Neurochem Res (2017) 42:1279–1287
DOI 10.1007/s11064-016-2169-5

OVERVIEW

An Overview of the Mechanisms of Abnormal GABAergic Interneuronal Cortical Migration Associated with Prenatal Ethanol Exposure

Botros B. Shenoda[1,2]

Received: 27 September 2016 / Revised: 25 December 2016 / Accepted: 27 December 2016 / Published online: 3 February 2017

Abstract GABAergic Interneuronal migration constitutes an essential process during corticogenesis. Derived from progenitor cells located in the proliferative zones of the ventral telencephalon, newly generated GABAergic Interneuron migrate to their cortical destinations. Cortical dysfunction associated with defects in neuronal migration results in severe developmental consequences. There is growing evidence linking prenatal ethanol exposure to abnormal GABAergic interneuronal migration and subsequent cortical dysfunction. Investigating the pathophysiological mechanisms behind disrupted GABAergic interneuronal migration encountered with prenatal alcohol exposure is crucial for understanding and managing fetal alcohol spectrum disorders. This review explores the molecular pathways regulating GABAergic interneuronal cortical migration that might be altered by prenatal ethanol exposure thus opening new avenues for further research in this topic.

Keywords GABAergic Interneurons · GABA · Prenatal Ethanol Exposure · Fetal Alcohol Spectrum Disorders

✉ Botros B. Shenoda
bbs39@drexel.edu

[1] Pharmacology and Physiology, Drexel University College of Medicine, 245 North 15th Street, Mail Stop 488, Philadelphia, PA 19102, USA

[2] Department of Pharmacology, Assiut University College of Medicine, Assiut, Egypt

Introduction

Proper development and functioning of the neocortex critically depends on the coordinated production and migration of excitatory and inhibitory neurons [1–3]. Representing 10–25% of total number of cortical neurons, GABAergic interneurons expressing parvalbumin (PV^+) and somatostatin (SOM^+) are the main source of inhibition. GABAergic interneurons control the activity of pyramidal neurons [4, 5] and play a crucial role in shaping cortical maturation at various stages of development [4]. Disruptions of cortical GABAergic circuitry at several stages of development contribute to various neurodevelopmental disorders [6] including autism [7, 8], epilepsy [1, 9, 10] and schizophrenia [8, 11].

During in utero development, GABAergic interneuronal system is vulnerable to several agents including prenatal ethanol exposure [12–14]. Prenatal ethanol exposure can alter the migration of GABAergic interneurons [14–16] which might represent a potential mechanism by which prenatal ethanol exposure can lead to the postnatal behavioral and cognitive dysfunctions encountered with Fetal Alcohol Spectrum Disorders (FASDs). The exact molecular mechanisms by which prenatal ethanol exposure can affect the GABAergic interneurons during their cortical migration are still unclear. This article discusses different molecular mechanisms by which prenatal ethanol exposure can alter GABAergic interneuronal cortical migration.

Embryology of GABAergic Interneurons

There are three distinct classes of GABAergic interneurons in the rodent neocortex according to the molecular markers they express: PV^+, somatostatin (SOM^+), and

5-hydroxytryptamine 3A receptor positive (5-HT3AR$^+$) cells [17, 18]. The vast majority of murine GABAergic interneurons in the neocortex are derived from the subpallium [19], in which PV$^+$ and SOM$^+$ cells originate from medial ganglionic eminence (MGE) [19] whereas most 5-HT3AR$^+$ cells originate from the caudal ganglionic eminence (CGE) [18] and preoptic area (POA) [20, 21].

MGE is the primary source of GABAergic cortical interneurons, accounting for 50–60% of cortical GABAergic interneurons [22, 23]. Following a tangential migration pattern, inhibitory GABAergic interneurons migrate throughout the developing telencephalon to reach the cortex [24, 25]. Migratory pathways followed by CGE- and POA-derived interneurons to reach their cortical destination are largely distinct from those used by MGE-derived interneurons. Whereas MGE-derived cells migrate toward the rostrocaudal regions of the neocortex [26], CGE-derived and POA-derived cells primarily migrate toward the caudal pole [27, 28], and rostral region of the neocortex [20] respectively. This suggests that interneurons born in the CGE and POA respond, at least in part, to a different set of guidance cues [29].The migration of GABAergic interneurons generated from MGE commences around embryonic day 9.5 (E9.5) with a peak at E13.5 -E16.5 [30] followed by the migration of neurons generated in other areas. GABAergic interneurons start reaching the cortex by E14. Upon reaching the cortex, GABAergic interneurons integrate themselves in an "inside-out" pattern where earlier coming older interneurons lie deeper to the newly coming younger ones [31–33]. MGE-derived interneurons are expected to reach their adult brain-like maturation by postnatal days 16–21 [31]. In humans, neuronal migration takes place predominantly between 12 and 20 weeks of gestation [34].

The migration of neurons from the subpallial origins to the cerebral cortex is a complicated process involving the activity of various motogens, chemotactic factors, transcription factors, as well as neurotransmitters [35, 36]. Chemical cues such as semaphorines and ephrins are expressed as gradients in the brain and serve as attracting or repelling signals for migrating cells [37, 38]. Several prenatal factors including stress [39] and pharmacological agents [40] can disrupt the GABAergic interneuronal system. This review will only focus on the effect of prenatal ethanol exposure on GABAergic interneuronal migration.

Fetal Alcohol Spectrum Disorders (FASDs)

Prenatal ethanol exposure results in neurodevelopmental deficits and lifelong disability in offspring [41]. FASDs, which encompasses fetal alcohol syndrome, alcohol-related birth defects, and alcohol-related neurodevelopmental disorder, are estimated to affect at least 1% of all births in the United States [42]. In pregnant women, the prevalence of any alcohol use and binge drinking in the past 30 days was 10.2 and 3.1%, respectively [43]. Animal studies showed that binge-like drinking patterns in pregnant females are particularly dangerous to fetal brain development, even if the total amount of ethanol consumed is less than that consumed in a more continuous drinking pattern [44]. Children with FASDs are often described as hyperactive, distractible, impulsive, with short attention spans, impaired cognitive functions and learning difficulties [45, 46]. Epidemiological studies have suggested that alcohol use problem of parents might be related to the hyperactivity or inattention symptoms in their children [47]. Prenatal ethanol exposure in experimental animals results in hyperactivity [48] and impaired executive functions [49]. The mechanism by which prenatal ethanol exposure contribexposure contributes to such myriad of symptoms is not fully understood.

Prenatal Ethanol Exposure Impacts GABAergic Interneuron Cortical Migration

Prenatal ethanol exposure results in profound effects on cortical neuronal migration [50, 51]. Several studies have suggested that abnormal migration of GABAergic cortical interneurons is involved in FASDs (Table 1). Monkeys exposed prenatally to ethanol once per week for 4 or 24 weeks starting from the first week of gestation showed reduced GABA expressing neurons in somatosensory cortex [52]. In guinea pigs, ethanol administered through almost the whole pregnancy (from day 2 until the day before delivery) was associated with reduced expression of glutamic acid decarboxylase (GAD), the protein marker for GABAergic neurons, in layers II–III of somatosensory cortex [53]. The involvement of superficial cortical layers (layers II–III) suggested that chronic prenatal ethanol treatment seems to affect mostly the late-generated GABAergic cells [16]. In rats, the offspring of pregnant females exposed to ethanol over the whole gestation showed 45% fewer PV$^+$ neurons in the anterior cingulate cortex [54]. Over all, it has been suggested that chronic prenatal ethanol consumption may result in reduced GABAergic cell density in specific cortical regions.

A different set of experiments came up with different conclusions. Prenatal ethanol exposure for 14 days (E0.5–E14.5) in mice resulted in increased density of GABAergic interneurons in all cortical layers of medial prefrontal cortex (mPFC) at E14.5 which was proposed to be due to increased tangential migration of GABAergic interneurons [14]. Sukorput et al. showed that gestational ethanol exposure during the peak of tangential migration

Table 1 Effect of prenatal ethanol exposure on the migration of GABAergic interneuron migration in experimental animals

Species	Prenatal ethanol exposure	Effect on GABAergic interneurons	Brain region affected	References
Guinea pigs	Chronic, throughout gestation (4 g/kg/day)	Decrease in the number of GAD-immunopositive neurons	Layers II/III of somatosensory cortex	[53]
Monkeys	Intermittent (once per week) for 4 or 24 weeks starting from the first week of gestation	Reduced GABA expressing neurons	Somatosensory cortex	[52]
Rats	Chronic ethanol over from G0–G21: ethanol comprised 35% of the total calories	Fewer PV^+ neurons	Anterior cingulate cortex	[54]
Mice	Ethanol exposure for 14 days (E0.5–E14.5) (1 or 2% (w/v)	Increased density of GABAergic interneurons	All cortical layers of medial prefrontal cortex	[14]
Mice	Acute binge like ethanol exposure (E13.5–E16.5)	Increased density of GABAergic interneurons	Layer V of mPFC	[15]
Mice	Ethanol exposure (E11 and E14)	Abnormal distribution of GABA expressing cells	Somatosensory cortex	[16]

of GABAergic interneurons (E13.5–E16.5 in mice corresponding to mid-first trimester in humans) resulted in increased density of GABAergic interneurons in layer V of mPFC. This was associated with significant electrophysiological and behavioral consequences. Mice exposed prenatally to ethanol during such critical period showed dysregulated neuronal excitability in the form of increased GABA-mediated inhibitory drive over pyramidal neurons. Behavioral deficits in the form of hyperactivity and long-term PFC-dependent executive dysfunction were also observed in these mice [15]. In another study done in mice, ethanol exposure between E11 and E14 produced mosaic abnormal distribution of GABA expressing cells in the somatosensory cortex at P10 and a tendency, though non-significant, for increased GABA expressing cells at P180 [16] which may suggest that alcohol may also alter cortical organization of already migrated GABAergic interneurons.

In summary, it seems that the type of exposure (chronic versus acute) could account for the differences observed in various models [16]. However, the mechanisms by which prenatal ethanol exposure can influence the programmed GABAergic migratory process is still poorly understood. This review proposes that ethanol can alter one or more of the factors regulating GABAergic interneuronal migration process which include neurotransmitters such GABA and dopamine, epigenetic and trophic factors.

GABAergic Pathway of Ethanol-Induced Abnormal GABAergic Interneuron Migration

There are two main categories of GABA receptors, the ionotropic GABA receptors, $GABA_A$ and $GABA_c$, and the metabotropic $GABA_B$ receptors. Activation of $GABA_A$ receptors causes the opening of a channel formed at the center of the receptor complex, allowing the diffusion of chloride ions across the cell membrane [55]. $GABA_B$ receptors are coupled to K^+ and/or Ca^{2+} channels via a G-protein mediated pathway or in a membrane delimited manner [56, 57]. There is clear evidence for the involvement of $GABA_A$ and $GABA_B$ receptors in neurodevelopmental disorders [57, 58]. Migration of GABAergic interneurons are largely controlled by GABAergic signaling [59, 60]. Reducing ambient GABA activity results in improper migration process with the accumulation of interneurons at the corticostriatal junction [61]. Migrating interneurons express $GABA_A$ and $GABA_B$ receptors, and their GABA responsiveness increases with the progression of the migration process [62]. In line with this, diazepam, a benzodiazepine which augments the activation of $GABA_A$ receptors, substantially increased the motility rate of migrating GABAergic interneurons [63]. The tangentially migrating GABAergic interneurons in the marginal zone of neonatal mice are also impaired after inhibition of $GABA_A$ receptors in vivo [63] demonstrating the important influence of endogenous GABA on the tangential migration.

It was suggested that tangentially migrating GABAergic neurons are themselves a source for GABA [59] which might constitute a promigratory signal autoactivating GABA receptors [64]. It has been shown that GABA can affect the migration process in a dose and receptor dependent manner and the differential role of GABA receptors on neuronal migration might differ according to type of targeted neuron [64–68]. Acting on GABAergic interneurons, GABA can have a selective action at individual layers, being able to generate action potentials in layers V–VI but not in layers II–III [69]. Overall, GABA seems to affect the migration and function of GABAergic interneurons.

GABAergic signaling is a well-known target of alcohol. Alcohol potentiates GABA-mediated signaling through different mechanisms including increasing GABA release and increasing $GABA_A$ receptor activity [70–72]. It has been

proposed that alcohol can increase the tangential migration by augmenting GABA signaling. In utero ethanol exposure elevated the ambient level of GABA and increased the sensitivity of MGE-derived cells to GABA promoting premature migration [14]. As different neurons respond differently to GABA, ethanol mimicking GABA action through the activation of $GABA_A$ could target preferentially the neurons that are more sensitive to GABA mediated depolarization i.e. layer V which might explain why prenatal ethanol exposure increased the migration to this particular cortical layer [15]. However, neurons less sensitive to $GABA_A$-mediated depolarization i.e. layers II–III might be modulated by alcohol through metabotropic GABA receptors producing an opposite effect on migration [53].

$GABA_B$ receptors have been identified in the developing cerebral cortex [73] with particularly high density in tangentially orientated neurons in the lower intermediate zone (LIZ) of the cortex [74]. Several lines of evidence suggest that $GABA_B$ receptors activation might play an important role in cortical development. Pharmacological studies indicate that $GABA_B$ receptors activation stimulates migration of neurons in immature cortical regions [75]. Blockade of $GABA_B$ receptors with a specific antagonist, CGP52432, resulted in a concentration-dependent accumulation of these tangentially migrating neurons in the ventricular/sub-ventricular zones of the cortex and fewer cells were observed in the cortical plate/marginal zone and LIZ indicating an important modulatory role of $GABA_B$ receptors in the migration of cortical interneurons [76]. The role of $GABA_B$ receptors in mediating effect of prenatal ethanol exposure on GABAergic interneuronal migration is to be identified.

Dopaminergic Pathway of Alcohol-Induced Abnormal GABAergic Interneuron Migration

Another possible mechanism by which ethanol can influence the migration of GABAergic interneuron is modulation of dopaminergic transmission. Dopaminergic signaling has been shown to modulate the migration of GABAergic interneurons which express D_1 and D_2 receptors. D_1 receptor normally functions to promote cortical interneuron migration while D_2 receptor knockouts possess increased migratory capability [77]. The dopaminergic system is known to be significantly influenced by ethanol [78, 79] including prenatal ethanol exposure [80]. Ethanol enhanced dopaminergic signaling mediated through D_1 [81]. Prenatal ethanol exposure led to the persistent abnormal synaptic plasticity via disturbing the balance between D_1 and D_2 mediated signaling, allowing more D_1 over D_2 activity [82]. Theoretically, altered dopaminergic signaling may provide a potential mechanism by which ethanol can influence the GABAergic interneurons migration. As dopamine receptors are widely distributed in the central nervous system, it might be difficult to use pharmacological agents to understand their contribution to prenatal ethanol-induced abnormal interneuronal migration. Selective knock down of dopamine receptors in migrating GABAergic neurons might be a more useful strategy in this context.

Prenatal Alcohol Exposure and Epigenetic Factors

Epigenetic regulation of gene expression has been shown to play a pivotal role in developmental processes. Recent studies have demonstrated epigenetic alterations in the etiology of FASDs [83]. Hyperactivity has been shown in offsprings of male mice exposed to preconception ethanol which may refer to the involvement of epigenetic factors [84]. Prenatal alcohol exposure caused altered DNA methylation pattern [84–86] and changed the expression of key epigenomic regulators e.g. DNA methyltransferase 1 (DNMT1), DNMT3a, and methyl CpG binding protein 2 (MeCP2) [87]. MeCP2 is a transcriptional regulator that binds to methylated DNA. MeCP2 regulates the expression of Brain-Derived Neurotrophic Factor (BDNF). BDNF is known to influence GABAergic interneuronal migration (see below), thus MeCP2 might be involved in the regulation of GABAergic interneuron maturation indirectly by regulating BDNF [88, 89]. MeCP2 regulates the transcription of DLX5, a transcription factor critical for the migration and maturation of PV^+ interneurons [90]. Thus, it is possible that ethanol influences the GABAergic interneuron migration through an altered DNA methylation-MeCP2-BDNF/DLX5 pathway.

MicoRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by binding to the 3′ untranslated region (3′UTR) of mRNA leading to its breakdown or translational repression. It has been shown that dysregulated miRNA mediated activity significantly influence GABAergic neuronal development and migration [91]. In vivo and in vitro studies showed that prenatal alcohol exposure resulted in several miRNA alterations both in the mother and the developing fetus [92, 93]. Alterations in miRNA expression were also found in primary neuronal cultures from the cortex of mice (E15) following chronic intermittent ethanol exposure and withdrawal [94]. Rats exposed to prenatal ethanol show altered miRNA expression in amygdala and striatum [95]. miRNAs have been implicated in the development of brain damage in response to prenatal ethanol exposure [96]. Experimental evidence indicates that the expression of miRNAs is altered following exposure to alcohol during development, and this may be one of the mechanisms underlying alcohol-related teratogenesis [97, 98]. miRNAs disrupted by ethanol exposure

during critical periods, can affect neuronal migration by regulating several biological pathways regulating interneuronal migration such as BDNF [92].

Prenatal Alcohol Exposure and Neurotrophic Factors

The guidance of GABAergic interneurons from the subpallium to the developing cortex relies on multiple factors [99, 100]. Several neuronal growth factors such as Hepatocyte Growth Factor (HGF) [101], BDNF [102] and glial cell line-derived neurotrophic factor (GDNF) [103, 104] regulate the migration of cortical GABAergic interneurons. By stimulating TrkB-mediated pathways, BDNF strongly influences tangential interneuronal migration in the developing nervous system [102]. GDNF, through its receptor, GFRalpha, mediated signaling has been implicated in the development of GABAergic interneurons. GFRalpha signaling guides the development of a subset of PV^+ expressing GABAergic interneurons in specific cortical regions [103]. HGF serves as an important molecular cue for the dispersion of ganglionic eminence-generated interneurons to their appropriate locations in the dorsal telencephalon. HGF receptor, MET, expression was evident in a polarized pattern on migrating cells from GE explants and its exogenous ligand disrupts normal cell migration [101].

Prenatal alcohol exposure has been found to influence the expression or the levels of these factors [105, 106] which may impact GABAergic interneuron migration. However, the effect of ethanol on the expression of these growth factors and their receptors is rather complex and there is clear deficit in our knowledge regarding their role in mediating the effects of prenatal alcohol exposure. Although adult mice showed reduced BDNF in response to prenatal ethanol exposure, neonatal rats that were exposed to ethanol throughout gestation [105] did not show change in BDNF levels in their cortex [107]. Other studies showed also that ethanol may reduce TrkB expression [108] thus indirectly influencing BDNF-mediated effects. The effect of alcohol on GDNF is also poorly understood. Alcohol increased expression of GDNF in ventral tegmental area [109] and cortex [105]. It reduced the expression of GDNF mRNA expression in neuronal progenitor cells generated from telencephalic tissue derived from E15–17 [106].

Currently, we cannot conclusively establish which of the different factors mentioned above (neurotransmitters, epigenetic regulators or trophic factors) and possibly others, are the major players linking prenatal alcohol exposure to abnormal GABAergic interneuronal migration (Fig. 1). The most probable is a complex interplay, with some of these factors being regulated in a maladaptive manner resulting in FASDs [16]. Despite the accumulating evidence about the involvement of GABAergic interneurons in the FASDs,

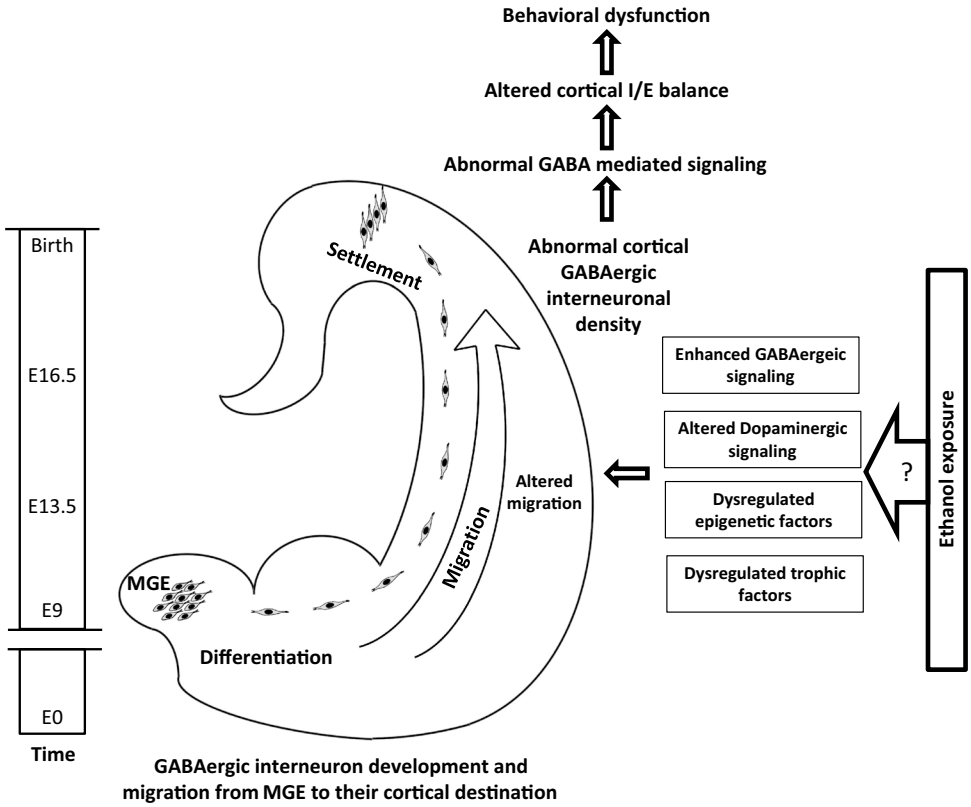

Fig. 1 Factors that might be involved in mediating the effect of prenatal ethanol exposure on GABAergic interneuronal migration

it has been shown that prenatal exposure to alcohol during early pregnancy (E0–E8) i.e. before the critical period of tangential migration can still produce persistent behavioral dysfunction [110], which suggests the multifactorial nature of FASDs. In addition, the prolonged inhibitory effect related to ethanol can develop due to enhanced postsynaptic GABA signaling [111], which renders the functional and electrophysiological impact of ethanol on GABAergic signaling more complex.

Conclusion and Future Directions

Prenatal ethanol exposure affects the cortical migration of GABAergic interneurons which impacts cortical function and development. Understanding the mechanisms by which prenatal alcohol exposure can influence GABAergic interneuronal migration process is not an easy task. First, the process of GABAergic interneuronal migration is a complex phenomenon controlled by precisely orchestrated pathways and several important aspects of which are not fully understand. Second, alcohol can affect several molecular pathways and neurotransmitter systems on almost every neuronal cell-type. Although alcohol-free pregnancy is the best choice for the mother and the newborn, it might be difficult to achieve, this necessitates clear understanding of the mechanism by which alcohol can cause a permanent neuroanatomical and functional impairment for the possible generation of a safe "antidote" that might be successful in preventing or at least minimizing ethanol's teratogenic effects.

Acknowledgements I would like to express my sincere thanks and appreciation to Dr. Seena Ajit, Drexel University College of Medicine for her continuous support and encouragement. I acknowledge the help of Diana Winters in editing the review. The author is a recipient of the Fulbright Foreign Student Program fellowship funded by the US Department of State, Bureau of Educational and Cultural Affairs and Dean's Fellowship for Excellence in Collaborative or Themed Research, Graduate School of Biomedical Sciences and Professional Studies, Drexel University.

Compliance with Ethical Standards

Conflict of interest The author has declared that no conflict of interest exists.

References

1. Powell EM, Campbell DB, Stanwood GD, Davis C, Noebels JL, Levitt P (2003) Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. J Neurosci 23(2):622–631
2. Bartolini G, Ciceri G, Marin O (2013) Integration of GABAergic interneurons into cortical cell assemblies: lessons from embryos and adults. Neuron 79(5):849–864. doi:10.1016/j.neuron.2013.08.014
3. Lodato S, Rouaux C, Quast KB, Jantrachotechatchawan C, Studer M, Hensch TK, Arlotta P (2011) Excitatory projection neuron subtypes control the distribution of local inhibitory interneurons in the cerebral cortex. Neuron 69(4):763–779. doi:10.1016/j.neuron.2011.01.015
4. Le Magueresse C, Monyer H (2013) GABAergic interneurons shape the functional maturation of the cortex. Neuron 77(3):388–405. doi:10.1016/j.neuron.2013.01.011
5. Varju P, Katarova Z, Madarasz E, Szabo G (2001) GABA signalling during development: new data and old questions. Cell Tissue Res 305(2):239–246
6. Rossignol E (2011) Genetics and function of neocortical GABAergic interneurons in neurodevelopmental disorders. Neural Plast 2011:649325. doi:10.1155/2011/649325
7. Reiner O, Karzbrun E, Kshirsagar A, Kaibuchi K (2016) Regulation of neuronal migration, an emerging topic in autism spectrum disorders. J Neurochem 136(3):440–456. doi:10.1111/jnc.13403
8. Lewis DA (2000) GABAergic local circuit neurons and prefrontal cortical dysfunction in schizophrenia. Brain Res Brain Res Rev 31(2–3):270–276
9. Guerrini R, Dobyns WB, Barkovich AJ (2008) Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options. Trends Neurosci 31(3):154–162. doi:10.1016/j.tins.2007.12.004
10. Guerrini R, Parrini E (2010) Neuronal migration disorders. Neurobiol Dis 38(2):154–166. doi:10.1016/j.nbd.2009.02.008
11. Lewis DA, Curley AA, Glausier JR, Volk DW (2012) Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci 35(1):57–67. doi:10.1016/j.tins.2011.10.004
12. Kato M, Dobyns WB (2003) Lissencephaly and the molecular basis of neuronal migration. Hum Mol Genet 12 Spec No 1:R89–R96
13. Crandall JE, Hackett HE, Tobet SA, Kosofsky BE, Bhide PG (2004) Cocaine exposure decreases GABA neuron migration from the ganglionic eminence to the cerebral cortex in embryonic mice. Cereb Cortex 14(6):665–675. doi:10.1093/cercor/bhh027
14. Cuzon VC, Yeh PW, Yanagawa Y, Obata K, Yeh HH (2008) Ethanol consumption during early pregnancy alters the disposition of tangentially migrating GABAergic interneurons in the fetal cortex. J Neurosci 28(8):1854–1864. doi:10.1523/JNEUROSCI.5110-07.2008
15. Skorput AG, Gupta VP, Yeh PW, Yeh HH (2015) Persistent interneuronopathy in the prefrontal cortex of young adult Offspring exposed to ethanol in utero. J Neurosci 35(31):10977–10988. doi:10.1523/JNEUROSCI.1462-15.2015
16. Isayama RN, Leite PE, Lima JP, Uziel D, Yamasaki EN (2009) Impact of ethanol on the developing GABAergic system. Anat Rec (Hoboken) 292 (12):1922–1939. doi:10.1002/ar.20966
17. Kawaguchi Y, Kubota Y (1997) GABAergic cell subtypes and their synaptic connections in rat frontal cortex. Cereb Cortex 7(6):476–486
18. Lee S, Hjerling-Leffler J, Zagha E, Fishell G, Rudy B (2010) The largest group of superficial neocortical GABAergic interneurons expresses ionotropic serotonin receptors. J Neurosci 30(50):16796–16808. doi:10.1523/JNEUROSCI.1869-10.2010
19. Fogarty M, Grist M, Gelman D, Marin O, Pachnis V, Kessaris N (2007) Spatial genetic patterning of the embryonic neuroepithelium generates GABAergic interneuron diversity in the adult cortex. J Neurosci 27(41):10935–10946. doi:10.1523/JNEUROSCI.1629-07.2007

20. Gelman DM, Martini FJ, Nobrega-Pereira S, Pierani A, Kessaris N, Marin O (2009) The embryonic preoptic area is a novel source of cortical GABAergic interneurons. J Neurosci 29(29):9380–9389. doi:10.1523/JNEUROSCI.0604-09.2009
21. Gelman DM, Marin O (2010) Generation of interneuron diversity in the mouse cerebral cortex. Eur J Neurosci 31(12):2136–2141. doi:10.1111/j.1460-9568.2010.07267.x
22. Wonders CP, Anderson SA (2006) The origin and specification of cortical interneurons. Nat Rev Neurosci 7(9):687–696. doi:10.1038/nrn1954
23. Welagen J, Anderson S (2011) Origins of neocortical interneurons in mice. Dev Neurobiol 71(1):10–17. doi:10.1002/dneu.20857
24. de Carlos JA, Lopez-Mascaraque L, Valverde F (1996) Dynamics of cell migration from the lateral ganglionic eminence in the rat. J Neurosci 16(19):6146–6156
25. Marin O (2013) Cellular and molecular mechanisms controlling the migration of neocortical interneurons. Eur J Neurosci 38(1):2019–2029. doi:10.1111/ejn.12225
26. Wichterle H, Turnbull DH, Nery S, Fishell G, Alvarez-Buylla A (2001) In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. Development 128(19):3759–3771
27. Yozu M, Tabata H, Nakajima K (2005) The caudal migratory stream: a novel migratory stream of interneurons derived from the caudal ganglionic eminence in the developing mouse forebrain. J Neurosci 25(31):7268–7277. doi:10.1523/JNEUROSCI.2072-05.2005
28. Rubin AN, Alfonsi F, Humphreys MP, Choi CK, Rocha SF, Kessaris N (2010) The germinal zones of the basal ganglia but not the septum generate GABAergic interneurons for the cortex. J Neurosci 30(36):12050–12062. doi:10.1523/JNEUROSCI.6178-09.2010
29. Tanaka DH, Nakajima K (2012) Migratory pathways of GABAergic interneurons when they enter the neocortex. Eur J Neurosci 35(11):1655–1660. doi:10.1111/j.1460-9568.2012.08111.x
30. Miyoshi G, Butt SJ, Takebayashi H, Fishell G (2007) Physiologically distinct temporal cohorts of cortical interneurons arise from telencephalic Olig2-expressing precursors. J Neurosci 27(29):7786–7798. doi:10.1523/JNEUROSCI.1807-07.2007
31. Del Rio JA, Soriano E, Ferrer I (1992) Development of GABA-immunoreactivity in the neocortex of the mouse. J Comp Neurol 326(4):501–526. doi:10.1002/cne.903260403
32. Rymar VV, Sadikot AF (2007) Laminar fate of cortical GABAergic interneurons is dependent on both birthdate and phenotype. J Comp Neurol 501(3):369–380. doi:10.1002/cne.21250
33. Faux C, Rakic S, Andrews W, Britto JM (2012) Neurons on the move: migration and lamination of cortical interneurons. Neurosignals 20(3):168–189. doi:10.1159/000334489
34. Liu JS (2011) Molecular genetics of neuronal migration disorders. Curr Neurol Neurosci Rep 11(2):171–178. doi:10.1007/s11910-010-0176-5
35. Faux C, Rakic S, Andrews W, Yanagawa Y, Obata K, Parnavelas JG (2010) Differential gene expression in migrating cortical interneurons during mouse forebrain development. J Comp Neurol 518(8):1232–1248. doi:10.1002/cne.22271
36. Kelsom C, Lu W (2013) Development and specification of GABAergic cortical interneurons. Cell Biosci 3(1):19. doi:10.1186/2045-3701-3-19
37. Bagnard D, Vaillant C, Khuth ST, Dufay N, Lohrum M, Puschel AW, Belin MF, Bolz J, Thomasset N (2001) Semaphorin 3A-vascular endothelial growth factor-165 balance mediates migration and apoptosis of neural progenitor cells by the recruitment of shared receptor. J Neurosci 21(10):3332–3341
38. Senturk A, Pfennig S, Weiss A, Burk K, Acker-Palmer A (2011) Ephrin Bs are essential components of the reelin pathway to regulate neuronal migration. Nature 472(7343):356–360. doi:10.1038/nature09874
39. Lussier SJ, Stevens HE (2016) Delays in GABAergic interneuron development and behavioral inhibition after prenatal stress. Dev Neurobiol. doi:10.1002/dneu.22376
40. Manent JB, Jorquera I, Mazzucchelli I, Depaulis A, Perucca E, Ben-Ari Y, Represa A (2007) Fetal exposure to GABA-acting antiepileptic drugs generates hippocampal and cortical dysplasias. Epilepsia 48(4):684–693. doi:10.1111/j.1528-1167.2007.01056.x
41. Naimi TS, Lipscomb LE, Brewer RD, Gilbert BC (2003) Binge drinking in the preconception period and the risk of unintended pregnancy: implications for women and their children. Pediatrics 111(5 Pt 2):1136–1141
42. May PA, Gossage JP (2001) Estimating the prevalence of fetal alcohol syndrome. A summary. Alcohol Res Health 25(3):159–167
43. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D (2015) Alcohol use and binge drinking among women of childbearing age - United States, 2011–2013. MMWR Morb Mortal Wkly Rep 64(37):1042–1046. doi:10.15585/mmwr.mm6437a3
44. Maier SE, West JR (2001) Drinking patterns and alcohol-related birth defects. Alcohol Res Health 25(3):168–174
45. Peadon E, Elliott EJ (2010) Distinguishing between attention-deficit hyperactivity and fetal alcohol spectrum disorders in children: clinical guidelines. Neuropsychiatr Dis Treat 6:509–515
46. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN (2007) Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 119(3):e733–e741. doi:10.1542/peds.2006-1606
47. Knopik VS, Sparrow EP, Madden PA, Bucholz KK, Hudziak JJ, Reich W, Slutske WS, Grant JD, McLaughlin TL, Todorov A, Todd RD, Heath AC (2005) Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a female twin study. Psychol Med 35(5):625–635
48. Schneider ML, Moore CF, Adkins MM (2011) The effects of prenatal alcohol exposure on behavior: rodent and primate studies. Neuropsychol Rev 21(2):186–203. doi:10.1007/s11065-011-9168-8
49. Marquardt K, Sigdel R, Caldwell K, Brigman JL (2014) Prenatal ethanol exposure impairs executive function in mice into adulthood. Alcohol Clin Exp Res 38(12):2962–2968. doi:10.1111/acer.12577
50. Miller MW (1993) Migration of cortical neurons is altered by gestational exposure to ethanol. Alcohol Clin Exp Res 17(2):304–314
51. Miller MW (1986) Effects of alcohol on the generation and migration of cerebral cortical neurons. Science 233(4770):1308–1311
52. Miller MW (2006) Effect of prenatal exposure to ethanol on glutamate and GABA immunoreactivity in macaque somatosensory and motor cortices: critical timing of exposure. Neuroscience 138(1):97–107. doi:10.1016/j.neuroscience.2005.10.060
53. Bailey CD, Brien JF, Reynolds JN (2004) Chronic prenatal ethanol exposure alters the proportion of GABAergic neurons in layers II/III of the adult guinea pig somatosensory cortex. Neurotoxicol Teratol 26(1):59–63. doi:10.1016/j.ntt.2003.08.002
54. Moore DB, Quintero MA, Ruygrok AC, Walker DW, Heaton MB (1998) Prenatal ethanol exposure reduces parvalbumin-immunoreactive GABAergic neuronal number in the adult rat cingulate cortex. Neurosci Lett 249(1):25–28
55. Knoflach F, Hernandez MC, Bertrand D (2016) GABAA receptor-mediated neurotransmission: not so simple after all. Biochem Pharmacol 115:10–17. doi:10.1016/j.bcp.2016.03.014

56. Misgeld U, Bijak M, Jarolimek W (1995) A physiological role for GABAB receptors and the effects of baclofen in the mammalian central nervous system. Prog Neurobiol 46(4):423–462
57. Wu C, Sun D (2015) GABA receptors in brain development, function, and injury. Metab Brain Dis 30(2):367–379. doi:10.1007/s11011-014-9560-1
58. Braat S, Kooy RF (2015) The GABAA receptor as a therapeutic target for neurodevelopmental disorders. Neuron 86(5):1119–1130. doi:10.1016/j.neuron.2015.03.042
59. Manent JB, Demarque M, Jorquera I, Pellegrino C, Ben-Ari Y, Aniksztejn L, Represa A (2005) A noncanonical release of GABA and glutamate modulates neuronal migration. J Neurosci 25(19):4755–4765. doi:10.1523/JNEUROSCI.0553-05.2005
60. Smith KM, Maragnoli ME, Phull PM, Tran KM, Choubey L, Vaccarino FM (2014) Fgfr1 inactivation in the mouse telencephalon results in impaired maturation of interneurons expressing parvalbumin. PLoS ONE 9(8):e103696. doi:10.1371/journal.pone.0103696
61. Cuzon VC, Yeh PW, Cheng Q, Yeh HH (2006) Ambient GABA promotes cortical entry of tangentially migrating cells derived from the medial ganglionic eminence. Cereb Cortex 16(10):1377–1388. doi:10.1093/cercor/bhj084
62. Cuzon Carlson VC, Yeh HH (2011) GABAA receptor subunit profiles of tangentially migrating neurons derived from the medial ganglionic eminence. Cereb Cortex 21(8):1792–1802. doi:10.1093/cercor/bhq247
63. Inada H, Watanabe M, Uchida T, Ishibashi H, Wake H, Nemoto T, Yanagawa Y, Fukuda A, Nabekura J (2011) GABA regulates the multidirectional tangential migration of GABAergic interneurons in living neonatal mice. PLoS ONE 6(12):e27048. doi:10.1371/journal.pone.0027048
64. Behar TN, Smith SV, Kennedy RT, McKenzie JM, Maric I, Barker JL (2001) GABA(B) receptors mediate motility signals for migrating embryonic cortical cells. Cereb Cortex 11(8):744–753
65. Behar TN, Schaffner AE, Scott CA, O'Connell C, Barker JL (1998) Differential response of cortical plate and ventricular zone cells to GABA as a migration stimulus. J Neurosci 18(16):6378–6387
66. Bony G, Szczurkowska J, Tamagno I, Shelly M, Contestabile A, Cancedda L (2013) Non-hyperpolarizing GABAB receptor activation regulates neuronal migration and neurite growth and specification by cAMP/LKB1. Nat Commun 4:1800. doi:10.1038/ncomms2820
67. Furukawa T, Yamada J, Akita T, Matsushima Y, Yanagawa Y, Fukuda A (2014) Roles of taurine-mediated tonic GABAA receptor activation in the radial migration of neurons in the fetal mouse cerebral cortex. Front Cell Neurosci 8:88. doi:10.3389/fncel.2014.00088
68. Heck N, Kilb W, Reiprich P, Kubota H, Furukawa T, Fukuda A, Luhmann HJ (2007) GABA-A receptors regulate neocortical neuronal migration in vitro and in vivo. Cereb Cortex 17(1):138–148. doi:10.1093/cercor/bhj135
69. Rheims S, Represa A, Ben-Ari Y, Zilberter Y (2008) Layer-specific generation and propagation of seizures in slices of developing neocortex: role of excitatory GABAergic synapses. J Neurophysiol 100(2):620–628. doi:10.1152/jn.90403.2008
70. Kumar S, Fleming RL, Morrow AL (2004) Ethanol regulation of gamma-aminobutyric acid A receptors: genomic and nongenomic mechanisms. Pharmacol Ther 101(3):211–226. doi:10.1016/j.pharmthera.2003.12.001
71. Santhakumar V, Wallner M, Otis TS (2007) Ethanol acts directly on extrasynaptic subtypes of GABAA receptors to increase tonic inhibition. Alcohol 41(3):211–221. doi:10.1016/j.alcohol.2007.04.011
72. Lobo IA, Harris RA (2008) GABA(A) receptors and alcohol. Pharmacol Biochem Behav 90(1):90–94. doi:10.1016/j.pbb.2008.03.006
73. Janigro D, Schwartzkroin PA (1988) Effects of GABA and baclofen on pyramidal cells in the developing rabbit hippocampus: an 'in vitro' study. Brain Res 469(1–2):171–184
74. Lopez-Bendito G, Shigemoto R, Kulik A, Paulsen O, Fairen A, Lujan R (2002) Expression and distribution of metabotropic GABA receptor subtypes GABABR1 and GABABR2 during rat neocortical development. Eur J Neurosci 15(11):1766–1778
75. Behar TN, Schaffner AE, Scott CA, Greene CL, Barker JL (2000) GABA receptor antagonists modulate postmitotic cell migration in slice cultures of embryonic rat cortex. Cereb Cortex 10(9):899–909
76. Lopez-Bendito G, Lujan R, Shigemoto R, Ganter P, Paulsen O, Molnar Z (2003) Blockade of GABA(B) receptors alters the tangential migration of cortical neurons. Cereb Cortex 13(9):932–942
77. Crandall JE, McCarthy DM, Araki KY, Sims JR, Ren JQ, Bhide PG (2007) Dopamine receptor activation modulates GABA neuron migration from the basal forebrain to the cerebral cortex. J Neurosci 27(14):3813–3822. doi:10.1523/JNEUROSCI.5124-06.2007
78. Trantham-Davidson H, Chandler LJ (2015) Alcohol-induced alterations in dopamine modulation of prefrontal activity. Alcohol 49(8):773–779. doi:10.1016/j.alcohol.2015.09.001
79. Engel JA, Jerlhag E (2014) Alcohol: mechanisms along the mesolimbic dopamine system. Prog Brain Res 211:201–233. doi:10.1016/B978-0-444-63425-2.00009-X
80. Fabio MC, Vivas LM, Pautassi RM (2015) Prenatal ethanol exposure alters ethanol-induced Fos immunoreactivity and dopaminergic activity in the mesocorticolimbic pathway of the adolescent brain. Neuroscience 301:221–234. doi:10.1016/j.neuroscience.2015.06.003
81. Rex EB, Rankin ML, Ariano MA, Sibley DR (2008) Ethanol regulation of D(1) dopamine receptor signaling is mediated by protein kinase C in an isozyme-specific manner. Neuropsychopharmacology 33(12):2900–2911. doi:10.1038/npp.2008.16
82. Zhou R, Wang S, Zhu X (2012) Prenatal ethanol exposure alters synaptic plasticity in the dorsolateral striatum of rat offspring via changing the reactivity of dopamine receptor. PLoS ONE 7(8):e42443. doi:10.1371/journal.pone.0042443
83. Ungerer M, Knezovich J, Ramsay M (2013) In utero alcohol exposure, epigenetic changes, and their consequences. Alcohol Res 35(1):37–46
84. Kim P, Choi CS, Park JH, Joo SH, Kim SY, Ko HM, Kim KC, Jeon SJ, Park SH, Han SH, Ryu JH, Cheong JH, Han JY, Ko KN, Shin CY (2014) Chronic exposure to ethanol of male mice before mating produces attention deficit hyperactivity disorder-like phenotype along with epigenetic dysregulation of dopamine transporter expression in mouse offspring. J Neurosci Res 92(5):658–670. doi:10.1002/jnr.23275
85. Kleiber ML, Diehl EJ, Laufer BI, Mantha K, Chokroborty-Hoque A, Alberry B, Singh SM (2014) Long-term genomic and epigenomic dysregulation as a consequence of prenatal alcohol exposure: a model for fetal alcohol spectrum disorders. Front Genet 5:161. doi:10.3389/fgene.2014.00161
86. Kim P, Park JH, Choi CS, Choi I, Joo SH, Kim MK, Kim SY, Kim KC, Park SH, Kwon KJ, Lee J, Han SH, Ryu JH, Cheong JH, Han JY, Ko KN, Shin CY (2013) Effects of ethanol exposure during early pregnancy in hyperactive, inattentive and impulsive behaviors and MeCP2 expression in rodent offspring. Neurochem Res 38(3):620–631. doi:10.1007/s11064-012-0960-5
87. Perkins A, Lehmann C, Lawrence RC, Kelly SJ (2013) Alcohol exposure during development: impact on the

epigenome. Int J Dev Neurosci 31(6):391–397. doi:10.1016/j.ijdevneu.2013.03.010
88. Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, Jaenisch R, Greenberg ME (2003) Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. Science 302(5646):885–889. doi:10.1126/science.1086446
89. Martinowich K, Hattori D, Wu H, Fouse S, He F, Hu Y, Fan G, Sun YE (2003) DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. Science 302(5646):890–893. doi:10.1126/science.1090842
90. Horike S, Cai S, Miyano M, Cheng JF, Kohwi-Shigematsu T (2005) Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. Nat Genet 37(1):31–40. doi:10.1038/ng1491
91. Tuncdemir SN, Fishell G, Batista-Brito R (2015) miRNAs are essential for the survival and maturation of cortical interneurons. Cereb Cortex 25(7):1842–1857. doi:10.1093/cercor/bht426
92. Gardiner AS, Gutierrez HL, Luo L, Davies S, Savage DD, Bakhireva LN, Perrone-Bizzozero NI (2016) Alcohol use during pregnancy is associated with specific alterations in microRNA levels in maternal serum. Alcohol Clin Exp Res 40(4):826–837. doi:10.1111/acer.13026
93. Balaraman S, Lunde ER, Sawant O, Cudd TA, Washburn SE, Miranda RC (2014) Maternal and neonatal plasma microRNA biomarkers for fetal alcohol exposure in an ovine model. Alcohol Clin Exp Res 38(5):1390–1400. doi:10.1111/acer.12378
94. Guo Y, Chen Y, Carreon S, Qiang M (2012) Chronic intermittent ethanol exposure and its removal induce a different miRNA expression pattern in primary cortical neuronal cultures. Alcohol Clin Exp Res 36(6):1058–1066. doi:10.1111/j.1530-0277.2011.01689.x
95. Ignacio C, Mooney SM, Middleton FA (2014) Effects of Acute Prenatal Exposure to Ethanol on microRNA Expression are Ameliorated by Social Enrichment. Front Pediatr 2:103. doi:10.3389/fped.2014.00103
96. Miranda RC, Pietrzykowski AZ, Tang Y, Sathyan P, Mayfield D, Keshavarzian A, Sampson W, Hereld D (2010) MicroRNAs: master regulators of ethanol abuse and toxicity? Alcohol Clin Exp Res 34(4):575–587. doi:10.1111/j.1530-0277.2009.01126.x
97. Sathyan P, Golden HB, Miranda RC (2007) Competing interactions between micro-RNAs determine neural progenitor survival and proliferation after ethanol exposure: evidence from an ex vivo model of the fetal cerebral cortical neuroepithelium. J Neurosci 27(32):8546–8557. doi:10.1523/JNEUROSCI.1269-07.2007
98. Wang LL, Zhang Z, Li Q, Yang R, Pei X, Xu Y, Wang J, Zhou SF, Li Y (2009) Ethanol exposure induces differential microRNA and target gene expression and teratogenic effects which can be suppressed by folic acid supplementation. Hum Reprod 24(3):562–579. doi:10.1093/humrep/den439
99. Marin O, Rubenstein JL (2003) Cell migration in the forebrain. Annu Rev Neurosci 26:441–483. doi:10.1146/annurev.neuro.26.041002.131058
100. Metin C, Baudoin JP, Rakic S, Parnavelas JG (2006) Cell and molecular mechanisms involved in the migration of cortical interneurons. Eur J Neurosci 23(4):894–900. doi:10.1111/j.1460-9568.2006.04630.x
101. Powell EM, Mars WM, Levitt P (2001) Hepatocyte growth factor/scatter factor is a motogen for interneurons migrating from the ventral to dorsal telencephalon. Neuron 30(1):79–89
102. Polleux F, Whitford KL, Dijkhuizen PA, Vitalis T, Ghosh A (2002) Control of cortical interneuron migration by neurotrophins and PI3-kinase signaling. Development 129(13):3147–3160
103. Canty AJ, Dietze J, Harvey M, Enomoto H, Milbrandt J, Ibanez CF (2009) Regionalized loss of parvalbumin interneurons in the cerebral cortex of mice with deficits in GFRalpha1 signaling. J Neurosci 29(34):10695–10705. doi:10.1523/JNEUROSCI.2658-09.2009
104. Pozas E, Ibanez CF (2005) GDNF and GFRalpha1 promote differentiation and tangential migration of cortical GABAergic neurons. Neuron 45(5):701–713. doi:10.1016/j.neuron.2005.01.043
105. Ceccanti M, Mancinelli R, Tirassa P, Laviola G, Rossi S, Romeo M, Fiore M (2012) Early exposure to ethanol or red wine and long-lasting effects in aged mice. A study on nerve growth factor, brain-derived neurotrophic factor, hepatocyte growth factor, and vascular endothelial growth factor. Neurobiol Aging 33(2):359–367. doi:10.1016/j.neurobiolaging.2010.03.005
106. Tyler CR, Allan AM (2014) Prenatal alcohol exposure alters expression of neurogenesis-related genes in an ex vivo cell culture model. Alcohol 48(5):483–492. doi:10.1016/j.alcohol.2014.06.001
107. Heaton MB, Mitchell JJ, Paiva M, Walker DW (2000) Ethanol-induced alterations in the expression of neurotrophic factors in the developing rat central nervous system. Brain Res Dev Brain Res 121(1):97–107
108. Light KE, Brown DP, Newton BW, Belcher SM, Kane CJ (2002) Ethanol-induced alterations of neurotrophin receptor expression on Purkinje cells in the neonatal rat cerebellum. Brain Res 924(1):71–81
109. Ahmadiantehrani S, Barak S, Ron D (2014) GDNF is a novel ethanol-responsive gene in the VTA: implications for the development and persistence of excessive drinking. Addict Biol 19(4):623–633. doi:10.1111/adb.12028
110. Sanchez Vega MC, Chong S, Burne TH (2013) Early gestational exposure to moderate concentrations of ethanol alters adult behaviour in C57BL/6 J mice. Behav Brain Res 252:326–333. doi:10.1016/j.bbr.2013.06.003
111. Diaz MR, Vollmer CC, Zamudio-Bulcock PA, Vollmer W, Blomquist SL, Morton RA, Everett JC, Zurek AA, Yu J, Orser BA, Valenzuela CF (2014) Repeated intermittent alcohol exposure during the third trimester-equivalent increases expression of the GABA(A) receptor delta subunit in cerebellar granule neurons and delays motor development in rats. Neuropharmacology 79:262–274. doi:10.1016/j.neuropharm.2013.11.020