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Late adolescent expression of GluN2B transmission in the prefrontal cortex is input-specific and requires postsynaptic PKA and D1 dopamine receptor signaling

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Abstract

Background—Refinement of mature cognitive functions such as working memory and decision-making typically take place during adolescence. The acquisition of these functions is linked to the protracted development of the prefrontal cortex (PFC) and dopamine facilitation of glutamatergic transmission. However, the mechanisms that support these changes during adolescence remain elusive.

Methods—Electrophysiological recordings (*in vitro* and *in vivo*) combined with pharmacological manipulations were employed to determine how NMDA transmission in the medial PFC changes during the adolescent transition to adulthood. The relative contribution of GluN2B transmission and its modulation by postsynaptic PKA and D1 receptor signaling were determined in two distinct age groups of rats: postnatal days (P) 25–40 and P50–80.

Results—We found that only NMDA receptor transmission onto the apical dendrite of layer V pyramidal neurons undergoes late adolescent remodeling due to a functional emergence of GluN2B function after P40. Both PKA and dopamine D1 receptor signaling are required for the functional expression of GluN2B transmission and to sustain PFC plasticity in response to ventral hippocampal, but not basolateral amygdala inputs.

Conclusion—Thus, the late adolescent acquisition of GluN2B function provides a mechanism for dopamine D1-mediated regulation of PFC responses in an input-specific manner.

Keywords

dopamine; NMDA; signaling; adolescence; hippocampus; amygdala

Introduction

Adolescence constitutes a period for enhancement of executive functions including working memory, decision-making, and inhibitory control (1). The neurobiological substrate

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underlying these changes is linked to the protracted development of the prefrontal cortex (PFC) (2) and the integration of glutamatergic inputs carrying contextual and emotional information from the ventral hippocampus and amygdala (3, 4). Such refinement of PFC-dependent functions has also been associated with the maturation of prefrontal dopamine signaling during adolescence (5–7). In particular, co-activation of dopamine D1 and NMDA receptors in the PFC is required for appetitive instrumental learning (8) and for enhancing plasticity in the ventral hippocampal-PFC pathway (9). In this regard, NMDA receptor-mediated transmission has long been recognized as a critical effector in a variety of cognitive behaviors, including those executed by the PFC in adulthood (10–13). Thus, it has been proposed that a periadolescent gain of D1 receptor-dependent facilitation of NMDA transmission in the PFC provides one key mechanism of synaptic plasticity that underlies the acquisition of mature prefrontal functions (5, 14). Nonetheless, the molecular mechanisms by which dopamine tone supports NMDA function in adult cortical circuits remain largely unknown.

It has been shown that the distinctive expression of NMDA subunits affects the plasticity of pyramidal output neurons in cortical circuits (15). Traditionally, the NR2A subunit has been seen as the predominant form of NMDA receptors in adult cortical networks from a variety of non-PFC regions (16, 17) whereas the GluN2B subunit has been regarded to contribute to synaptic transmission only in the developing brain (see reviews (16, 18)). However, recent studies have highlighted a critical role for NMDA-GluN2B receptors in the adult PFC in sustaining working memory-associated persistent activity (17, 19) and trace conditioning (20). Thus, it is not unexpected that the developmental regulation of NMDA receptor subunit composition in the PFC follows a different postnatal trajectory to that seen in other cortical circuits. Here, we performed *in vitro* and *in vivo* electrophysiological recordings combined with pharmacological manipulations to determine how NMDA receptor-mediated transmission and plasticity in the medial PFC change during the periadolescent transition to adulthood. For this purpose, we examined the relative contribution of GluN2B transmission and its modulation by postsynaptic PKA and D1 receptor signaling in two distinct age groups of rats: postnatal days (P) 25–40 (juvenile-early adolescence) and P50–80 (late adolescence-adulthood).

Methods and Materials

All experimental procedures were approved by the Rosalind Franklin University Institutional Animal Care and Use Committee according to the USPHS Guide for Care and Use of Laboratory Animals. Male Sprague-Dawley rats (Harlan, Indianapolis, IN) from P25 to P85 were allowed to acclimate to the animal facility for at least 5 days before being used, group-housed (2–3 rats/cage) with food and water available *ad libitum*, and maintained at 21–23°C in a 12 hour light-dark cycle. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO) except forskolin and GLYX-13 that were obtained from Tocris Bioscience/R&D Systems (Minneapolis, MN). The peptides inhibitors (PKI[5–24], PKI[19–36], St-Ht31) were obtained from Calbiochem/Millipore (Billerica, MA).

Whole-cell patch-clamp recordings

Coronal PFC slices (350µm thick) were obtained and recordings of layer V pyramidal neurons were conducted at 33–35°C using patch electrodes filled with a Cs-based internal solution to increase the space clamping as previously described (Supplemental Material) (21, 22). Electrically-evoked excitatory postsynaptic currents (EPSC) were elicited in the presence of 10 µM picrotoxin (GABA-A antagonist) every 10 s using a teflon-coated bipolar electrode placed ~200 µm following the apical or basolateral dendrites of the neuron. The stimulation intensity (0.05 to 0.15 mA; 0.3 ms square pulses) was chosen from the minimum

current required to elicit an EPSC_{-70mV} with <15% variability in amplitude. Only neurons exhibiting stable EPSC_{-70mV} responses (10–15 min) were included. During baseline, 2 sets of depolarizations at 3–5 min interval were applied to assess the reversal potential, and the AMPA (EPSC_{-70mV}) and NMDA (EPSC_{+60mV}) components of response. Typically, 5–8 sweeps of EPSC_{+60mV} were obtained per set of depolarization. Relative changes to baseline EPSC_{+60mV} amplitude (onset to peak) and duration (onset to half-decay amplitude) were measured following 10 min bath application of APV (NMDA receptor antagonist), ifenprodil (GluN2B antagonist), SCH23390 (D1 receptor antagonist), or GLYX-13 (partial agonist of the glycine binding site) in 2 sets of depolarizations from –70mV to +60mV. APV-treated cells were further used to estimate the EPSC_{NMDA} component by digitally subtracting the average baseline EPSC_{+60mV} traces from that recorded in the presence of APV. Data were analyzed using pCLAMP 10.1 (Molecular Devices, Sunnyvale, CA), and the location of the recorded cell was determined through Neurobiotin staining (Supplemental Material) (21, 22).

Local field potential recordings in vivo

PFC plasticity were assessed by means of local field potential (LFP) recordings as previously established (23, 24) (Supplemental Material). The slope of all evoked LFP was measured following local infusion of picrotoxin to pharmacologically isolate glutamatergic transmission. All infusions were delivered in 1 µl at 0.1 µl/min through a 28-gauge cannula (Plastics One Inc., Roanoke, VA) secured to the recording electrode and filled with aCSF-containing picrotoxin (50 µM in 0.1% DMSO), picrotoxin + APV (50 µM), picrotoxin + ifenprodil (5 µM), picrotoxin + St-Ht31 (20 µM), or picrotoxin + SCH23390 (10 µM). Long-lasting changes in LFP were assessed upon the delivery of a high-frequency stimulation (HFS) protocol into the ventral hippocampal or the basolateral amygdala (4 × 50 pulses/100 Hz/15 s). Typically, a 12–15 min baseline of single-evoked LFP (elicited every 15 s) was collected before HFS followed by a post-HFS LFP recording period of at least 40 min (23, 24) (Supplemental Material).

Statistical analysis

Data are expressed as mean ± SEM. Student's t-test was used for two-group comparisons whereas ANOVA was applied to determine effects along two or more variables. Differences were considered statistically significant when $p < 0.05$.

Results

We first examined whether glutamatergic transmission onto the apical dendrite of layer V medial PFC pyramidal neuron is developmentally regulated during the transition from juvenile/early adolescence (P25–40) to late adolescence/adulthood (P50–80). Analyses of the evoked response revealed that both age groups exhibit similar EPSC amplitude at the –70mV (EPSC_{-70mV}) and at the +60mV (EPSC_{+60mV}) holding potentials (Fig. 1A). Similarly, the EPSC_{-70mV} duration was indistinguishable among neurons from P25–40 and P50–80 (Fig. 1B). However, pyramidal neurons recorded from the P50–80 age group exhibited a significantly longer EPSC_{+60mV} duration to that obtained in the P25–40 group (Fig. 1B, C). Typically, the EPSC_{+60mV} duration elicited from the apical stimulation is <100 ms (duration to half amplitude) in the P25–40 age group whereas all neurons recorded from the P50–80 group showed EPSC_{+60mV} durations >100 ms (Fig. 1C). We next asked whether a similar facilitation of EPSC_{+60mV} occurs at glutamatergic synapses onto the basolateral dendrites of layer V medial PFC pyramidal neuron. In contrast to the results obtained with the apical stimulation (Fig. 1B–C), we found that neither the amplitude (Fig. 1D) nor the duration (Fig. 1E–F) of the basolateral-evoked EPSC differed between the two age groups

studied. These results indicate that only the apical glutamatergic synapses undergo developmental facilitation during the adolescent transition to adulthood.

A change in EPSC_{+60mV} kinetic indicates that NMDA receptor-mediated transmission contributes to the age dependent facilitation of glutamatergic synaptic response elicited from the apical stimulation. Indeed, bath application of the NMDA receptor antagonist APV significantly reduced EPSC_{+60mV} amplitude (Fig. 2A) and duration (Fig. 2B) in all cells tested from both P25–40 and P50–80 age groups. Following NMDA receptor blockade, the characteristic age difference in EPSC_{+60mV} duration is no longer apparent (Fig. 2B). Further analyses of the apical-evoked EPSC_{+60mV} revealed that pyramidal neurons in the P50–80 PFC exhibited a markedly prolonged NMDA component to that from the P25–40 group (Fig. 2C; see **Methods and Materials** for details). Accordingly, the duration of the evoked EPSC_{+60mV} is positively correlated with the duration of the NMDA component (Fig. 2D), further indicating that a change in NMDA receptor-mediated function underlies the late adolescent facilitation of apical glutamatergic transmission observed in layer V pyramidal neurons of the PFC.

We next asked whether a postsynaptic protein kinase-dependent signaling contributes to the prolonged NMDA-mediated EPSC_{+60mV} observed in the P50–80 age group (Fig. 3A). Recordings conducted with internal solution containing the PKC inhibitor peptide PKI[19–36] or the PKA inhibitor peptide PKI[5–24] revealed that postsynaptic PKA, not PKC, signaling pathway is required for sustaining the increased EPSC_{+60mV} duration characteristic of layer V pyramidal neuron in response to apical stimulation (Fig. 3B). In the presence of PKI[5–24], the EPSC_{+60mV} duration in the P50–80 age group became markedly reduced and indistinguishable from that recorded in the P25–40 PFC. A similar effect on EPSC_{+60mV} duration was observed in the presence of the PKA anchor protein inhibitor St-Ht31 (Fig. 3B), further supporting the finding that postsynaptic PKA-dependent signaling is selectively involved in the facilitation of NMDA receptor function after P50. In the P25–40 group, postsynaptic inhibition of either PKA or PKC signaling failed to change the EPSC_{+60mV} duration (Fig. 3C). In addition, bath application of the positive modulator of the PKA signaling forskolin also failed to prolong the EPSC_{+60mV} duration in the P25–40 PFC to that seen after P50 (Fig. 3C). However, a significant 33% increase in EPSC_{+60mV} amplitude was observed following bath application of forskolin (from 62.4 ± 10.4 pA to 83.4 ± 16.3 pA, $p < 0.02$, paired t-test). Together, these results indicate that postsynaptic PKA signaling is necessary for maintaining the prolonged NMDA-mediated transmission onto layer V pyramidal neuron's apical dendrite in the P50–80 age group, but not sufficient to elicit such augmented response in the juvenile/early adolescent PFC.

Among the different NMDA receptor subunits, the GluN2B-containing receptor is of great interest because of its characteristic slow decay kinetics and its responsiveness to postsynaptic PKA signaling (25, 26). We therefore asked whether the distinctive apical-evoked long-lasting NMDA-mediated EPSC_{+60mV} recorded in layer V pyramidal neurons from the P50–80 PFC could be attributable to an age-dependent increase in the relative contribution of GluN2B-containing NMDA receptor function. Towards this goal, we found that bath application of the selective NMDA-GluN2B receptor antagonist ifenprodil markedly reduced the duration of the evoked EPSC_{+60mV} only in pyramidal neurons recorded from the P50–80 PFC whereas no apparent changes in EPSC_{+60mV} duration were observed in the P25–40 group (Fig. 4A). The age-dependent effect of ifenprodil was not associated with a change in EPSC_{+60mV} amplitude (non-significant age x treatment interaction, $p = 0.98$, two-way ANOVA) since a similar degree of EPSC_{+60mV} amplitude attenuation was observed in both age groups (P25–40: from 49.4 ± 5.9 pA to 45.0 ± 6.1 pA, $p < 0.05$ paired t-test; P50–80: from 51.4 ± 6.7 pA to 47.7 ± 5.7 pA, $p < 0.05$ paired t-test). Further analyses of the recordings obtained from the P50–80 age group revealed a

significant positive linear correlation between baseline EPSC_{+60mV} duration and the ifenprodil-sensitive component of the apical-evoked response (Fig. 4B). We next asked whether there is a mechanistic association between the emergence of GluN2B transmission and postsynaptic PKA signaling in the P50–80 PFC. As shown in Fig. 3A, the inclusion of PKI[5–24] or St-Ht31 into the recording electrode significantly reduced the duration of apical-evoked EPSC_{+60mV}. However, ifenprodil failed to further reduce the shortened EPSC_{+60mV} response induced by intracellular application of PKI[5–24] or St-Ht31 (Fig. 4C). This occlusion effect indicates that a postsynaptic PKA-dependent mechanism is required for the functional expression of GluN2B transmission in the apical dendrite of layer V pyramidal neuron of the PFC after P50. In contrast, GluN2B-containing receptors do not contribute to the basolateral-EPSC_{+60mV} duration (baseline: 82.9 ± 1.4 ms vs. ifenprodil: 83.2 ± 1.5 ms, $n=5$), but a significant 20% attenuation in EPSC_{+60mV} amplitude was observed following bath application of ifenprodil (from 67.8 ± 7.9 pA to 53.5 ± 6.1 pA, $p=0.03$ paired t-test).

Among the different classes of G protein-coupled receptors known to enhance NMDA-mediated responses in the PFC, the D1 dopamine receptor is of great interest because its modulation increases after P45 and involves postsynaptic PKA signaling (5, 22). It is therefore plausible that a change in D1 receptor tone contributes to the prolonged GluN2B-mediated EPSC_{+60mV} response observed in the P50–80 PFC. We found that bath application of the D1 receptor antagonist SCH23390 (10–15 min) selectively reduced the duration of apical-evoked EPSC_{+60mV} in layer V pyramidal neurons of the P50–80 PFC (Fig. 5A). Such an age-dependent effect on EPSC_{+60mV} duration is not due to the lack of D1 receptor tone in the P25–40 PFC. Further analyses revealed a significant 20% attenuation of EPSC_{+60mV} amplitude following bath application of SCH23390 in both age groups (P25–40: from 53.6 ± 3.7 pA to 41.7 ± 5.1 pA; P50–80: from 59.1 ± 7.0 to 45.6 ± 5.0 pA; significant main treatment effect, $p=0.02$, two-way ANOVA). Interestingly, ifenprodil completely occluded the effect of SCH23390 on apical-evoked EPSC_{+60mV} duration in the P50–80 PFC. When recordings were conducted in the presence of ifenprodil, bath application of SCH23390 failed to further reduce the already shortened EPSC_{+60mV} duration (from 76.2 ± 1.2 to 74.8 ± 1.7 ms; $n=6$; Fig 5B). We next assessed the impact of the D1 agonist SKF38393 (10 μ M, 10–15 min) in the P25–40 PFC and found that D1 receptor stimulation significantly increased EPSC_{+60mV} amplitude (from 52.6 ± 5.3 to 64.5 ± 2.7 pA; $p=0.02$, paired t-test, $n=6$) but failed to prolong EPSC_{+60mV} duration (from 91.7 ± 3.7 to 95.7 ± 3.2 ms). A similar facilitation of apical-evoked EPSC_{+60mV} amplitude (from 64.9 ± 4.1 to 95.4 ± 9.2 pA; $p=0.02$, paired t-test, $n=4$) without further increasing EPSC_{+60mV} duration (from 136.6 ± 7.9 to 133.6 ± 6.8 ms) was observed in the P50–80 PFC following SKF38393. Together, these results indicate that a D1 receptor tone in the PFC is necessary (Fig 5A), but not sufficient to sustain the characteristic apical-evoked long-lasting EPSC_{+60mV} response, which is dictated by the presence of GluN2B-mediated transmission (Fig 5B) in layer V pyramidal neuron after P50.

To further assess whether a differential expression of GluN2B function contributes to the age-dependent response of layer V pyramidal neuron in the PFC, we examined the effects of GLYX13, a partial agonist of the glycine-binding site also known to enhance GluN2B transmission (27). We found that GLYX13 effectively increased the duration of apical-evoked EPSC_{+60mV} only in pyramidal neurons recorded from the P50–80 PFC (Fig. 6A). Such an age-dependent facilitation of EPSC_{+60mV} response by GLYX13 is lacking when recordings were conducted in the presence of ifenprodil. Baseline EPSC_{+60mV} duration was 81.3 ± 4.3 ms in brain slices pre-incubated with ifenprodil and 79.8 ± 4.2 ms following the addition of GLYX13 ($n=5$; Fig. 6B). Thus, prefrontal GluN2B-containing receptors become functionally available only after late adolescence to sustain glutamatergic transmission in the apical dendrite of layer V pyramidal neurons.

We next determined whether the late adolescent emergence of GluN2B transmission contributes to regulation of synaptic plasticity in the PFC *in vivo*. Specifically, we assessed the age-dependent impact of ventral hippocampal high-frequency stimulation on medial PFC local field potential (LFP) responses (Fig. 7A). We found that high-frequency stimulation of the ventral hippocampus resulted in long-term potentiation (LTP) of LFP in the P50–80 PFC, a form of plasticity that is absent in P25–40 rats (Fig. 7B). The hippocampal-induced prefrontal LTP was completely blocked when recordings were conducted following local PFC microinfusions of aCSF_{ptx}-containing APV, ifenprodil, the AKAP inhibitor or the D1 receptor antagonist SCH23390 (Fig. 7C–D). However, basolateral amygdala-induced LTP was unaffected by PFC blockade of GluN2B and D1 receptors, but blunted by APV (Fig. 7E–F). Interestingly, the basolateral amygdala-dependent LTP is already enabled by P30 (28). In sum, a late adolescent emergence of prefrontal GluN2B function is required for sustaining plasticity in the adult PFC in response to ventral hippocampal inputs. Such input-specific modulation of glutamatergic transmission is dependent on local prefrontal PKA and D1 receptor signaling.

Discussion

In the present study, we found that NMDA-mediated transmission onto the apical dendrite of layer V pyramidal neuron in the medial PFC undergoes a specific developmental upregulation during the adolescent transition to adulthood. Both postsynaptic PKA signaling and local prefrontal D1 receptor tone are necessary, but not sufficient to sustain the characteristic long-lasting NMDA response that begins to emerge ~P45 (Fig. 8A–B). Our results also indicate that such developmental facilitation is dictated by the functional availability of GluN2B transmission in the apical dendrite of layer V pyramidal neurons. When examined *in vivo*, the protracted emergence of prefrontal GluN2B function is required for the late adolescent, input-specific expression of LTP in response to ventral hippocampal stimulation. Local PFC inhibition of PKA and D1 receptor signaling blocked GluN2B-dependent LTP. Thus, the gain of GluN2B function provides a mechanism for D1 receptor regulation of PFC plasticity in an input-specific manner, and contributes to the manifestation of dopamine actions on prefrontal-dependent executive functions that occurs during adolescence.

It is generally accepted that the overall expression of the GluN2B subunit in cortical circuits increases sharply during the first 2 weeks of postnatal development in rodents (25, 29–31). However, the relative contribution of GluN2B function to NMDA transmission in cortical synapses decreases over the course of postnatal development to adulthood concurrent with subsequent increases of the NR2A subunit (16, 18). Thus, the relative loss of GluN2B function is thought to signal the end of plasticity in sensory cortices (16, 18). Nonetheless, the slow kinetic properties of GluN2B-containing receptors (26) have been proposed as ideal for computing input integration (32) and have been recently implicated in a variety of PFC-dependent functions (19, 20). To the best of our knowledge, our study is the first to demonstrate that an upregulation of GluN2B transmission in cortical glutamatergic synapses emerges late in adolescence and enables LTP in the medial PFC in an input-specific manner. Our results indicate that the late adolescent acquisition of prefrontal GluN2B function is required for the expression of ventral hippocampal-induced LTP, but not basolateral amygdala-mediated plasticity. Interestingly, afferents originating from the ventral hippocampus are critical for amplifying PFC-dependent cognitive processes (3, 4). These include working memory, decision-making, and inhibitory control, all of which are refined during the adolescent transition to adulthood (1), and require prefrontal D1 receptor function (8, 33, 34). Thus, a key neurobiological step towards the maturation of PFC functioning could be the emergence of input-specific regulation of GluN2B-dependent plasticity by D1 receptors during the late adolescent period.

In addition to the input-specific GluN2B transmission observed in the PFC *in vivo*, our results indicate that only glutamatergic synapses onto the apical dendrite of layer V pyramidal neurons undergo late adolescent expression of GluN2B function. Interestingly, such compartment-specific remodeling of NMDA transmission coincides with the developmental period during which the apical dendrite of layer V pyramidal neurons in the neocortex reaches maturity (35). Although major changes in apical dendrite's length and complexity have been completed by P30 (22, 35), its functional maturation continues through adolescence as evidenced by a switch in apical dendritic regenerative potentials from mainly Na⁺-dependent to both Na⁺- and Ca⁺⁺-dependent after P42 (35). Consequently, the apical dendrite becomes functionally coupled to the soma, and integration of amplified-distal synaptic inputs is enabled in layer V pyramidal neurons (35). Thus, the late adolescent incorporation of GluN2B transmission into a functionally mature apical dendrite is expected to enhance the temporal summation of context-dependent inputs and facilitate neuronal ensembles in the adult PFC to sustain working memory-related functions.

We had previously observed that the periadolescent facilitation of NMDA-mediated plateau depolarizations by D1 receptors in the medial PFC is largely dependent on PKA signaling (5). Similarly, a critical level of postsynaptic PKA signaling and prefrontal D1 receptor tone is needed to sustain the prolonged GluN2B-dependent NMDA transmission in layer V pyramidal neurons after P50. The fact that PKA inhibition was sufficient to occlude the effect of ifenprodil indicates that the functional expression of GluN2B transmission in the PFC is PKA-dependent. Ifenprodil also occluded the effect of the D1 receptor antagonist SCH23390, suggesting a common signaling mechanism that involves the AKAP-PKA signaling pathway. These results are consistent with the facilitatory role of PKA and D1 receptor stimulation on GluN2B subunit phosphorylation, trafficking and surface expression as well as dendritic localization and clustering, all of which result in enhanced GluN2B transmission (36–38). It is therefore possible that a differential innervation of dopamine terminals onto apical vs. basolateral dendrites in the PFC contributes to the developmental changes observed here, yet no anatomical data are currently available to support this view. However, the sole activation of PKA or D1 receptors in the juvenile/early adolescent PFC failed to recapitulate the prolonged EPSC_{+60mV} response found in adult prefrontal neurons, indicating that other mechanisms are positioned to enable GluN2B function in the adult PFC. One likely mechanism is that the functional availability of GluN2B transmission is lacking in the juvenile/early adolescent group and emerges late in adolescence. To test this, we took advantage of the glycine-binding site partial agonist GLYX-13 known to enhance GluN2B-containing receptors (39, 40) and found that the facilitation of GluN2B transmission can only be elicited in layer V pyramidal neurons from the P50–80 PFC. Thus, the characteristic late adolescent onset of long-lasting NMDA transmission found in the apical dendrite of layer V pyramidal neurons appears to be dictated by the expression of GluN2B receptors.

The fact that a differential age-dependent EPSC_{+60mV} response can be elicited through a focal/non-selective extracellular afferent stimulation indicates that synaptic transmission onto the apical and basolateral dendrites is different. In this regard, these results do not reject nor support the possibility that the developmental regulation is attributable to afferents that selectively synapse onto the apical dendrite. One plausible model resulting from integrating the *in vitro* and the *in vivo* data is that afferents originating from the ventral hippocampus may synapse preferentially onto the apical dendrite whereas the basolateral dendrites receive primarily inputs from the basolateral amygdala (Fig. 8C). Data supporting a subcellular compartmentalization of these inputs are currently lacking, yet a wealth of anatomical and physiological studies clearly show convergence of these inputs onto layer V pyramidal neurons in the PFC (3, 41–44). Alternatively, glutamatergic inputs from the ventral hippocampus and basolateral amygdala could converge to drive the apical dendrite of layer

V pyramidal neurons, but they remain functionally segregated as hippocampal afferents may preferentially synapse onto GluN2B-containing postsynaptic sites (Fig. 8C). Future studies are warranted to determine the precise anatomical basis for supporting the GluN2B-dependent input-specific plasticity in the PFC, although the two models proposed here are not mutually exclusive.

As one of the last cortical regions to reach maturity (45) it is not surprising that NMDA transmission in the PFC continues its functional remodeling during adolescence through a gain of GluN2B function. The striking differential sensitivity of ventral hippocampal vs. basolateral amygdala-dependent plasticity to D1 and GluN2B receptor antagonists suggests that the hippocampal-PFC pathway undergoes unique changes in plasticity during late adolescence. Conversely, the lack of D1 and GluN2B receptor modulation on amygdala-PFC plasticity during this period suggests that this pathway has achieved relative maturity by adolescence (28). Thus, the late adolescent emergence of GluN2B transmission allows D1 receptor signaling in the adult PFC to selectively amplify contextually salient information originating from ventral hippocampus. We speculate that a failure to gain GluN2B function in the PFC during adolescence would result in reduced control of prefrontal-dependent goal-directed tasks as observed when ventral hippocampal modulation is lacking (46, 47) and reminiscent of teenagers behavior (48, 49). In summary, we have uncovered a novel mechanism that integrates current knowledge on how changes in NMDA transmission and D1 receptor signaling during adolescence impact adult PFC functioning through a GluN2B-dependent, input-specific manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Best JR, Miller PH. A developmental perspective on executive function. *Child Dev.* 2010; 81:1641–1660. [PubMed: 21077853]
2. Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. *Child Dev.* 2004; 75:1357–1372. [PubMed: 15369519]
3. Ishikawa A, Nakamura S. Convergence and interaction of hippocampal and amygdalar projections within the prefrontal cortex in the rat. *J Neurosci.* 2003; 23:9987–9995. [PubMed: 14602812]
4. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry.* 2003; 54:504–514. [PubMed: 12946879]
5. Tseng KY, O'Donnell P. Post-pubertal emergence of prefrontal cortical up states induced by D1-NMDA co-activation. *Cereb Cortex.* 2005; 15:49–57. [PubMed: 15217899]
6. Tseng KY, Lewis BL, Lipska BK, O'Donnell P. Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. *Biol Psychiatry.* 2007; 62:730–738. [PubMed: 17207473]
7. Naneix F, Marchand AR, Di Scala G, Pape JR, Coutureau E. Parallel maturation of goal-directed behavior and dopaminergic systems during adolescence. *J Neurosci.* 2012; 32:16223–16232. [PubMed: 23152606]
8. Baldwin AE, Sadeghian K, Kelley AE. Appetitive instrumental learning requires coincident activation of NMDA and dopamine D1 receptors within the medial prefrontal cortex. *J Neurosci.* 2002; 22:1063–1071. [PubMed: 11826135]

9. Gurden H, Takita M, Jay TM. Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses in vivo. *J Neurosci*. 2000; 20:RC106. [PubMed: 11069975]
10. Dalton GL, Ma LM, Phillips AG, Floresco SB. Blockade of NMDA GluN2B receptors selectively impairs behavioral flexibility but not initial discrimination learning. *Psychopharmacology (Berl)*. 2011; 216:525–535. [PubMed: 21384103]
11. Gilmartin MR, Helmstetter FJ. Trace and contextual fear conditioning require neural activity and NMDA receptor-dependent transmission in the medial prefrontal cortex. *Learn Mem*. 2010; 17:289–296. [PubMed: 20504949]
12. Murphy ER, Dalley JW, Robbins TW. Local glutamate receptor antagonism in the rat prefrontal cortex disrupts response inhibition in a visuospatial attentional task. *Psychopharmacology (Berl)*. 2005; 179:99–107. [PubMed: 15678364]
13. Stefani MR, Groth K, Moghaddam B. Glutamate receptors in the rat medial prefrontal cortex regulate set-shifting ability. *Behav Neurosci*. 2003; 117:728–737. [PubMed: 12931958]
14. O'Donnell P. Adolescent maturation of cortical dopamine. *Neurotox Res*. 2010; 18:306–312. [PubMed: 20151241]
15. Zhao MG, Toyoda H, Lee YS, Wu LJ, Ko SW, Zhang XH, et al. Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory. *Neuron*. 2005; 47:859–872. [PubMed: 16157280]
16. Dumas TC. Developmental regulation of cognitive abilities: modified composition of a molecular switch turns on associative learning. *Prog Neurobiol*. 2005; 76:189–211. [PubMed: 16181726]
17. Wang H, Stradtman GG 3rd, Wang XJ, Gao WJ. A specialized NMDA receptor function in layer 5 recurrent microcircuitry of the adult rat prefrontal cortex. *Proc Natl Acad Sci U S A*. 2008; 105:16791–16796. [PubMed: 18922773]
18. Yashiro K, Philpot BD. Regulation of NMDA receptor subunit expression and its implications for LTD, LTP, and metaplasticity. *Neuropharmacology*. 2008; 55:1081–1094. [PubMed: 18755202]
19. Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, et al. NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron*. 2013; 77:736–749. [PubMed: 23439125]
20. Gilmartin MR, Kwapil JL, Helmstetter FJ. NR2A- and NR2B-containing NMDA receptors in the prelimbic medial prefrontal cortex differentially mediate trace, delay, and contextual fear conditioning. *Learning & Memory*. 2013
21. Heng L, Beverley JA, Steiner H, Tseng KY. Differential developmental trajectories for CB1 cannabinoid receptor expression in limbic/associative and sensorimotor cortical areas. *Synapse*. 2011; 65:278–286. [PubMed: 20687106]
22. Heng LJ, Markham JA, Hu XT, Tseng KY. Concurrent upregulation of postsynaptic L-type Ca(2+) channel function and protein kinase A signaling is required for the periadolescent facilitation of Ca(2+) plateau potentials and dopamine D1 receptor modulation in the prefrontal cortex. *Neuropharmacology*. 2011; 60:953–962. [PubMed: 21288471]
23. Cass DK, Thomases DR, Caballero A, Tseng KY. Developmental Disruption of Gamma-Aminobutyric Acid Function in the Medial Prefrontal Cortex by Noncontingent Cocaine Exposure During Early Adolescence. *Biol Psychiatry*. 2013
24. Thomases DR, Cass DK, Tseng KY. Periadolescent exposure to the NMDA receptor antagonist MK-801 impairs the functional maturation of local GABAergic circuits in the adult prefrontal cortex. *J Neurosci*. 2013; 33:26–34. [PubMed: 23283319]
25. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron*. 1994; 12:529–540. [PubMed: 7512349]
26. Vicini S, Wang JF, Li JH, Zhu WJ, Wang YH, Luo JH, et al. Functional and pharmacological differences between recombinant N-methyl-D-aspartate receptors. *J Neurophysiol*. 1998; 79:555–566. [PubMed: 9463421]
27. Burgdorf J, Kroes RA, Weiss C, Oh MM, Disterhoft JF, Brudzynski SM, et al. Positive emotional learning is regulated in the medial prefrontal cortex by GluN2B-containing NMDA receptors. *Neuroscience*. 2011; 192:515–523. [PubMed: 21645591]

28. Caballero A, Thomases DR, Flores-Barrera E, Cass DK, Tseng KY. Emergence of GABAergic-dependent regulation of input-specific plasticity in the adult rat prefrontal cortex during adolescence. *Psychopharmacology*. 2013 In Press.
29. Williams K, Russell SL, Shen YM, Molinoff PB. Developmental switch in the expression of NMDA receptors occurs in vivo and in vitro. *Neuron*. 1993; 10:267–278. [PubMed: 8439412]
30. Sheng M, Cummings J, Roldan LA, Jan YN, Jan LY. Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. *Nature*. 1994; 368:144–147. [PubMed: 8139656]
31. Quinlan EM, Olstein DH, Bear MF. Bidirectional, experience-dependent regulation of N-methyl-D-aspartate receptor subunit composition in the rat visual cortex during postnatal development. *Proc Natl Acad Sci U S A*. 1999; 96:12876–12880. [PubMed: 10536016]
32. Wang XJ. Synaptic basis of cortical persistent activity: the importance of NMDA receptors to working memory. *J Neurosci*. 1999; 19:9587–9603. [PubMed: 10531461]
33. Floresco SB, Phillips AG. Delay-dependent modulation of memory retrieval by infusion of a dopamine D1 agonist into the rat medial prefrontal cortex. *Behav Neurosci*. 2001; 115:934–939. [PubMed: 11508732]
34. Seamans JK, Floresco SB, Phillips AG. D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *J Neurosci*. 1998; 18:1613–1621. [PubMed: 9454866]
35. Zhu JJ. Maturation of layer 5 neocortical pyramidal neurons: amplifying salient layer 1 and layer 4 inputs by Ca²⁺ action potentials in adult rat tuft dendrites. *J Physiol*. 2000; 526(Pt 3):571–587. [PubMed: 10922009]
36. Hallett PJ, Spoelgen R, Hyman BT, Standaert DG, Dunah AW. Dopamine D1 activation potentiates striatal NMDA receptors by tyrosine phosphorylation-dependent subunit trafficking. *J Neurosci*. 2006; 26:4690–4700. [PubMed: 16641250]
37. Schilstrom B, Yaka R, Argilli E, Suvarna N, Schumann J, Chen BT, et al. Cocaine enhances NMDA receptor-mediated currents in ventral tegmental area cells via dopamine D5 receptor-dependent redistribution of NMDA receptors. *J Neurosci*. 2006; 26:8549–8558. [PubMed: 16914681]
38. Yaka R, Tang KC, Camarini R, Janak PH, Ron D. Fyn kinase and NR2B-containing NMDA receptors regulate acute ethanol sensitivity but not ethanol intake or conditioned reward. *Alcohol Clin Exp Res*. 2003; 27:1736–1742. [PubMed: 14634488]
39. Burgdorf J, Zhang XL, Nicholson KL, Balster RL, Leander JD, Stanton PK, et al. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology*. 2013; 38:729–742. [PubMed: 23303054]
40. Burgdorf J, Zhang XL, Weiss C, Matthews E, Disterhoft JF, Stanton PK, Moskal JR. The N-methyl-D-aspartate receptor modulator GLYX-13 enhances learning and memory, in young adult and learning impaired aging rats. *Neurobiol Aging*. 2011; 32:698–706. [PubMed: 19446371]
41. Bacon SJ, Headlam AJ, Gabbott PL, Smith AD. Amygdala input to medial prefrontal cortex (mPFC) in the rat: a light and electron microscope study. *Brain Res*. 1996; 720:211–219. [PubMed: 8782914]
42. Carr DB, Sesack SR. Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopamine terminals. *J Comp Neurol*. 1996; 369:1–15. [PubMed: 8723699]
43. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. *J Comp Neurol*. 2002; 453:116–130. [PubMed: 12373778]
44. Gabbott P, Headlam A, Busby S. Morphological evidence that CA1 hippocampal afferents monosynaptically innervate PV-containing neurons and NADPH-diaphorase reactive cells in the medial prefrontal cortex (Areas 25/32) of the rat. *Brain Res*. 2002; 946:314–322. [PubMed: 12137936]
45. Huttenlocher PR. Morphometric study of human cerebral cortex development. *Neuropsychologia*. 1990; 28:517–527. [PubMed: 2203993]
46. Abela AR, Dougherty SD, Fagen ED, Hill CJ, Chudasama Y. Inhibitory Control Deficits in Rats with Ventral Hippocampal Lesions. *Cereb Cortex*. 2012

47. Chudasama Y, Doobay VM, Liu Y. Hippocampal-prefrontal cortical circuit mediates inhibitory response control in the rat. *J Neurosci.* 2012; 32:10915–10924. [PubMed: 22875926]
48. Casey BJ, Jones RM, Hare TA. The adolescent brain. *Ann N Y Acad Sci.* 2008; 1124:111–126. [PubMed: 18400927]
49. Geier C, Luna B. The maturation of incentive processing and cognitive control. *Pharmacol Biochem Behav.* 2009; 93:212–221. [PubMed: 19593842]

Figure 1.

(A) Electrical stimulation of glutamatergic synaptic transmission onto the apical dendrite of layer V medial PFC pyramidal neuron revealed no apparent age differences in the amplitude of EPSC_{-70mV} and EPSC_{+60mV} (n=10, P25–40; n=14, P50–80). (B) However, the duration of apical stimulation-evoked EPSC_{+60mV} (duration to half amplitude) in the P50–80 age group was significantly longer to that recorded in the P25–40 group (****p*<0.0005, unpaired t-test). (C) Average traces of apical stimulation-evoked synaptic response illustrating the age-dependent increase in EPSC duration recorded at the +60 mV holding potential (calibration bars: 50 pA, 50 ms). (D–E) Bar graph summarizing the results obtained from the basolateral stimulation revealed similar EPSC kinetics across cells recorded from both age groups (n=7, P25–40; n=14, P50–80). (F) Average traces of basolateral-evoked EPSC recorded at the +60 mV holding potential (calibration bars: 50 pA, 50 ms).

Figure 2.

(A) Bath application of the NMDA receptor antagonist APV (50 μ M, 10 min) significantly reduced the amplitude of apical-evoked EPSC_{+60mV} in all cells tested from both P25–40 (n=10) and P50–80 (n=14) age groups (*** p <0.001 vs. baseline, paired t-test; main effect of treatment p <0.0006, $F_{(1,46)} = 13.65$; no significant age $\times$ treatment interaction, two-way ANOVA). (B) Similarly, APV markedly reduced the duration of apical-evoked EPSC_{+60mV} in both age groups (+++ p <0.0005 vs. P25–40, *** p <0.0005 vs. baseline, Fisher LSD post-hoc test; significant age $\times$ treatment interaction p <0.0005, $F_{(1,46)} = 24.92$, two-way ANOVA). Note that the late-adolescent increase in EPSC_{+60mV} duration is no longer detectable following bath application of APV. (C) Analyses of the APV-sensitive component digital subtraction of control vs. APV treatment revealed that the prolonged EPSC_{+60mV} duration recorded in the P50–80 PFC is due to a facilitation of the NMDA-mediated EPSC (*** p <0.0005 vs. P25–40, unpaired t-test). Insets are example traces showing the prolonged EPSC_{NMDA} obtained in the P50–80 PFC (calibration bars: 15 pA, 100 ms). (D) Further analyses revealed a significant positive correlation between the duration of the pre-APV EPSC_{+60mV} and the EPSC_{NMDA} component (P25–40: white circles; P50–80: black circles).

Figure 3.

(A) Diagram summarizing the experimental design used to assess the contribution of postsynaptic PKA and PKC signaling in mediating the late-adolescent facilitation of NMDA-mediated transmission onto medial PFC layer V pyramidal neuron apical dendrite. (B) In the P50–80 age group, the inclusion of PKI[19–36] (PKC inhibitor, 10 μ M; $n=7$) failed to alter the characteristic prolonged EPSC_{+60mV} duration obtained in response to apical stimulation (control internal solution, $n=11$). However, the inclusion of the PKA inhibitor PKI[5–24] ($n=12$) or the AKAP inhibitor St-Ht31 ($n=10$) into the recording electrode markedly reduced the duration of apical-evoked EPSC_{+60mV} (** $p<0.0005$ vs. control, Fisher LSD post-hoc test after significant one-way ANOVA, $F_{(3,36)} = 31.61$, $p<0.0005$), resembling that observed in the P25–40 medial PFC. (C) In contrast, the inclusion of PKI[19–36] (10 μ M; $n=7$), PKI[5–24] (20 μ M; $n=10$) or St-Ht31 (10 μ M; $n=7$) into the recording electrode did not affect the duration of apical-evoked EPSC_{+60mV} in the P25–40 age group (control internal solution, $n=13$). In addition, bath application of forskolin failed to increase the duration of the evoked EPSC_{+60mV} to the P50–80 age group level (10–20 μ M, $n=7$; 50 μ M, $n=6$).

Figure 4.

(A) Age-dependent effect of the selective GluN2B antagonist ifenprodil on apical stimulation-evoked EPSC_{+60mV} duration recorded from layer V medial PFC pyramidal neuron (age x treatment interaction, $p < 0.0005$, $F_{(1,44)} = 17.59$, two-way ANOVA). Bath application of ifenprodil (ifen 5 μM ; 10 min) markedly reduced the duration of apical-evoked EPSC_{+60mV} only in the P50–80 age group ($n = 11$; *** $p < 0.0001$ vs. baseline, +++ $p < 0.0005$ vs. P25–40, Fisher LSD post-hoc test). In contrast, ifenprodil failed to further reduce the duration of apical-evoked EPSC_{+60mV} in the P25–40 PFC ($n = 13$, $p = 0.95$, Fisher LSD post-hoc test). Insets are traces of apical-evoked responses illustrating the age-dependent effect of ifenprodil on EPSC_{+60mV} duration (calibration bars: 50 pA/50 ms). (B) Further analyses revealed a significant positive correlation between EPSC_{+60mV} duration (pre-ifenprodil) and the ifenprodil/GluN2B-sensitive component of the evoked response. (C) The inclusion of the PKA inhibitor PKI[5–24] (20 μM , $n = 9$) or AKAP inhibitor St-Ht31 (5 μM , $n = 8$) into the recording electrode (10–15 min) was sufficient to occlude the effect of ifenprodil on EPSC_{+60mV} duration.

Figure 5.

(A) Age-dependent effect of the D1 receptor antagonist SCH23390 (SCH) on apical stimulation-evoked EPSC_{+60mV} in layer V pyramidal neuron of the medial PFC (age x treatment interaction, $p < 0.0001$, $F_{(1,20)} = 105.8$, two-way ANOVA). Bath application of SCH23390 (10 μ M; 10–15 min) markedly reduced EPSC_{+60mV} duration in all pyramidal neurons recorded from the P50–80 PFC ($n=6$; *** $p < 0.0005$ vs. baseline, +++ $p < 0.0005$ vs. P25–40, Fisher LSD post-hoc test). In contrast, SCH23390 failed to reduce the duration of the evoked EPSC_{+60mV} in the P25–40 age group ($n=6$, $p=0.97$, Fisher LSD post-hoc test). Inset traces are examples of apical-evoked EPSC_{+60mV} illustrating the age-dependent effect of SCH23390 (calibration bars: 50 pA/50 ms). (B) Bar graph summarizing the percent change (% change) to baseline of the results shown in A. Overall, SCH23390 reduced the duration of apical-evoked EPSC_{+60mV} by ~40% in the P50–80 age group whereas a non-significant ~5% change was observed in the P25–40 PFC. Notably, SCH23390 failed to further reduce EPSC_{+60mV} duration in the P50–80 age group when recordings were conducted from slices pre-incubated with ifenprodil (5 μ M, $n=6$; *** $p < 0.0005$ vs. P25–40 or P50–80 + ifenprodil, Fisher LSD post-hoc test after significant one-way ANOVA, $p < 0.0001$, $F_{(2,15)} = 128.9$).

Figure 6.

(A) Age-dependent effect of GLYX13 on apical-evoked EPSC_{+60mV} duration recorded from layer V medial PFC pyramidal neurons (age x treatment interaction, $p < 0.0005$, $F_{(1,24)} = 18.98$, two-way ANOVA). Bath application of GLYX13 (1 μ M; 10 min) significantly increased the duration of the evoked EPSC_{+60mV} only in prefrontal pyramidal neurons recorded from the P50–80 age group ($n = 6$; $***p < 0.0005$ vs. baseline, $+++p < 0.0005$ vs. P25–40, Fisher LSD post-hoc test). All neurons recorded from the P25–40 PFC remained unchanged following bath application of GLYX13 ($n = 8$, $p = 0.97$, Fisher LSD post-hoc test). Insets are example traces of apical-evoked responses illustrating the age-dependent effect of GLYX13 on EPSC_{+60mV} duration (calibration bars: 50 pA/50 ms). (B) Bar graph summarizing the results shown in A as percent change (% change) to baseline. Overall, GLYX13 increased the duration of apical-evoked EPSC_{+60mV} by ~30% in the P50–80 age group whereas a non-significant ~5% change was observed in the P25–40 PFC. Note that the facilitatory effect of GLYX13 observed in the P50–80 age group failed to occur in brain slices pre-incubated with ifenprodil (5 μ M, $n = 5$; $***p < 0.0005$ vs. P25–40 or P50–80 + ifenprodil, Fisher LSD post-hoc test after significant one-way ANOVA, $p < 0.0001$, $F_{(2,16)} = 30.2$).

Figure 7.

(A) Diagram illustrating the recording arrangement used to study ventral hippocampal high-frequency stimulation (HFS)-induced plasticity in the medial PFC by means of local field potential (LFP) recordings *in vivo* (IL: infralimbic; PL: prelimbic; calibration bars: 2 μ V/50 ms). To pharmacologically isolate glutamatergic transmission, all recordings were conducted following local prefrontal microinfusion of aCSF-containing picrotoxin (aCSF_{ptx}; see details in **Methods and Materials**). (B) In the P50–80 age group (aCSF_{ptx}, $n=7$), ventral hippocampal HFS typically elicited a sustained facilitation of the evoked LFP response in the medial PFC. Such LTP of the evoked LFP response was not observed in the medial PFC of P25–40 rats (aCSF_{ptx}, $n=6$). (C) Summary of the effects of ventral hippocampal HFS following single local prefrontal microinfusion of aCSF_{ptx}-containing APV (50 μ M, $n=6$), ifenprodil (5 μ M, $n=6$), St-Ht31 (10 μ M, $n=6$) or SCH23390 (10 μ M, $n=6$). Note that the characteristic LFP-LTP observed in the P50–80 PFC is not longer present after prefrontal removal of NMDA-GluN2B transmission, PKA signaling and D1 receptor tone. (D) Bar graph summarizing the statistical analyses of the results shown in C (average from the last 20 min; *** $p < 0.0005$ vs. P25–40 or any treatment group, Fisher LSD post-hoc test after significant one-way ANOVA, $p < 0.0005$, $F_{(5,31)} = 5.86$). (E) Diagram illustrating the recording arrangement used to study basolateral amygdala (BLA)-induced plasticity in the medial PFC by means of LFP recordings *in vivo* (calibration bars: 2 μ V/50 ms). As in A, all prefrontal LFP recordings were conducted following local microinfusion of aCSF_{ptx} into the PFC. (F) BLA-HFS also elicited LTP in the PFC of P50–80 rats (aCSF_{ptx}, $n=6$), a form plasticity that was blocked by the NMDA receptor antagonist APV (50 μ M, $n=5$). However, prefrontal infusions of ifenprodil (5 μ M, $n=5$) or SCH23390 (10 μ M, $n=5$) failed to block BLA-induced LTP in the medial PFC.

Figure 8.

(A) Summary of the baseline EPSC_{+60mV} duration of all layer V pyramidal neurons recorded from the medial PFC included in the present study. Additional data obtained from the P41–49 age gap were included to highlight that the gain of long-lasting NR2B transmission begins to emerge ~P45. Note that all PFC cells recorded after P50 exhibit EPSC_{+60mV} duration >100 ms (dashed line). (B) Simplified diagram illustrating how dopamine D1 receptor signaling and AKAP-PKA interacts to facilitate (directly or indirectly) GluN2B transmission in the apical dendrite of layer V PFC pyramidal neurons. (C) Two plausible scenarios for explaining the GluN2B-dependent input-specific LTP observed in the adult PFC following HFS of the ventral hippocampus. Model 1 suggests that ventral hippocampal inputs to the PFC may synapse preferentially onto the apical dendrite whereas afferents from the basolateral amygdala may synapse preferentially onto the basolateral dendrites. Model 2 proposes a convergence of inputs originating from both structures onto the apical dendrite of layer V pyramidal neurons. However, a functional segregation of these two afferents is determined by the emergence of GluN2B transmission preferentially at hippocampal synapses.