps. **B.** Testing of the other direction of the same pair. Spikes in the lower neuron do not elicit EPSPs in the upper neuron. **C.** Absolute EPSP amplitude at Week 2 and Week 4 *in vitro* ($n=10, 12$). $F_{4,80}=3.9$, $p=0.006$ (interaction). **D:** Normalized EPSP amplitude. $F_{1,20}=12$, $p=0.002$ (main effect of week). **E.** Correlation between PPR and EPSP amplitude is age-dependent. There is a significant correlation at Week 2 ($p=0.039$) but not at Week 4 ($p=0.319$).

Figure 2. Developmental change in cellular properties. **A.** Examples of intrinsic excitability in Week 2 (left) and Week 4 (right). **B.** There was a significant developmental decrease in intrinsic excitability ($p=0.0005$). **C.** There was a significant decrease in resting membrane potential ($t_{143}=3.282$, $p=0.001$). **D.** There was no significant change in input resistance.

Figure 3.

Quantitative analysis of STP. **A.** Example of a fit of the data to the Tsodyks-Markram model of STP (upper, middle, and lower panels correspond to 20 Hz, 10 Hz, and 5 Hz respectively). **B.** There was a significant developmental decrease in the U parameter ($t_{17}=3.75$, $p=0.0016$). **C.** There were no significant changes in the value of τ_{rec} .