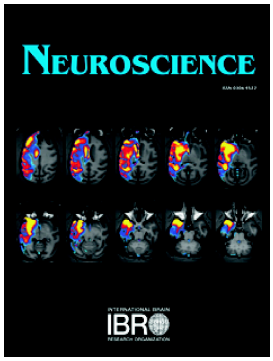

The Role of the Subplate in Schizophrenia and Autism: A Systematic Review

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PII: S0306-4522(19)30207-6
DOI: https://doi.org/10.1016/j.neuroscience.2019.03.049
Reference: NSC 18974

To appear in: *Neuroscience*

Received date: 21 August 2018
Accepted date: 20 March 2019

Please cite this article as: M. Serati, G. Delvecchio, G. Orsenigo, et al., The Role of the Subplate in Schizophrenia and Autism: A Systematic Review, Neuroscience, https://doi.org/10.1016/j.neuroscience.2019.03.049

The Role of the Subplate in Schizophrenia and Autism: a Systematic Review

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Financial Disclosure

Drs. Serati, Del Vecchio, Orsenigo, Mandolini, Lazzaretti, and Scola, Prof. Brambilla, and Prof. Triulzi do not have any affiliation with or financial interest in any organization that might pose a conflict of interest with the present article.

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Abstract

The subplate (SP) represents a transitory cytoarchitectural fetal compartment containing most subcortical and cortico-cortical afferents, and has a fundamental role in the structural development of the healthy adult brain. There is evidence that schizophrenia and autism may be determined by developmental defects in the cortex or cortical circuitry during the earliest stages of pregnancy. This article provides an overview on fetal SP development, considering its role in schizophrenia and autism, as supported by a systematic review of the main databases. The SP has been described as a cortical amplifier with a role in the coordination of cortical activity, and sensitive growth and migration windows have crucial consequences with respect to cognitive functioning. Although there are not enough studies to draw final conclusions, improved knowledge of the SP's role in schizophrenia and autism spectrum disorders may help to elucidate and possibly prevent the onset of these two severe disorders.

Keywords: development; cerebral cortex; gray matter; white matter; magnetic resonance imaging; subplate

Introduction

The subplate (SP) is a transient cerebral wall compartment, in which progenitor cells and afferents of the thalamus and cerebral areas segregate and grow; it is one of the first zones to develop in the human cerebral cortex (Kostović and Jovanov-Milošević, 2008; Marín Padilla, 2014; Hoerder-Suabedissen and Molnár, 2015; Ohtaka-Maruyama et al., 2016; Žunić Išasegi et al., 2018). Neurons usually migrate from their places of origin to more superficial cortical layers, and start to differentiate after migration, with the exception of axonal outgrowth. Interestingly, some neurons stop in the preplate or SP, while others enter the cortical plate (CP) (Hadders-Algra, 2018; Scola et al., 2018). The initial studies on the SP were carried out by Molliver (1973), Kostovic and Molliver (1974) and Kostović and Rakic (1980); they described the SP as rich in fibers but containing few cells, and situated at the developing cortical-subcortical interface, between the intermediate zone and the cortex (an area visible from the third month of pregnancy). The SP is more represented in somatosensorial areas than in visual ones, reaching the major development at the end of the third trimester (peak at 30 weeks) (Kostović and Rakic, 1990). After this period, the SP decreases in thickness due to the movement of ascending thalamo-cortical axons to the CP (Molliver et al., 1973), and undergoes several additional modifications throughout the first year of life (Jovanov Milošević et al., 2014; Kostović et al., 2014). Between-species comparison revealed that the SP has grown during mammalian evolution; in the human fetus, this growth is due to augmentation with cortico-cortical fibers (Kostović and Rakic, 1990; Marín Padilla, 2001; Kerschensteiner, 2014). The SP survives longer in regions subjacent to associatied cortices containing cortico-cortical and callosal connections (Kostović and Rakic, 1990).

The SP has been defined as a pacemaker for the maturation of cortical circuitry subserving cognitive development (Luhmann et al., 2009; Luhmann et al., 2016). Indeed, it has three major functions: (1) receiving corticothalamic and intracortical afferents (McConnell et al., 1989; Allendoerfer and Shatz, 1994); (2) acting as a ‘waiting room’ for afferents from the thalamus, contralateral and ipsilateral hemispheres, basal forebrain, and monoaminergic brainstem nuclei (Kostović et al., 2011); and (3) supporting cognitive processes as a pacemaker for maturation of the cerebral cortex (Kostović and Judaš, 2006; Luhmann et al., 2009). Moreover, the SP has been involved in fetal behavior, such as general movements’ activity (Hadders-Algra, 2007) and precise adjustments to cortical connectivity (Allendoerfer and Shatz, 1994). The SP neurons contain glutamatergic and GABAergic interstitial white matter neurons (IWMNs) (Kostović and Rakic, 1990; Kostović et al., 2011) that, in the postnatal human brain, stay at the cortical/white matter interface as SP remnant, functioning as auxiliary interneurons and gating cortical input (Kostović and Rakic, 1980; Suárez-Solá et al., 2009; Judaš et al., 2010a; Judaš et al., 2010b).

The morphological organization of the SP has been investigated in major psychiatric disorders, including schizophrenia and autism spectrum disorders (ASDs) (Akbarian et al., 1993a; Akbarian et al., 1993b; Akbarian et al., 1996; Anderson et al., 1996; Kirkpatrick et al., 1999; Eastwood and Harrison, 2003; Kirkpatrick et al., 2003; Rioux et al., 2003; Eastwood and Harrison 2005; Eastwood and Harrison 2006; Hutsler et al., 2007; Avino and Hutsler, 2010; Yang et al., 2011). Neuroimaging studies have been conducted using structural in vitro magnetic resonance imaging (MRI) (Kostović and Judaš, 2002; Kostović and Judaš, 2006; Kostović and Jovanov-Milošević, 2008; Kostović and Vasung, 2009; Wright et al., 2014; Vasung et al., 2016). Evidence from available studies suggests that schizophrenia and ASDs are determined by alterations in the early SP synaptic circuitry due to genetic load (Harkin et al., 2017). Abnormal neuronal migration and myelination usually occur during the earliest stages of pregnancy, a crucial period for determining correct functioning of the neural circuitry and cortical growth (Molliver et al. 1973; Kostović et al., 2011). Indeed, a migration perturbation or apoptosis in the SP can alter normal cortical connections (Jones, 1995; Rakic, 2006). Moreover, the second trimester of pregnancy has been considered the "window period of vulnerability", during which several factors can produce alterations in cortical development (Bunney et al., 1997), as the transient fetal SP zone is more susceptible to pathogenetic insult (Katz and Shatz, 1996; López-Bendito and Mólnar, 2003; Kostović and Judaš, 2007; Luhmann et al., 2009; Kanold and Luhmann, 2010; Luhmann et al., 2016).

Given the importance of the SP during the perinatal period, the aim of this review is to give a perspective on its development and elucidate its role in schizophrenia and ASDs.

Methods

In order to provide an updated overview, a search in main databases (Pubmed, ISIWEB of Knowledge, PsycINFO) was performed. Suitable articles were sourced from a comprehensive literature search and from references identified through other studies. Keywords were “subplate” matched with “schizophrenia”, “autism”, “fetal brain”, “adolescence”, “child development”, “magnetic resonance imaging”, “diffusion tensor imaging”, “early cortical circuits”, “psychiatric disorders”, and “childhood”. Studies were excluded if they included animals or patients with diagnoses different from schizophrenia or autism in order to better focus on the impact of the SP on adult development in autism and schizophrenia.

This review covers findings from 1980 to December 2018, with the majority of papers reviewed being published prior to 2011. After applying the inclusion and exclusion criteria, a total of 147 papers were included in the review.

The subplate and brain development

Human brain development and maturation are complex events characterized by cellular proliferation, migration, and network formation (Molliver et. al., 1973; Toga et al., 2006; Mailath-Pokorny et al., 2012). Fetal cerebral lamination and its different developmental stages have been explored histologically with postmortem in vitro studies and morphologically with MRI and diffusion tensor imaging (DTI) investigations, which allow the investigation of specific changes in the prenatal brain at different gestational ages (Zhan et al., 2013; Scola et al., 2018). Histological studies showed that during radial migration, cerebral axonal connections develop in each cerebral area; during the midgestation phase in particular, the development of transitional structures, including the SP, is aimed at controlling axonal proliferation and cellular migration (Kostović and Jovanov-Milošević, 2006; Kostović and Jovanov-Milošević, 2008; Scott et al., 2011). In the SP zone, synaptogenesis occurs (Kostović and Rakic, 1980; Bourgeois et al., 1989; Zecevic et al., 1989; Kostović and Rakic, 1990; Zecevic and Rakic, 1991; Rakic et al., 1994) and long cortical pathways expand (Kostović and Judaš, 2002; Kostović and Judaš, 2007; Kostović and Judaš, 2010). Kostović and Jovanov-Milošević (2006) compared histological versus MRI data on fetal development, subdividing laminar organization from 20 weeks to 45 weeks into four phases: fetal phase (<24 weeks), early preterm (24–32 weeks), late preterm (33–35 weeks), and neonatal phase (>35 weeks). With regard to the SP, the authors reported that thalamo-cortical afferents grew outside the CP during the fetal phase, whereas these fibers penetrate the CP during the early preterm phase (synchronous with lamination). During the late preterm phase, long cortico-cortical and callosal fibers grew and the SP reached its maximum extension (45% of the telencephalic volume), four times thicker than the CP (De Graaf-Peters and Hadders-Algra, 2006). The neonatal phase is characterized by a reorganization of cortical circuitry, with axonal arborization of the CP and growth of the short cortico-cortical connections. The SP gradually decreases in size through programmed cell death, although it continues to differentiate and participate in endogenous circuitry facilitating functional interactions of cortico-cortical fibers in the frontal and associative cortices (the last cortices to mature permanently), and then disappearing during adulthood (Kostović and Jovanov-Milošević, 2006; Perkins et al., 2008; Kerschensteiner, 2014; Kostović et al., 2014; Krsnik et al., 2017). Similarly (and consistent with histological studies), a retrospective study evaluating the sonographic appearance of laminar organization at 17–38 weeks of gestation reported that the SP disappears after 34 weeks (Pugash et al., 2012).

Longitudinal pre- and post-natal imaging studies have been applied to delineate physiological changes in the SP over time (Figure 1) (Kostović et al., 2002,; Radoš et al., 2006;

Kostović et al., 2014; Vasung et al., 2016). Nossin-Manor and colleagues (2015) described the relation between microstructural changes and maturational processes using magnetization transfer imaging (MTI). This technique is sensitive to the concentration of semisolids in tissues, and showed changes in lamination pattern during gestation that were not visible on structural MR images after 28 gestational weeks (Figure 2) (Glenn, 2009; Scola et al., 2018). This finding corroborates previous histological and MRI data supporting the application of multimodal MRI in the assessment of brain evolution. A recent MRI in vivo study reported that the 20–week fetal period is characterized by the reinforcement of both intra- and inter-hemispheric macro-connectivity (Jakab et al., 2014). In particular, the authors reported augmented connectivity between 21–38 weeks, with a peak in inter-hemispheric connectivity between 26–29 weeks. Moreover, another MRI investigation performed to quantify cortical growth in utero between 21–38 weeks in healthy subjects showed rapid growth in the parietal and temporal cortices compared with slow development of the frontal and temporal medial areas (Wright et al., 2014). In contrast, a post mortem study using high angular resolution DTI on human brains (17–40 weeks) showed an initial regression of radial organization, with intracerebral connectivity evolving sequentially from dorsal-posterior brain areas in the antero-ventral direction and ending in the inferior temporal/frontal lobes (Takahashi et al., 2012).

Moreover, several strands of evidence have shown that normal SP maturation is necessary in order to have correct connectivity between cortical and subcortical areas (Kostović and Rakic, 1990; Meyer et al., 2000; Kostović and Judaš, 2006; Kostović and Judaš, 2007; Kostović et al., 2015; Vasung et al., 2016; González-Arnay et al., 2017; Žunić Išasegi et al., 2018). Indeed, various injuries (e.g., perinatal and obstetric complications, such as preterm birth) can lead to alterations in the periventricular white matter and SP, areas more vulnerable to hypoxic/ischemic lesions (Volpe, 2009a; Polo-Kantola et al., 2014; Laurens et al., 2015; Buoli et al., 2016; Millar et al., 2017; Žunić Išasegi et al., 2018). This vulnerability could be due to the high metabolic energy required by the SP to reach its developmental peak (McQuillen and Ferriero, 2005; Perkins et al., 2008; Marret et al., 2013). In this regard, an interesting follow-up study reported a significant association between birth weight and cognitive functions: patients with low birth weight had less inhibitory control and reduced surface area of the orbitofrontal cortex and caudate nucleus compared to patients with normal birth weight (Schlotz et al., 2014). Similarly, two studies in preterm brains conducted by the same group, showed that the presence of altered structural connections between selective cortical and subcortical regions were associated with functional impairments in information flow, rule learning, verbal IQ and memory deficits (Hadders-Algra, 2007; Karolis et al., 2016; Nosarti and Froudist-Walsh, 2016). Moreover, abnormal gray matter found in these subjects might be due to SP

dysfunction damaging efferent motor connections in periventricular white matter. Indeed, prenatal lesions, stress, and pain seem to influence development of the emotional fronto-limbic circuitry (Anand and Hickey, 1987; Fitzgerald, 2005; Lee et al., 2005; Slater et al., 2006). This can alter the number of SP neurons during the perinatal period, which in turn is a causal factor in schizophrenia (or at least, for a subgroup of schizophrenics with deficiency syndrome) (Kostović et al., 2015).

In conclusion, SP physiological development, cellular migration, and apoptosis, beyond other maturation processes, seem to be fundamental for a mature and correct pediatric cognitive, behavioral and emotional growth (Volpe, 2009b; Kostović et al., 2011). Studying grey and white matter quality in pregnancy and childhood represents a good tool to investigate the evolution of the nervous system, given the key role of gray/white matter augmentation and plasticity in mentalization, flexibility, and the pediatric development of cognitive abilities, representing a possible prevention tool (Hüppi, 2010; Studholme, 2015; Thomason et al., 2015).

The subplate and schizophrenia

Schizophrenia is a neurodevelopmental disorder characterized by altered connectivity in the cerebral white matter (Weinberger, 1987; Eastwood and Harrison, 2003; Schmitt et al., 2011), that could result from aberrant connections or alterations in synaptic plasticity during development, or to the persistence of SP neurons (Stephan et al., 2009; Schmitt et al., 2011; Corradi-Dell'Acqua et al., 2012; Kostović et al., 2015). Leading causes of the altered connections observed in schizophrenia could include alterations in cerebral cortical development, pathological migration of SP neurons (also through the SP), the establishment/refinement of cortical connections, or programmed cell death (Stolp et al., 2012). In particular, in adolescents and adults with schizophrenia, numerous SP neurons survive in the superficial white matter as so-called interstitial neurons, possibly altering input gating (Chun and Shatz, 1989; Judaš et al., 2010a; Judaš et al., 2010b; Kostović et al., 2011).

IWMNs are thought to represent the few adult SP remnants (Chun and Shatz, 1989; Allendoerfer and Shatz, 1994; Kanold et al., 2003). Changes in their density/distribution have been reported in several brain regions in schizophrenia (Akbarian et al., 1993a; Akbarian et al., 1993b; Akbarian et al., 1996; Anderson et al., 1996; Kirkpatrick et al., 1999; Eastwood and Harrison, 2003; Kirkpatrick et al., 2003; Rioux et al., 2003; McQuillen and Ferriero, 2005; Kostović et al., 2011). In particular, IWMNs seem to cause the inhibition of augmented prefrontal cortical neurons, potentially altering the limbic input "gating" with altered connections between prefrontal cortex and limbic areas (Kostović and Molliver, 1974; Kostović and Jovanov-Milošević, 2008; Perkins et al., 2008; Kostović and Judaš, 2010; Kostović et al., 2011; O'Donoghue et al., 2015).

Specifically, Kostović and colleagues (2011) proposed that schizophrenic individuals have increased GABAergic interstitial neurons at the cortical/white matter interface, where limbic and afferent pathways penetrate the prefrontal cortex. The strategic location of IWMNs appears to cause significant inhibition of the prefrontal cortical neurons (Kostović et al., 2011), as inhibitory dysfunction of the prefrontal cortex is one pathogenetic hypothesis of schizophrenia (Lewis et al., 2005). Moreover, the density of IWMNs seems to be greater in patients with negative symptoms (Kirkpatrick et al., 1999; Kirkpatrick et al., 2003).

Regarding dopaminergic neuronal systems in the forebrain, which are implicated in schizophrenia, Unis (1993) found that specific and saturable dopamine receptor antagonists stratified in the SP between the CP and the intermediate zone are already present at gestational week 17. Altogether, these findings seem to confirm the evidence reported by Weinberger in 1987 suggesting that prefronto-limbic dysconnectivity might sustain the emotion/decision processing failure observed in schizophrenic individuals during adolescence and young adulthood.

In order to identify the role of IWMNs in schizophrenia, different studies have evaluated their density and distribution using immunohistochemical methods, based on the antigen-antibody conjugation principle, in addition with detection systems (enzymatic, fluorescent) that render the reaction visible under a microscope. Different molecular markers have been identified, including the neuronal nuclear antigen (NeuN), a marker of mature neurons (Mullen et al., 1992; Sarnat et al., 1998), and the monoclonal antibody anti-microtuble associated protein 2 (MAP2), which is involved in microtubule assembly (an essential step in neurogenesis) (Dehmelt and Halpain, 2005).

Studies by Eastwood and Harrison that used NeuN as immunomarker reported increased IWMN density (Eastwood and Harrison, 2003), particularly in the dorsolateral prefrontal cortex (DPFC) (Eastwood and Harrison, 2005) in patients with schizophrenia; no changes have been detected in deep white matter. Similarly, always using NeuN as an immunomarker, Yang and colleagues (2011) reported increased IWMN density in DPFC white matter. This study provided the first evidence of a correlation between increased IWMN density and gray matter interneuron deficit, suggesting that the migration of interneurons from white matter to the cortex might be altered in schizophrenia. Other studies quantified the density and distribution of MAP2-expressing neurons; a post mortem study by Anderson and colleagues (1996) reported greater density in the prefrontal superficial white matter in schizophrenics compared to controls. This finding might reflect a premature arrest of SP neuron migration or an abnormality in apoptosis. Similarly, Rioux and colleagues (2003) used a monoclonal antibody against MAP2 to label IWMNs, reporting altered migration of IWMNs in the anterior parahippocampal gyrus instead of their normal positions in the CP and their survival in this ectopic position in individuals suffering from schizophrenia.

Moreover, IWMNs seem to reduce the mRNA expression of reelin, a secretory protease that has a major role in neurodevelopmental plasticity, in schizophrenia (Eastwood and Harrison, 2006). Reelin reportedly contributes to the synaptic pathology of schizophrenia, particularly regarding GABA-ergic and glutamatergic transmission within the hippocampal-DLPFC network (Harrison, 1999; Rice and Curran, 2001; Fatemi, 2005; Eastwood and Harrison, 2006; Ishii et al., 2016).

In conclusion, both neuroimaging and clinical studies support the conception of schizophrenia as a neurodevelopmental disorder (Murray and Lewis, 1987; Fatemi and Folsom, 2009; Andreasen, 2010; Gupta and Kulhara, 2010; Owen et al., 2011). Developmental defects leading to schizophrenia might include defects in cerebral cortical development that are due, at least in part, to alterations in the SP, specifically with respect to the density and/or distribution of IWMNs.

The Subplate and autism

Autism and ASDs are neurodevelopmental and lifelong disorders featuring onset of symptoms within the first 3 years of life (Brambilla et al., 2004; Matson et al., 2016). Autism and ASD are characterized by altered cortical developmental trajectory and connectivity, as reported in several studies (Bailey et al., 1998; Casanova et al., 2002; Brambilla et al., 2003; Geschwind and Levitt, 2007; Hutsler et al., 2007; Hutsler and Zhang, 2010; Calderoni et al., 2016; Crippa et al., 2016; Hutsler and Casanova, 2016). A potential role for the SP in autism has been outlined, but has been only partially explored.

In ASDs, the boundary between gray/white matter is not clearly delineated (Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Geschwind, 2009). It has been hypothesized that this inability to distinguish the transition zone between gray and white matter in individuals with ASDs may be driven by the presence of supernumerary SP neurons (Avino and Hutsler, 2010; Kemper, 2010).

An excess of neuronal cell bodies within the SP in autistic subjects has been a major finding (Hutsler and Casanova, 2016). Indeed, this condition might be related to neuronal overproduction, reduced apoptosis, or problems with radial/tangential migration (Hutsler and Casanova, 2016). Although processes underlying these changes have not been identified, some authors have suggested that altered migration may have an important role due to the retention of transient SP neurons within the subcortical white matter (Bauman and Kemper, 1985; Courchesne, 1988; Kemper, 1988; Chun and Shatz, 1989; Piven et al., 1990; Avino and Hutsler, 2010; Kemper, 2010). Moreover, cell pattern modifications and layer constitution, identified in ASD subjects through the detection of reelin and serotonin, have been involved in ASD etiopathogenesis (Fatemi et al., 2002;

Zhang et al., 2002; Janusonis et al., 2004; Fatemi et al., 2005; Skaar et al., 2005; Serajee et al., 2006).

Furthermore, with regard to cortical thickness, a post mortem study by Hutsler et al. (2007) reported similar cortical thickness values between ASD and control subjects. On the other hand, increased brain volumes have been reported in different ASD studies (Piven et al., 1995; Piven et al., 1996; Courchesne et al., 2001; Cody et al., 2002; Courchesne et al., 2003). However, the boundary between cortex and white matter is sometimes indistinct in ASD; thus, MRI measures might overestimate cortical thickness due to a lower border (Hutsler et al., 2007; Hutsler and Avino, 2013). Therefore, as recently underlined by Hutsler and Casanova (2016), studies of cortical development in the context of ASD could link microanatomical circuitry and atypical ASD behaviors, permitting the application of targeted interventions very early in life.

Similarly to schizophrenia, the role of the SP in autism is actually under-explored; although some hypotheses describe it as a "cortical amplifier" with altered coordination of cortical activity (Hutsler et al., 2007; Avino and Hutsler, 2010), there are too few studies to draw clear conclusions.

The SP displays several functions during fetal gestation, including correct radial and tangential thalamocortical and corticothalamic migration to the CP, which previous studies have shown may play a role in the pathogenesis of major psychiatric disorders. SP neurons are involved in short cortico-cortical connections until the second postnatal year, with axonal, synaptic, and dendritic branch reorganization in response to environment. Therefore, these modifications have crucial consequences regarding the development of language, cognition, and self-awareness, particularly regarding the social interaction of an infant with their environment (Kostović et al., 2014; Kostović et al., 2015). In this context, longitudinal pre- and postnatal imaging studies may make it possible to describe and quantify changes in the SP zone over time. In particular, recent articles have proposed to evaluate retrospective imaging studies in relation to diagnoses made in early childhood in order to identify atypical developmental pathways and SP maturation (Nossin-Manor et al., 2015; Hutsler and Casanova, 2016). Improved knowledge of the impact of the SP in schizophrenia and ASDs would help to elucidate and possibly prevent or reduce the onset of these two severe disorders (Judaš et al., 2013).

In conclusion, the availability of molecular, genetic, and neuroimaging techniques could bring forth new insights on the role of the SP, allowing early interventions and possibly diminishing the impact of SP development on brain maturation. As already shown in preterm neonates, it is important to emphasize how subtle cognitive disabilities caused by neurodevelopmental defects

(e.g., decreased brain surface area) usually appear at school age, but might be be visible earlier with neuroimaging studies (Ajayi-Obe et al., 2000; Kapellou et al., 2006; Perkins et al., 2008).

Schizophrenia and autism disorders have heterogeneous etiologies, different clinical and neurobiological presentations. Neuroimaging studies, performed in the early stages of life (e.g., fetal MRI) (Triulzi et al., 2011), might help in the future to identify specific patients subgroups with particular altered brain patterns and clinical needs.

Acknowledgements

PB was partially supported by grants from the Italian Ministry of Health (RF-2011-02352308).

References

Ajayi-Obe M, Saeed N, Cowan FM, Rutherford MA, Edwards AD (2000) Reduced development of cerebral cortex in extremely preterm infants. Lancet 356(9236):1162-3.

Akbarian S, Bunney Jr WE, Potkin SG, Wigal SB, Hagman JO, Sandman CA, Jones EG (1993a) Altered distribution of nicotinamide–adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry 50,169 – 177.

Akbarian S, Kim JJ, Potkin SG, Hetrick WP, Bunney WEJ, Jones EG (1996) Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Arch Gen Psychiatry 53, 425 – 436.

Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney WEJ, Jones EG (1993b) Distorted distribution of nicotinamide–adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry 50, 178 – 187.

Allendoerfer KL, Shatz CJ (1994) The subplate, a transient neocortical structure: its role in the development of connections between thalamus and cortex. Annu Rev Neurosci 17,185 – 218.

Anand KJ, Hickey PR (1987) Pain and its effects in the human neonate and fetus. N Engl J Med 317, 1321–1329.

Anderson SA, Volk DW, Lewis DA (1996) Increased density of microtubule associated protein 2-immunoreactive neurons in the prefrontal white matter of schizophrenic subjects. Schizophr Res 19(2-3):111-9.

Andreasen NC (2010) The lifetime trajectory of schizophrenia and the concept of neurodevelopment. Dialogues Clin Neurosci 12 (3): 409-15.

Avino TA, Hutsler JJ (2010) Abnormal cell patterning at the cortical gray-white matter boundary in autism spectrum disorders. Brain Res 1360:138-46.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P (1998) A clinicopathological study of autism. Brain 121(Pt 5):889 –905.

Bauman M, Kemper TL (1985) Histoanatomic observations of the brain in early infantile-autism. Neurology 35, 866–874.

Bourgeois JP, Jastreboff PJ, Rakic P (1989) Synaptogenesis in visual cortex of normal and preterm monkeys: evidence for intrinsic regulation of synaptic overproduction. Proc Natl Acad Sci USA 86, 4297–4301.

Brambilla P, Hardan A, di Nemi S, Perez J, Soares J, Barale F (2003) Brain anatomy and development in autism: review of structural MRI studies. Brain Res Bull 61:557–569.

Brambilla P, Hardan AY, di Nemi SU, Caverzasi E, Soares JC, Perez J, Barale F (2004) The functional neuroanatomy of autism. Funct Neurol 19(1):9-17.

Bunney BG, Potkin SG, Bunney WE (1997) Neuropathological studies of brain tissue in schizophrenia. J Psychiatr Res 31(2):159-73.

Buoli M, Bertino V, Caldiroli A, Dobrea C, Serati M, Ciappolino V, Altamura AC (2016) Are obstetrical complications really involved in the etiology and course of schizophrenia and mood disorders? Psychiatry Res 241:297-301.

Calderoni S, Billeci L, Narzisi A, Brambilla P, Retico A, Muratori F (2016) Rehabilitative Interventions and Brain Plasticity in Autism Spectrum Disorders: Focus on MRI-Based Studies. Front Neurosci 10:139.

Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002) Minicolumnar pathology in autism. Neurology 58(3):428-32.

Chun JJM, Shatz CJ (1989) Interstitial-cells of the adult neocortical white matter are the remnant of the early generated subplate neuron population. J Comp Neurol 282, 555–569.

Cody H, Pelphrey K, Piven J (2002) Structural and functional magnetic resonance imaging of autism. Int J Dev Neurosci 20:421– 438.

Corradi-Dell'Acqua C, Tomelleri L, Bellani M, Rambaldelli G, Cerini R, Pozzi-Mucelli R, Balestrieri M, Tansella M et al. (2012) Thalamic-insular dysconnectivity in schizophrenia: evidence from structural equation modeling. Hum Brain Mapp 33(3):740-52.

Courchesne E (1988) Cerebellar changes in autism. In: Disorders of the Developing Nervous System: Changing Views on Their Origins, Diagnoses, and Treatments (18th Albany Birth Defects Symposium) (Swann JW, Messer A, eds), 1st ed. Liss Albany NY pp. 93–110.

Courchesne E, Carper R, Akshoomoff N (2003) Evidence of brain overgrowth in the first year of life in autism. JAMA 290:337–344.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P et al. (2001) Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57:245–254.

Courchesne E, Pierce K (2005) Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 15(2):225-30.

Crippa A, Del Vecchio G, Busti Ceccarelli S, Nobile M, Arrigoni F, Brambilla P (2016) Cortico-Cerebellar Connectivity in Autism Spectrum Disorder: What Do We Know So Far? Front Psychiatry 7:20.

De Graaf-Peters VB, Hadders-Algra M (2006) Ontogeny of the human central nervous system: what is happening when? Early Hum Dev 82: 257–66.

Dehmelt L, Halpain S (2005) The MAP2/Tau family of microtubule-associated proteins. Genome Biol 6: 204.

Eastwood SL, Harrison PJ (2003) Interstitial white matter neurons express less reelin and are abnormally distributed in schizophrenia: Towards an integration of molecular and morphologic aspects of the neurodevelopmental hypothesis. Mol Psychiatry 8:821-731.

Eastwood SL, Harrison PJ (2005) Interstitial white matter neuron density in the dorsolateral prefrontal cortex and parahippocampal gyrus in schizophrenia. Schizophr Res 79(2-3):181-8.

Eastwood SL, Harrison PJ (2006) Cellular basis of reduced cortical reelin expression in schizophrenia. Am J Psychiatry 163(3):540-2.

Fatemi SH (2005) Reelin glycoprotein: structure, biology and roles in health and disease. Mol Psychiatry 10(3):251-7.

Fatemi SH, Folsom TD (2009) The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull 35(3):528-48.

Fatemi SH, Snow AV, Stary JM, Araghi-Niknam M, Reutiman TJ, Lee S, Brooks AI, Pearce DA (2005) Reelin signaling is impaired in autism. Biol Psychiatry 57(7):777-87.

Fatemi SH, Stary JM, Egan EA (2002) Reduced blood levels of reelin as a vulnerability factor in pathophysiology of autistic disorder. Cell Mol Neurobiol 22(2):139-52.

Fitzgerald M (2005) The development of nociceptive circuits. Nat Rev Neurosci 6, 507–550.

Geschwind DH (2009) Advances in autism. Annu Rev Med 60, 367–380.

Geschwind DH, Levitt P (2007) Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol 17, 103–111.

Glenn OA (2009) Normal development of the fetal brain by MRI. Semin Perinatol 33(4):208-19.

González-Arnay E, González-Gómez M, Meyer G (2017) A Radial Glia Fascicle Leads Principal Neurons from the Pallial-Subpallial Boundary into the Developing Human Insula. Front Neuroanat 11:111.

Gupta S, Kulhara P (2010) What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis. Indian J Psychiatry 52(1):21-7.

Hadders-Algra M (2007) Putative neural substrate of normal and abnormal general movements. Neurosci Biobehav Rev 31(8):1181-90.

Hadders-Algra M (2018) Neural substrate and clinical significance of general movements: an update. Dev Med Child Neurol 60(1):39-46.

Harkin LF, Lindsay SJ, Xu Y, Alzu'bi A, Ferrara A, Gullon EA, James OG, Clowry GJ (2017) Neurexins 1-3 Each Have a Distinct Pattern of Expression in the Early Developing Human Cerebral Cortex. Cereb Cortex 27(1):216-232.

Harrison PJ (1999) The neuropathology of schizophrenia: a critical review of the data and their interpretation. Brain 122:593– 624.

Hoerder-Suabedissen A, Molnár Z (2015) Development, evolution and pathology of neocortical subplate neurons. Nat Rev Neurosci 16(3):133-46.

Hüppi PS (2010) Growth and development of the brain and impact on cognitive outcomes. Nestle Nutr Workshop Ser Pediatr Program 65:137-49; discussion 149-51.

Hutsler JJ, Avino TA (2013) Sigmoid fits to locate and characterize cortical boundaries in human cerebral cortex. J Neurosci Methods 212(2):242-6.

Hutsler JJ, Casanova MF (2016) Review: Cortical construction in autism spectrum disorder: columns, connectivity and the subplate. Neuropathol Appl Neurobiol 42(2):115-34.

Hutsler JJ, Love T, Zhang H (2007) Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. Biol Psychiatry 61(4):449-57.

Hutsler JJ, Zhang H (2010) Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Res 1309:83-94.

Ishii K, Kubo KI, Nakajima K (2016) Reelin and Neuropsychiatric Disorders. Front Cell Neurosci 10:229.

Jakab A, Schwartz E, Kasprian G, Gruber GM, Prayer D, Schöpf V, Langs G (2014) Fetal functional imaging portrays heterogeneous development of emerging human brain networks. Front Hum Neurosci 8:852.

Janusonis S, Gluncic V, Rakic P (2004) Early serotonergic projections to Cajal-Retzius cells: relevance for cortical development. J Neurosci 24(7):1652-9.

Jones EG (1995) Cortical development and neuropathology in schizophrenia. Ciba Found Symp 193:277-95.

Jovanov Milošević N, Judaš M, Aronica E, Kostovic I (2014) Neural ECM in laminar organization and connectivity development in healthy and diseased human brain. Prog Brain Res 214:159-78.

Judaš M, Sedmak G, Pletikos M (2010a) Early history of subplate and interstitial neurons: from Theodor Meynert (1867) to the discovery of the subplate zone (1974). J Anat 217(4):344-67.

Judaš M, Sedmak G, Pletikos M, Jovanov-Milošević N (2010b) Populations of subplate and interstitial neurons in fetal and adult human telencephalon. J Anat 217(4):381-99.

Judaš M, Sedmak G, Kostović I (2013) The significance of the subplate for evolution and developmental plasticity of the human brain. Front Hum Neurosci 7:423.

Kanold PO, Kara P, Reid RC, Shatz CJ (2003) Role of subplate neurons in functional maturation of visual cortical columns. Science 301, 521 – 525.

Kanold PO, Luhmann HJ (2010) The subplate and early cortical circuits. Annual Review of Neurosci 33, 23–48.

Kapellou O, Counsell SJ, Kennea N, Dyet L, Saeed N, Stark J, Maalouf E, Duggan P et al. (2006) Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. PLoS Med 3(8):e265.

Karolis VR, Froudist-Walsh S, Brittain PJ, Kroll J, Ball G, Edwards AD, Dell'Acqua F, Williams SC et al. (2016) Reinforcement of the Brain's Rich-Club Architecture Following Early Neurodevelopmental Disruption Caused by Very Preterm Birth. Cereb Cortex 26(3):1322-35.

Katz LC, Shatz CJ (1996) Synaptic activity and the construction of cortical circuits. Science 274, 1133–1138.

Kemper TL (1988) Neuroanatomic studies of dyslexia and autism. In: Disorders of the Developing Nervous System: Changing Views on Their Origins, Diagnoses, and Treatments (18th Albany Birth Defects Symposium) (Swann JW, Messer A, eds), 1st ed. Liss Albany NY pp. 125–154.

Kemper TL (2010) The developmental neuropathology of autism. In: The neurochemical basis of autism (Blatt GJ, eds). Springer New York pp. 69–82.

Kerschensteiner D (2014) Spontaneous network activity and synaptic development. Neuroscientist 20: 272–90.

Kirkpatrick B, Conley RC, Kakoyannis A, Reep RL, Roberts RC (1999) Interstitial cells of the white matter in the inferior parietal cortex in schizophrenia: an unbiased cell-counting study. Synapse 34, 95 – 102.

Kirkpatrick B, Messias NC, Conley RR, Roberts RC (2003) Interstitial cells of the white matter in the dorsolateral prefrontalcortex in deficit and nondeficit schizophrenia. J Nerv Ment Dis 191, 563 – 567.

Kostović I, Jovanov-Milošević N (2006) The development of cerebral connections during the first 20-45 weeks' gestation. Semin Fetal Neonatal Med 11(6):415-22.

Kostović I, Jovanov-Milošević N (2008) Subplate zone of the human brain: historical perspective and new concepts. Coll Antropol 32 Suppl 1:3-8.

Kostović I, Jovanov-Milošević N, Radoš M, Sedmak G, Benjak V, Kostović-Srzentić M, Vasung L, Čuljat M et al. (2014) Perinatal and early postnatal reorganization of the subplate and related cellular compartments in the human cerebral wall as revealed by histological and MRI approaches. Brain Struct Funct 219(1):231-53.

Kostović I, Judaš M (2002) Correlation between the sequential ingrowth of afferents and transient patterns of cortical lamination in preterm infants. Anat Rec 267(1):1-6.

Kostović I, Judaš M (2006) Prolonged coexistence of transient and permanent circuitry elements in the developing cerebral cortex of fetuses and preterm infants. Dev Med Child Neurol 48(5):388-93.

Kostović I, Judaš M (2007) Transient patterns of cortical lamination during prenatal life: do they have implications for treatment? Neurosci Biobehav Rev 31(8):1157-68.

Kostović I, Judaš M (2010) The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatr 99(8):1119-27.

Kostović I, Judaš M, Radoš M, Hrabaè P (2002). Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. Cereb Cortex 12, 536–544.

Kostović I, Judaš M, Sedmak G (2011) Developmental history of the subplate zone, subplate neurons and interstitial white matter neurons: relevance for schizophrenia. Int J Dev Neurosci 29(3):193-205.

Kostović I, Kostović-Srzentić M, Benjak V, Jovanov-Milošević N, Radoš M (2014) Developmental dynamics of radial vulnerability in the cerebral compartments in preterm infants and neonates. Front Neurol 5:139.

Kostović I, Molliver ME (1974) A new interpretation of the laminar development of cerebral cortex: synaptogenesis in different layers of neopallium in the human fetus. Anat Rec 178, 395.

Kostović I, Rakic P (1980) Cytology and time of origin of interstitial neurons in the white matter in infant and adult human and monkey telencephalon. J Neurocytol 9, 219–242.

Kostović I, Rakic P (1990) Developmental history of transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 297, 441–470.

Kostović I, Sedmak G, Vukšić M, Judaš M (2015) The relevance of human fetal subplate zone for developmental neuropathology of neuronal migration disorders and cortical dysplasia. CNS Neurosci Ther 21(2):74-82.

Kostović I, Vasung L (2009) Insights from in vitro fetal magnetic resonance imaging of cerebral development. Semin Perinatol 33(4):220-33.

Krsnik Ž, Majić V, Vasung L, Huang H, Kostović I (2017) Growth of Thalamocortical Fibers to the Somatosensory Cortex in the Human Fetal Brain. Front Neurosci 11:233.

Laurens KR, Luo L, Matheson SL, Carr VJ, Raudino A, Harris F, Green MJ (2015) Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. BMC Psychiatry 15:205.

Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA (2005) Fetal pain: a systematic multidisciplinary review of the evidence. JAMA 294, 947–954.

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312–324.

López-Bendito G, Mólnar Z (2003) Thalamocortical development: how are we going to get there? Nat Rev Neurosci 4, 276–289.

Luhmann HJ, Kilb W, Hanganu-Opatz IL (2009) Subplate cells: amplifiers of neuronal activity in the developing cerebral cortex. Front Neuroanat 3:19.

Luhmann HJ, Sinning A, Yang JW, Reyes-Puerta V, Stüttgen MC, Kirischuk S, Kilb W (2016) Spontaneous Neuronal Activity in Developing Neocortical Networks: From Single Cells to Large-Scale Interactions. Front Neural Circuits 10:40.

Mailath-Pokorny M, Kasprian G, Mitter C, Schöpf V, Nemec U, Prayer D (2012) Magnetic resonance methods in fetal neurology. Semin Fetal Neonatal Med 17(5):278-84.

Marín Padilla M (2001) The evolution of the structure of the neocortex in mammals: a new theory of cytoarchitecture. Rev Neurol 33(9):843-53.

Marín Padilla M (2014) The mammalian neocortex new pyramidal neuron: a new conception. Front Neuroanat 7: 51.

Marret S, Marchand-Martin L, Picaud JC, Hascoët JM, Arnaud C, Rozé JC, Truffert P, Larroque B et al. (2013) Brain injury in very preterm children and neurosensory and cognitive disabilities during childhood: the EPIPAGE cohort study. PLoS One 8(5):e62683.

Matson JL, Cervantes PE, Peters WJ (2016) Autism spectrum disorders: management over the lifespan. Expert Rev Neurother 16(11):1301-1310.

McConnell SK, Ghosh A, Shatz CJ (1989) Subplate neurons pioneer the first axon pathway from the cerebral cortex. Science 245(4921):978-82.

McQuillen PS, Ferriero DM (2005) Perinatal subplate neuron injury: implications for cortical development and plasticity. Brain Pathol 15 (3): 250-260.

Meyer G, Schaaps JP, Moreau L, Goffinet AM (2000) Embryonic and early fetal development of the human neocortex. J Neurosci 20(5):1858-68.

Millar LJ, Shi L, Hoerder-Suabedissen A, Molnár Z (2017) Neonatal Hypoxia Ischaemia: Mechanisms, Models, and Therapeutic Challenges. Front Cell Neurosci 11:78.

Molliver ME, Kostović I, van der Loos H (1973) The development of synapses in cerebral cortex of the human fetus. Brain Res 28;50(2):403-7.

Mullen RJ, Buck CR, Smith AM (1992) NeuN, a neuronal specific nuclear protein in vertebrates. Development 116:201–211.

Murray RM, Lewis SW (1987) Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) 295(6600): 681–682.

Nosarti C, Froudist-Walsh S (2016) Alterations in development of hippocampal and cortical memory mechanisms following very preterm birth. Dev Med Child Neurol 58 Suppl 4:35-45.

Nossin-Manor R, Card D, Raybaud C, Taylor MJ, Sled JG (2015) Cerebral maturation in the early preterm period-A magnetization transfer and diffusion tensor imaging study using voxel-based analysis. NeuroImage 112:30-42.

Ohtaka-Maruyama C, Nakajima K, Pierani A, Maeda N (2016) Editorial: Mechanisms of Neuronal Migration during Corticogenesis. Front Neurosci 10:172.

O'Donoghue S, Cannon DM, Perlini C, Brambilla P, McDonald C (2015) Applying neuroimaging to detect neuroanatomical dysconnectivity in psychosis. Epidemiol Psychiatr Sci 24(4):298-302.

Owen MJ, O'Donovan MC, Thapar A, Craddock N (2011) Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 198(3):173-5.

Perkins L, Hughes E, Srinivasan L, Allsop J, Glover A, Kumar S, Fisk N, Rutherford M (2008) Exploring cortical subplate evolution using magnetic resonance imaging of the fetal brain. Dev Neurosci 30(1-3): 211-20.

Piven J, Arndt S, Bailey J, Havercamp S (1995) An MRI study of brain size in autism. Am J Psychiat 152:1145.

Piven J, Arndt S, Bailey J, Andreasen N (1996) Regional brain enlargement in autism: A magnetic resonance imaging study. J Amer Acad Child Adoles Psychiat 35:530 –536.

Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S (1990) Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. Am J Psychiat 147:734 –739.

Polo-Kantola P, Lampi KM, Hinkka-Yli-Salomäki S, Gissler M, Brown AS, Sourander A (2014) Obstetric risk factors and autism spectrum disorders in Finland. J Pediatr 164(2):358-65.

Pugash D, Hendson G, Dunham CP, Dewar K, Money DM, Prayer D (2012) Sonographic assessment of normal and abnormal patterns of fetal cerebral lamination. Ultrasound Obstet Gynecol 40(6):642-51.

Radoš M, Judaš M, Kostović I (2006) In vitro MRI of brain development. Eur J Radiol 57, 187–198.

Rakic P (2006) A century of corticoneurogenesis: from silver impregnation to genetic engineering. Cereb Cortex 16, i3–i17.

Rakic P, Bourgeois JP, Goldman-Rakic PS (1994) Synaptic development of the cerebral cortex: implications for learning, memory and mental illness. Prog Brain Res 102, 227–243.

Rice DS, Curran T (2001) Role of the reelin signaling pathway in central nervous system development. Annu Rev Neurosci 24:1005–1039.

Rioux L, Nissanov J, Lauber K, Bilker WB, Arnold SE (2003) Distribution of microtubule-associated protein MAP2-immunoreactive interstitial neurons in the parahippocampal white matter in subjects with schizophrenia. Am J Psychiatry 160(1):149-55.

Sarnat HB, Nochlin D, Born DE (1998) Neuronal nuclear antigen (NeuN): A marker of neuronal maturation in early human fetal nervous system. Brain Dev 20:88 –94.

Schlotz W, Godfrey KM, Phillips DI (2014) Prenatal origins of temperament: fetal growth, brain structure, and inhibitory control in adolescence. PLoS One 9(5):e96715.

Schmitt A, Hasan A, Gruber O, Falkai P (2011) Schizophrenia as a disorder of disconnectivity. Eur Arch Psyhiatry Clin Neuroscience 261 Suppl 2:S150-4.

Scola E, Conte G, Palumbo G, Avignone S, Cinnante CM, Boito S, Persico N, Rizzuti T et al. (2018) High resolution post-mortem MRI of non-fixed in situ foetal brain in the second trimester of gestation: Normal foetal brain development. Eur Radiol 28(1):363-371.

Scott JA, Habas PA, Kim K, Rajagopalan V, Hamzelou KS, Corbett-Detig JM, Barkovich AJ, Glenn OA et al. (2011) Growth trajectories of the human fetal brain tissues estimated from 3D reconstructed in utero MRI. Int J Dev Neurosci 29(5):529-36.

Serajee FJ, Zhong H, Mahbubul Huq AH (2006) Association of Reelin gene polymorphisms with autism. Genomics 87(1):75-83.

Skaar DA, Shao Y, Haines JL, Stenger JE, Jaworski J, Martin ER, DeLong GR, Moore JH et al. (2005) Analysis of the RELN gene as a genetic risk factor for autism. Mol Psychiatry 10(6):563-71.

Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, Fitzgerald M (2006) Cortical pain responses in human infants. J Neurosci 26(14):3662-6.

Stephan KE, Friston KJ, Frith CD (2009) Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 35(3):509-27.

Stolp H, Neuhaus A, Sundramoorthi R, Molnár Z (2012) The Long and the Short of it: Gene and Environment Interactions During Early Cortical Development and Consequences for Long-Term Neurological Disease. Front Psychiatry 3:50.

Studholme C (2015) Mapping the developing human brain in utero using quantitative MR imaging techniques. Semin Perinatol 39(2):105-112.

Suárez-Solá ML, Gonzáles-Delgado FJ, Pueyo-Morlans M, Medina-Bolivar OC, Hernandez-Acosta NC, Gonzáles-Gomez M, Meyer G (2009) Neurons white matter of the adult human neocortex. Front Neuroanat 3, 1–6.

Takahashi E, Folkerth RD, Galaburda AM, Grant PE (2012) Emerging cerebral connectivity in the human fetal brain: an MR tractography study. Cereb Cortex 22(2):455-64.

Thomason ME, Grove LE, Lozon TAJr, Vila AM, Ye Y, Nye MJ, Manning JH, Pappas A et al. (2015) Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. Dev Cogn Neurosci 11:96-104.

Toga AW, Thompson PM, Sowell ER (2006) Mapping brain maturation. Trends Neurosci 29(3):148-59.

Triulzi F, Manganaro L, Volpe P (2011) Fetal magnetic resonance imaging: indications, study protocols and safety. Radiol Med 116(3):337-50.

Unis AS (1993) Concentration and distribution of [3H]-SCH23390 and [3H]-YMO9151-2 binding sites in midgestational human fetal cortex. Psychopharmacol Bull 19 (3): 415-25.

Vasung L, Lepage C, Radoš M, Pletikos M, Goldman JS, Richiardi J, Raguž M, Fischi-Gómez E et al. (2016) Quantitative and Qualitative Analysis of Transient Fetal Compartments during Prenatal Human Brain Development. Front Neuroanat 10:11.

Volpe JJ (2009a) Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 8: 110–24.

Volpe JJ (2009b) The encephalopathy of prematurity–brain injury and impaired brain development inextricably intertwined. Semin Pediatr Neurol 16, 167–178.

Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44, 660–669.

Wright R, Kyriakopoulou V, Ledig C, Rutherford MA, Hajnal JV, Rueckert D, Aljabar P (2014) Automatic quantification of normal cortical folding patterns from fetal brain MRI. Neuroimage 91:21-32.

Yang Y, Fung SJ, Rothwell A, Tianmei S, Weickert CS (2011) Increased interstitial white matter neuron density in the dorsolateral prefrontal cortex of people with schizophrenia. Biol Psychiatry 69(1):63-70.

Zecevic N, Bourgeois JP, Rakic P (1989) Changes in synaptic density in motor cortex of rhesusmonkey during fetal and postnatal life. Dev Brain Res 50, 11–32.

Zecevic N, Rakic P (1991) Synaptogenesis in monkey somatosensory cortex. Cereb Cortex 1, 510–523.

Zhan J, Dinov ID, Li J, Zhang Z, Hobel S, Shi Y, Lin X, Zamanyan A et al. (2013) Spatial-temporal atlas of human fetal brain development during the early second trimester. NeuroImage 82:115-26.

Zhang H, Liu X, Zhang C, Mundo E, Macciardi F, Grayson DR, Guidotti AR, Holden JJ (2002) Reelin gene alleles and susceptibility to autism spectrum disorders. Mol Psychiatry 7(9):1012-7.

Žunić Išasegi I, Radoš M, Krsnik Ž, Radoš M, Benjak V, Kostović I (2018) Interactive histogenesis of axonal strata and proliferative zones in the human fetal cerebral wall. Brain Struct Funct 223(9):3919-3943.

FIGURE 1 SCHEMATIC DIAGRAM ILLUSTRATING NEOCORTICAL DEVELOPMENT MAJOR STAGES [ADAPTED FROM KIRISCHUK ET AL., 2017]

FIGURE 2 FETAL MRI IN VIVO AND POST-MORTEM. PHYSIOLOGICAL SP CHANGES, AT 22 WEEKS OF GESTATION (MAXIMUM EXTENSION) AND AT 28 WEEKS OF GESTATION (SP NO LONGER IDENTIFIABLE FROM THE UNDERLYING INTERMEDIATE ZONE). SP SIGNAL INTENSITY CHANGE ON MRI PRECEDES THE DATE OF DISSOLUTION OF THE SP ZONE BASED ON HISTOLOGICAL STUDIES.

Table 1. SP and Schizophrenia

Author, year	Sample	Methods / Knowledges	Neuronal stain [a]	Conclusions
Akbarian et al., 1993	5 schizophrenic and 5 control subjects	Prefrontal cortex WM characterized by histochemical study	NAPDH	Findings are consistent with a SP disturbance during development with compromised programmed cell death.
Akbarian et al., 1996	20 schizophrenic patients and 20 matched control subjects	WM middle frontal gyrus characterized by histochemical study	NAPDH, MAP2	Nicotinamide adenine dinucleotide phosphate-diaphorase neurons were reduced in superficial WM and showed variable densities in deeper WM.
Anderson et al., 1996	5 schizophrenics and 5 matched control subjects	prefrontal WM Immunoreactivity	MAP2	The mean density of MAP2-immunoreactive neurons was greater in the superficial WM of schizophrenic subjects compared to matched controls.
Kirkpatrick et al., 1999	9 schizophrenia subjects (3 deficit and 6 nondeficit) and 9 matched control subjects	IWMN density inferior parietal cortex compared in schizophrenia subjects and matched controls Immunoreactivity	MAP2	IWMN density was significantly greater in the deficit syndrome subjects compared to other groups.
Eastwood and Harrison, 2003	12 subjects with schizophrenia and 14 control subjects	Abnormal distribution of neurons in superior temporal cortex. Immunoreactivity	NeuN	IWMNs distribution and density was increased in the superficial WM in schizophrenia.
Kirkpatrick et al., 2003	3 subjects with deficit schizophrenia, 4 subjects with nondeficit schizophrenia and 5 control subjects	Postmortem tissue from the dorsolateral prefrontal cortex. Immunoreactivity	MAP2	The deficit group differed significantly from the other two groups.

Rioux et al., 2003	41 schizophrenics and 15 control subjects	IWMN in the anterior region of the parahippocampal gyrus, gray matter/WM boundary	MAP2	The number of IWMN decreased with increasing WM depth in both groups, but significantly more slowly in the schizophrenia group. IWMN located deeper in WM in schizophrenics
Eastwood and Harrison, 2005	11 schizophrenics and 12 control subjects	IWMN density in the dorsolateral prefrontal cortex and parahippocampal gyrus.	NeuN	IWMN density was found to be increased in schizophrenia in the superficial dorsolateral prefrontal cortex WM.
Eastwood and Harrison, 2006	13 schizophrenics and 12 control subjects	reelin mRNA in the hippocampal formation and dorsolateral prefrontal cortex.	reelin mRNA	IWMN contribute to the reduction in reelin mRNA in schizophrenia.
Yang et al., 2011	29 schizophrenics and 37 control subjects	IWMN densities determined in the dorsolateral prefrontal cortex	NeuN, SST	IWMNs density is increased in superficial WM in schizophrenia, gray matter interneuron deficit

Legend: WM: white matter; IWMN: interstitial white matter neurons

[a] NeuN: anti-neuronal nuclei; MAP2: anti-microtuble associated protein 2; NAPDH: nicotinamide–adenine dinucleotide phosphate-diaphorase; SST: somatostatin

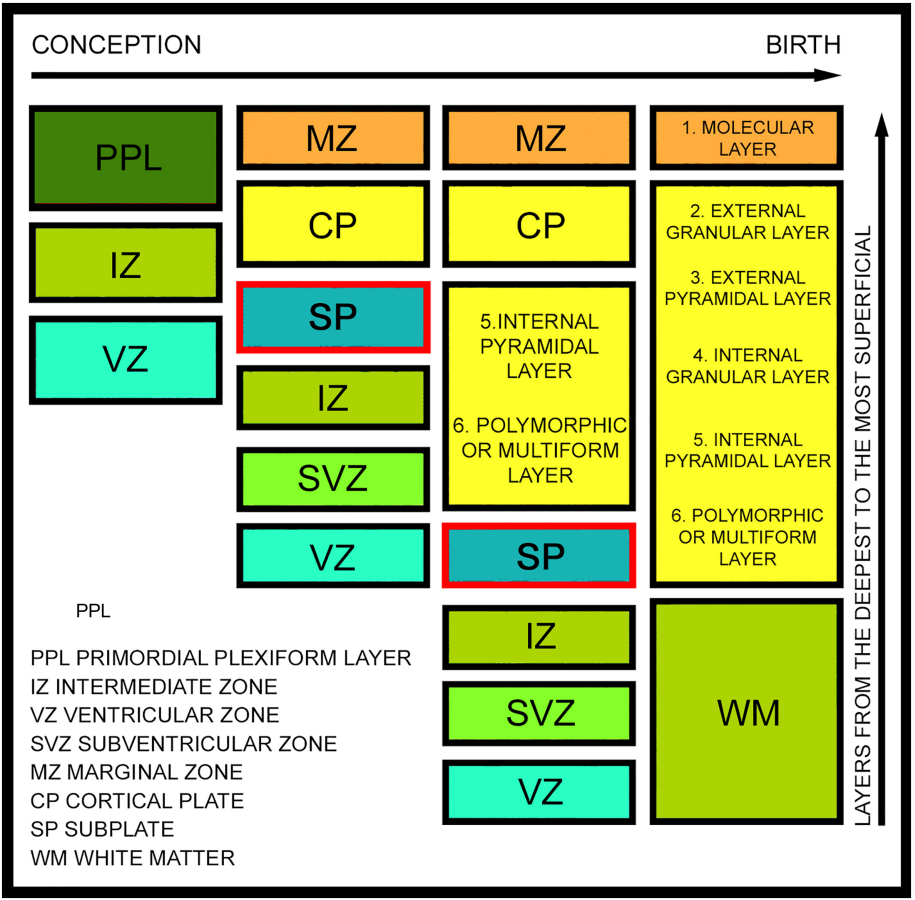
Table 2. SP and Autism

Author, year	Sample	Methods / Knowledges	Results
Hutsler et al., 2007	16 postmortem ASD individuals and 16 age-matched control subjects	MRI evaluate total cortical thickness, and histological samples evaluate the pattern of cortical layering.	Qualitative examination revealed evidence of cell clustering and supernumerary cells in layer I and the SP in ASD.
Avino and Hutsler, 2010	8 ASD and 8 control subjects	Digital photomicrographs of the gray-white matter boundary	Supernumerary neurons presence in cortical plate could be the result of migration deficits or failed apoptosis in the SP region.

Legend: MRI: Magnetic resonance imaging; ASD: autism spectrum disorders

Highlights

- Subplate (SP) represents a transitory cytoarchitectonic fetal compartment
- SP critical maturation period is between the 15th till 24th weeks after conception
- SP is visible with Diffusion Tensor Imaging (DTI) and Magnetic Resonance Imaging (MRI)
- Fetal SP neurons surviving in postnatal period are visible in schizophrenia/autism with MRI
- SP residual may alter cortical activity, ultimately affecting cognition


CONCEPTION
BIRTH
PPL
IZ
VZ
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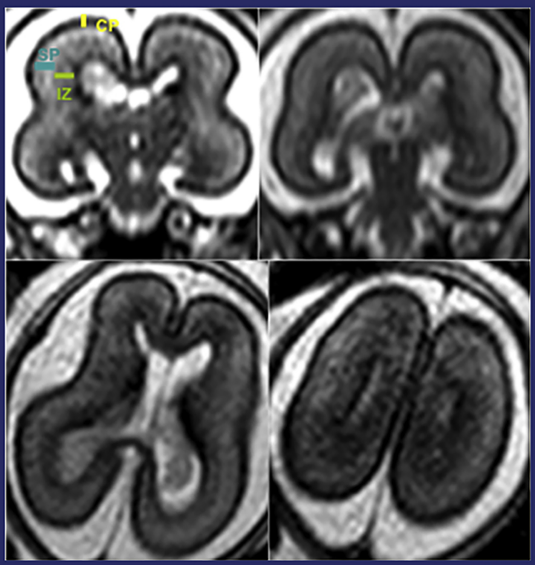
CP
SP
IZ
SVZ
VZ
MZ
CP
5.INTERNAL PYRAMIDAL LAYER
6. POLYMORPHIC OR MULTIFORM LAYER
SP
IZ
SVZ
VZ
1. MOLECULAR LAYER
2. EXTERNAL GRANULAR LAYER
3. EXTERNAL PYRAMIDAL LAYER
4. INTERNAL GRANULAR LAYER
5. INTERNAL PYRAMIDAL LAYER
6. POLYMORPHIC OR MULTIFORM LAYER
WM
LAYERS FROM THE DEEPEST TO THE MOST SUPERFICIAL
PPL
PPL PRIMORDIAL PLEXIFORM LAYER
IZ INTERMEDIATE ZONE
VZ VENTRICULAR ZONE
SVZ SUBVENTRICULAR ZONE
MZ MARGINAL ZONE
CP CORTICAL PLATE
SP SUBPLATE
WM WHITE MATTER

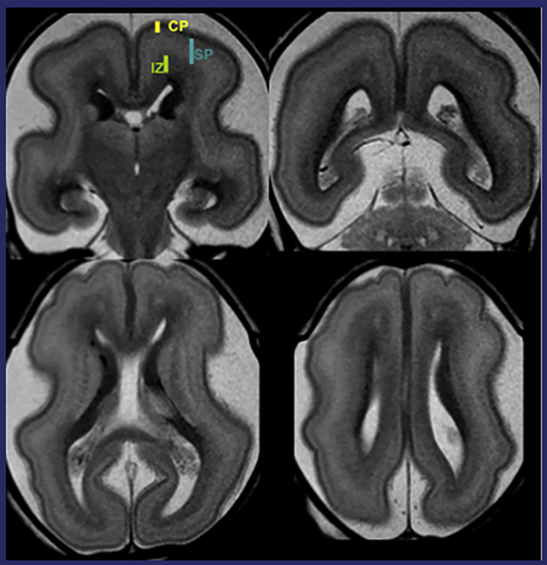
Figure 1

22 GESTATIONAL WEEKS

FETAL MRI IN VIVO



FETAL MRI POST PORTEM



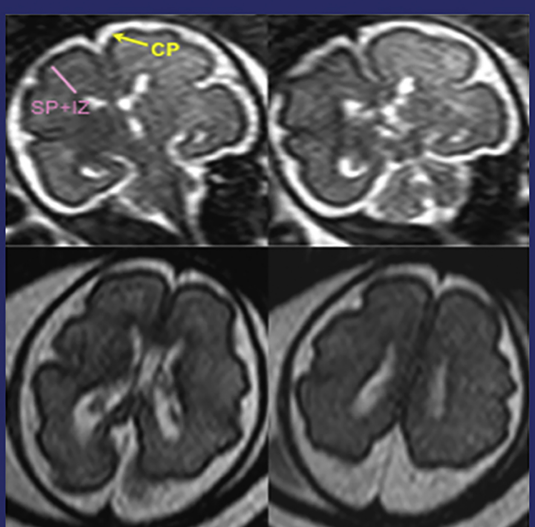
CP CORTICAL PLATE

SP SUBPLATE

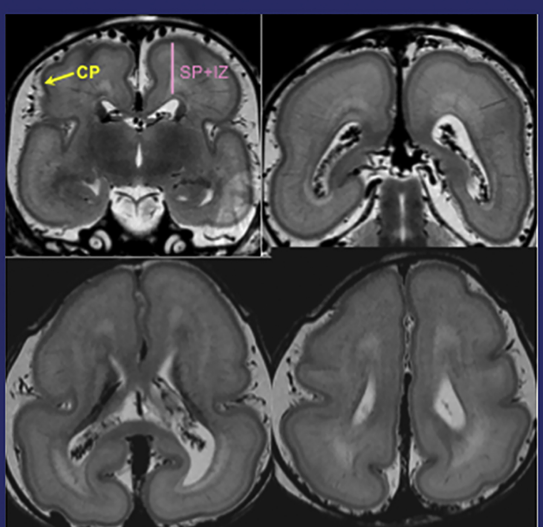
IZ INTERMEDIATE ZONE

28 GESTATIONAL WEEKS

FETAL MRI IN VIVO



FETAL MRI POST PORTEM



CP CORTICAL PLATE

SP+IZ SUBPLATE AND INTERMEDIATE ZONE

Figure 2