



Review

Three lessons from Philip Teitelbaum and their application to studies of motor development in humans and mice

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ABSTRACT

In this paper we present a number of studies, some with humans and some with animals that have been directly influenced by the work of Philip Teitelbaum. As appropriate for a festschrift, we integrate a number of contributions from different fields (specifically, clinical psychopathology and neurobiology) and present the studies, not so much chronologically, but in ways that illustrate some of the key lessons that we have learned from Philip Teitelbaum. We would summarize these lessons as follows: (1) Complex and precise tools are required to assess the complexity of specific behaviors; using simplified tools will bias our understanding of the behavior itself. (2) Studying a specific behavior in atypical brain conditions is required to fully understand that behavior and how the brain controls it. (3) Considering the evolutionary basis of human behavior, studying corresponding behaviors in other mammalian species is required to strengthen and deepen our knowledge of specific human behaviors. In this paper we describe studies on motor development in humans and mice and their implication for the diagnosis of autism and early parental care that illustrate these three lessons.

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1. Introduction

In this paper we present a number of studies, some with humans and some with animals that have been directly influenced by the work of Philip Teitelbaum. As appropriate for a festschrift, we integrate a number of contributions from different fields (specifically, clinical psychopathology and neurobiology) and present the studies, not so much chronologically, but in ways that illustrate some of the key lessons that we have learned from Philip Teitelbaum, either by reading his works or by interacting and working directly with him. We would summarize these lessons as follow: (1) Complex and precise tools are required to assess the complexity of specific behaviors; using simplified tools will bias our understanding of the behavior itself. (2) Studying a specific behavior in atypical

brain conditions is required to fully understand that behavior and how the brain controls it. (3) Considering the evolutionary basis of human behavior, studying corresponding behaviors in other mammalian species is required to strengthen and deepen our knowledge of specific human behaviors. In the remainder of this paper, we describe studies on motor development in humans and mice and their implication for the diagnosis of Autism that illustrate these three lessons.

Autism indicates a severe and lifelong developmental condition characterized by impaired social and communicative skills as well as restricted interests and repetitive behaviors [1]. Manifestation of autism varies in severity and it is generally agreed that there is a spectrum of disorders (autism spectrum disorder, ASD). More recently it has been suggested that the term “Autisms” [2] might be even more appropriate than ASD because the diverse symptomatology of ASD seem to correlate with very different neural pathways, different etiopathogenesis, and different prognosis.

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Many studies during the past two decades have investigated early diagnosis of ASD [3–10]. Among the potential early indicators of ASD that have been investigated, motor development, in particular, has gained international attention [3,4]. Independent groups in the USA [3,5], Canada [6], Australia [7,8], France [9], and Italy [10] have found that motor anomalies may be an early sign of ASD, one that precedes social or linguistic abnormalities. It should be noted, however, that Ozonoff and colleagues [4] did not find elevated rates of movement abnormalities in infants later diagnosed with autism. Thus, the debate on the importance of early motor abnormalities as indicators of possible ASD is still open.

In the following paragraphs, we present a brief review of some recent studies, along with some yet unpublished results, regarding a specific aspect of motor development, the development of motor symmetry.

1.1. Lesson 1. Using precise tools

To capture the complexity of a specific behavior, complex and precise tools are required to assess that behavior using simplified tools will bias our understanding of the behavior itself. In order to assess motor performance in rodents and humans, starting from the late seventies Philip Teitelbaum [e.g. 11] began to utilize the Eshkol–Wachman Movement Notation [12]. The EWMN was created in Israel by Noa Eshkol (dance theorist) and Avraham Wachman (professor of architecture). The EWMN assumes one general form that will stand conceptually for all bodies; in that form, each limb is reduced to its longitudinal axis, an imaginary straight line of unchanging length; these axes are analogous to the skeletal structure of the body. Using a spherical coordinate system, the relationship of the axes is described in three-dimensional space (analogous to latitude and longitude on a globe) and is able to capture the complexity of motor patterns over time. Thanks to the Teitelbaum application of EWMN in science, the system has come to be used in many fields, including physical therapy, animal behavior, and child psychopathology [see for example Figs. 1–4].

Before toddlerhood, the baby's main task is the development of motor autonomy, a process that proceeds in distinct stages. Each stage is characterized by a motor milestone—specifically, (i) lying; (ii) rolling; (iii) sitting; (iv) standing and (v) walking—and mastering each stage prepares the infant's progression for the next one. The EWMN has proven to be a useful tool for describing the motor milestones of infancy and, in particular, for assessing the importance of postural symmetry in acquiring those milestones [3,13]. By definition, postural symmetry occurs when corresponding limbs (an arm and the other arm, a leg and the other leg) are positioned the same.

Lying is an active posture, even in the first few days of life. Casaer has highlighted [14] how newborns maintain specific active

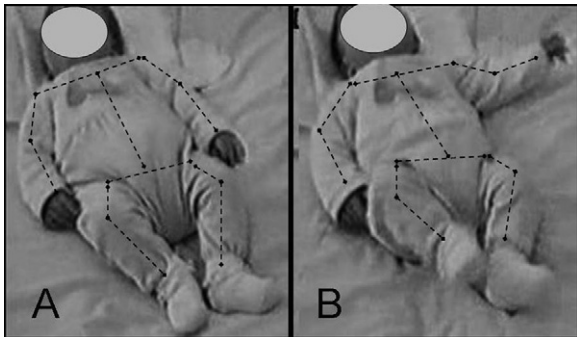


Fig. 1. The images show (A) symmetric and non-symmetric (B) postures of a 5-month-old infant while lying. The symmetric and non-symmetric postures were assessed using the Eshkol–Wachman Movement Notation (EWMN). (Reproduced from Ref. [15]).

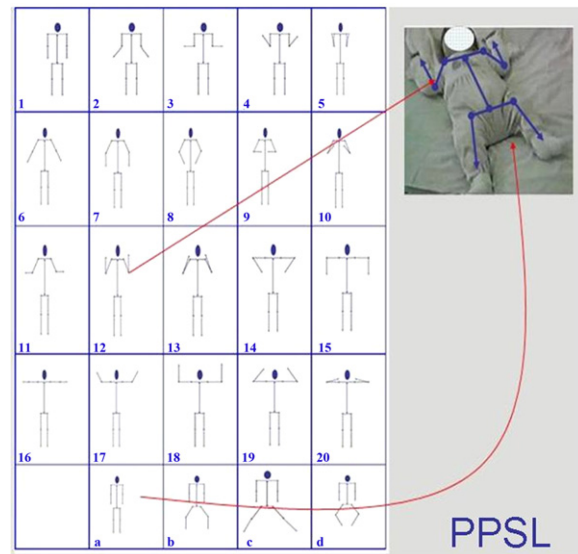


Fig. 2. The positional pattern for symmetry during lying (PPSL) represents all the possible symmetric positions of a body in a supine position in a 2D image. Considering the degree of freedom for movement during the supine position the PPSL contemplates 20 symmetric positions for the arms and 4 symmetric positions for the legs. A total of 80 symmetrical position of the whole body are possible. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.) (Reproduced from Ref. [15]).

postures while lying. Lying can also be seen as the first occasion for infants to exercise their vestibular system. Indeed, in typical infants a general symmetry, defined as similarity in the position of the two sides of the body, can be seen [13].

Rolling. Although there is considerable variability, from the first few weeks of life infants evidence the “rolling” movement, a movement important for the infant's increasing strength and coordination. Two patterns are typically seen: rolling from front to back and rolling from back to front. For some typically developing infants, this pattern may not emerge until seven or eight months of age [3].

Sitting. By about 7–8 months, on average, typically developing infants are able to sit without external support. This movement

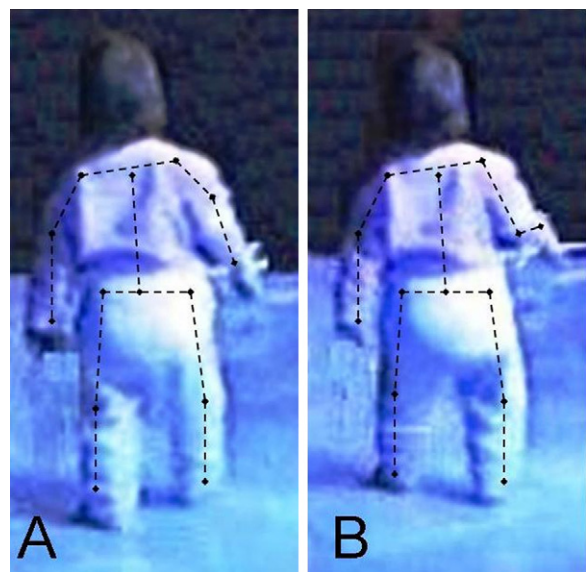


Fig. 3. The images show (A) symmetric and non-symmetric (B) postures of a 12-month-old infant while walking. The symmetric and non-symmetric postures were assessed using the Eshkol–Wachman Movement Notation (EWMN). (Reproduced from Ref. [15]).

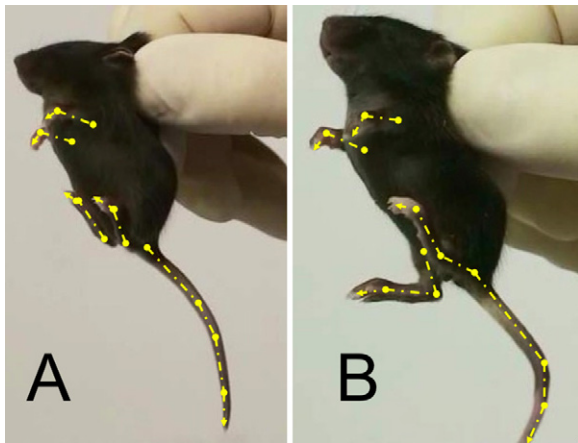


Fig. 4. The images show (A) symmetric and (B) non-symmetric postures of a P10 pup assessed using the EWMN. A symmetrical posture of the pup's body is a position for which similarity of relative positions for corresponding limbs (right upper-limb with the left upper-limb, right lower-limb with the left lower-limb,) is showed with an accuracy of 45°.

requires integration among the vestibular centers and the muscles that control the trunk and hips. Although the sitting posture is usually achieved during the second half of the first year of life, its emergence is a continuous process. Indeed, during the first 2 months, an infant's muscles have not yet developed adequate strength to sit. At about 6–7 months of age, typically developing infants begin to show the righting reflex. This reflex, which is shared with other nonhuman primates, is the ability to resume an optimal position when there has been a departure from it. For example, in the case of sitting, when infants are held around the chest and their bodies are tilted, they extend their arms in an attempt to keep balance. After the activation of this reflex, infants develop several skills that provide the opportunity to sit.

Standing. Around the 10th month of life the ability to stand usually emerges. It represents perhaps the most important motor skill infants learn during their first year of life. Once able to stand, infants have the opportunity to observe the environment from a totally different perspective.

Walking. Between 12 and 15 months of age most babies learn to walk. The reflexes that form the foundation for walking are probably active since birth. However, children cannot walk until their muscles have grown and developed enough strength to sustain their body weight.

By using the EWMN [15,16], we have been able to document a consistent developmental pattern, one that characterizes all of the motor developmental milestones just described. It appears that at the beginning all the motor milestones are performed in a very asymmetric way (i.e., a lack of balance or “patterned self-similarity” among the position of the limbs). Then, as the motor expertise of the child progresses and the muscles become stronger, the movement is produced in a more symmetrical way. Indeed, asymmetric postures persist only in atypical development [17].

1.2. Lesson 2. Comparing typical with atypical

In the previous section, we noted that typical development of motor milestones involves initial asymmetry that becomes outgrown, but that persistent asymmetry may be a sign of neurological deficit. Following this argument, analysis of an atypical behavior is useful not only to elucidate the mechanisms behind the atypical behavior itself, but also to gain a better understanding of the typical behavior. In other words—and this is Philip Teitelbaum's second lesson—to really understand what a specific typical behavior is and how the brain controls it, one needs to analyze the same specific

behavior in atypical brain conditions. Influenced by this idea and the hypothesis that asymmetry in motor development may be an early indicator of neurological disorders, Teitelbaum and colleagues [3,17], and subsequently some of his former students [15,16], employed a number of studies to (i) describe motor developmental milestones in children with ASD compared to Typically Developing (TD) children and (ii) evaluate whether early asymmetry in motor development may constitute an early marker of ASD. These studies investigated lying, rolling, sitting, standing, and walking.

Lying. Analysis of static and dynamic symmetry during lying [15] was conducted with retrospective home videos, recorded during the first 5 months of life, of children with ASD and other developmental delay (DD) and TD children. For each child, selected scenes from these retrospective home videos were assembled, split into frames with a rate of 4 frames for second, and coded. Two coders using the positional pattern for symmetry during lying (PPSL) coding scheme (Fig. 2) coded each frame. The general framework for the PPSL was the same as that used by Teitelbaum and colleagues: the EWMN. This study suggested that different pattern of motor functioning probably relate to different pathways to ASD. It was hypothesized that the low levels of symmetry from the 1st month of life could be related to the loss of the Purkinje cells described in ASD.

Rolling. Impairments in rolling in children with ASD have been described [3,17]. They note that some children cannot perform rolling at all, whereas some others can begin a rotation pattern but are unable to complete the motor sequence. Furthermore, even children with ASD who were able to perform the complete motor sequence showed quite a different pattern from the pattern described in TD children [13].

Sitting. In their 1998 study Teitelbaum and colleagues [3] showed that not all the children with ASD at 6 months of age were able to maintain sitting stability, whereas typically developing children of this age usually can. Furthermore, for children with ASD who were able to maintain a sitting position, their posture showed persistent asymmetry (i.e., their weight was often not distributed equally on both sides). A successive independent study was subsequently conducted in 2009 [13] for which frames captured from retrospective home videos taken when infants were sitting at 5–7 months of age (ASD, TD, and DD) were analyzed. The results of this study showed marked differences among the AD, TD, and DD groups for sitting. In particular, children with a diagnosis of ASD showed more asymmetric posture. Moreover, internal variability (i.e., the standard deviation) for the ASD group was much larger than that for the TD and DD groups.

Standing. Very few studies report data about standing in infants with ASD during the first year of life. We found only two. Teitelbaum and colleagues [3] described signs of akinesia (a signal of motor disorder) in a girl later diagnosed with ASD who “stood in one place leaning her back against a heavy piece of furniture for periods as long as 15 min at a time”. The second study [13], which employed EWMN assessment of frames captured from retrospective home videos taken when infants were 9–11 months of age (ASD, TD, and DD), did not find any significant differences in the level of motor symmetry in the three groups analyzed. The authors commented that the analysis of standing between 9 and 11 months of age did not show differences because all three groups showed low levels of symmetry. In fact it is possible that all children in this developmental stage (9–11 months) are learning how to stand and maintain balance and for this reason they show high levels of asymmetry. This result also agrees with the idea that, at the beginning of each developmental motor milestone, movement is characterized by a persistent lack of symmetry. Probably standing, which is compromised in older children with ASD [18], is not a useful marker during the first year of life.

Walking. The first studies on walking and ASD were conducted in the late 1970s. Damasio and Maurer [19] showed that

children with ASD between 3 and 10 years of age walk somewhat like Parkinsonian adults (i.e. more slowly, short steps). Nonetheless, the existence of such a Parkinsonian-type disturbance was disputed by Hallett et al. [20], who identified movement abnormalities in persons with ASD suggestive of a cerebellar disturbance (decreased range of motion of the ankle, decreased knee flexion in early stance, and gait irregularity). Other symptoms that may resemble extrapyramidal impairments include delays in the initiation, change, or arrest of a motor sequence. Correspondingly, Allen and Courchesne [21], using functional Magnetic Resonance, found that certain areas of the cerebellar vermis are incompletely developed in children with autism. This also supports the view that movement disorders might play a role in ASD. Teitelbaum and colleagues [3,17] have reconsidered the Parkinsonian gait hypothesis in children with ASD, as related to a dopaminergic system deficit. They found asymmetric patterns of gait in all the children with ASD in their sample. Other studies [8,9] have stressed the importance of the dopaminergic system and of the basal ganglia as well. In particular, Vernazza-Martin and colleagues [9], using a kinematic gait analysis (ELITE system), have indicated that, rather than gait parameters or balance control, the locomotion component most affected in children with ASD was the definition of the trajectory (probably due to an impairment of motor planning). In two successive studies using independent samples, Esposito and Venuti [10,16] investigated walking performances in ASD. In the first study [10], the authors analyzed gait in toddlers with ASD, TD, and DD using the walking observation scale (WOS) after 6 months of independent walking (~18 months of age). The WOS includes 11 items that analyze gait through three axes: foot movements, arm movements and global movements. Their results highlighted that after 6 months of independent walking, different patterns in gait among the groups were evident. In the second study [16], using EWMN (see Fig. 3) the authors identified gait pattern disturbances in ASD at an even earlier age (after 1 week of walking autonomy, ~12 months of age). Furthermore, the results of both studies showed that the standard deviation for the ASD group was much larger than that for the TD and DD groups, highlighting the existence of different subgroups among persons with ASD. This finding could be of some clinical value, since the different subgroups could be related to multiple etiological and neuropathological mechanisms that lead to ASD. Indeed the autism spectrum suggests that different neuronal pathways exist [22].

In general, several studies suggest that anomalies in specific motor milestones (such as lying, sitting, and walking) may serve as early markers for a diagnosis of ASD (or at least for a specific subgroup of children with ASD). Furthermore, these results support the idea that there are some specific neural mechanisms, implied in motor control, which play a role in the motor anomalies shown by a subgroup of children with ASD. In some previous studies, Purkinje cell disruption has been proposed as one possible mechanism that compromises motor development in ASD. Indeed general agreement exists that the microscopic anatomic pathology of ASD involves Purkinje cell loss and neuron size reductions in the cerebellum. Furthermore, in a report by Kern [23] it is speculated some children may develop ASD from neuronal cell death or brain damage occurring postnatally due to injuries. Purkinje cells in the cerebellum can be selectively vulnerable to certain types of insult (e.g., hypoxia, excitotoxicity [24]) and they may play a role in motor disturbances in children with ASD.

1.3. Lesson 3. Employing animal and human studies

Philip Teitelbaum's third lesson is that, considering the evolutionary basis of human behavior, studying corresponding behaviors in other mammalian species is required to strengthen and deepen our knowledge of specific human behaviors [see for example 25]. To demonstrate the importance of this lesson, we now present

new data from an experiment with laboratory mice [26]. Because certain basic behaviors and physiological functions are conserved through mammalian evolution, some similarities are present in the neural mechanisms for these functions across mice and humans. Furthermore, in mice, genetic-engineering techniques, such as the production and use of a gene knockout mouse for behavioral analysis, are readily available. The application of genetic engineering in behavioral neuroscience enables us to make typical-atypical comparisons in a highly controlled manner, and to use the results to speculate about the human nervous system. Indeed, Philip Teitelbaum's emphasis on the importance of paying attention to the details of behavior led him to insist that one should manipulate the brain to understand behavior, rather than the reverse. An evident consequence, based on the data presented by Teitelbaum and colleagues [17], is that early asymmetry in infants with neurological damage can create a bias in the way these infants interact with the environment in general, and with the caregiver in particular. Based on this idea, we wanted to use an animal model to test whether motor asymmetry in early infancy could modify the pup behavior and subsequently the pup-caregiver interaction.

A rodent mother carries her young by grasping the pup's dorsal skin in her mouth. Neonatal pups are transported passively, but they soon become actively involved in the process by showing the "transport response (TR)", which is a compact posture characterized by postural immobility and hindlimb flexion [26–29] see also Fig. 4.

Therefore, maternal retrieval behavior and pup's TR are a mutually dependent, dynamic process. To investigate this dyadic interaction more closely, we implemented a new behavioral task of "maternal rescue of pups from a cup" (Fig. 5), in which the pups were experimentally put in a plastic cup and the mother had to retrieve the pups from a cup back to the nest [26,27]. This experimental setting was intended to mimic a challenging situation in the wild, in which the mutual cooperation of the mother and her pups are required for pup survival.

Using this behavioral task, we tested not only typical mouse pups but also the atypical homozygous *Reeler* mutant mice. *Reeler* is a spontaneous loss-of-function mutation in Reelin gene encoding an extracellular matrix protein [30]. Homozygous *Reeler* mutant mice are viable but display severe architectonic abnormalities in the cortical structures of the cerebrum [31], hippocampus [32] and cerebellum [33]. The behavioral phenotypes of *Reeler* mice are characterized as: (i) hypotonia, (ii) loss of motor coordination, and

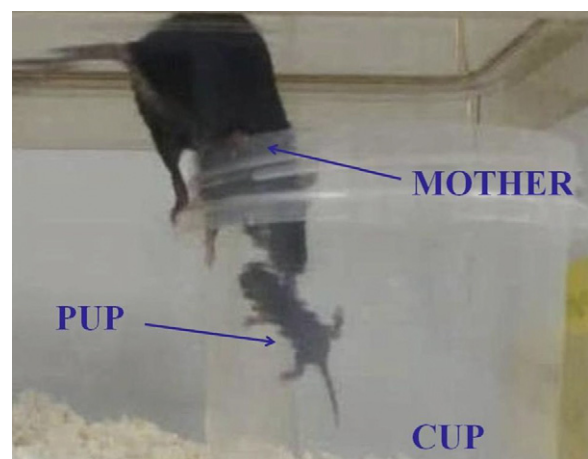


Fig. 5. A transparent plastic cup (125 mm × 90 mm) is fixed in the breeding cage from postnatal day 3 (P3). The task is for the mother to retrieve the pup by grasping and lifting to take it completely outside of the cup; it is complete when the mother has successfully removed the pup from inside of the cup to the ground outside of the cup and the mother's four limbs are also touching the ground.

(iii) high frequency tremor. Because TR includes fine motor coordination, we hypothesized that Reeler mutant pups should be defective in some aspects of body control during maternal transport that would influence their mother's retrieval performance.

Our results highlighted that the *Reeler* mutant pups showed a poor level of postural symmetry during maternal transport, compared with wild-type littermates [26]. Among the various phenotypes of *reeler* mice, the cerebellar malformation might be responsible for this abnormal postural regulation during TR. This notion will be further verified by additional experiments.

We also found that the maternal efficacy of pup retrieval from the cup was reduced for *reeler* mutant pups compared to wild-type littermates [26]. The causal relationship of this prolonged maternal retrieval with the postural asymmetry of *reeler* mutant pups needs to be shown in future studies. Nevertheless, the delay in maternal retrieval of a pup may result in failure or abandonment when attempting to rescue the particular pup. In this sense, the present data are in support of the idea, posed by Teitelbaum and colleagues [3], that early asymmetry in infancy can create a bias in the way these infants interact with the caregiver (i.e. higher infant asymmetry > more difficulties for parents while holding them).

Although the preliminary results here discussed present some limitations (i.e. data await a full airing in the peer review process; results have not yet been replicated), we believe that continuing this line of research can be worth for learning brain mechanisms of the "transport response". Finally we can suggest that, "transport response" which represents an early attachment behavior in laboratory mice can be studied using the behavioral task "maternal rescue of pups from a cup" implemented here.

2. General conclusions

In this paper we have presented several studies of both human and animals in order to illustrate some of the key lessons that the authors have learned from Philip Teitelbaum, either by direct instruction in person or from his literature. From his early work on the hypothalamic control of food and water intake, to the more recent application of movement notation to the study of Autism, Philip Teitelbaum has been (and continues to be) an influential figure in the field of comparative and physiological psychology. His papers have been influential for many researchers around the world. Although some of his more recent works on Autism have been criticized for the lack of control data [4], they have nonetheless shown new directions in the study of Autism [15], and have provided alternative points of view.

We strongly believe that in the fast-developing field of Behavioral Neuroscience, where new techniques and tools are created every month, Philip Teitelbaum's lessons remain very valuable and can benefit students and young scholars. While we have sophisticated tools to analyze brain functions (e.g. genetic engineering, fMRI, MEG) for behavioral analysis we still depend largely on observation. Indeed, one of the challenges new scholars should face in modern Behavioral Neuroscience is probably best represented by the postulate: "If meaningful correlations are to be made between brain mechanisms and behavior, then the analysis of behavior will require as much sophistication and attention to detail as the analysis of the brain" (Philip Teitelbaum).

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