The importance of touch in development

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Developmental delay is common in children deprived of normal sensory stimulation – for example, in premature neonates and some institutionalized children. Touch has emerged as an important modality for the facilitation of growth and development; positive effects of supplemental mechanosensory stimulation have been demonstrated in a wide range of organisms, from worm larvae to rat pups to human infants. Animal models are being used to elucidate the cellular and molecular mechanisms underlying these effects. In rats, the amount of maternal licking received as a pup has a profound impact on the behaviour and physiology of the adult; in the microscopic roundworm *Caenorhabditis elegans*, physical interactions with other worms promote growth and increase adult responsiveness to mechanosensory stimuli. By understanding the underlying mechanisms, as well as the timing and degree of stimulation required to fully reverse the effects of early childhood deprivation, strategies can be developed to best help those in need.

Key Words: Caenorhabditis elegans; *Kangaroo mother care; Maternal patterns of care; Preterm birth; Rats; Sense of touch*

L'importance du toucher pour le développement

Le retard de développement est courant chez les enfants privés de stimulation sensorielle normale, par exemple, chez les nouveau-nés prématurés et certains enfants institutionnalisés. Le toucher a émergé comme une modalité importante pour favoriser la croissance et le développement. Les effets positifs d'une stimulation mécanosensorielle supplémentaire sont démontrés chez toute une série d'organismes, des larves de vers aux nourrissons humains en passant par les ratons. On utilise des modèles animaux pour élucider les mécanismes cellulaires et moléculaires à l'origine de ces effets. Chez les rats, la quantité de léchage que reçoit le raton de sa mère a d'importantes répercussions sur son comportement et sa physiologie à l'âge adulte. Chez les nématodes *Caenorhabditis elegans* microscopiques, les interactions physiques avec d'autres vers favorisent la croissance et augmentent la réceptivité de l'adulte aux stimuli mécanosensoriels. Si on comprend les mécanismes sous-jacents, le moment et le degré de stimulation nécessaires pour supprimer entièrement les effets d'une privation pendant la première enfance, on pourra élaborer des stratégies pour aider les enfants dans le besoin.

Developmental delay is often seen in children receiving inadequate or inappropriate sensory stimulation. For example, orphaned infants exposed to the bleakest of conditions in eastern European institutions exhibited impaired growth and cognitive development, as well as an elevated incidence of serious infections and attachment disorders (1). Much evidence now points to the importance of touch in child development and suggests the possibility that these orphaned infants are not suffering from maternal deprivation, per se, but from sensory deprivation, and more specifically a deprivation of mechanosensory stimulation. In early studies on human infants, Hopper and Pinneau (2) found that 10 min of additional handling per day resulted in a significant reduction in regurgitation. In addition, Casler (3) reported that institutionalized infants receiving an additional 20 min of tactile stimulation per day for 10 weeks had higher scores on developmental assessments. Since then, several studies have documented mechanosensory stimulation facilitating growth and development in children deprived of normal sensory stimulation, such as premature neonates.

Premature infants are often isolated in incubators and deprived of much of the mechanosensory stimulation they would otherwise receive. Field et al (4) and Scafidi et al (5) investigated the effects of tactile and kinesthetic stimulation on the development of premature/low birth weight neonates. In the studies, 20 preterm neonates, recently transferred from the neonatal intensive care unit to the transitional care unit, were given 15 min of mechanosensory stimulation three times per day for 10 days. The procedure was tightly controlled: infants received body stroking for the first and final 5 min of stimulation, and their limbs were gently flexed upward during the intervening 5 min. Several clinical and behavioural variables were monitored, and the stimulated infants were compared with unstimulated controls equivalent in their gestational age (approximately 31 weeks), birth weight (approximately 1.27 kg) and duration of intensive care (approximately 20 days). The data showed that extra mechanosensory stimulation led to superior growth and developmental performance. Although caloric consumption did not differ between the two groups, infants receiving mechanosensory stimulation averaged 47% greater weight gain per day than the unstimulated controls and were discharged an average of six days earlier. The stimulated infants also spent more time awake and active, and exhibited more mature habituation, orientation, motor and range-of-state behaviours on the Brazelton Neonatal Behavioral Assessment Scale. The positive effects appear to be persistent; when retested eight and 12 months after treatment, the stimulated infants were in a higher weight percentile group, scored better on the Bayley mental and motor assessment tests, and had a reduced incidence of neurological soft signs (minor neurological abnormalities indicating nonspecific cerebral dysfunction).

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Research on the benefits of touch for premature infants has already led to procedural changes at many hospitals, with the implementation of 'kangaroo care' as a standard care option for both premature and full-term infants. In kangaroo care, the infant only wears a diaper and is held upright against the bare chest of the carrier. Feldman et al (6) studied the long-term effects of this technique and found that premature infants who had received at least 1 h of kangaroo care daily for at least two weeks, beginning between 31 and 34 weeks postconception, scored higher on both the mental and motor domains of the Bayley assessment tests at six months. The importance of mechanosensory stimulation in development is a highly conserved phenomenon, and current work on animal models is beginning to elucidate the underlying cellular and molecular mechanisms.

THE IMPORTANCE OF TOUCH FOR RAT PUPS: BEHAVIOURAL STUDIES

In 1922, in one of the earliest studies on the benefits of touch, Hammett (7) reported that rats that were infrequently handled were more timid, apprehensive and high strung than rats that had been 'petted and gentled'. They were also six times less likely to survive thyroidectomy. For the developing rat pup, mothers and littermates are the major sources of sensory input. A useful approach to evaluating the importance of this input is to remove it completely and observe what happens. Gonzalez et al (8) compared the adult behaviour of maternally reared rats with those isolated in plastic cups, from postnatal days 4 to 20. Despite receiving comparable nutritional input, the pups raised in cups weighed less at weaning. Although this difference did not persist into adulthood, early deprivation did affect adult maternal and emotional behaviour. Compared with maternally reared controls, isolate-reared rats were less attentive to their own offspring, performing fewer pup retrievals and spending less time licking and crouching over pups and spending more time digging, biting the cage, hanging from the top of the cage, eating and tail chasing. In an attempt to reverse the effects of isolation on adult behaviour, the pups in cups were stroked with a warm wet paintbrush to simulate maternal licking. The minimally stimulated pups received 45 s of anogenital stroking twice a day to promote urination and defecation. The maximally stimulated pups received 2 min of full-body stroking five times per day. When the pups were studied as adults and the way they mothered their own offsprings was examined, it was found that full-body stroking partially rescued the behavioural deficits of isolation, with the maximally stimulated pups exhibiting maternal behaviours of durations intermediate to those of the maternally reared and minimally stimulated pups. Thus, tactile stimulation can ameliorate some of the deficits resulting from isolate rearing in rats.

Based on the behavioural profile of rats reared in cups, it was hypothesized that early isolation impaired their attentional processing. Lovic and Fleming (9) assessed the performance of isolate-reared rats on two attentional tasks: prepulse inhibition of the startle response and attentional set shifting. Isolate-reared rats showed decreased prepulse inhibition and more trials to criterion in several stages of the attentional set-shifting task. These results suggest that sensory deprivation as a pup leads to attentional deficits later in life; however, Lovic and Fleming (9) demonstrated that these deficits could be reversed by tactile stimulation with a paintbrush: isolated pups who received paintbrush stroking for 2 min eight times per day performed as well as maternally reared controls on these tasks. In summary, isolate-reared rats were hyperactive, easily distracted and less attentive to their own pups – behaviours which could be rescued by introducing licking-like stimulation with a paintbrush.

Licking is clearly an important component of maternal care in rats. A number of studies (10-13) have monitored natural variation in maternal licking/grooming (LG) of rat pups. Mothers whose frequency scores for LG were more than 1 SD above the mean were considered to be high lickers/groomers, while those whose frequency scores for LG were more than 1 SD below the mean were considered to be low lickers/groomers. Francis et al (10) compared adult offspring of low and high LG mothers, and found that LG behaviour was transmitted across generations, because female offspring of high LG mothers licked/groomed their own pups more than those of low LG mothers. Furthermore, cross-fostering experiments demonstrated that the mechanism of inheritance was nongenomic: biological female offspring of low LG mothers fostered into the litter of high LG mothers displayed increased LG levels comparable with unfostered offspring of high LG mothers and vice versa. What then are the long-term effects of being licked more or less? Compared with offspring of high LG mothers, those reared by low LG mothers displayed impaired learning and memory in the Morris water maze and in object recognition (11,12), and showed substantially more fearful behaviour, as measured by a longer latency to eat food in a novel environment and decreased open-field exploration (13,10). These behavioural studies demonstrate that mechanosensory stimulation can alter the developing rat brain. The next series of studies highlights some of the cellular and molecular mechanisms underlying the behavioural changes that have been described.

THE IMPORTANCE OF TOUCH FOR RAT PUPS: CELLULAR AND MOLECULAR MECHANISMS

A study by Liu et al (14) showed that maternal licking altered the pup's hypothalamic-pituitary-adrenal (HPA) stress reactivity through changes in gene expression in areas of the brain that regulate the behavioural and endocrine response to stress. Adult offspring of low LG mothers had higher HPA responses to restraint stress than those of high LG mothers. An elevated HPA stress response highlights the importance of early intervention programs for children; elevated exposure to stress hormones has been implicated in the development of many conditions, including visceral obesity, hypertension, diabetes, depression, anxiety, drug addiction and multiple forms of coronary artery disease. Before policies are drafted for practical applications in humans, a better understanding of the cellular and molecular mechanisms underlying mechanosensory-mediated developmental plasticity is needed.

Briefly, in response to stressors, the periventricular nucleus of the hypothalamus secretes corticotrophin-releasing hormone (CRH). In the pituitary, CRH stimulates the synthesis and release of adrenocorticotropic hormone, which in turn induces the release of glucocorticoids from the adrenal gland. A negative feedback loop for this stress response is initiated by the binding of glucocorticoids to glucocorticoid receptors (GR) in the hippocampus. Liu et al (14) showed that as adults, the offspring of low LG mothers had decreased GR expression in the hippocampus, resulting in diminished glucocorticoid feedback sensitivity and increased CRH synthesis and release of plasma adrenocorticotropic hormone. Weaver et al (15) demonstrated that maternal care programs GR gene expression levels in the hippocampus for the lifespan of the animal via epigenetic modification of the GR gene. Beyond GR levels, maternal LG has widespread effects on gene expression in the brain, basically increasing the expression of genes that provide metabolic support, mediate experience-dependent neuronal activation, and support the growth and survival of synapses (16). Thus, licking-like stimulation has also been studied in the context of brain injury.

Stroking has been shown to facilitate functional recovery and synaptic organization following brain lesions in rat pups. In one study (17), rats were given medial prefrontal cortex (mPFC) or posterior parietal cortex lesions on postnatal day 3. It was found that administering 15 min of tactile stimulation with a small brush three times per day resulted in increased dendritic spine density in animals with mPFC lesions and increased dendritic length in animals with posterior parietal lesions. The mechanism of action appears to be the release of fibroblast growth factor-2 (FGF-2), because both FGF-2 and its receptor were upregulated in the skin and brain of stimulated rats (17). FGF-2 is produced in the skin, but can pass the blood-brain barrier, where it is hypothesized to stimulate synaptic changes. In support of this hypothesis, animals receiving FGF-2 showed better recovery following mPFC or posterior parietal lesions than vehicle-treated animals (17). Remarkably, stroking a pregnant mother rat also ameliorated the effects of future cortical lesions in her pups, as did prenatal pretreatment with FGF-2 (17). These findings hold great promise for medicine, but translational research requires continued work on the fundamental biology in model systems.

THE IMPORTANCE OF TOUCH FOR A WORM

The benefits of touch have become a recurring theme in human, monkey and rat development, but the importance of physical contact is not limited to mammals. Rose et al (18) showed that a microscopic nematode, known as *Caenorhabditis elegans*, is also sensitive to touch deprivation. Approximately 40 years ago, Sydney Brenner chose C *elegans* as the ideal model system for studies in developmental biology and neuroscience. Now, the worm is one of the best understood organisms on the planet. It is morphologically very simple, which has allowed researchers to create a complete neural wiring diagram and cell lineage: the adult hermaphrodite has only 959 cells, 302 of which are neurons forming approximately 5000 chemical synapses, 600 gap junctions and 2000 neuromuscular junctions (19). Furthermore, its small size (approximately 1 mm), short life cycle (less than three days) and ability to survive being frozen for long-term storage make it highly amenable to laboratory research.

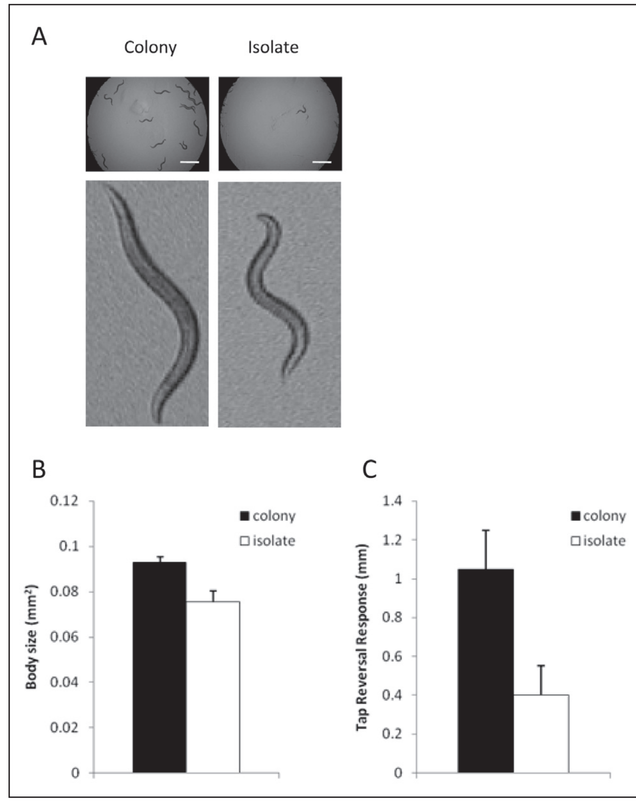

Figure 1) A *Adult colony worms reared in groups (left) and an adult isolate worm reared alone (right). Scale bars represent 1 mm. Isolated worms were smaller than colony worms (***B***) and were less responsive to a tap delivered to the side of their petri plate (***C***)*

Similar to the studies in rats and humans described above, Rose et al (18) found that worms reared in isolation had a smaller body size (Figures 1A and 1B) and a delayed onset of egg laying compared with colony worms reared in groups of 30 to 40. C *elegans* develops from egg to the adult stage in three days, going through four larval stages – L1, L2, L3 and L4 – and then a young adult stage. Rai and Rankin (20) found that the body size of isolated worms could be rescued if they were transferred into colonies before the end of stage L3. This suggests that exposure to other worms alters adult body size and that there is a critical period (stages L1 to L3) for this exposure to have its effect.

Growing up alone on a smooth agar surface in an insulated incubator, isolated worms, similar to premature neonates, were deprived of mechanosensory stimulation. As a result, they showed significantly smaller withdrawal responses (backward swimming) to a tap delivered to the side of their petri plate (Figure 1C). In an attempt to rescue the effects of isolation on withdrawal behaviour, isolated worms were given supplemental mechanosensory stimulation during development. This was done with 30 taps at a 10 s interstimulus interval (5 min of stimulation). Administering this nonlocalized mechanosensory stimulation at any point during development, rescued responses to tap in the isolated adult worms, although their body size remained smaller than worms reared in colonies (20). This suggests that development of the neural circuitry underlying the tap withdrawal response is activity dependent. Looking at pre- and postsynaptic markers within the mechanosensory circuit, Rose et al (18) found that worms reared in isolation had weaker synapses than colony-reared worms, but 30 taps administered early in development were sufficient to strengthen them. As the worm aged, progressively greater amounts of stimulation were required to fully reverse the effects of isolation – 400 taps at stage L2 or L3 and 800 taps at stage L4 or the young adult stage (20). Thus, in attempting to reverse the effects of early deprivation, it is important to remember that different aspects of development require different amounts and timing of supplemental stimulation. A major advantage of using C *elegans* is the ability to relate animal behaviour to changes in identified neurons.

CONCLUSION

Organisms need sensory stimulation for normal development. Mechanosensory stimulation has proven to be exceptionally important – a fact demonstrated in organisms across phylogeny. In rats and worms, researchers are able to examine the effects of sensory deprivation from the behavioural to the molecular level. These studies have shown that sensory stimulation can alter many aspects of development by a number of different mechanisms. Reversing the effects of early deprivation is not simple, but the importance of touch is undeniable. Finally, you need not be a worm larvae, rat pup or even human child to reap the rewards of touch. For example, employees receiving chair massages showed a significant reduction in blood pressure (21), anxiety (22) and job stress, and had increased speed and accuracy on math problems (23). Furthermore, patients with ailments ranging from burns (24) to eating disorders (25) have been shown to benefit from massage therapy, with reductions in stress hormone levels, anxiety and clinical symptoms; HIV-positive men receiving daily massages had an increased number of immune cells to combat the virus (26). To paraphrase, a kiss may just be a kiss, a sigh may just be a sigh, but a touch can change your life (or at least your nervous system)!

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