Placebo

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Synonyms

Placebo effect; Placebo response

Definition

A simulated intervention (often a drug but potentially other interventions) used as a control/comparison in research studies. As suggested in the title of a book on the subject (Shapiro & Shapiro, 2000), the effects of such treatment can be powerful (what is termed to placebo response or effect). In drug studies, for example, the use of a placebo (inert agent that is packaged so as to be indistinguishable from the drug being studied) control provides one of the most stringent tests in demonstrating drug efficacy.

As Volkmar and Wiesner (2009) note that the nature of the placebo response in studies involving children with autism reflects several factors: high levels of attention from parents, teachers, and clinicians; provision of high-quality care during a study; variation in symptoms over time; and the effects of expecting a change with a new treatment (see also Volkmar, 2001). The effects of placebo treatments can be quite strong, as demonstrated in studies of secretin which did not significantly outperform secretin (Sandler & Bodfish 2000); on the other hand, studies of agents like risperidone (McCracken et al., 2002), the active drug, proved significantly better than placebo even after only a few weeks of administration.

See Also

- ▶ Risperidone
- ▶ Secretin

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Placebo Effect

- ▶ Placebo

Placebo Response

- ▶ Placebo

Placement-Pending Requirement

- ▶ Stay-Put Requirement

Placenta

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Definition

If we could noninvasively analyze the detailed neuroanatomy of all newborns at a cellular, synapse by synapse level, we might be able to

identify those children who will go on to have an autistic spectrum disorder (ASD). As that is unlikely to be possible anytime soon, doctors seek surrogates that can make the same diagnoses. Luckily, the placenta, an organ that is often routinely discarded at birth, may be able to identify those babies who will exhibit overt signs of autism months or years later.

The human placenta is not only an integral part of the fetus during all of pregnancy, but it also shares in the vast majority of cases the exact genetic makeup of the fetus. As such, it offers the potential to reveal abnormal morphologic patterns that may be at the basis of ASD and other genetic and developmental abnormalities.

Historical Background

Formation of the Placenta

Humans start off as a symmetrical ball of cells. Even as our first few dozen cells begin to separate into an inner cell mass (which will become the embryo, fetus, and eventually baby) and the trophoblasts (which will become the placenta), genes are regulating the creation of the developmental axes that will form the basis of the entire organism (Kliman, 1999). Defects in the genes that regulate these processes lead to a wide range of embryonic, fetal, and neonatal defects from minor cosmetic abnormalities to disasters that terminate pregnancy within a few days to weeks after fertilization.

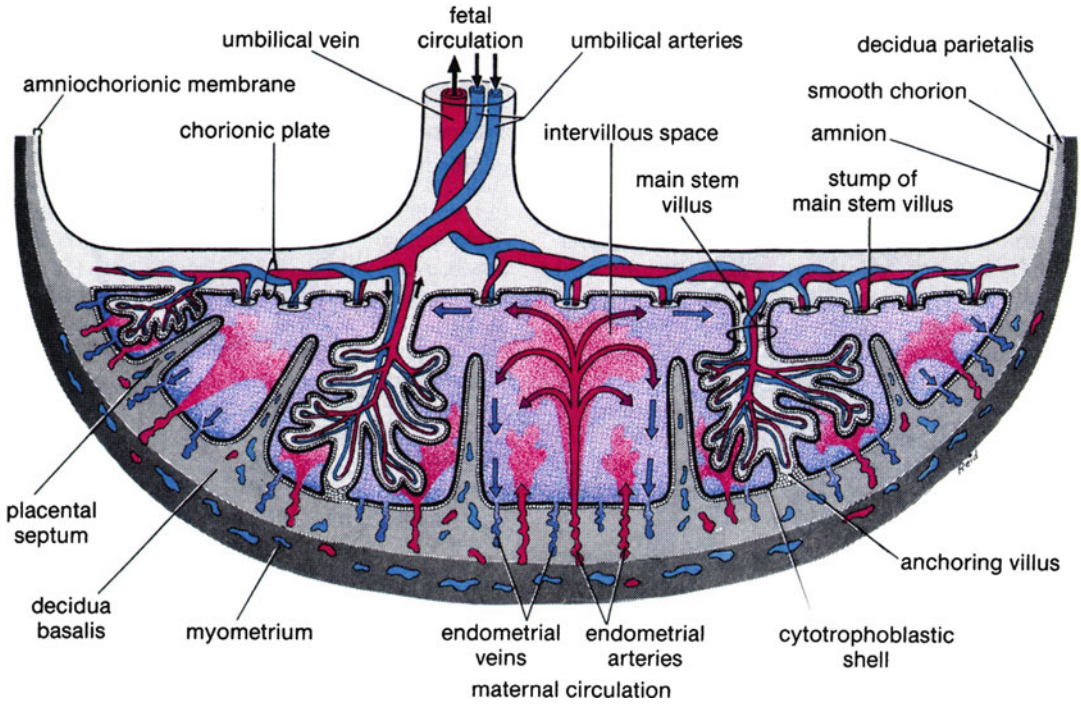
By 21 days after fertilization, the trophoblasts have begun to sort themselves into what will become the treelike structures that make up the placenta: the chorionic trees, branches, and villi (Fig. 1). The terminal villi (from the Latin for shaggy hair) are fingerlike structures that are covered with a double cell layer. This trophoblast bilayer is made up of an inner cytotrophoblast layer made of single nucleated cells and an outer syncytiotrophoblast layer made of giant multinucleated sheets (Fig. 2). Starting with purified cytotrophoblasts, we demonstrated using in vitro time lapse cinematography that cytotrophoblasts fuse to form syncytiotrophoblast (Kliman, Nestler, Sermasi, Sanger, & Strauss, 1986) (Fig. 3), an observation that has been confirmed in situ (Huppertz, Tews, & Kaufmann, 2001). The critical conclusion from these studies is that only the cytotrophoblasts proliferate, making the growth of the syncytiotrophoblast layer completely dependent on the absorption of fusing cytotrophoblasts (Fig. 4).

Current Knowledge

Trophoblast Inclusions

The relative rates of cytotrophoblast proliferation and incorporation into the outer syncytiotrophoblast layer appear to determine the morphology of the fingerlike chorionic villi (Huppertz et al., 2001; Kliman & Segel, 2003; Rejniak, Kliman, & Fauci, 2004). In the normal placenta, new villus branches are formed by outward bending bulges of the trophoblast bilayer (Fig. 5). However, when these critical processes go awry, the bilayer can inappropriately bulge inward into the villi, creating invaginations (Fig. 6) and trophoblast inclusions (Fig. 7) that can be readily detected upon histological examination of sectioned placental tissue.

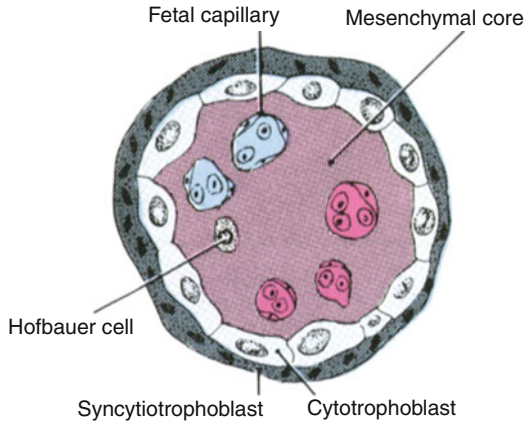
The basis of trophoblast invaginations and inclusions, therefore, appears to be an imbalance between the rate of cytotrophoblast proliferation and fusion (Rejniak et al., 2004). This could be the result of either an increased rate of proliferation – due to either endogenous genetic factors within these cells or exogenous factors such as increased exposure to paracrine or endocrine growth factors – or the result of a decreased rate of fusion – due to decreased production of the factors that facilitate cell fusion. Endogenous cell proliferation rates may be affected by genes that regulate the mitotic cycle, such as the cyclins (Gillett & Barnes, 1998). Equally potent are hormones that regulate cellular proliferation, such as growth hormone and insulin. Abnormalities of cytotrophoblast fusion have been shown in the placentas of Down syndrome (trisomy 21) children, showing a direct relationship between this particular genetic disorder and placental morphogenesis (Malassine, Frendo, & Evain-Brion, 2010).



Placenta, Fig. 1 *Diagram of the human placenta.* The placenta, which is part of the fetus, attaches to the maternal decidua via the anchoring villi. The maternal blood is injected into the intervillous space where it circulates around the chorionic villi and then returns to the maternal circulation via the endometrial veins. The fetus pumps its blood into the placenta via the umbilical arteries, which branch in the chorionic plate and eventually dive down to form the villus trees. The fetal circulation terminates in the fingerlike chorionic villi, which are covered by a layer of trophoblast cells (see Fig. 2). (From Moore KL, The Developing Human, 4th edition, WB Saunders, 1988, used with permission)

Understanding how trophoblast invaginations and inclusions are formed helps to identify them in placental tissues and leads to criteria for diagnosing these dysmorphic features. In almost all cases of invagination, there is an increased number of cytotrophoblasts at the point of infolding compared to the density of cytotrophoblasts away from the invagination (Fig. 8). Likewise, careful examination of a trophoblast inclusion reveals a central region of syncytiotrophoblasts, surrounded by cytotrophoblasts (Fig. 8). Like an epidermal inclusion cyst, which continues to get larger and larger over time, the cytotrophoblasts continue to proliferate and fuse with the adjacent syncytiotrophoblasts, which in some cases leads to very large trophoblast inclusions (see Fig. 7d). Adherence to the criteria of identifying increased numbers of cytotrophoblasts along the invagination and around the syncytiotrophoblast core of an inclusion helps to distinguish trophoblast invaginations and inclusions from tangential sections of curved chorionic villus surfaces.

Although trophoblast inclusions were first described as a marker of triploid gestations (a complete extra one set of chromosomes) (Szulman, Philippe, Boue, & Boue, 1981), it is now appreciated that the presence of trophoblast inclusions in placentas is associated with a long list of genetically abnormal gestations, including tetraploidy (a complete extra two sets of chromosomes), trisomies (an extra individual chromosome, such as trisomy 21 or Down syndrome, trisomy 18, and trisomy 13), Turner's syndrome (female with one X chromosome missing), and even genetic diseases without obvious chromosome abnormalities (Honore, Dill, & Poland, 1976; Novak et al., 1988; Silvestre, Cusi, Borras, & Antich, 1996; Szulman, 1984; van Lijnschoten,



Placenta, Fig. 2 *Diagrammatic cross section of first-trimester chorionic villus*. The villus core of villi contains fetal capillaries embedded in a loose matrix which contains fibroblasts and macrophages (also called Hofbauer cells). In the first trimester, a villus cross section reveals two distinct trophoblast layers, the outer syncytiotrophoblast layer which is in direct contact with maternal blood and the inner cytotrophoblast layer, the stem cell of the placenta and the source of new trophoblasts. (Modified from Moore KL, The Developing Human, 4th edition, WB Saunders, 1988, used with permission)

Arends, De La Fuente, Schouten, & Geraedts, 1993). Thus, many different genetic defects manifest themselves in the placenta as trophoblast inclusions. Since cytotrophoblast proliferation and absorption is no doubt regulated by many genes, it appears that abnormalities in any part of these multigene processes may result in these villus dysmorphic features.

Frequency of Trophoblast Inclusions

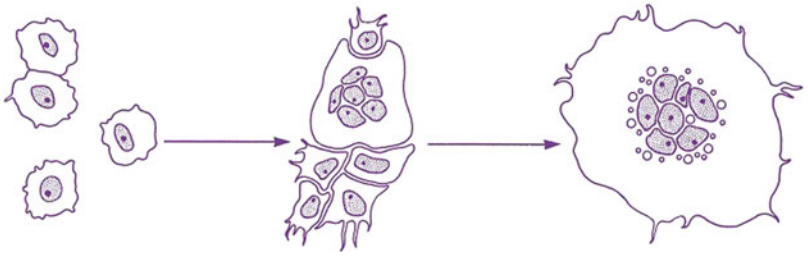
Fewer than 3% of placentas from uncomplicated, normal gestations manifest trophoblast inclusions. But 70% of placentas of fetuses with known chromosomal abnormalities exhibit inclusions (Kliman et al., 2003). Since the presence of a normal karyotype does not exclude the possibility of a genetic defect (e.g., cystic fibrosis, Tay-Sachs, sickle cell disease), it should not be surprising that trophoblast inclusions are also seen in cases with a normal karyotype. The most common example of the later situation is a spontaneous pregnancy loss where the karyotype is normal, but clearly, there is something abnormal about the gestation. The genetic basis of such losses is reinforced by the finding of both a high recurrence risk for these families and the fact that the losses almost always occur at the same gestational age for each particular family, suggesting a specific programming error.

The more severe the genetic abnormality, or the earlier the pregnancy loss, the more inclusions are found (Fig. 9). This is consistent with studies that have concluded that over 90% of first-trimester losses are secondary to genetic causes (Zhang et al., 2009). As pregnancies progress from the first to the third trimester, the likelihood of a genetic basis for a pregnancy loss decreases but does not go to zero even at term. Not surprisingly, the number of trophoblast inclusions seen in cases that reach term are fewer than those that terminate early in pregnancy. This is most likely related to the severity of the genetic abnormality, with the most severe terminating before 13 weeks of gestation.

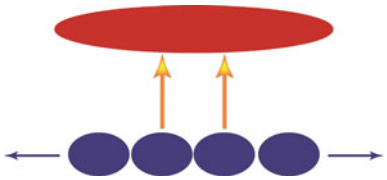
The only documented nongenetic cause for trophoblast inclusions appears to be gestational diabetes. In such cases, it is believed that increased glucose and insulin levels lead to increased cytotrophoblast proliferation, which as described above, would lead to invagination of the trophoblast bilayer. This is consistent with the observation that cultured cytotrophoblasts grow better in high glucose media compared to normal media (Kliman et al., 1986). It is also of interest that diabetics have a much higher fetal anomaly rate (Correa et al., 2008), suggesting that the high glucose insulin environment leads not only to abnormalities in the placenta but also in the fetus. This has been confirmed in rat gestations where it has been shown that high glucose levels alone can lead to both deformed fetuses and pregnancy terminations (Reece, Pinter, Homko, Wu, & Naftolin, 1994).

Trophoblast Inclusions and Autism

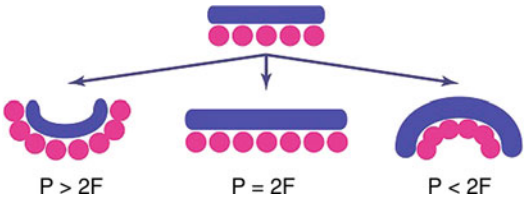
It was in the context of trophoblast inclusions as a general marker of genetic and developmental abnormalities that the association of trophoblast inclusions and autism was first suggested. The linkage was first observed anecdotally in two cases of Asperger's syndrome, which was then followed by a retrospective study. Trophoblast



Placenta, Fig. 3 *In vitro conversion of cytotrophoblasts into syncytiotrophoblasts*. Individual cytotrophoblasts (*left*) migrate like amoeba, eventually making contact with each other. Once in contact, the cytotrophoblasts form aggregates (*middle*), and in time, the cells fuse to form syncytiotrophoblasts. Eventually, all the cytotrophoblasts have merged and fused to make a large syncytiotrophoblast (*right*). (From Kliman HJ, Nestler JE, Sermasi E, Sanger JM, and Strauss JF III. (1986) Purification, characterization and in vitro differentiation of cytotrophoblasts from human term placentae. Endocrinology 118: 1567–1582, used with permission. *Copyright 1986, The Endocrine Society*)



Placenta, Fig. 4 *Cytotrophoblast proliferation and fusion*. Cytotrophoblasts (*blue*) either proliferate to increase the number of trophoblastic stem cells (*blue arrows*) or occasionally fuse upward (*gold arrows*) into the multinucleated syncytiotrophoblast layer (*red*). The balance of these two processes – proliferation and fusion – determines the overall morphology of the placenta's chorionic villi (see also Fig. 5)



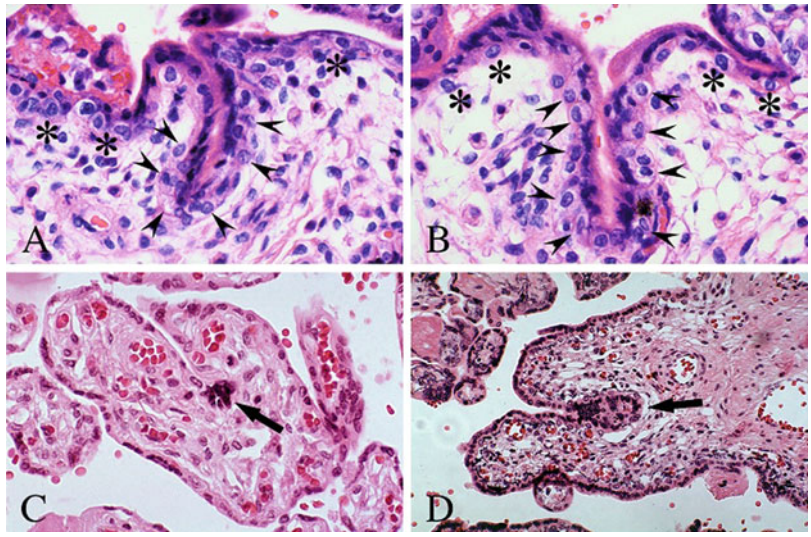
Placenta, Fig. 5 *Proliferation fusion model*. A model illustrating the different ratios of proliferation (*P*) and fusion (*F*). Cytotrophoblasts (*pink circles*) proliferate and intermittently fuse into the upper syncytiotrophoblast layer (*blue bars*). Stability (relative flatness) of the bilayer is maintained at, or near, an ideal ratio: P = 2F. Normal outward budding (evagination) is observed from the ratio: P < 2F, while an abnormal trophoblast inclusion (invagination) results from the ratio: P > 2F. (Kliman HJ, Segel L. (2003) The placenta may predict the baby. J Ther Biol, 225: 143–145, used with permission)

inclusions were found in significantly more cases of ASD than would be predicted from the normal population (Anderson, Jacobs-Stannard, Chawarska, Volkmar, & Kliman, 2007).

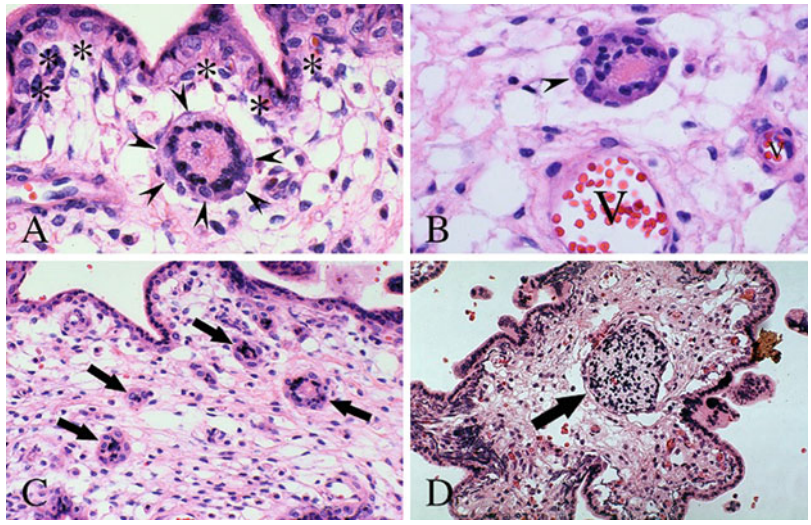
This result fits into the consensus view that ASD is largely genetically based. It also suggests that this seemingly polygenetic, heterogeneous condition may ultimately be caused by subtle abnormalities in common morphogenetic processes, such as bilayer folding.

A Problem of Folding

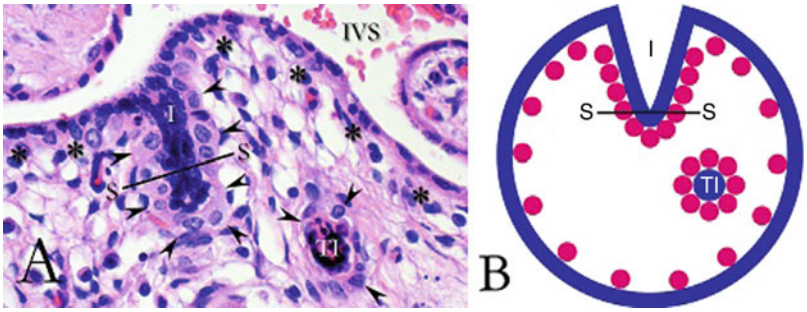
There are only a few developmental processes in the embryology tool box. These include cell proliferation, cell death, cell migration, cell hypertrophy, differentiation, fusion, and cellular dissociation. With these tools, all the various organs and body parts are made. One of the common problems in development is how to increase surface area. There are two basic solutions to this problem: increased branching or increased folding. In both cases, these are most often achieved by differential growth of layers of cells, which due to increased tension being built up in one layer or another, results in bending. This is exactly how the placenta forms new buds and villi to make the villus tree. It is also how the heart forms, the bronchi branch in the lung, the kidney tubules form, the gut surface area



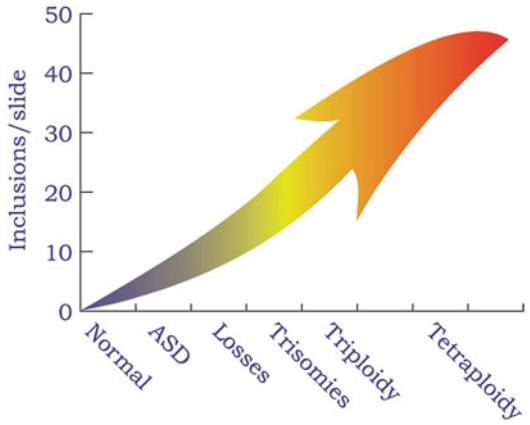
Placenta, Fig. 6 *Trophoblast invaginations.* (**a**, **b**) Trophoblast invaginations forming cleft-like structures. Note the many cytotrophoblasts lining the invaginations (*arrowheads*) and the fewer cytotrophoblasts underlying the normal bilayers (*). (**c**) Invagination ending in an area of increased syncytiotrophoblasts (*arrow*). Even though the bilayer is invaginated, syncytiotrophoblasts still form. (**d**) Bulb-like prominence of syncytiotrophoblasts at base of an invagination (*arrow*). (Kliman HJ, Segel L. (2003) The placenta may predict the baby. J Ther Biol, 225: 143–145, used with permission)



Placenta, Fig. 7 *Trophoblast inclusions.* (**a**) Trophoblast inclusion within the villous core. Note how the cytotrophoblasts of the bilayer (*arrowheads*) and the cytotrophoblasts of the inclusion (*) both are adjacent to the villous core. (**b**) Trophoblast inclusion with a prominent syncytiotrophoblast layer and a lone cytotrophoblast (*arrowhead*). Fetal vessels (*V*). (**c**) Chorionic villous with four prominent trophoblast inclusions (*arrows*). (**d**) Trophoblast inclusion with very expanded syncytiotrophoblast component (*arrow*). (Kliman HJ, Segel L. (2003) The placenta may predict the baby. J Ther Biol, 225: 143–145, used with permission)



Placenta, Fig. 8 *Formation of trophoblast invaginations and inclusions*. (**a**) Histologic section of a placental villus which exhibits both a trophoblast invagination (*I*) and inclusion (*TI*). Note the increased numbers of cytotrophoblasts (*arrow heads*) beneath the syncytiotrophoblast layer in the region of the invagination and their paucity away from the invagination (*). When an invagination is sectioned perpendicular to its long axis (*S-S*), it appears as an inclusion (*TI*), with dark syncytiotrophoblast nuclei in its center surrounded by cytotrophoblasts (*arrow heads*). *IVS* Intervillus space. (**b**) Diagram of a villus cross section showing the outer syncytiotrophoblast layer (*blue*) and inner cytotrophoblast layer (*pink cells*) with a trophoblast invagination (*I*) and inclusion (*TI*) illustrating the relevant morphology and disposition of cytotrophoblasts in the region of the invagination. (From Anderson GM, Jacobs-Stannard A, Chawarska K, Volkmar FR, Kliman HJ. (2007) Placental Trophoblast Inclusions in Autism Spectrum Disorder, Biological Psychiatry, 61:487–491, used with permission)



Placenta, Fig. 9 *Trophoblast inclusions as a function of genetic abnormality severity*. Normal placentas rarely exhibit trophoblast inclusions. As the degree of genetic abnormality increases, the more trophoblast inclusions can be identified per unit area of placenta examined. The earlier the pregnancy loss, the more frequent the inclusions. Many pregnancy losses reveal normal karyotypes; however, a significant number of trophoblast inclusions can be seen in many of these cases. The trisomies (e.g., trisomy 21, 13, 18) may or may not lead to an early pregnancy loss, depending on which chromosome is affected. In very abnormal gestations, such as triploidy and tetraploidy, as many as 50 or more inclusions per slide can be seen. ASD, a subtle condition that does not lead to pregnancy loss, usually exhibits only 1–3 trophoblast inclusions per placenta slide examined

increases, and most dramatically how the brain, especially the human brain, fits into the skull.

Since the upper limit of human skull diameter is directly related to the size of the female pelvis, increases in brain surface area could only be achieved by folding. And the human brain is one of the most folded brains in the animal kingdom (Hilgetag & Barbas, 2006). Behind this folded structure are the cellular processes that lead to differential growth in the many neural layers that make up the brain. Could the developmental abnormalities that lead to abnormal folding and trophoblast inclusions in the placenta also be at work in the brains of ASD children?

Researchers have demonstrated significantly abnormal brain folding in children on the autism spectrum using surface mapping and magnetic resonance imaging (MRI) (Awate, Win, Yushkevich, Schultz, & Gee, 2008; Kates, Ikuta, & Burnette, 2009; Nordahl et al., 2007). These abnormalities may in part explain the observation of increased head size in ASD children (Awate et al., 2008; McCaffery & Deutsch, 2005). Basically, with less folding, the brain tissue has no other option but to expand the skull to make up for the less compact nature

of the neural tissue. Translating this gross macroscopic observation to cellular processes and ultimately to abnormal behaviors is much harder. However, neuropathologists have described abnormalities in ASD children at the tissue level of the brain that may be associated with these macroscopic changes (Bauman & Kemper, 2003, 2005; Kemper & Bauman, 1998; Whitney, Kemper, Rosene, Bauman, & Blatt, 2009).

Future Directions

If one of the basic pathologies in ASD is related to problems in tissue folding, then we should see evidence for this in any tissue where folding is a critical part of the anatomy or function of that tissue. Some organs may be impervious to low frequencies of misfolding, such as the liver, which does not have a critical requirement for multilayer cellular organization. Other organs, such as the gut, may not function as well if its folded structure is disrupted. If commonalities can be ascertained in cases of ASD, then candidate genes could be sought that control and regulate these processes. Further, in the future, one might anticipate that genetic or medical interventions might be forthcoming that can ameliorate the abnormalities that may exist in ASD children. In the meantime, knowing that trophoblast inclusions are related to ASD could lead to early identification and intervention before overt symptoms arise.

See Also

► Developmental Change

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PL-ADOS

► Prelinguistic Autism Diagnostic Observation Schedule

Planning and Placement Team (PPT)

► Interdisciplinary Team

Plasticity, Neural

Joshua Trachtenberg and Peyman Golshani
David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Synonyms

Cortical remapping; Cortical rewiring; Neural reorganization

Structure

Autism spectrum disorders are characterized by profound impairments in language acquisition and social interaction that are often comorbid with repetitive behaviors and sensory and motor abnormalities. Communicative and social skills emerge in early childhood and grow exponentially in complexity. The establishment of appropriate neural circuitry in the cerebral cortex subserving language acquisition, social interaction, and indeed, all aspects of cortical function, including vision and motor control, relies on the proper execution of genetic programs that regulate neural proliferation, migration, differentiation, axon guidance, and recognition of synaptic targets. A characteristic conserved between these disparate systems is that this circuitry is ineffective at birth. Sensory experience within specified sensitive or so-called "critical" periods during development sculpts the fine structure and function of cortical circuitry. However, the timing and influence of these critical periods varies dramatically among the functional domains of the cerebral cortex. This entry examines recent advances in our understanding of how autism-candidate genes regulate neural growth, synaptic plasticity, and the closure of critical periods.

Anatomical Plasticity of Neural Structure

The establishment of precise neural circuitry in the cortex hinges on five major events. First, neurons must be born in correct numbers. Second, these neurons must migrate to appropriate