

1 Embodied Brain Model for Understanding Functional Neural Development of Fetuses and Infants

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Early functional neural development is increasingly recognized as important for revealing the developmental origins of human cognitive-motor function and related disorders. Previous studies focusing on fetuses and neonates have revealed sophisticated behaviors and cognitive repertoires, indicating that fetuses begin learning through sensorimotor experience even inside the uterus. Despite accumulating evidence supporting the importance of sensorimotor experience in neural development as early as the fetal period, the developmental mechanisms by which intrauterine sensorimotor experience guides cortical learning, including factors in prenatal experience that are needed for normal development, remain unclear. However, investigating causal links between sensorimotor experience and cortical learning is particularly challenging in human fetuses owing to technical and ethical difficulties. Therefore, computational approaches based on comprehensive biological data about nervous system, body, and environment have been developed to probe mechanisms underlying early functional brain development. In this chapter, we show how an embodied approach focusing on interactions among brain, body, and environment offers opportunities to explore relations between functional neural development and sensorimotor experience.

1.1 The Origins of Cognitive/Motor Development and Learning

Developmental science has revealed the cognitive/motor abilities of infants (Adolph & Berger, 2006; Piaget, 1952; Rochat, 2009; Tomasello, 2009; von Hofsten, 2007). Many studies have reported that some amazing abilities can be observed in infants soon after birth, including neonatal imitation (Meltzoff & Moore, 1977), recognition of the difference between self- and other-derived stimulation in the rooting reflex (Rochat & Hespos, 1997),

predictive mouth movements when sucking a pacifier (Rochat, 2009), orientation towards sound (Clifton, Morrongiello, Kulig, & Dowd, 1981), hand–eye coordination in reaching (van der Meer, 1997; von Hofsten, 1982), and leg movement adjustment in response to visual stimulation (Barbu-Roth et al., 2014). These findings indicate that human infants are not born as a *tabula rasa* (i.e., blank slate), but come into the world with various cognitive, motor, perceptual, and social abilities.

From this early competence perspective, fetal development has been investigated as well. Ultrasound imaging and observational studies reveal that the sensory systems except for vision are already functionally mature in the fetal period (Purves, 2012). Additionally, visual perception has been reported; fetuses can feel light and show a preference to engage with face-like stimuli in the third trimester of pregnancy (Gerhard, 2013; Reid et al., 2017). Collectively, these studies suggest that fetuses already sense the world with multiple sensory organs and adapt their movements accordingly. Further, spontaneous movements and somatosensory responses can be observed as early as 8 weeks before the formation of a spinal reflex circuit (Bradley & Mistretta, 1975; Lüchinger, Hadders-Algra, van Kan, & de Vries, 2008). Ultrasound imaging studies show that fetuses show structured movements (Butterworth & Hopkins, 1988; Kurjak et al., 2003; Reissland, Francis, Aydin, Mason, & Schaal, 2014), predictive mouth opening during hand–mouth coordination (Myowa-Yamakoshi & Takeshita, 2006), and planned hand movements (Zoia et al., 2007), suggesting that even fetuses possess sophisticated behaviors and cognitive repertoires (Reissland et al., 2014; Rochat, 2011).

Moreover, fetuses learn from sensorimotor experiences. For example, fetuses distinguish their own mother's voice and rhythms (DeCasper, Lecanuet, Busnel, Granier-Deferre, & Maugeais, 1994; Kisilevsky et al., 2003), recognize music heard prenatally during the neonatal period (James, Spencer, & Stepsis, 2002), and distinguish the taste/smell of amniotic fluid (Hepper, 1996; Schaal, Marlier, & Soussignan, 1998). Although few human studies have addressed motor learning based on prenatal sensorimotor experience, there have been multiple animal studies on this topic, including investigations of coordinated peristaltic movements in zebrafish embryos (Warp et al., 2012), motor learning in fetal/neonatal rats (Brumley & Robinson, 2013; Granmo, Petersson, & Schouenborg, 2008; Robinson, Kleven, & Brumley, 2008), and spontaneous movement and somatotopic map formation in rats and human preterm infants (Khazipov et al., 2004; Milh et al., 2006)). These reports suggest that cognitive/motor development (learning) based on sensorimotor–environment interactions starts during the early fetal phase.

1.1.1 A Key to Understanding Developmental Disorders: Clinical, Epidemiological, and Policy Perspectives

With reference to clinical, epidemiological, and policy considerations, a deeper understanding of early human development would inform prevention and

intervention. Neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), have recently increased in prevalence and have received considerable attention (Fombonne, 2009; Gaugler et al., 2014). Long-term follow-up studies have shown that perinatal environmental factors and diverse genetic factors influence the risk of developmental disorders later in life (Gaugler et al., 2014). Related studies suggest that even preterm infants without apparent brain injuries experience motor, cognitive, and learning difficulties and are at a greater risk of developmental disorders than their term-born counterparts (Larroque et al., 2008). Additionally, functional connectivity studies document differences between preterm infants and full-term neonates at term-equivalent ages, suggesting that preterm infants follow different trajectories of brain development from those of full-term neonates (Fuchino et al., 2013; Smyser et al., 2010). These studies suggest that abbreviated intrauterine periods and early exposure to extrauterine environments contribute to developmental disorders in later life. However, the causal links between sensorimotor experiences and atypical brain development remain unknown.

Additionally, care for preterm infants at high risk has been a challenge. In neonatal intensive care units, clinical staffs or caregivers often implement positioning or swaddling methods that are designed to provide a sense of containment similar to the intrauterine environment. In contrast, novel clinical techniques and devices such as artificial wombs (Partridge et al., 2017), which have been developed to support extremely premature infants, provide different forms of developmental care and may be associated with improved longer-term developmental outcomes. Although some studies report positive effects of early intervention with respect to reduced mortality or cognitive outcome (Lawn, Mwansa-Kambafwile, Horta, Barros, & Cousens, 2010; Ludington-Hoe, 2013), meta-analyses and systematic reviews report mixed evidence regarding the effects of early developmental intervention programmes on long-term cognitive or motor outcomes (Sizun & Westrup, 2004; Spittle, Orton, Doyle, & Boyd, 2007; Wallin & Eriksson, 2009). Thus, in the case of preterm human infants, the impact of developmental care on neuronal development remains controversial (Ohlsson & Jacobs, 2013). To improve current developmental care, research on the mechanisms underlying early functional brain development, including the types of prenatal experience that contribute to normal development, is needed.

1.1.2 Large-Scale Datasets for Understanding Human Brain Development: Neuroscience Perspectives

To date, knowledge about the process of fetal brain development has been mainly gained through histological/immunochemical studies using human fetal specimens at a microscopic level (Gerhard, 2013; Kanold & Luhmann, 2010; Tau & Peterson, 2010). In addition, recent methodological advances in neuroimaging such as diffusion tensor imaging and high-angular resolution

diffusion tractography allow investigators to study the architecture of the human fetal brain (Dubois, Hertz-Pannier, Dehaene-Lambertz, Cointepas, & Le Bihan, 2006; Takahashi, Folkerth, Galaburda, & Grant, 2011; Takahashi, Hayashi, Schmahmann, & Grant, 2014). In Europe, the Developing Human Connectome Project launched in 2013 aims to create a dynamic map of human brain connectivity from 20 to 44 weeks post-conceptional age, which will link imaging, clinical, behavioral, and genetic information (Developing Human Connectome Project, n.d.). This longitudinal project plans to investigate the relation between developmental change in brain structure and neurodevelopmental disease. Additionally, the BRAIN Initiative project published an open-source atlas of gene expression across the developing brain using laser microdissection or DNA microarray technology (Miller et al., 2014). The creation of this open database of gene expression in the brain has made it possible to conduct allied investigations when new discoveries regarding developmental disorders and psychiatric disorders occur. Although these large-scale datasets of the prenatal human brain help to elucidate typical and atypical trajectories of human brain formation, investigations of brain structure alone do not directly address how sensorimotor experiences, arising from brain, body, and environment interactions, influence and guide brain development.

1.1.3 Sensorimotor Experiences of Embodied Interactions

We define the interactions among the brain, body, and environment as “embodied interactions.” The term “embodied interactions” has been used to emphasize the role of “the body” with the environment when considering intelligence, including cognitive-motor function and its development. This concept has also been used to understand differences in brain function related to intelligence. Ideas relating to embodiment have developed in various fields, including philosophy, cognitive science, psychology, and robotics (Gallagher & Zahavi, 2007; Gibson, 1979; Merleau-Ponty & Smith, 1996; Varela, Rosch, & Thompson, 1992). In the field of developmental science, Thelen and Smith (1994) proposed a “dynamic systems approach,” which argued that the development of thinking was part of a larger integrated system involving the development of the body and action as well as the brain. Byrge, Sporns, and Smith (2014) proposed a network-based account of developmental process in terms of nested dependencies and interdependent timescales of change within structural and functional brain networks. Consistent with these embodied approaches, studies to explain early human development from the perspective of complex body, nervous system, and environment interactions have been undertaken.

For instance, in the field of robotics, Brooks (1991) provided empirical evidence that intelligence can be constructed by using sensorimotor interactions in the environment even without detailed representations of the world as internal models. In keeping with this idea, embodiment cognitive science has

tried to understand intelligence as an embodied system that dynamically utilizes the structure of the body and the environment (Pfeifer & Scheier, 2001). Furthermore, a novel field called “developmental robotics,” which is based on embodiment notions in cognitive science, has emerged and focuses on mechanisms that underlie the development of intelligence (Asada, MacDorman, Ishiguro, & Kuniyoshi, 2001; Kuniyoshi, 1994; Kuniyoshi & Berthouze, 1998; Lungarella, Metta, Pfeifer, & Sandini, 2003; Weng et al., 2001) and other developmental phenomena such as reaching (Caligiore, Parisi, & Baldassarre, 2014; Pitti, Mori, Yamada, & Kuniyoshi, 2010), body image (Hoffmann et al., 2010; Sasaki, Yamada, Tsukahara, & Kuniyoshi, 2013), joint attention (Nagai, Hosoda, Morita, & Asada, 2003), and imitation (Demiris, Rougeaux, Hayes, Berthouze, & Kuniyoshi, 1997; Kuniyoshi, Cheng, & Nagakubo, 2003; Kuniyoshi, Yorozu, Inaba, & Inoue, 2003). These studies reveal how embodied interactions that exploit body and environmental constraints enable various behaviors to emerge and how incremental developmental processes can be explained with just simple control and learning rules.

We next show how an embodied approach focusing on brain, body, and environment interactions engendered by sensorimotor experience can be used to understand the mechanisms that underlie functional neural development in human fetuses and infants. We first describe the development of the nervous system (spinal cord and cortex) from the fetal to the infancy stage. Second, we explain development and learning based on sensorimotor experiences occurring from the embryonic to the infancy stage. Third, we present novel, integral embodied brain models of the human fetus and infant and show how these models provide insights into the mechanisms by which sensorimotor experience influences and is influenced by functional neural development.

1.2 Development of the Human Embryo and Fetus

In this section, we highlight the functional development of the sensory modalities, bodily movements, and nervous system during the early fetal and infancy periods, particularly in relation to learning based on sensorimotor experience.

1.2.1 Development of Sensory Modalities

To consider learning based on sensorimotor experiences in the embryonic and fetal periods, we first explain the development of the sensory modalities. Although it takes most sensory organs several years to fully mature after birth, sensory systems begin to work functionally even in the fetal period (Vauclair, 2012). Here, we consider the development of tactile perception, proprioception, equilibrium sensation, taste, olfaction, auditory, and vision during the fetal period.

Relative to all the sensing modalities, somatosensory perception such as tactile perception and proprioception matures earliest. With regard to tactile perception, Hooker (1952) reported developmental differences in tactile sensation after aborted fetuses were stimulated with a von Frey hair. Before 7 weeks after conception, the fetus did not respond to tactile stimulation. After 7 weeks post-conception, the fetus responded to tactile stimulation on the lip. At 10.5 weeks after conception, the fetus responded to hand, foot, and upper limb stimulation. At 11 weeks after conception, the fetus responded to stimulation on the face and all limbs. Approximately 14 weeks after conception, the fetus responded to stimulation on the whole body except for the top of the head and back.

Proprioception is the sense of self-movement and body position and its developmental emergence has been mainly investigated through study of muscle spindles. The muscle spindle is embedded in skeletal muscle fibres and senses information related to muscle length and its change. The structure of the muscle spindle appears at 11 weeks after conception and matures by 30 weeks after conception (Cuajunco, 1940). The stretch reflex, which is the most representative monosynaptic reflex induced by an afferent signal from the muscle spindle, is reported to mature by 25 weeks (Hakamada, Hayakawa, Kuno, & Tanaka, 1988). Although there is no study investigating when sensory feedback of the muscle spindle begins to induce the reflex in the human fetus, several studies suggest that it begins to work and affect neural learning in the spinal nervous system from around the end of first trimester (Clancy, Darlington, & Finlay, 2001; Robinson et al., 2008; Sarnat, 2003). For example, Sarnat (2003) suggested that the human fetus at its earliest stages can register proprioceptive feedback based on findings that: (i) the stretch reflex emerges at the same time as the formation of muscle spindle in the rat fetus, and (ii) sensory branches reach to the anterior horn of the spinal cord at 8 weeks in the human fetus. In addition, the rat fetus shows motor learning based on proprioceptive feedback at embryonic day 19 (Robinson et al., 2008). Because this period in the rat fetus is estimated to be equivalent to 11–13 weeks after conception in the human fetus (Clancy et al., 2001), these findings also suggest the beginning of proprioceptive feedback in the human fetus.

In the visual system, basic structures such as the eyeball and retina start to form by 7 weeks after conception; the optic nerve reaches the cerebral cortex at 16 weeks after conception (Bremner, Lewkowicz, & Spence, 2012). Although the maturation of these structures continues throughout infancy (Bremner et al., 2012), some visual function has been reported in the early fetal stage. Preterm infants showed eye tracking for visual stimulation from 22 to 28 weeks after conception and cortical activity in response to a flash of light (Bremner et al., 2012). Moreover, a recent study reported that the human fetus looked towards face-like stimulation projected through the uterine wall in the middle of third trimester (Reid et al., 2017).

The sense of equilibrium starts to function at 8 weeks after conception and functionally matures by 25 weeks after conception (Hakamada et al., 1988). In this phase, we can observe the righting reflex, which reflects the functioning of the vestibular sensory system (Bremner et al., 2012). Stimulation to the vestibular system in the fetus and preterm infant may affect state regulation, which plays an essential role in early functional development.

Gustatory and olfactory organs start to function approximately 14 weeks after conception (Vauclair, 2012). Regarding the auditory system, the cochlea is formed 9 weeks after conception and matures functionally at 24 weeks (Bremner et al., 2012). For example, some studies report that the fetus begins to respond to sounds at 24 weeks after conception, whereas others report auditory evoked cortical responses in preterm infants at 21 weeks after conception (Bremner et al., 2012). Regarding these three sensory modalities, many studies have suggested the possibility of fetal learning based on sensory experiences (James, 2010).

In summary, the central nervous system is capable of receiving almost all sensory inputs from peripheral organs in the third trimester. Further, somato-sensory perception is the first of all the sensing modalities to mature and already begins to function in the early fetal period.

1.2.2 Development of Fetal and Infantile Bodily Movements

One of the earliest studies of fetal movement was done by Wilhelm Preyer in 1885. He noticed stepping-like movements by fetuses that were removed from the womb (Robinson & Kleven, 2005). After his original study, many researchers investigated fetal behaviors, especially behavioral responses to stimulation. Such attempts were carried out extensively from 1925 to 1940, which is known as “The golden age of behavioral embryology” (Robinson & Kleven, 2005). Due to technical and ethical difficulties associated with human studies, most studies were conducted on animals such as rodents and pigs. Researchers investigated movements of embryos and fetuses outside their mother’s body with intact umbilical cords (Robinson et al., 2008). Results showed that fetal movements in response to chemical and tactile stimulation were coordinated and structured. In addition to behavioral responses to stimulation, researchers found that animal embryos and fetuses exhibit spontaneous movements without overt stimulation. Spontaneous movements were actively investigated especially around the 1960s. For example, Hamburger, Wenger, and Oppenheim (1966) studied early spontaneous movements in the chick embryo and quantitative changes in spontaneous movements during development. In addition, they reported that movements can be observed even in embryonic isolation of the spinal cord from the brain. These animal studies showed that embryos and fetuses generate various types of movements including structured behavioral responses to stimuli as well as spontaneous movements.

Observational studies of movements by human fetuses in the intrauterine environment became more feasible with techniques such as ultrasonic measurement. In 1982, de Vries, Visser, and Prechtl conducted a systematic longitudinal observation of fetal motility for 11 pregnancies during the first 20 weeks of gestation. They reported that 16 distinct movement patterns could be observed by 15 weeks of gestation. Regarding the emergence of spontaneous bodily movements, recent studies indicate that these movements emerge as early as muscles function (Lüchinger et al., 2008). Specifically, spontaneous movements started from 7 weeks and 2 days after conception in an in-vitro fertilized fetus (Hadders-Algra, 2007; Lüchinger et al., 2008). The formation of the reflective arc in the spinal cord occurs at 8 weeks (Okado, 1984), indicating that spontaneous fetal movements emerge prior to maturation of the nervous system (Hadders-Algra, 2007).

Spontaneous movements have been characterized qualitatively in terms of “complexity” (the spatial variation of movement), “variation” (the temporal variation of the movement), and “fluency” (the presence of smooth, supple, and graceful movements) (Hadders-Algra et al., 2004; Prechtl, 1990). Clinical studies reveal that atypical variation in these qualitative features of spontaneous movement can be associated with neurological dysfunction, including cerebral palsy and neurodevelopmental disorders in later life (Groen, de Blécourt, Postema, & Hadders-Algra, 2005). In neonates and infants, spontaneous movements have also been described quantitatively by using marker-based motion capture systems and accelerometers (Vaal, van Soest, Hopkins, Sie, & van der Knaap, 2000). In such studies, researchers find that infants with brain injuries or at risk for neurological dysfunction evidence disorganized limb trajectories characterized by chaoticity and fractal properties (Ohgi, Morita, Loo, & Mizuike, 2007; Stephen et al., 2012).

1.2.3 Neural Development Related to Sensory-Motor Learning

Next, we consider the development of the nervous system during the embryo, fetal, and perinatal periods. We emphasize neural learning via sensorimotor experiences and focus on the spinal circuit and cerebral cortex.

1.2.3.1 *Development of the Spinal Nervous System*

The spinal nervous system relays afferent signals from peripheral sensory organs to the central nervous system, including the primary sensory and motor cortex. It is also the final pathway of the motor system, conducting efferent signals from the motor cortex to muscle. The most representative monosynaptic reflex named the stretch reflex is induced by α and γ motor neurons in this system. The former activates skeletal muscle, and the latter activates muscle spindles. Various other spinal circuits, which comprise several excitatory and inhibitory interneurons, process information from afferent and efferent signals to and from the peripheral organs and the central nervous system. The spinal

cord integrates and relays the afferent signals of somatosensory inputs, leading to complex motor responses including reflexes and locomotion behaviors.

From morphological studies, muscle spindle afferents start to reach the motor neuron pools by 8 weeks and project to the ventral horn in the intermediate zone between 11 and 19 weeks. Because the human fetus starts to move as early as 7 to 8 weeks (Lüchinger et al., 2008), efferent output of alpha motor neurons also starts to reach the muscle at the similar time period (Sarnat, 2003). Although the development of interneuronal connectivity remains poorly understood, the neuromuscular loop for the stretch reflex emerges and matures by 25 weeks (Hakamada et al., 1988). Among the descending inputs to spinal circuits, the corticospinal tract, which is the descending pathway from the motor cortex to alpha motoneurons, has been most actively investigated. Morphological studies demonstrate that corticospinal axons have reached their most distant destination by 24 weeks post-conceptual age (Eyre, Miller, Clowry, Conway, & Watts, 2000; Sarnat, 2003). Following a waiting period of up to a few weeks, there is extensive innervation of spinal neurons, including motor neurons. Neurophysiological studies also provide evidence for prenatal and neonatal functional corticospinal projections (Eyre et al., 2000; Kanazawa et al., 2014).

The spinal circuit consists of excitatory and inhibitory interneurons, like all circuits. Early in development, GABAergic and glycinergic interneurons drive depolarization of postsynaptic neurons, while they act as inhibitory neurons and produce hyperpolarization after maturation (Ben-Ari, Gaiarsa, Tyzio, & Khazipov, 2007; Blaesse, Airaksinen, Rivera, & Kaila, 2009). These interneurons with recurrent connections exhibit a spontaneous rhythmic activity before the formation of the afferent and efferent projections, which is thought to play an important role in generating spontaneous bodily movements (Blankenship & Feller, 2010). Animal studies have shown that developmental changes in movement patterns generated by the spinal circuits proceed in progressive phases (Yvert, Branchereau, & Meyrand, 2004). Initially, activities of all hind-limb muscle groups are synchronized, followed by a phase in which left–right alternation of the limbs increases, proceeding finally to a pattern of intermuscular coordination within individual limbs (e.g., flexor–extensor alternation). In part, this phasic progression has been explained by a switch in signaling sign of the GABAergic and glycinergic interneurons because these inhibitory neurons are responsible for patterning the interneuron and motor output that directs left–right and flexor–extensor alternation in adult mammalian species (Grillner & Jessell, 2009). Although little is known about how the spinal circuit generates spontaneous rhythmic activity and how it changes developmentally, these networks are usually referred to as central pattern generators (CPGs) or neural oscillators. They are considered the neural basis of spontaneous bodily movements of fetuses and infants, and for locomotion behaviors as well (Hadders-Algra, 2007).

Recent animal studies have reported activity-dependent neural development and learning in the spinal circuit. Observations of spontaneous activity

suggest that such activity could play essential roles in the maturation of the nervous system including neuron differentiation, migration, synaptic formation, and maturation of neuromuscular junction (Gonzalez-Islas & Wenner, 2006; Hanson, Milner, & Landmesser, 2008; Spitzer, 2006). In addition, recent studies on mice suggest that proprioceptive sensory feedback is required for the formation of antagonistic circuits at the level of premotor interneurons (Tripodi, Stepien, & Arber, 2011). The finding that even the distribution of premotor neurons is affected by activity-dependent factors suggests that the development of functional neural circuits is dependent on both genetic and activity-dependent factors.

Bodily movements generated by spontaneous activity in the spinal circuit have also attracted attention due to their important role in neural development and learning. Studies on neonatal rats have shown that spontaneous movements play an essential role in the formation of a body representation in the spinal nervous system as well as in the spinal circuit for the withdrawal reflex (Granmo et al., 2008; Petersson, Granmo, & Schouenborg, 2004; Petersson, Waldenström, Fåhræus, & Schouenborg, 2003). Other studies have documented the important role of bodily movements in the formation of spinal circuits engendering locomotion behaviors. For example, studies on the zebrafish embryo have shown that spontaneous movements are needed for the proper development of coordinated patterns of activity in the motor system (Warp et al., 2012). Studies on *Drosophila* larvae also have revealed the essential role of the movements for maturation of a spinal circuit engendering coordinated crawling-like behavior (Crisp, Evers, & Bate, 2011; Suster & Bate, 2002). Interestingly, these studies also suggest that adequate patterns of activity may be required for the normal maturation of the spinal circuit since synchronized stimulation leads to delay or prevents it. Likewise, Robinson et al. (2008) showed that fetal rats can modify patterns of interlimb coordination based on sensorimotor experience and feedback before birth. Collectively, these studies show that the development of spinal circuits is highly dependent on activity from the earliest stages of development. They also suggest that sensorimotor experience plays an essential role in the formation of the spinal circuits that are used to perceive sensory information and control movements, including reflex movements and locomotion behaviors.

1.2.3.2 *Development of the Cortex*

Next, we describe cortical development by focusing on neocortex, which is a distinctive feature of the mammalian brain. Cortical neurons are mainly generated from neural progenitors through cell proliferation, migration, and differentiation. In the human fetus, cortical neurons proliferate between 10 weeks and 22 weeks from the ventricular zone. Neuronal migration peaks between 12 and 20 weeks and is largely complete by 26–29 weeks. The number of neurons peaks at 28 weeks, and approximately half of these cells decrease with apoptosis and naturally occurring cell death by adolescence. The synaptic density