ATTENUATING THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE WITH POSTNATAL INTERVENTIONS: CRITICAL REVIEW OF ANIMAL STUDIES AND APPLICATIONS TO CLINICAL RESEARCH

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ABSTRACT

Background
Alcohol exposure during pregnancy is associated with central nervous system dysfunction and behavioural problems. Animal studies provide researchers with a good analogy of fetal alcohol exposure in which more control can be asserted over the conditions of exposure and treatment, and where neurological outcomes can be examined in greater detail than in humans. The objective of this review is to identify possible evidence-based interventions that may be eventually applied to children exposed to alcohol in utero.

Methods
A search was conducted using Medline for all animal studies which examined interventions for the treatment of prenatal alcohol exposure. Interventions included environmental enrichment (EE), postnatal handling (PH), exercise, and therapeutic motor training (TMT). All publications matching the search criteria were included regardless of duration, timing or amount of exposure or of animal type. Literature is summarized and discussed critically.

Results
Several non-pharmacological interventions have been tested on rodents exposed to alcohol in utero with varying degrees of success. Postnatal EE may attenuate hind limb gait problems and ameliorate water maze learning, but neuroanatomical explanations for these findings are lacking. PH has been shown, in one study, to improve learning, but shows inconsistent results regarding HPA axis regulation. Exercise, in one study, was found to be a useful intervention for maze learning and long-term potentiation. Postnatal TMT is also an effective intervention tool as it permits exposed rats to perform at the same as non-exposed rats on tasks normally affected by prenatal alcohol.

Conclusions
All of the reviewed interventions hold some promise. It appears that a controlled simulation study in humans is a logical next step in examining these new and exciting findings.

Keywords: fetal alcohol syndrome, animal studies, postnatal interventions, neuroplasticity, in-utero exposure

The four diagnostic components of Fetal Alcohol Spectrum Disorder (FASD) are facial dysmorphology, pre- or post-natal growth retardation, central nervous system (CNS) dysfunction and a confirmed history of maternal drinking.\textsuperscript{1,3}

Even though facial abnormalities may be the most pathognomonic features of a FASD, the most crippling are CNS dysfunctions, which commonly exist even in the absence of classic facial characteristics. CNS dysfunctions range from sensorimotor problems to behavioural problems and beyond.\textsuperscript{4} It has been reported that prenatal ethanol exposure could be the leading cause of mental retardation in the western world\textsuperscript{5} and that each individual with FASD in the U.S.A. costs $2 million.\textsuperscript{6} Clearly, prevention and recovery from FAS are important issues.

Most challenging in the diagnosis of FASD is the inability to confirm in utero exposure to alcohol. In the absence of facial signs, maternal drinking is an important diagnostic clue.\textsuperscript{2}
However, new research into biomarkers, specifically Fatty Acid Ethyl Esters (FAEEs), is emerging as an accurate method of detecting maternal drinking during pregnancy. By examining meconium or maternal hair, the presence of FAEEs may indicate problem drinking during pregnancy. Because maternal drinking is necessary to confirm FASD, the tool will allow for early screening of at-risk children. During the last decade, evidence has emerged that early diagnosis of FASD is a strong predictor of favourable outcome in affected children. Early screening may provide an opportunity for early intervention and treatment which may reduce the physical, emotional, social and economic burden of FASD.

This paper will review novel animal studies that describe the therapeutic effects of postnatal environmental enrichment (EE), handling (PH), exercise and therapeutic motor training (TMT) on in-utero ethanol (EtOH)-exposed animals. These studies have the advantage of allowing randomized control trials, in-depth brain examinations, and tightly controlled conditions.

The Effects of FASD

In order to understand the potential power of rehabilitation following fetal alcohol exposure, one must first understand the damage that prenatal alcohol inflicts on the CNS. For an exhaustive review, the reader may refer to Riley and McGee.

Damage caused by prenatal ethanol varies depending partially on the time and duration of exposure. Heavy exposure during the first trimester affects migration, proliferation and organization of cerebral cortex nerve cells, as demonstrated in humans and rats. The same exposure in the third trimester (a period of intense brain growth) affects the cerebellum, hippocampus, and prefrontal cortex of both humans and rats.

Several studies have found a lower cerebellar volume in EtOH-exposed human offspring. In children affected by alcohol, the cerebellum was 15% smaller, specifically in the anterior vermis. The corpus callosum is among the most adversely affected brain areas in humans. It is smaller, thinner, not fully developed and displaced in location following prenatal alcohol exposure. The caudate nucleus in the basal ganglia is also reduced in size. Brain size is affected by a reduction in white matter (accompanied by an increase in grey matter) in the perisylvian cortex, and rat studies show neuron loss in the extended hippocampal diecephalic circuit. Part of this circuit, the Anterior Thalamic Nuclei (ATN) shows a long-term volume reduction of 60%. The ability to carry out long term potentiation (LTP– a mechanism for learning) in the CA1 region of the hippocampus is also compromised by prenatal alcohol in rat brains. Finally, human and rat studies suggest that the HPA axis is over-active following prenatal alcohol exposure.

The CNS insult caused by prenatal EtOH may be expressed in humans as impairments in IQ, memory, language, attention, reaction time, visuospatial abilities, executive functioning (cognitive flexibility and abstract reasoning), fine/gross motor skills and social/adaptive functioning. Affected children have particular difficulty in set shifting, because of damage to the cerebellar vermis. Damage to the cerebellum has also resulted in poor hand-eye coordination, tremors, weak grip and poor balance. Children with FASD rely on somatosensory information heavily and have difficulty compensating for it with visual or vestibular information. FASD is often associated with attention deficit/hyperactivity disorder.

Many of the problems caused by EtOH consumption during pregnancy in children could be reproduced in animals. It is therefore promising that some postnatal interventions in animals following fetal alcohol exposure may partly attenuate brain and behaviour changes. Postnatal environment, handling, exercise and therapeutic motor training have been experimented in animal models and bear tremendous promise for clinical intervention in alcohol-affected young children. This research will be reviewed in detail.

Methods Employed by Reviewed Studies

In general, the procedure for studying in-utero alcohol exposure in rodents is to divide pregnant dams into one of three conditions:
1. Alcohol Exposed (AE),
2. Pair-fed controls (PF), or
3 food/water controls (C). AE dams are fed alcohol either by intubation, artificial rearing, voluntary consumption of a
liquid diet or, in one case, vapours. PF control dams are fed identically to AE rodents except with sucrose or a dextrose-maltose solution to provide the calories otherwise derived from alcohol. C animals are allowed access to food and water ad lib. Upon birth, pups are usually suckled by their respective dams until weaning (P21-P28, depending on animal type and experimental manipulation). The exceptions to this are two studies that added a fostering condition where some pups were cross fostered by other dams before weaning. Postnatal handling is the only therapeutic intervention that is implemented prior to weaning (with the exception of EE in Mothes et al. and Opitz et al.). Most interventions are given postweaning by dividing the rats or mice into two groups – one receiving the intervention and the other denied it. Following the intervention, researchers test the animals behaviourally (using mazes, learning paradigms, balance tests, or measures of activity) and/or physiologically (using blood tests or brain examinations).

Human versus Rodent Exposure
One of the advantages of using rodents for studies of prenatal alcohol exposure is that the effects of timing and dose of prenatal EtOH have been more strongly established than in humans, and that these doses can be reached in a controlled condition. Rats and mice experience a growth spurt for two weeks after birth, where the same growth spurt occurs in humans during the third trimester and several years after birth. During this time, the developing brain is particularly sensitive to alcohol exposure. In rats, maintaining a blood alcohol concentration of 200mg/dL for 4 hours during this period is enough to cause massive neurodegeneration. However, as little as 83mg/dL throughout gestation has been shown to negatively affect performance on the Morris water maze.

The studies reviewed here utilize exposures ranging from 100mg/dL to 278mg/dL at various points throughout gestation (18-22 days in mice, 21-23 days in rats) and the brain growth spurt (2 weeks after birth). Most states and provinces in North America allow individuals to operate a motor vehicle with a blood alcohol level of 80-100mg/dL and it is common for individuals to reach much higher levels following an episode of binge drinking. Therefore, the animal models employed for this study may be considered somewhat realistic in terms of alcohol consumption quantities.

Environmental Enrichment
Animal models of environmental enrichment (EE) consist of 8 to 12 animals housed together (after weaning) with toys that are changed regularly. Animals not put into an enriched environment are put into an isolated condition, which consists of one animal per cage without toys or other stimulation. EE in early postnatal life has long been known to be beneficial in rats. Rats exposed to a stimulating environment show increased numbers of glial cells and dendritic branching.

As in humans, stimulation of neurons is necessary in early life in order that they not be lost to synaptic pruning. EE has been found to increase cortical depth, numbers of dendritic spines in cerebral neurons, dendritic branching, the number of synapses per neuron, and improve performance on maze learning. Presently, the results of studies examining EE in rehabilitation of brain insults caused by prenatal EtOH in rodents have been generally positive. The earliest study of EE following prenatal alcohol exposure was carried out by Osborne et al. and found a negative result. AE rats were different from non-AE rats in that they were over active and learned faster in a Y-maze. These differences were not reduced by fostering or EE. However, the finding that AE rats learned faster was unusual and may be partly explained by the poor timing of exposure (~238.9mg/dL, G10-14). Wainwright et al. found that mice given EE after weaning had a trend toward heavier brains than those that were isolated regardless of prenatal exposure status. Prenatal alcohol exposure affected brain weight negatively – specifically due to a thinner occipital cortex. Increases in brain weight resulting from EE were not related to increases in cortical depth; perhaps because cortical depth is too crude a measure to pick up fine details about brain changes. The study also involved behavioural testing on the Morris water maze. While prenatal alcohol did not worsen performance on the water maze (possibly because alcohol exposure was only “moderate” – 6.25% EDC on G5 to 25% on G16, 12.5% on G17, BEC>100mg/dL, or because males and females...
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were grouped together), EE did decrease latency for learning the water maze. This suggests that prenatal alcohol exposure does not block the behavioural benefits of EE, but does not suggest that EE attenuates the effects of prenatal alcohol.

Hannigan et al. examined the effect of EE on maze learning as well as hind limb gait in alcohol-exposed rats. The study employed only two prenatal treatment groups: AE rats (4g/kg/day, ~155-220mg/dL, G8-G20), and PF rats. Exposed rats exhibited hind limb ataxia in the non-enriched condition, but showed no signs of it in the EE condition by the end of the study (8-12 weeks). Not only did all EE rats appear the same regardless of prenatal exposures, they performed better in all cases than IC rats on the Morris water maze and radial arm maze. However, it is worth noting that prenatal alcohol did not negatively affect maze performance. Therefore, it can be said that EE is beneficial despite prenatal EtOH, but not that EE attenuates AE effects.

In a follow-up study, Berman et al. examined the hippocampus of rats given EE, only using three prenatal treatment groups instead of two (AE - 6g/kg/day, ~155-220mg/dL, G8-G20; PF; or C). They found that, despite improving behavioural outcomes (maze learning) following EtOH exposure, EE only increased the dendritic spine density of hippocampal neurons in non-AE animals. The benefits of EE in this respect, therefore, were denied to animals prenatally exposed to alcohol. Another explanation for the behavioural improvements was investigated more recently in a study by Choi et al. The study examined the possibility that EE increased the survivability of newly generated hippocampal neurons and found that this was not the case in AE mice (13.2g/kg/day, ~121mg/dL, throughout gestation) although it was in non-AE mice. Further investigation into the neuroanatomical explanation for improved maze learning following EE is needed.

Mothes et al. and Opitz et al. studied the effects of EE on AE mice’s over activity and inability to learn conditioned taste aversion. Both of these problems stem from the observation that AE rodents have response inhibition deficits. EE, in these studies, consisted of housing two dams and litters together before weaning (as opposed to one) and extending the weaning period from P21 to P28. A relatively low amount of alcohol was administered to AE dams during pregnancy (1.58-3.16g/kg/day, 100.2-162.1mg/dL, G14-G18). Mice were observed post-weaning, after being separated into cages housing 2 individuals. Measures of hyperactivity included coded observation in an ‘open-field’ or in their home cages. Taste aversion learning was studied by administering the mice a saccharin solution and making them ill, and then re-introducing the solution to see how readily they consumed it again.

Results showed that AE rats only displayed more hyperactivity in their home cage and that EE made no difference in the expression of this behaviour. However, in the open field, where AE mice showed only slightly more hyperactivity (not statistically significant), EE did reduce it significantly for all. The lack of hyperactivity displayed by AE rats in the open field, the authors argue, was due partly to the short duration of the test (not long enough to get over the fear of novelty) and the relatively low amount of alcohol exposure. In terms of taste aversion learning, the authors found that AE mice were poorer learners, but that EE attenuated this deficit (although due to a small sample size, the PF group was dropped from the analysis). These studies show some promising results, especially in terms of early interventions that may be applied pre-weaning.

Taken together, studies of the effects of EE on EtOH-exposed rats suggest that it is beneficial in terms of learning and behaviour. However, a neuroanatomical explanation for these changes is still lacking. In addition, the available evidence has not consistently shown that EE is more helpful to rodents with prenatal alcohol exposure than to all rodents. Many studies found a benefit of EE in all rats, without finding a negative effect of prenatal alcohol. Therefore it is not possible, in these cases, to conclude that EE negated the effect of alcohol, but only to conclude that alcohol did not prevent the animals from benefiting from EE. More studies, repeating similar designs of the successful experiments, will be needed to allow robust conclusions.

Postnatal Handling
Rats exposed to alcohol in utero have a hyper responsive HPA axis and reduced response inhibition. Prenatal alcohol exposure leads to
increased open-field activity\textsuperscript{58}, running wheel activity\textsuperscript{59}, exploratory behaviour\textsuperscript{60} and startle reactivity.\textsuperscript{61} The HPA reacts to shock,\textsuperscript{62} restraint stress,\textsuperscript{63} cardiac puncture,\textsuperscript{64} and noise\textsuperscript{65} with an above-average release of adrenocorticotropin hormone (ACTH) and corticosterone (CORT), and AE rats have higher steady-state corticotrophin releasing factor mRNA levels. Early postnatal handling (PH) of animals makes them better able to regulate HPA responses. Handled animals show a reduced CORT and ACTH response to mild stressors, such as novelty or restraint, but an increased response following severe stressors, such as shock.\textsuperscript{66-69} Handling also enhances behavioural performance and reduces neuron loss due to aging in the hippocampus.\textsuperscript{68} Several studies have investigated the use of handling as a therapeutic technique for treating prenatally EtOH-exposed rats.

Animal models of PH take place pre-weaning, and involve removal of the pups and dam from their home cage each day and placing them in individual cages for either 3 minutes or 15 minutes (depending on the study), before returning them. The first study to examine the effects of postnatal handling on AE rats\textsuperscript{70} found that AE rats performed worse on a step-down avoidance task and that the deficit was eliminated following early PH. In 1995, Weinberg and colleagues\textsuperscript{63} tested the possibility that PH in rats (3 minutes in individual cages, P2-P15) may improve stress responses to an EtOH injection or restraint (putting a rat in a closed tube) at 70 to 100 days of age. They found that PH attenuated the hypothermic response to postnatal EtOH injection in AE (9.5-12.2g/kg/day, \textasciitilde145-155mg/dL, throughout gestation) and PF male rats. It also accelerated recovery from the injection in C and PF females (not AE females). Handling increased CORT release following EtOH injection – possibly because a large stressor triggers a higher CORT release following PH.

Previous work on responses to ether and cardiac puncture\textsuperscript{64} confirm the finding that handling can result in increased CORT. However, prenatal alcohol had no effect on CORT response. When rats were restrained, PH was found to attenuate the increased stress response in AE female rats only, and was not found to attenuate the more prolonged CORT levels seen in AE rats. There is a well established sex difference between the HPA responses of male and female rats that may partly explain these results.

One study\textsuperscript{38} found that postnatal handling interacted with prenatal alcohol exposure and fostering to affect ACTH and CORT responses to stress in different directions. As expected, AE rats responded to foot shock with above-average ACTH release, and handled control rats responded to foot shock with less ACTH release. But handled fostered AE rats responded with even higher ACTH any other group during foot shock. Shortly following foot shock, it was promising to see that all handled animals had equal ACTH levels regardless of prenatal treatment, indicating an ability to recover from stress despite prenatal alcohol. Furthermore, handled fostered male AE rats showed a reduced CORT response to foot shock. The disparity of these results may be partly explained by the important methodological differences between this study and most other PH studies. In this study, alcohol exposure was relatively low and poorly timed (\textasciitilde188.7mg/dL, G8-G15), alcohol was administered by vapour instead of feeding or intubation, stress was induced by foot shock instead of restraint or EtOH injection, handling involved being put in a separate cage for 15 minutes instead of 3 minutes each day, non-handled rats were moved to a new cage once a week (which required some handling) and rats were tested on P22 (immediately after weaning) instead of P70-P100.

Gabriel et al.\textsuperscript{71}, created a different test for evaluating the effectiveness of handling in alcohol-exposed rat pups. Instead of only exposing the rats to stressful situations (i.e. EtOH injection or restraint in a tube), they preceded restraint stress with an injection of saline (SAL) or dexamethasone-21-phosphate (DEX). DEX generally inhibits HPA activity and SAL does not. As expected AE rats (10.3-13.4g/kg/day, \textasciitilde145-155mg/dL, G1-G21) expressed HPA hyper responsiveness to stress when preceded by SAL (a greater increase in ACTH and CORT than controls), but not DEX (which block CORT and ACTH release). AE females were the only exception to this finding. They over responded to stress even following DEX administration. Handled animals (3 minutes per day, P1-P15) had lower CORT and ACTH plasma levels in general. However, handling did not attenuate the over responsiveness of female AE rats following DEX,
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as it did with males. The sex differences in the HPA responsiveness of AE rats was further underlined by this study and it also showed that handling can be therapeutic but does not always eliminate functional problems. In 2001, the same team, using the same prenatal exposure and subsequent intervention, found that handling AE rats worsened their already poor ability to learn conditioned taste aversion (in a non-deprived condition). This is because handling reduces emotionality and fear in rats – thereby increasing the likelihood that they will re-try dangerous food. They also reported that, in a stressful situation, CORT levels do not rise as much in handled as non-handled rats overall. In a subsequent study, the team determined that prenatal alcohol increased corticotrophin releasing factor mRNA levels and that the PH intervention they applied reduced these levels in PF and C males only (AE males, and all females were unaffected by PH).

In summary, published data from the literature on postnatal handling of AE rats are not consistent. The studies to date do demonstrate that early postnatal handling is beneficial to HPA responsiveness of normal rats and mice, but when applied specifically to pups exposed to alcohol in utero the picture becomes less clear. HPA axis responsiveness is different in male and female rats, and handling may change the strength and direction of stress hormone levels given certain interactions between treatment, exposure, gender and fostering condition. The theory that handling affects responses to small stressors differently than large stressors may partly explain these results, but methodological differences may also be responsible for this widely variant data. Studies thus far do not show that handling is a consistently positive intervention for negating the effects of prenatal alcohol exposure across all groups and genders.

Exercise and Therapeutic Motor Training

It has been said that “a healthy body leads to a healthy mind”. In our context, several studies support this statement. Brain improvements resulting from exercise or motor training can specifically affect areas damaged by prenatal alcohol exposure. Walking has been demonstrated in rats to increase hippocampal LTP and to increase spatial learning abilities. Running also facilitates spatial learning via the hippocampus and neurogenesis in the dentate gyrus.

One study specifically addressed the use of exercise as a therapeutic intervention following prenatal alcohol toxicity in rats. In the study, AE rat pups (10.51g/kg/day, ~184mg/dL, G0-G22), PF rat pups and C rat pups were divided into two subgroups (after weaning): rats given a running wheel and rats not given a running wheel. Only male rats were chosen to participate in the study and all participants were housed individually. After just over a month, the rats were tested for five days on the Morris water maze and it was found that AE rats performed worst on the maze (especially on the first day), but that AE rats housed with a running wheel performed at the same level as non-AE rats with a running wheel. In order to explain the results, the perforant path to the dentate gyrus pathway of the rats was examined for its capacity to carry out long-term potentiation. As expected, AE rats had a reduced capacity for long-term potentiation in the hippocampus, but this capacity was increased by voluntary exercise (even in rats exposed to alcohol).

Klintsova and colleagues showed, in a series of studies, that therapeutic motor training is a very effective intervention for rats exposed to alcohol in pregnancy. Rats were exposed to alcohol (4.5g/kg/day, ~225-278mg/dL, P4-P9), to a maltose-dextrin solution of equal calories, or to ordinary rat chow, shortly after birth during the brain growth spurt (P4-P9). At 6 months of age, rats were given TMT (forced obstacle course learning) or no chance to do exercise. In one study a second control group was added where rats were given forced exercise (of equivalent distance to the obstacle course). The training course was specifically challenging for rats with cerebellar damage (as is the case for those exposed to high alcohol levels during the brain growth spurt). Impressively, AE rats given motor training performed consistently equivalent to other rats given motor training, despite their cerebellar damage. Not only did the AE rats given TMT eventually perform the obstacle course as quickly and effectively as the others, they performed equivalently on a novel parallel bar test, a rope-walking test and a rotating rod-walking test. These are tests that specifically call on the use of the
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cerebellum and that were new to all rats. AE rats who did not receive therapeutic motor training performed significantly worse than their non-exposed counterparts. In the study with a forced exercise condition, the authors found that simply exercising did not improve performance on these tasks. Although it is worth noting that the tests were heavily cerebellum-dependant and Christie et al.\textsuperscript{28} found that exercise had hippocampal benefits. It was also found that AE rats, even when receiving TMT, had an approximate 40% loss of purkinje cells from the paramedian lobule of the cerebellum. However, AE rats with TMT appear to have compensated for the loss with a greater number of synapses per neuron. Increased synaptogenesis following rehabilitation of this sort is expected based on previous research\textsuperscript{74,84-85}\textsuperscript{54} and may be due in part to an increase in the number of presynaptic mitochondria.\textsuperscript{85} This suggests that TMT can attenuate some cerebellar effects of alcohol exposure during the brain growth spurt.

Evidence regarding TMT and exercise following early (or prenatal) ethanol exposure is promising. But, while the effects of motor training were verified by a series of studies with consistent, positive results, they have yet to be studied by other laboratories or in other contexts. The same is true of exercise, which has only been validated in one study of prenatal alcohol exposure.

**DISCUSSION**

As highlighted in this review, increased EE, PH, exercise, and TMT are all useful in improving, to some extent, the outcomes of AE rodents. EE, TMT and exercise are the most promising postnatal interventions as they have yielded the most consistent positive outcomes. EE can improve hindlimb stride, learning, memory, over activity and possibly overall brain weight. TMT can improve balance, coordination and synaptogenesis in the cerebellum. Exercise can attenuate maze learning deficits and increase the capacity for long-term potentiation in the hippocampus. However, no postnatal intervention has demonstrated the consistent ability to regulate stress responses across all groups.

Where prenatal alcohol is used to insult the brain, differing administration routes (intubation, artificial rearing, vapours, etc.) and, more importantly, times and durations are employed. While the administration of alcohol by vapour inhalation is an effective method of maintaining high blood alcohol levels throughout the exposure period, as well as maintaining the growth of the rats, it is less analogous to the actual method of human exposure.\textsuperscript{86} Furthermore, gastric intubation of EtOH during pregnancy appears to result in healthier and heavier rat pups than artificial rearing.\textsuperscript{87} Some variation between findings may also be explained by the use of different animals. When mice are given EtOH, their blood ethanol concentrations (BEC) tends to rise and fall fairly sharply whereas rats experience a more gradual increase and decline in BEC.\textsuperscript{13} As well, most of the studies reviewed here (with the exception of TMT studies) did not expose rodents to alcohol during the early postnatal period (a time of intense CNS development in rats and mice). This may account for some of the results where prenatal alcohol exposure did not significantly affect rodent behaviour.

FASD in humans has some important differences from rodents. In humans, the corpus callosum is one of the most affected brain areas, but in the studies reviewed here, the corpus callosum was not addressed. As well, motor abilities in humans with FASD are strong, relative to their verbal abilities (although both are affected). However, all of the rodent studies must necessarily focus on motor abilities as rodents have no capacity for language. In addition, human prenatal alcohol exposure is hardly ever as simple as exposure in a controlled experiment. Human exposure is inconsistent, usually punctuated by several binges, and accompanied by other drug use as well. This is another hurdle that needs to be overcome before these interventions may be applied to humans.

Practical difficulties in translating therapeutic techniques from animals to humans also exist. Animal studies examining EE tend to compare animals in isolation with those in more ‘normal’ conditions. Real life human environments are seldom as isolating as the ones found in these studies. Even if results were consistently positive in response to EE, it is likely that we are witnessing a negative effect of deprivation as opposed to a positive effect of an enriched environment. What this may mean is that children...
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with FASD have a lower chance of developing normally if they are raised in neglectful environments, rather than necessarily developing better in rich environments. Still, this is a useful finding as, sadly, children with FASD are more likely to be born into a neglectful environment. A direct translation of PH to humans seems difficult to derive. Much research exists to show the beneficial effects of early human stimulation but rodent studies simplify handling to such a degree that it may be considered an entirely different manipulation. In rats and mice, PH means removing a pup from its home cage, transferring it to a separate cage for a period of time, and then returning it. In humans, handling newborn babies in this manner is unlikely to have the same effect. More studies are needed to describe an effective analogy of PH for humans.

Defining a human analogy of TMT and exercise, as well as determining when they may be applied are important next steps in the future of this line of research. TMT, in animal models, essentially consists of motor skills learning. Intensive motor skills training is possible in humans as well, but with humans being compromised in executive functioning and verbal skills following an FASD diagnosis, it may be helpful to expand the concept of TMT to include cognitive training. The question of timing for these interventions is also important. Both exercise and TMT were applied when the rats were no longer young (Exercise at P54, and TMT at P180), and human treatments are likely to be more effective if they can be applied at an early age.

Implications to Human FASD Research and Practice
The animal studies presented here indirectly support the data by Streissguth, showing that the earlier the diagnosis of FASD, the better the prognosis, presumably due to earlier interventions. Babies and children afflicted by FASD are being typically reared in two extreme and opposing contexts: 1. by their natural mothers, in which case they are likely to be negatively affected by poverty, neglect and numerous other determinants associated with poor developmental outcomes; or 2. by adopting families, motivated to create optimal conditions with enrichment, support and encouragement, which are associated with good developmental outcomes.

It appears that the next logical step in translating the exciting preliminary animal results to humans is to randomize young children reared by their natural mothers to receive either the current standard follow-up program, or an enriched stimulatory program, possibly using techniques which were proven effective in other forms of neurological rehabilitation.

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