The Effects of Prenatal and Postnatal Environmental Interaction: Prenatal Environmental Adaptation Hypothesis

Running title: Prenatal environmental adaptation

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Abstract

Adverse antenatal maternal environments during pregnancy influence fetal development that consequently increases a risk of mental health problems including psychiatric disorders in offspring. Therefore, behavioral and brain alterations caused by adverse prenatal environmental conditions are generally considered as deficits. In this article, we propose a novel hypothesis, along with summarizing a body of literatures supporting it, that fetal neurodevelopmental alterations, particularly synaptic network changes occurring in the prefrontal cortex, associated with adverse prenatal environmental conditions may be adaptation to cope with expected severe postnatal environments, and therefore, psychiatric disorders may be able to be understood as adaptive strategies against severe environmental conditions through evolution. It is hoped that the hypothesis presented in this article stimulate and open a new venue on research toward understanding of biological mechanisms and therapeutic treatments of psychiatric disorders.

Key words: Evolution; Neurodevelopment; Prefrontal cortex; Hippocampus; Synaptic network; microRNA; Psychiatric disorder; Epigenetics; Cognitive function

1. Introduction

Extensive investigation has now unveiled that antenatal maternal environments during pregnancy substantially influences fetal brain development that could ultimately cause mental health problems in offspring. Epidemiological studies have shown that prenatal exposure to adverse environmental factors such as stress, famine, and virus infection, is associated with increased risks of psychiatric disorders such as schizophrenia, attention deficit/hyperactivity disorder (ADHD), and autism in offspring (Malaspina et al., 2008; Rice et al., 2010; Kinney et al., 2008; Ronald et al., 2011; van Os and Selten, 1998; Rodriguez and Bohlin, 2005; Khashan et al., 2008; Brown et al., 1995a; Brown et al., 2000; Susser et al., 1996; Favaro et al., 2011; Mednick et al., 1988; Brown et al., 1995b; Brown, 2006; Machon et al., 1997).

It is generally agreed that behavioral and brain changes caused by prenatal exposure to adverse environmental conditions are "deficits", "impairments", and "abnormalities". However, this doctrine may be challenged by the following two apprehensions. First, the fetal brain is likely to be highly plastic. For instance, even in the adult brain in which plasticity, an ability of the system to be modulated by experience and environments, would be more limited than that in the fetal brain, the plasticity mechanism try to recover damages caused by stroke or ischemia (Kolb and Whishaw, 1998; Hallett, 2001; Hosp and Luft, 2011). If there is any defect in the process of brain development, plasticity mechanism should overcome such a deficit. Nevertheless, studies have found no trace of any compensatory action that correct a deficit, interruption, or deviation of fetal brain development incurred by prenatal exposure to environmental insults. This provokes a question of why the highly dynamic plasticity mechanism in the fetal brain does not fix developmental changes that produce unfavorable consequences. Second, if maternal exposure to environmental insults yields negative influences

on fetal development, why does the biological system has to be existent that deliberately transmits adverse environmental information from mothers to fetuses that produces unfavorable changes in fetuses?   Existence of such an unfavorable system is especially inexplicable from the evolutionary biological perspective.

One possible answer to the above questions is a hypothesis that fetal developmental changes caused by prenatal exposure to environmental insults are not deficits, but adaption to prepare for expected severe environmental conditions after birth.   Indeed, we usually consider prenatally-induced alterations as deficits in a daily postnatal environmental condition (the environmental condition that the majority of lifetime is spent).   In contrast, we have missed to consider how prenatally-induced changes could fit into a rather unusual postnatal environmental condition.

The idea that fetal developmental alterations with adverse prenatal environmental conditions may be adaptation to prepare for postnatal severe environments is, although barely considered in the field of neuroscience, in fact not a new, but it has been originally proposed by the UK medical scientist, David Barker, and therefore known as Barker hypothesis.   The finding that led him to propose the hypothesis is a significant association between low birth weight and adverse adult health outcomes such as coronary heart disease and diabetes (Barker, 1997; Godfrey and Barker, 2000).   This observation can be explained as following.   Thus, low birth weight in fetuses may indicate insufficient nutrition during pregnancy.   To cope with low nutrition, fetal metabolism is lowered to conserve more energy.   However, when such offspring with low metabolism is exposed to adequate nutrient after birth, it results in abnormally excessive energy conservation and consequently causes health problems.   Increasing empirical

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evidence has now supported this hypothesis (for instance, see review papers such as Lumey et al, 2011, for the summary of research supporting the Barker hypothesis).

2. Prenatal stress as environmental adaptation

2.1. Effects of prenatal stress in humans

A huge body of literatures has unveiled the effects of prenatal stress on fetal development and consequent postnatal behavioral changes in both humans and animals (for instance, summaries of human and rodent studies can be found in the review papers by Kingston et al., 2012 and Weinstock, 2008). It is not possible to review all of these findings, and also not the scope of this paper. Instead, here we summarize some of major findings on prenatal stress-induced behavioral alterations and discuss them in the context of environmental adaptation.

Both retrospective and prospective studies have been conducted to examine the relationship between prenatal stress/anxiety and offspring behaviors in human subjects. These studies found that prenatal stress/anxiety causes increased rate of low birth weight and preterm deliveries (Wadhwa et al., 1993), and augmented stress responses in offspring (Vrekoussis et al., 2010; Austin and Leader, 2000; Knackstedt et al., 2005; Phillips and Jones, 2006).

Whether a single, severe stress exposure during pregnancy may impact offspring behavior was investigated in mothers exposed to disasters. In the study with mothers who were stressed by Chernobyl exposure, offspring born from such stressed mothers were found to show slower motor and mental development as infants (Huizink et al., 2007). Children born from mothers exposed to Canadian ice storm exhibit altered pattern of play, lower general IQ, and language abilities than control groups, although whether these children have deficits in specific domain of cognitive functions other than language has remained unclear (Laplante et al., 2008).

The study with mothers exposed to World Trade Center attack during pregnancy has reported that among these mothers, those who had subsequently developed post-traumatic stress disorder (PTSD) was found to exhibit lower baseline stress hormone level than others who did not develop PTSD (Yehuda and Bierer, 2008). Offspring born from such mothers who had developed PTSD have lower cortisol level and are more likely to develop PTSD than offspring born from the mothers without PTSD (Yehuda and Bierer, 2008).

Other studies examined the effects of prenatal stress with milder, but more prolonged exposure. Convergent evidence from various studies (for examples, O'Connor et al., 2002; Niederhofer, 2004; Rieger et al., 2004; Huizink et al., 2007) suggests that maternal anxiety/stress level during pregnancy is correlated with emotionality in offspring. Thus, offspring born from mothers with high anxiety/stress during pregnancy exhibit heightened anxiety and greater negative emotional behaviors. In contrast, whether maternal stress/anxiety during pregnancy affects cognitive function in human offspring has essentially remained unclear. For instance, maternal stress/anxiety during pregnancy has been also shown to increase intra-individual variability in performance of the reaction-time task in boys, but not girls (Loomans et al., 2011). This finding, however, does not necessarily mean that these offspring have cognitive impairments. Bergman and colleagues have reported that offspring born from mothers with higher stress hormone level during pregnancy exhibit greater fearfulness and slower cognitive development than offspring without prenatal stress. Moreover, these changes are more prominent in offspring born from stressed mothers experience insecure infant-mother attachment (Bergman et al., 2008). Niederhofer and colleagues have examined motor responses to vibroacoustic stimuli in the third trimester fetuses (Niederhofer, 2004). They found that the responses were attenuated in fetuses of mothers exposed to stress. Although they have

suggested based on this finding that such attenuated responses to stimuli may be associated with learning impairments, this is apparently over-interpretation of the results.

Based on these studies, one seemingly convergent conclusion is, unlike animal studies discussed in the next section, the effects of prenatal stress on any specific domain of cognitive function in human offspring are not clear, whereas prenatal stress-induced alterations on emotionality are documented in some extent. Thus, a caution has to be given not to overtly apply findings of prenatal stress effects on cognitive impairments made in animals into human cases.

2.2. Effects of prenatal stress in rodents and non-human primates

A majority of animal studies investigating prenatal stress effects is conducted in rodents (mostly in rats), and less extent in non-human primates (mostly in rhesus macaques). Although in human studies, increased rate of lower birth weight and preterm deliveries are relatively consistently observed, these are controversial in rodents. Although one study has reported that prenatal stress results in smaller size of newborn pups (Drago et al., 1999), others were unable to find smaller pups (Guo et al., 1993; D'Mello and Liu, 2006) and altered duration of gestation (D'Mello and Liu, 2006), suggesting that general effects of stress on pregnancy may slightly differ between human subjects and rodents. However, similar to human offspring born from stressed mothers, stress response in rodent (Weinstock et al., 1992; Vallee et al., 1999; Koenig et al., 2005; Mastorci et al., 2009) and primate (Clarke et al., 1994) offspring exposed to prenatal stress seem more robust (i.e. prolonged stress hormone release) than that in animals without prenatal stress.

An assortment of behavioral alterations, some of which are relatively consistently reported and others are controversial, has been reported to be caused by prenatal stress in rodents and non-human primates.   These prenatal stress-induced behavioral alterations include deficits in cognitive function such as spatial learning (Vallee et al., 1999) and working memory (Vallee et al., 1999), affective function such as heightened anxiety (Vallee et al., 1997), fear-related behavior (Lehmann et al., 2000; Griffin et al., 2003), and abnormal social behaviors (Clarke and Schneider, 1993; Lee et al., 2007), and auditory sensory gating (Hunter et al., 2012; Koenig et al., 2005).

2.3. Is spatial learning deficit adaptive behavioral change?

Whether the behavioral alterations mentioned above are adaptation to cope with expected postnatal stressful condition is not apparent.   Moreover, most of these altered behavioral phenotypes are clearly disadvantages in the non-stressful environmental condition.   However, a cautious consideration on the relationship between stressor types and induced alterations may be able to provide a novel insight that indicates a possibility of adaptation, rather than deficit, of brain function to cope with an expected postnatal stress condition.   In this context, it is interesting to note that majority of rodent studies examining prenatal stress effects have utilized restraint stress procedure.

Spatial learning and memory in rodents born from dams exposed to stress during gestation has been extensively investigated.   In almost all studies utilizing restraint stress procedure, spatial memory has been reported to be impaired in offspring born from mothers exposed to prolonged, repeated restraint stress [for examples (Bustamante et al., 2010; Lui et al., 2011; Szuran et al., 1994; Vallee et al., 1999; Lemaire et al., 2000; Son et al., 2006;

Hosseini-Sharifabad and Hadinedoushan, 2007; Yaka et al., 2007)], whereas there are also several studies showing enhancement of spatial memory with prenatal restraint stress (Fujioka et al., 2001; Cannizzaro et al., 2006), in which, however, restraint stress given to dams was milder (e.g. only single exposure) than the more commonly used procedure. Strikingly, spatial memory appears to be relatively intact or even enhanced with repeated exposure to stressors other than restraint such as exposure to stressful sensory stimuli (Kapoor et al., 2009), unfamiliar social group (Aleksandrov et al., 2001), and psychological stress by observation of other rodents being electrically shocked (Abe et al., 2007). Moreover, prenatal administration of glucocorticoids (Salomon et al., 2011) or dexamethasone (Brabham et al., 2000), does not affect spatial memory in offspring. These studies collectively indicate that spatial memory deficits may not be in fact "deficit" but rather "adaptation". Indeed, the most characteristic feature of restraint stress is rigorous limitation of spatial information processing while pregnant rodents are exposed to stress. If restraint stress given to dams is prolonged and repeated (i.e. it is inescapable from stress by moving to other place), and this is the stress condition that offspring expects to encounter postnatally, spatial learning ability may be less important as it is inescapable from stress by moving to other places, and attenuated spatial learning ability may actually enable to better cope with anxiety/stress response associated with place-specific stress encountering. On the other hand, when stress is milder and brief (i.e. the condition that stress can be avoided by moving to another place), the most important action is to escape from and not to return to the place where stress is provoked. Thus, enhanced spatial learning may increase a chance to escape from danger or stress-provoking place. Adaptation, but not deficit, of spatial learning caused by prenatal restraint stress may be further supported by sexually dimorphic effects of prenatal stress. Although spatial memory is impaired in male offspring with severe

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prenatal restraint stress, it is conversely enhanced in female offspring (Bowman, 2005; Zuena et al., 2008). If altered spatial learning with prenatal restraint stress is a deficit, the reason of sexual dichotomy of prenatal stress-induced alterations on spatial learning is less clear. Indeed, enhancement of spatial memory may yield advantages to female animals, since information of a particular location is critical to them for assurance of resources (i.e. foods and shelters) for perseveration of the species even in the severe stress condition (New et al., 2007).

2.4. Gender-associated behavioral changes as adaptation to social stress

A further support that behavioral changes caused by prenatal stress may be adaptation to postnatal stress condition comes from a series of studies by Kaiser and colleagues investigating the effects of prenatal social stress in guinea pigs. In their studies, dams were exposed to social stress by placing them in unfamiliar groups of animals. Female offspring born from socially stressed dams exhibit a trait of masculinization such as high level of male-typical courtship behavior, increased testosterone level, and male-like (increased) androgen receptor distribution in the limbic system (Kaiser et al., 2003b). In contrast, male offspring born from socially stressed dams exhibit a trait of infantalizaiton/demasculinization such as less sexually-motivated courtship behavior, delayed maturation of the male hormonal system, infant-typical behavior such as resting with body contact on other animals, and down-regulation of androgen receptor expression in the limbic system (Kaiser et al., 2003a). Based on these observations, they have proposed that these gender-related changes in offspring caused by prenatal social stress may be adaptation to cope with a socially stressful (crowding) environment expected to encounter after birth (Kaiser and Sachser, 2009). Thus, masculinization may enable females to facilitate the attainment of dominant social class that may benefit securing of foods and shelters in the

crowding environment. In contrast, infantilization/demasculinization may enable males to avoid agonistic encounters at early age and thereby increase a chance of later siring in the group and reproduction.

2.5. Cognitive impairments with prenatal variable unpredictable stress

The studies by Koenig and colleagues have utilized variable unpredictable stress to examine the effects of prenatal stress on offspring behaviors (Markham et al., 2010; Koenig et al., 2005). Variable unpredictable stress procedure employs exposure to different types of stressors over gestation. Interestingly, these studies found a wide range of behavioral alterations from sensory gating deficit to working and long-term memories, which are not to be reported in other studies with repeated exposure to a single modality of stress. There must be reasons that such various behavioral alterations are produced with exposure to variable prenatal stressors, and it may be adaptation to cope with expected postnatal stress condition, but such stress is originated in variable sources. For instance, decreased social interaction and working memory impairments caused by prenatal stress appear to cause only disadvantages, and there is no apparent benefit at all. Nevertheless, for instance, a stressful environment expects less survivors and poor social organization than the non-stressful condition. In such condition, prenatal stress-induced decrease of social interaction may increase a chance of survival with less social-dependence and greater resistance against social isolation. In a life-threatening severe environment, analytical and critical thinking that depends on working memory may not be much useful, whereas almost automatic stimulus-response (escape) behavior may even increase a chance of survival.

3. Biological mechanisms of maternal-to-fetal communication of stress

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Studies often report variable, and sometimes even opposite, effects of prenatal stress.   It is believed that such differential stress effects may be associated with timing, severity, and duration of stress exposure, as well as stressor types.   In prenatal stress effects, timing of stress exposure appears to be the greatest concern, as depending on when maternal stress is given during pregnancy, stress may affect different developmental stages in fetuses, leading of distinct outcomes.   However, timing of stress exposure alone apparently does not explain all differences of prenatal stress-induced alterations, as the results of studies with prenatal stress given at the identical developmental stage are still mixed (Charil et al., 2010; Grizenko et al., 2008; Kinney et al., 2008; Weinstock, 2008).

In contrast, from both human and animal studies described above, it appears that behavioral changes caused by prenatal stress are significantly associated with stressor types. This challenges the generally accepted belief that prenatal stress-induced alterations in fetuses are achieved by maternal-to-fetal transfer of stress hormones (Charil et al., 2010; Avishai-Eliner et al., 2002).   Indeed, some alterations in offspring born form dams exposed to stress may be associated with maternal-to-fetal transfer of stress hormones.   Such alterations would be mutually produced by exposure to stress regardless of stressor types.   In contrast, behavioral changes associated with a specific stress modality may involve molecules other than stress hormones.   For instance, this is clearly supported by the studies showing that, unlike restraint stress, administration of stress hormones, corticosterone (Salomon et al., 2011) or dexamethasone (Brabham et al., 2000), to dams does not impair spatial memory in offspring.

One potential candidate of such molecules may be microRNA (miRNA).   miRNA is an endogenous, short, double strand, RNA (Carthew and Sontheimer, 2009).   miRNA has been shown to be an important regulator of brain development (Sayed and Abdellatif, 2011; Coolen

and Bally-Cuif, 2009).   miRNA can circulate the body with exosome encapsulation, and plays important role on cell-cell communications (Valadi et al., 2007; Mitchell et al., 2008). Moreover, specific classes of miRNA are dynamically expressed in the placenta throughout pregnancy (Chiu and Lo, 2010; Miura et al., 2010; Chim et al., 2008), and their pregnancy-related expression are altered by maternal conditions such as smoking (Maccani et al., 2010) and hypoxia (Mouillet et al., 2010).   Indeed, placenta-derived exosomes have been implicated to influence fetal growth (Mincheva-Nilsson and Baranov, 2010).   Collectively, maternal-to-fetal transfer of miRNA may be involved in maternal-to-fetal communication and produce environmentally-specific alterations on fetal development.

4. Adaptation to other environmental factors

The effects of prenatal exposure to various environmental factors other than stress on offspring health outcomes have been also examined.   These include prenatal exposure to immunotoxicants including viruses and allergens.   Consistent findings are potentiated responses to postnatal exposure to the stimuli that are exposed in utero.   Thus, organisms exposed to immunotoxicants in utero exhibit heightened immune and inflammatory activation, often expressed as autoimmune diseases (Holladay, 1999).   Children born from mothers exposed to allergens during pregnancy exhibit greater allergic responses, but also improved respiratory function (Woodcock et al., 2004).   Potentiated responses to environmental stimuli could add a significant advantage in organisms for survival in the adverse environmental conditions by enabling early detection of threats, and escape from them.   Moreover, prenatal exposure to environmental stimuli such as viruses, famine, and stress produces various behavioral changes in offspring, some of which are, however, mutually observed regardless of exposure to completely

distinct environmental stimuli. These mutual behavioral changes caused by distinct prenatal environmental factors may therefore be considered as adaptation to generalized adversities or threats independent of a modality of environmental conditions.

Adaptation to environmental stimuli may also happen at the perinatal and neonatal periods as well as even in adulthood. Obstetric complications, especially the case that involves hypoxia, have been shown to induce behavioral changes in offspring (Boksa, 2004). Such hypoxia-induced alterations may be similar to prenatal exposure to high altitude that could alter uterine artery blood flow and arterial PCO_2/O_2 saturation (Julian et al., 2007), but hypoxia in obstetric complication is more brief and severe than the high altitude condition. Studies of cerebral ischemia in adult brains suggest that glial cells play a major role on protective (adaptive) response to ischemia (Nedergaard and Dirnagl, 2005). Thus, if obstetric complication may induce adaptive changes, it may alter glial function, which in turn alters behaviors of offspring. In this context, it is interesting to note that obstetric complication is a robust risk factor of schizophrenia [e.g. 10-fold greater likelihood of developing schizophrenia in offspring (Verdoux et al., 1997)], and altered glial function has been implicated in the pathology of schizophrenia (Mitterauer, 2011; Moises and Gottesman, 2004; Rothermundt et al., 2007).

5. Prenatal environmental adaptation hypothesis

Collectively from the studies described above, it appears that behavioral alterations observed in offspring born from mothers exposed to a particular environmental condition follow a specific modality of that environmental factor. Thus, for instance, if prenatal stress-induced alterations are adaptation (i.e. preparing to anticipated postnatal stressful life) rather than deficits, offspring born from mothers exposed to stress may be benefited with the alterations in the postnatal

stressful condition, whereas these individuals may have disadvantages with the alterations in the non-stressful environmental condition. In contrast, the phenotypes that develop during environmental conditions without stress could be also adaptive. This leads to a hypothesis that prenatal environmental conditions influence the development of behavioral phenotypes in offspring that can represent adaptations that match with expected postnatal environmental conditions. Indeed, such a hypothesis is not a new, but has been already proposed by others (Kaiser and Sachser, 2009).

6. Prenatal and postnatal stress interaction

The hypothesis implicates the importance of longitudinal investigation of stress effects, which has been barely conducted previously. Extensive studies have been conducted to examine the effects of prenatal or postnatal stress alone. In contrast, there are only few studies examining stress effects with multiple times of exposure along different ages. Indeed, stress exposure is not a single life event, but more likely to be multiple times throughout the life. In particular, whether alterations caused by stress are deficits or adaptation must be withdrawn only by examining how alterations produced at the first time of stress exposure impact on responses to subsequent stress exposure.

Several studies have investigated interaction between the effects of prenatal stress and postnatal stress; however, almost all of them are limited during the neonatal period. A line of evidence has argued that expression of at least some aspects of behavioral alterations caused by prenatal stress requires a neonatal stress condition such as decreased maternal care. This is based on the finding that dams exposed to stress provide less maternal care to pups than non-stressed mothers (Champagne and Meaney, 2006). Moreover, cross-fostering of pups born

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from stressed dams to non-stressed dams diminishes prenatal stress-induced behavioral alterations (Del Cerro et al., 2010; Maccari et al., 1995; Barbazanges et al., 1996; Burton et al., 2006). It has been also shown that prenatal stress effects are reversed by neonatal handling (Wakshlak and Weinstock, 1990). These studies suggest that neonatal period may be a window to match with prenatal and postnatal environmental condition, with early postnatal stress such as insufficient mother-infant attachment augmenting, whereas better than the expected environmental condition such as sufficient mother-infant attachment reversing, the effects of prenatal stress.

Modulation of prenatal stress effects by postnatal environmental condition also supports that alterations caused by prenatal stress are adaptation. If prenatal stress-induced alterations are "deficits", ceiling effects are expected (e.g. maternal deprivation has smaller effects on prenatal stress-induced alterations). Moreover, it appears that potentiation by maternal deprivation, and reversal by increased maternal care, of prenatal stress effects may be best interpreted as the process that maternal deprivation (i.e. matching with prenatal and postnatal conditions as stressful) ensures the necessity of behavioral changes caused by prenatal stress, whereas prenatal stress-induced alterations are reversed because the postnatal environmental condition does not meet with the prenatal stressful condition. Indeed, in this context, that stressed mothers provide less maternal care to pups is more reasonably understandable.

7. Biological substrate of prenatal environmental adaptation

Development of synaptic connections in the cortex and limbic structures starts during the prenatal period. In human prefrontal cortex (PFC), synaptogenesis and synaptic proliferation continues up around 5~6 year olds, and subsequently subjected for synaptic pruning throughout

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adolescence for fine tuning of the network (Huttenlocher, 1984; Rakic et al., 1986). Thus, development and maturation of PFC synaptic network continues from the prenatal period to early adulthood, and thereby, dynamic synaptic changes can be influenced by both prenatal and postnatal environmental conditions. A similar pattern of over-production of synaptic connections followed by pruning is also observed in limbic structures such as the hippocampus of rodents (Afadlal et al., 2010), although this appears to be less clear in the human hippocampus (Eastwood et al., 2006).

Prenatal stress (Afadlal et al., 2010; Mychasiuk et al., 2012; Murmu et al., 2006) and malnutrition (Diaz-Cintra et al., 1994) have been shown to decrease synaptogenesis in the cortex/hippocampus, whereas prenatal viral infection and associated immune activation appears to produce more complex patterns of alterations through development and maturation of the brain (Soumiya et al., 2011; Baharnoori et al., 2009). Such alterations are generally accepted as neurodevelopmental deficits that cause brain function. However, if fetal alterations caused by prenatal environmental exposure is adaptation, decreased synaptogenesis should be also interpreted as adaptation, which (i) may be a form of accelerated brain maturation (e.g. decreased synaptic connections may be considered a similar state to adult brain after pruning, or the amount of synaptogenesis and pruning may be smaller, and thereby maturation is achieved quicker), advantaging the organisms to survive the severe environmental condition during early postnatal period, and/or (ii) may provide protective effects on behavioral and brain changes caused by postnatal environmental threats. There has been no evidence so far that whether and how alterations of PFC synaptic development and maturation caused by prenatal and postnatal stress may interact. However, the ingenious study by Lueba and Rabinowicz indirectly supports these possibilities (Leuba and Rabinowicz, 1979). They found that postnatal under-nutrition caused

dendritic atrophy and decreased number of dendritic spines in the mouse cortex, which persisted into adulthood. However, postnatal under-nutrition was combined with maternal under-nutrition during pregnancy, cortical cell dendritic alterations were, although they were still present during the juvenile period, not observed when offspring reached adulthood. Further investigation on how prenatal and postnatal environmental interaction shapes cortical and limbic synaptic network would be a promising venue.

8. Psychiatric disorders as environmental adaptation

One dilemma, if prenatal/neonatal changes are adaptation process to environments, is since prenatal exposure to environmental insults such as exposure to stress, famine, and viral infection are suggested to increase the risks of psychiatric disorders such as schizophrenia, ADHD, and autism, these psychiatric disorders associated with prenatal environmental insults and involving PFC dysfunction may consequently be considered as environmental adaptation, rather than deficits, of the brain. This deviant idea from the generally accepted belief of psychiatric disorders as brain dysfunction may be reconciled by consideration of the evolutionary biology/medicine.

Evolutionary biology/medicine suggests that psychiatric disorders may in fact arise by environmental adaption through evolution to bring benefits on survival and fecundity of organisms. Thus, although the symptoms of several psychiatric conditions are incompatible with the modern society, they may benefit in certain specific environmental conditions. It is also possible that psychiatric disorders may still be disadvantageous if it is a by-product of evolution (i.e. an extreme variant of adaptive behavior).

For instance, Jensen and colleagues have suggested that the core symptoms of ADHD such as hyperactivity, impulsivity, and attention deficit, although these symptoms are clearly problems in the modern society, bring significant benefits on survival of organisms in a specific environment where dangers and threats are approaching (Jensen et al., 1997). Thus, hyperactivity enables greater exploration of surrounding environments for threats and opportunities. Impulsivity enables quick response to environmental cues while not considering alternative responses to the cues to escape form dangers and threats. Attention deficit observed in ADHD subjects is inability to sustain attention to a particular object. However, this in turn results in shifting of attention and scanning from one object to another rapidly to monitor dangers and threats.

Andrews and Thomson have proposed that the symptoms of major depressive disorder MDD are beneficial behavioral changes (Andrews and Thomson, 2009). Patients with MDD are known to exhibit highly persistent and analytical thinking on a particular issue (i.e. rumination). Moreover, primary MDD symptoms are social withdrawal/isolation and loss of pleasure on other activities. These behavioral phenotypes, however, enable to prevent interruption of thinking, and therefore, MDD patients can concentrate on overcoming the problem that gives stress and causes MDD. They further suggests that, since serotonin (5HT) 1A receptor is involved in the pathologies of MDD, 99% identical composition of the functional part of $5HT_{1A}$ receptor between rodents and human subjects supports emergence of MDD as positive evolutionary selection. However, it is important to note that $5HT_{1A}$ receptor also plays an important role in cognitive processing (Beste et al., 2010; Winstanley et al., 2003; Meneses and Perez-Garcia, 2007), and therefore, the argument that conservation of $5HT_{1A}$ receptor may explain the positive evolutionary selection of MDD is overstretching.

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From the evolutionary perspective, it is also interesting to note some similarities between MDD and hibernation. First, occurrence of MDD is higher during the winter term with shorter day light (Blehar and Rosenthal, 1989). In addition, one of the major symptoms of MDD is sleep problems (Thase, 1998). During hibernation, circadian rhythm is suppressed (Hut et al., 2002). Disruption of circadian rhythm is also observed in MDD (Monteleone et al., 2011). Hibernation is the mechanism of energy conservation with lower metabolic rate. In MDD patients, the metabolic syndromes such as type II diabetes are frequent co-morbid disorders (Musselman et al., 2003). Finally, MDD and hibernation appear to have the common biological mechanisms that involve 5HT transmission and $5HT_{1A}$ stimulation in the hippocampus (Albert and Lemonde, 2004; Horrigan et al., 1997; Naumenko et al., 2008) as well neuronal activity in the epithalamic nucleus, habenula (Li et al., 2011; Yu et al., 2002). Although there are indeed clear differences between MDD and hibernation, it may not be too much anomalous to think based on the similarities that MDD may be a trace of hibernation that has remained through evolution in human subjects as the energy conservation mechanisms with the MDD symptoms such as withdrawal from the society and decreased interest to various activities. Indeed, hibernation is a strategy that some animals take for energy conservation during the winter time while not many foods are available. In this regard, MDD may be also considered as an energy conservation strategy, which makes MDD patients await without loss of much energy until that the problems that the subjects are facing with pass away (Schmale and Engel, 1975).

9. Psychiatric disorders involving neurodevelopmental changes

It is interesting to note that psychiatric disorders appear to be strongly associated in neuorodevelopmental changes. Even in psychiatric disorders such as MDD, anorexia nervosa,

and schizophrenia, in which symptoms typically emerge in adolescence or young adulthood, epidemiological studies have shown the increased risks of these disorders in offspring with low birth weight (Abel et al., 2010; Cnattingius et al., 1999; Mick et al., 2002; Costello et al., 2007), obstetric complication [anorexia nervosa (Favaro et al., 2006) and schizophrenia (Geddes and Lawrie, 1995), but not for MDD (Bain et al., 2000; Preti et al., 2000)], and exposure to prenatal environmental factors such as stress (Ronald et al., 2011; van Os and Selten, 1998; Rodriguez and Bohlin, 2005; Khashan et al., 2008; Malaspina et al., 2008), famine (Brown et al., 1995b; Brown et al., 2000; Susser et al., 1996), and virus infection (Favaro et al., 2011; Mednick et al., 1988; Brown et al., 1995a; Brown, 2006; Machon et al., 1997).   Thus, prenatal period may be the critical time window for environmental adaptation incorporated into evolution, which in turn may originate psychiatric conditions that bring benefits for survival of organisms in severe environmental conditions.

10. PFC dysfunction in psychiatric disorders

The PFC is thought to be the brain region that is evolutionarily the latest and most complex area (Smaers et al., 2011; Teffer and Semendeferi, 2012).   The PFC plays a central role on executive function, along with integration of information from other parts of the brain such as limbic structures, basal ganglia, cerebellum, and other corticies (Fuster, 2001; Wood and Grafman, 2003).   Allometric analysis of brain structures suggest that the human PFC is approximately twice larger, and almost six times larger than predicted based on overall brain and body sizes, respectively, of other non-human primates (Deacon, 1988; Stephan et al. 1988; McBride et al., 1999; Rilling, 2006; Semendeferi et al., 2002).

In particular, dysfunction of the PFC has been implicated in almost all psychiatric disorders (Pietrini et al., 2011; Weinberger et al., 1994; Seidman et al., 2005; Drevets, 2000).   It is surprising that just one brain region is involved in various distinct psychiatric symptoms. However, this could be explained by that the PFC has extensive connections with many other parts of the brain, such that deficits in other brain structures are reflected in activity of the PFC, even if there is no deficit in the PFC itself.

Alterations in developmental trajectory of PFC synaptic network have been suggested in the disorders such as schizophrenia (Eastwood and Harrison, 2005) and ADHD (Shaw et al., 2007).   Indeed, the PFC is highly plastic brain region and altered by various prenatal and postnatal environmental conditions including stress (Lyons et al., 2002; Murmu et al., 2006). Moreover, development of PFC synaptic network starts from the prenatal period, continues to develop even after birth, and does not mature up until adulthood (Petanjek et al., 2011). Therefore, the PFC synaptic network may be particularly sensitive for both prenatal and postnatal environmental conditions.

Collectively, PFC synaptic network appears a crucial neural substrate through which prenatal and postnatal environmental adaptation can take place.

11. Psychiatric disorders in evolution

The Darwinian evolutionary theory, which has been widely accepted, argues that the primary driving force of evolution is stochastic, random genetic drifts, which create various phenotypes. These variable phenotypes are subjected for natural selection, and organisms with the phenotype that is most suitable to the specific environment have been inherited into descendents. Nevertheless, such stochastic genetic drifts appear to be unfavorable explanation for emergence

of psychiatric disorders in evolution. For instance, malaria infection and sickle-cell trait are the well-documented example of evolution (Kwiatkowski, 2005). Malaria infection is a common fatal disorder in Africa, and sickle-cell trait is thought to emerge in African people to reduce the risk of death by Malaria infection. It has been shown that approximately 10% of African people possesses sickle-cell trait. In contrast, however, only about 4% in African-Americans, who are five generation descendants of African people immigrated to US, exhibit such a trait (Hassell, 2010). Indeed, Malaria is an uncommon disease, and therefore, sickle-cell is unnecessary trait for people living in US, suggesting that evolution of the sickle-cell trait was subjected for natural selection. On the other hand, evolution of psychiatric disorders appears to be challenged by the fact of high constant prevalence in population all over the world throughout the history (World Health Organization, 2000). If psychiatric disorders are evolved by stochastic genetic drifts with subsequent natural selection, it is likely that prevalence of disorders decreases because of mismatch with the modern human society.

12. Epigenetic-based mechanisms of transgenerational inheritance of behaviors

The French naturalist, Lamarck proposed the mechanism of evolution that was different from the Darwinian theory. In Lamarckian inheritance, the primary driving force of evolution is adaptation of organisms to their specific environments in the life, and acquired phenotypes are inherited into descendants. This theory was once doomed as incorrect, and only few people have supported it. However, emerging evidence has proved that Lamarckian-like inheritance does occur.

In human studies, it has been shown that offspring of mothers who exposed to Dutch famine in 1943-1947 in utero exhibit increased neonatal adiposity and poor health outcomes such

as autoimmune, respiratory, infectious, and dermatological problems, later in life (Painter et al., 2008). Similarly, offspring of mothers who exposed to diethylstilbestrol in utero have higher rate of hypospadias (Brouwers et al., 2006), suggesting that maternal lineage of transmission of changes caused by prenatal environmental insults across generation.

Animal studies further supports transgenerational inheritance of behavioral phenotypes caused by prenatal exposure to environmental stimuli. Such transgenerational transmission was first reported by Wehmer and colleagues (Wehmer et al., 1970). They found that progenies (F_2) of female rats (F_0) subjected for foot shock stress before mating and during pregnancy exhibited hyperactivity compared to F_2 descendants of non-stressed F_0 mothers. More recently, Drake and colleagues examined the effects of maternal administration of stress hormone during pregnancy (Drake et al., 2005). Male and female progenies (F_2, F_3) of fathers and mothers (F_1) exposed to stress hormone in utero were found to be smaller in birth weight and develop glucose tolerance with increased phosphoenolpyruvate carboxykinase activity. Similarly, the study by Morgan and colleagues has shown that male offspring (F_2) of fathers (F_1) exposed to stress in utero exhibit more female-like gene expression pattern than that in male progenies of non-prenatally stressed fathers, suggesting paternal lineage of transgenerational transmission of alterations (Morgan and Bale, 2011).

Studies have also shown transgenerational inheritance of phenotypes in response to prenatal exposure to environmental stimuli other than stress. In one study, pregnant rats (F_0) were exposed to protein restriction diet (Bertram et al., 2008). Female offspring (F_1) born from such dams with protein restriction were grown up with either protein restriction or adequate diet. Insulin resistance was observed in male offspring (F_2) of F_1 females grown with protein restriction, whereas female offspring (F_2) of F_1 females grown with adequate diet exhibited

insulin resistance. Zambrano and colleagues investigated maternal nutrient restriction diet during pregnancy in guinea pigs (Zambrano et al., 2005). Female offspring (F_1) were grown up in the adequate nutrient and mated with non-nutrition restricted males to produce progenies (F_2). F_1 and F_2 male offspring exhibited altered cardiovascular function and elevated stress response compared to descendants of adequate nutrition across generation.

Transgenerational transmission of behavioral phenotypes appears not constricted to those associated with prenatal environmental conditions, but neonatal or even adult environments. Thus, descendants of fathers exposed to maternal deprivation during the neonatal period have been shown to exhibit behavioral phenotypes associated with depression (Franklin et al., 2010). Moreover, in these descendants, DNA methylation on corticotrophin-releasing factor receptor 2 and cannabinoid receptor-1 are inherited from the fathers exposed to maternal deprivation. Another study examined the effects of neonatal exposure to lipopolysaccharide (LPS), which has been shown to induce anxiety-like behavior, in male and female rats. Offspring of female rats who received LPS was found to exhibit heightened anxiety-like behavior and potentiated stress response, whereas offspring of male rats with neonatal LPS exhibited anxiety-like phenotype, but no alteration on stress response (Walker et al., 2012). Whether behavioral changes caused by chronic stress given in adult rodents were also transmitted into offspring was examined in the study by Dietz and colleagues. They found that male offspring of stressed fathers, but not mothers, exhibited increased stress hormone level, as well as increased anxiety and decreased reward seeking behavior (Dietz et al., 2011). This finding in rodents is, however, slightly different from the human case (Yehuda and Bierer, 2008), which reports that offspring of Holocaust survivors with PTSD demonstrate lower stress hormone level than offspring of

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Holocaust survivors without PTSD, this is inherited from female survivors rather than male survivors.

Epigenetic mechanisms play a central role of Lamarckian-like transgenerational inheritance of behavioral phenotypes. Epigenetic regulation of gene expression usually involves chromatin modification such as histone acetylation and DNA methylation (Borrelli et al., 2008). Although inheritance of typical chromatin modification across generation has been confirmed in some studies (Franklin et al., 2010), it appears that miRNA transmitted across generation through gametes also plays significant role on this type of inheritance (Daxinger and Whitelaw, 2012; Rechavi et al., 2011; Rassoulzadegan et al., 2006).

13. Transgenerational epigenetic inheritance as evolutionary biological bases of psychiatric disorders

Collectively from the studies described above, we propose a hypothesis that rapid, epigenetic-based mechanisms of environmental adaptation, especially during the prenatal period, may be the primary driving force for generation of psychiatric disorders in evolution. Thus, psychiatric disorders may be better understood under the concept of environmental adaptation of fetal development with epigenetic reprogramming.

This hypothesis has both pros and cons. Pros of the hypothesis are non-Mendelian pattern of expression of transmitted genes (Morgan et al., 1999; Sutherland et al., 2000), which is consistent with the observed non-Mendelian inheritance of psychiatric disorders. Moreover, epigenetic transgenerational inheritance also has an explanatory value on parental imprinting. It is often suggested that psychiatric disorders such as schizophrenia and autism are paternal or maternal origin (Shelton et al., 2010; Brown et al., 2002; Crespi and Badcock, 2008). Cons of

the hypothesis include unknown mechanisms transferring epigenetic changes into equivalent DNA changes. However, the mechanisms such as that proposed by Baldwin (Baldwin and Mark, 1896), and genetic assimilation that Waddington has experimentally demonstrated for stimulus-dependent (i.e. heat shock-induced) to stimulus-independent inheritance of crossveinless in drosophila (Waddington, 1953) would enable transfer of epigenetic changes into DNA changes. In addition, investigation of epigenetic inheritance and its mechanisms has been mostly conducted in rodents and lower vertebrates/invertebrates. It still remains to be examined that similar epigenetic-based inheritance mechanisms may be observed in primates. It is of particular interest to investigate whether any commonality may be found on epigenetic patterns of transgenes between psychiatric patients and subjects exposed to adverse environmental conditions.

14. Conclusion

In this article, we have proposed the two hypotheses. First, neurodevelopmental changes particularly occurring in the PFC of fetuses with exposure a specific prenatal environmental condition may be adaptation to cope with the environment that is anticipated in postnatal life. Extensive studies have unveiled the effects of prenatal environmental effects on offspring behaviors and brain function. These studies, however, took environmental exposure as a single life event, and did not consider the longitudinal aspect of environmental exposure. Taking this into account, it is important to consider how alterations caused by the first exposure of a specific environmental condition interact with re-exposure to the identical or even different environmental condition to fully understand the significance of the environment-associated alterations occurring in organisms.

The second hypothesis is that psychiatric disorders may be emerged through evolution as environmental adaptation with epigenetic inheritance. In particular, presence of the mechanism that can auspiciously transmit a defect across generation is unfavorable. Thus, epigenetic-based transgenerational inheritance of behavioral phenotypes prefers the explanation that such inherited alterations may not be deficits, but rather adaptation, to cope with environmental threats. Investigation and understanding of alterations in the context of such views will bring a novel insight on our understanding of psychiatric disorders.

Conflict of interest

None

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