Original Article

The Cytokine CXCL12 Promotes Basket Interneuron Inhibitory Synapses in the Medial Prefrontal Cortex

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Abstract

Prenatally, the cytokine CXCL12 regulates cortical interneuron migration, whereas its postnatal functions are poorly understood. Here, we report that CXCL12 is expressed postnatally in layer V pyramidal neurons and localizes on their cell bodies in the medial prefrontal cortex (mPFC), while its receptors CXCR4/CXCR7 localize to the axon terminals of parvalbumin (PV) interneurons. Conditionally eliminating CXCL12 in neonatal layer V pyramidal neurons led to decreased axon targeting and reduced inhibitory perisomatic synapses from PV+ basket interneurons onto layer V pyramidal neurons. Consequently, the mPFC of Cxcl12 conditional mutants displayed attenuated inhibitory postsynaptic currents onto layer V pyramidal neurons. Thus, postnatal CXCL12 signaling promotes a specific interneuron circuit that inhibits mPFC activity.

Key words: axon targeting, CXCR4/CXCR7, layer V pyramidal neurons, parvalbumin interneurons, schizophrenia

Introduction

The proper balance of excitation and inhibition in the prefrontal cortex (PFC) is essential for optimal cognitive functioning (Uhlhaas and Singer 2010; Cho and Sohal 2014). Disturbances in PFC inhibitory gamma-aminobutyric acid-containing (GABAergic) cortical interneurons (CINs), such as those expressing parvalbumin (PV) and somatostatin (SST), are implicated in neuropsychiatric disorders, including schizophrenia (Lewis et al. 2012; Volk and Lewis 2014). PV+ and SST+ CINs are generated in the medial ganglionic eminence (MGE), from where they tangentially migrate in the prenatal mouse brain [embryonic day (E) ~12–18]. Once in the cortex, they radially migrate into their appropriate layers [-E18–postnatal day (P) 6], where they receive and make synaptic connections with excitatory pyramidal neurons (Bartolini et al. 2013).

The axons from diverse CIN subtypes form synapses with different subdomains of pyramidal neurons. For example, layer V pyramidal neuron somata are innervated by PV+ basket CINs, while PV+ chandelier CINs target the axon initial segments (AIS), and SST+ Martinotti CINs innervate distal dendrites (Huang et al. 2007). These processes are controlled by transcription factors (Kessaris et al. 2014), and extracellular cues such as cytokine and neuregulin signaling (Marin 2013).

The cytokine C-X-C motif ligand 12 (CXCL12; also known as stromal cell-derived factor-1, SDF-1) regulates the immune system (Nagasawa et al. 1996; Ara et al. 2003; Greenbaum et al. 2013), and the nervous system (Marin 2013). In embryonic mouse neocortex, Cxcl12 is expressed in the meninges and the subventricular zone/intermediate zone (SVZ/IZ), where it attracts CINs and directs their tangential migration along two
The brains were then removed and post-fixed in the same fixative for 3 h. Fixed brains were sectioned at a thickness of 50 μm with a vibratome (Leica VT1200S, Leica).

For immunohistochemistry (IHC), free-floating sections were washed with PBS supplemented with 3% H2O2, 10% methanol, and 0.25% Triton X-100 for 15 min to quench endogenous peroxidases. Sections were then incubated with a blocking solution (5% normal goat serum or horse serum, 0.25% Triton X-100, and 0.2% gelatin in PBS) for 2 h, primary antibodies at 4°C overnight, and secondary antibodies for 2 h. Sections were incubated in ABC solution (Vector Laboratories) for 1 h, rinsed three times in PBS, and placed into 0.005% 3,3′-diaminobenzidine tetrahydrochloride (DAB; Sigma) with 0.001% H2O2 in PBS for 3–5 min. Reactions were stopped with PBS. Sections were washed, mounted, air-dried overnight, and coverslipped with Permount (Fisher Scientific).

For immunofluorescence, sections were blocked with 5% BSA and 0.25% Triton X-100 in PBS for 2 h, incubated with the primary antibodies at 4°C overnight, and then with secondary antibodies for 2 h. Sections were washed, mounted, and coverslipped with mounting medium with DAPI (Vector Laboratories). All primary and secondary antibodies were diluted in blocking solutions.

**Antibodies**

Primary antibodies: chicken anti-GFP (1:2000, Aves Lab, #GFP-1020); goat anti-somatostatin (1:400, Santa Cruz, #sc-7819), goat anti-CXCL12 (1:200, Santa Cruz, #sc-6193) (Bhattacharyya et al. 2008); mouse anti-GAD65 (1:500, Millipore, #MAB351) (Fazzari et al. 2010), mouse anti-CXCR7 (11G8, 1:200, R&D Systems, #MAB42273) (Sanchez-Alcaniz et al. 2011); rabbit anti-GFP (1:2000, Invitrogen, #A11122), rabbit anti-parvalbumin (1:2000, Swant, #PV 25) (Vogt et al. 2014), rabbit anti-phospho-IκBα (1D4, 1:300, Cell Signaling, #2859) (Fazzari et al. 2010); rat anti-RFP (5F8, 1:2000, ChromoTek, #5F8), rat anti-CXCR4 (1:200, BD biosciences, #551852). The IHC secondary antibodies were biotinylated goat anti-rabbit or horse anti-goat (1:200, Vector Laboratories), and the immunofluorescence secondary antibodies were Alexa Fluor 488-, 594-, or 647-conjugated (1:300, Invitrogen).

**Materials and Methods**

**Mice**

All animal care and procedures were performed according to the University of California at San Francisco (UCSF) Laboratory Animal Research Center guidelines. Mice were housed at a density of 2–5 adults/cage or 1–2 adults with 1 litter/cage. The light-dark cycle was 12:12 hours. All mice strains have been previously reported: Cxcl12<sup>GFP</sup>+/− (Ara et al. 2003), Nkx2.1-Cre (Xu et al. 2008), Ai14 (Madisen et al. 2010), and Cxcr4<sup>lox/lox</sup> (Greenbaum et al. 2013). Rbp4-Cre was obtained from the Gene Expression Nervous System Atlas Project (GENSAT, founder line KL100), Cxcl12<sup>GFP</sup>−/− and Nkx2.1-Cre mice were maintained on a C57BL/6J background. Mice of both genders were used.

**Histology**

Embryos were removed from pregnant females. Next, the embryonic brains were dissected and fixed in 4% paraformaldehyde (PFA) in phosphate-buffered saline (PBS) at 4°C overnight. For postnatal study, animals were anesthetized with CO2 (>P3) or ice (<P3), and perfused with PBS, followed by 4% PFA in PBS.
Slice Preparation
Slice preparation and intracellular recording followed our published protocol (Sohal and Huguenard 2005). Coronal slices, 250 μm thick, from P42–49 mice of either sex were cut in a chilled slicing solution in which Na+ was replaced by sucrose, then incubated in warmed ACSF at 30–31°C for 15 min and then at least 1 h at room temperature before being used for recordings. ACSF contained (in mM): 126 NaCl, 26 NaHCO3, 2.5 KCl, 1.25 NaH2PO4, 1 MgCl2, 2 CaCl2, and 10 glucose. Slices were secured by placing a harp along the midline between the two hemispheres.

Intracellular Recording
Somatic whole-cell patch recordings were obtained from visually identified neurons in layer V of infralimbic or prelimbic cortex using differential contrast video microscopy on an upright microscope (BX51WI; Olympus). Recordings were made using a Multiclamp 700A (Molecular Devices). Patch electrodes (tip resistance = 2–6 MOhmS) were filled with the following (in mM): 130 K-gluconate, 10 KCl, 10 HEPES, 10 EGTA, 2 MgCl2, 2 MgATP, and 0.3 NaGTP (pH adjusted to 7.3 with KOH). All recordings were at 32.5 ± 1 °C. Series resistance was usually 10–20 MΩ, and experiments were discontinued above 30 MΩ. Experiments were performed blind to genotype.

Injection of Virus for DlxI12b-mCherry Expression
To visually identify interneurons, we injected an adeno-associated virus (AAV) vector that drives mCherry expression using the DlxI12b enhancer, which restricts expression to GABAergic interneurons (Potter et al. 2009; Lee et al. 2014) (hereafter abbreviated as I12b). We injected 0.5 μl of virus following previously-described procedures (Sohal et al. 2009). We waited at least 4 weeks after virus injection before preparing brain slices. Coordinates for injection into mPFC were (in millimeters relative to bregma): 1.7 anterior-posterior, 0.3 mediolateral, and −2.75 dorsoventral. Injections were performed blind to genotype.

Injection of Virus for ChR2 Expression
To express ChR2 specifically in interneurons, we used an AAV that drives I12b-dependent expression of a ChR2-eYFP fusion protein (Cho et al. 2015). For the in vitro slice experiments, we injected 0.75 μl of virus following previously-described procedures (Sohal et al. 2009), then waited at least 4 weeks after virus injection before preparing brain slices. Coordinates for injection into mPFC were (in millimeters relative to bregma): 1.7 anterior-posterior, 0.3 mediolateral, and −2.75 dorsoventral. Injections were performed blind to genotype.

In Vitro ChR2 Stimulation
We stimulated ChR2 in interneurons using ~4–5 mW flashes of light generated by a Lambda DG-4 high-speed optical switch with a 300 W Xenon lamp (Sutter Instruments), and an excitation filter set centered around 470 nm, delivered to the slice through a ×40 objective (Olympus). Illumination was delivered across a full high-power (×40) field. To measure inhibitory currents, we made voltage-clamp recordings at a holding potential of +10 mV while stimulating ChR2 using trains of light flashes (5 ms/flash, 40 Hz). Experiments were performed blind to genotype.

Analysis of Intrinsic Properties
Intrinsic properties were calculated based on the current clamp responses to a series of 250 ms current pulse injections from −200 to 450 pA (50 pA/increment). Input resistance was calculated from the voltage response to a −50 pA, 250 ms current pulse. Spiking properties were calculated based on the response to a current pulse that was 100 pA above the minimal level that elicited spiking.

As described above, we identified interneurons based on the expression of mCherry driven by AAV and the DlxI12b enhancer (Potter et al. 2009). Recorded interneurons were therefore subdivided into fast-spiking (FS) or non-FS based on electrophysiological properties. Specifically, we classified an interneuron as FS if the adaptation ratio was <1.3, and the input resistance was <350 MΩms. Type A neurons were distinguished by their voltage sag and rebound afterdepolarization (ADP) following hyperpolarizing current pulses (~200 pA, 250 ms): type A neurons were defined based on a combined sag and rebound ADP >2.5 mV.

Statistics
Data were analyzed using Prism 6 (Graph Pad), SPSS 15 (IBM), and Excel (Microsoft). Lamination data were analyzed using two-tailed χ2 test, while the other data, which followed a normal distribution, were analyzed using two-tailed unpaired Student’s t-test with or without Welch’s correction, depending on the results of variance tests (F-test). P < 0.05 was considered statistically significant.

Results
Cxcl12 is Expressed Postnatally in Layer V Pyramidal Neurons
Neocortical Cxcl12 expression was assessed in postnatal mice (P1–P84) using the Cxcl12fllox/− allele, in which GFP was expressed under the control of the endogenous Cxcl12 locus (GFP knockin mice; Ara et al. 2003). Cxcl12-GFP was expressed in the meninges, blood vessel endothelial cells, and layer V pyramidal neurons (Ara et al. 2003; Vogt et al. 2014) (Fig. 1a–f and Supplementary Fig. 2a–b), but not in PV+ or SST+ CINs (Supplementary Fig. 2c–d and d′–d″). While meningeal Cxcl12-GFP gradually decreased after P7, Cxcl12-GFP persisted in layer V pyramidal neurons (Vogt et al. 2014) (Fig. 1c–f). During this postnatal period, CINs migrate radially to specific cortical layers. We explored whether Cxcl12 expression by layer V pyramidal neurons regulated CIN radial migration. Cxcl12fllox/− mice, which carry the Cxcl12 conditional allele (Greenbaum et al. 2013), were crossed to Rbp4-Cre mice. Within the neocortex, Rbp4-Cre is specifically expressed in layer V pyramidal neurons (GENSAT). Rbp4-Cre activity was detected using the Ai14 reporter (Ai14fllox/−), which expresses tdTomato following Cre-mediated recombination (Madisen et al. 2010). Rbp4-Cre neocortical activity was first detected at E17.5 (Fig. 1a′–d′ and Supplementary Fig. 1b). In the somatosensory cortex, ~56% of Cxcl12-GFP+ neurons co-expressed tdTomato at P1, and this increased to ~75% after P7, suggesting that ~75% of Cxcl12-GFP+
layer V pyramidal neurons co-expressed Rbp4-Cre at P7 (Supplementary Fig. 1a–b).

Next, we examined CIN lamination using immunohistochemistry for SST at P7 and P14, and PV at P14. We found no differences in the lamination pattern of SST+ and PV+ CINs in the somatosensory cortex between Rbp4-Cre; Cxcl12GFP/+ (control) and Rbp4-Cre; Cxcl12GFP/lox/lox (Cxcl12 conditional knockout, termed Cxcl12 CKO hereafter) (Supplementary Fig. 1c–e). On the contrary, when we challenged Cxcl12 CKOs by transplanting E14.5 MGE (source of PV+ and SST+ CINs) labeled using Nkx2.1-Cre; Ai14flox/+ into P2 control and Cxcl12 CKO neocortex, we observed that Cxcl12 CKO had an increased fraction of the transplanted cells in layer II/III and a decreased fraction in layer V at 7 days post-transplantation (DPT7). Thus, Cxcl12 can regulate neocortical lamination of Nkx2.1-lineage CINs derived from transplanted MGE cells (Supplementary Fig. 1f–g).

CXCL12 Localizes on the Extracellular Surface of Pyramidal Neuron Cell Bodies, while CXCR4/7 are Present on CIN Axon Terminals in the mPFC

Next, we explored whether CXCL12 expression by layer V pyramidal neurons regulated other CIN properties. We focused on the mPFC, rather than other cortical areas, because after P14, CXCL12-GFP was greatly reduced in cortical areas other than the mPFC until P84 (Fig. 1a–e and Supplementary Fig. 2a–b). In the P14 mPFC, ~85% of CXCL12-GFP+ pyramidal neurons had reduced CXCL12 (Fig. 2a, a′, b, and b′), consistent with the fact that ~85% of CXCL12-GFP+ layer V pyramidal neurons co-expressed Rbp4-Cre.
Next, we investigated subcellular CXCL12 and CXCR4/7 expression in the postnatal mPFC. We found that most CXCL12 appeared around the extracellular surface or inside the cell bodies of layer V pyramidal neurons, while less CXCL12 was detected on the AIS [labeled by phospho-IκBα (pIκBα)] (Fazzari et al. 2010) and distal dendrites in layer I (Fig. 2c–d). Both CXCR4 and CXCR7 were found in the cell bodies and all of the assessed axon terminals of PV+ interneurons (Fig. 2e–e″ and Supplementary Fig. 3a–a″).

**CXCL12 Promotes Targeting of PV+ CIN Axons to Layer V Pyramidal Neurons in the mPFC**

We next studied targeting of PV+ interneuron axons using PV immunofluorescence and confocal imaging. PV+ axon terminal punctae encircled the cell bodies of CXCL12-GFP+ pyramidal neurons in control mPFCs (Fig. 3a, right panel). The number of perisomatic PV+ punctae was decreased ~28% in Cxcl12 CKOs (Fig. 3a–b and Supplementary Fig. 4a–c), providing evidence that CXCL12 promotes targeting of PV+ CIN axons to layer V pyramidal neurons in the mPFC.

**CXCL12 Enhances Inhibitory Perisomatic Synapses onto mPFC Layer V Pyramidal Neurons**

To determine whether the decreased axon targeting led to a reduction of inhibitory synapses onto layer V pyramidal neurons, we used immunofluorescence with the inhibitory presynaptic marker, glutamate decarboxylase 65 (GAD65) (Fazzari et al. 2010). Confocal z-stack images showed that Cxcl12 CKO had a ~31% reduction in the number of perisomatic GAD65+ punctae at P16 (Supplementary Fig. 5a–b). These results indicate that CXCL12 promotes the formation of inhibitory perisomatic synapses onto layer V pyramidal neurons. Furthermore,
CXCL12 Mediates Evoked IPSCs onto Layer V Pyramidal Neurons in the mPFC

To test if the reduction in inhibitory synapses resulted in altered feedforward inhibition onto Cxcl12 CKO pyramidal neurons, we compared evoked inhibitory currents in layer V pyramidal neurons within the mPFC of control and Cxcl12 CKO. To activate inhibitory interneurons, we transduced mPFC interneurons using an adeno-associated virus (AAV) vector encoding the D1d2b enhancer (Cho et al. 2015) driving channelrhodopsin2 (ChR2-eYFP) expression. We optogenetically-activated these interneurons while simultaneously recording inhibitory currents from layer V pyramidal somata innervated specifically by PV⁺ basket CINs (Huang et al. 2007), which were voltage-clamped at +10 mV. We delivered 40 Hz light flashes (to preferentially recruit PV⁺ FSIN outputs) across a high power field to optogenetically-evoke inhibitory currents (Cardin et al. 2009), and assay the ability of layer V microcircuits to generate high frequency inhibition. The amplitudes of optogenetically-evoked IPSCs onto the Cxcl12 CKO pyramidal neurons (n = 32) were significantly lower than IPSCs onto controls (n = 31) throughout a 40 Hz train (Fig. 3).

Layer V pyramidal neurons in the mPFC can be divided into at least two subtypes: thick-tufted, subcortically-projecting type A neurons, with prominent h-current, and thin-tufted, callosally-projecting type B neurons, which lack prominent h-current. (Gee et al. 2012). PV⁺ fast-spiking interneurons (FSINs) preferentially inhibit type A neurons, i.e., optogenetic stimulation of PV⁺ interneurons elicits more inhibitory current in type A than type B neurons, and the inhibitory connection probability is higher for FSINs-type A pairs than for FSINs-type B pairs (Lee et al. 2014). When we subdivided layer V pyramidal neurons into type A vs. type B neurons (using electrophysiological criteria), we found that optogenetically-evoked IPSCs were selectively compromised in type A neurons of Cxcl12 CKOs (n = 26) compared to controls (n = 28; Fig. 5b). By contrast, evoked IPSCs onto type B cells were similar across genotypes (control: n = 3; Cxcl12 CKO: n = 6; Fig. 5c). This represents an internal control that suggests the levels of ChR2 expression were not different between controls and Cxcl12 CKO mice. Similar to what was previously reported, in control mice we found that the IPSC amplitude in type A neurons was approximately double that in type B neurons (Lee et al. 2014) (Fig. 5b–c, black bars). Furthermore, we found that while all type A neurons were Cxcl12-GFP⁺, only ~55% of type B neurons had Cxcl12-GFP expression in both control and Cxcl12 CKO mice at P14-21. These results suggest that CXCL12 specifically promotes inhibition onto type A neurons.

To further explore whether this reduction in IPSCs might reflect decreased connectivity between FSINs and type A neurons, we made paired recordings from individual FSINs (identified by their electrophysiological properties) in current clamp while simultaneously recording from type A neurons in voltage clamp at +10 mV. Consistent with our previous study in which FSINs inhibited nearby type A neurons with a probability ~50% (Lee et al. 2014), we found that the connection probability of FSINs onto type A neurons was 47% (7/15 pairs) in control mice (Fig. 5d). We observed a reduced FSIN-type A neuron connection probability of 30% (7/23 pairs) in Cxcl12 CKO mice (Fig. 5d). Although it did not reach statistical significance, this 36% reduction in connection probability is consistent with the 36% reduction in IPSC amplitude we observed earlier. Finally, we did not observe differences in intrinsic properties for FSINs, type A neurons, or type B neurons, between Cxcl12 CKO mice and controls (FSINs, control: n = 17, Cxcl12 CKO: n = 27, Fig. 5e; type A, control: n = 68, Cxcl12 CKO: n = 60, Fig. 5f; type B, control: n = 16, Cxcl12 CKO: n = 12, Fig. 5g). Thus, the reduction in PV⁺ inhibitory synapses seems to selectively disrupt inhibition onto type A pyramidal neurons, without affecting connections onto type B neurons, or the intrinsic properties of pyramidal neurons or FSINs.
Discussion

Here, we report a novel regulatory mode of mPFC activity by CXCL12. We show that in the postnatal mouse mPFC, CXCL12 was predominantly expressed in layer V pyramidal neurons, and highly localized on their cell bodies. Importantly, CXCL12 promoted the specific innervation and synapse formation of CXCR4/7-expressing PV+ interneurons onto the somata, but not distal dendrites or AIS, of layer V pyramidal neurons. Furthermore, CXCL12 enhanced evoked IPSCs onto layer V pyramidal neurons. Thus, reduced CXCL12 expression specifically affected innervation by PV+ basket interneurons (Fig. 6, scheme). Given the role of mPFC activity in cognitive function, this study implies that defects in CXCL12-CXCR4/7 signaling could underlie some symptoms of neuropsychiatric disorders.

CXCL12 Regulates Synaptic Transmission and Neuronal Activity through Multiple Mechanisms

In addition to promoting cell migration, several lines of evidence suggest that CXCL12 mediates synaptic transmission and neuronal activity through a variety of mechanisms (Guyon 2014). First, there is in vitro evidence that CXCL12 promotes axon elongation and pathfinding from entorhinal cortical neurons to the dentate gyrus, and thus enhances excitatory synaptic formation in the dentate gyrus (Ohshima et al. 2008). This concept is supported by our in vivo finding that CXCL12 promotes axon targeting of PV+ basket CINs. Second, CXCL12 is localized in GABA+ synaptic vesicles, and GABAergic transmission is partially dependent on co-released CXCL12 in the adult dentate gyrus (Bhattacharyya et al. 2008). Furthermore,
Bhattacharyya et al. reported that CXCL12 treatment increased GABAergic transmission. Similarly, CXCL12 application enhanced inhibitory postsynaptic currents onto serotonin neurons in the rat dorsal raphe nucleus (Heinisch and Kirby 2010), and newly developing neurons induced by transient ischemia (Ardelt et al. 2013). Third, in cultured rat cortical neurons, CXCL12 inhibits NR2B expression, a subunit of N-methyl-D-aspartic acid (NMDA) receptors, through activating histone deacetylases (HDACs), and thus decreases NMDA-induced calcium responses (Nicolai et al. 2010). Fourth, in rat hippocampal neurons, CXCL12 activates the voltage-gated potassium channel Kv2.1 through altering its phosphorylation and plasma membrane localization, thereby enhancing Kv2.1 currents (Shepherd et al. 2012). Lastly, like CXCR4 and CXCR7, the GABAB receptors, GABAB1 and GABAB2, are G-protein-coupled receptors (GPCRs). It is hypothesized that these receptors may regulate synaptic currents by directly interacting through heterodimerization, or indirectly through activating common signaling pathways.
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Evidence that CXCL12 Regulates CIN Lamination

CXCL12 is well characterized as a chemoattractant for cell migration (Sanchez-Martin et al. 2013), including tangential migration of immature CINs (Stumm et al. 2003; Tiveron et al. 2006; Sanchez-Alcaniz et al. 2011; Wang et al. 2011). We postulated that CXCL12 may regulate CIN radial migration for several reasons, including its neonatal expression in layer V pyramidal neurons (Vogt et al. 2014) (Supplementary Fig. 1b). Although we did not observe a CIN lamination defect in Cxcl12 CKOs (Supplementary Fig. 1c–e), we did find abnormal CIN lamination using the MGE transplantation assay (Supplementary Fig. 1f–g). These discrepant results may be due to a few reasons. First, the transplanted cells were from E14.5 MGE cells and their response to the cortical environment of Cxcl12 CKOs might be different than the endogenous P2 CINs. Second, Rbp4-Cre may be expressed too late to remove sufficient Cxcl12. Indeed, at P1 only 56% of Cxcl12-GFP cells co-expressed Rbp4-Cre (Supplementary Fig. 1b), a stage when CINs have already migrated into the cortex (Bartolini et al. 2013). Consequently, a layer V-specific Cre that is expressed earlier may answer whether Cxcl12 regulates CIN radial migration.

Altered CXCL12-CXCR4/7 Signaling Might Contribute to Neuropsychiatric Disorders

Higher levels of cognitive control require gamma (30–80 Hz) oscillations, which is dependent on PV+ basket CIN inhibitory inputs onto pyramidal neurons. As a result, dysfunction of PV+ CINs is likely to be deleterious for cognition (Lewis et al. 2012). Consistently, defects in FFC PV+ interneuron may be a risk factor for schizophrenia (Volk and Lewis 2014). CXCL12-CXCR4/7 signaling defects, based on abnormal Cxcr4/7 expression in the FFC, are postulated to contribute to CIN dysfunction in schizophrenia (Volk et al. 2015). Moreover, Cxcr2 expression is decreased in the olfactory neuronal layers of schizophrenia patients (Toritsuka et al. 2013). CXCL12-CXCR4 signaling is implicated in CIN migration deficits in the mouse models of 22q11 deletion syndrome (22q11DS), a chromosome disorder frequently associated with bipolar disorder and schizophrenia (Meechan et al. 2012; Toritsuka et al. 2013). Furthermore, Cxcr4 depletion in PV+ CINs increases motor stereotypy, a behavior found in autism and schizophrenia (Cash-Padgett et al. 2016). These studies, taken together with our finding that CXCL12 promotes IPSCs onto layer V pyramidal neurons in the mPFC, provide substantial evidence that CXCL12-CXCR4/7 signaling regulates mPFC function, and disruption of this signaling may contribute to neuropsychiatric disorders.

Author Contributions


Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org.

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Notes

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References


