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REVIEW ARTICLE

Timing of Thyroid Hormone Action in the Developing Brain: Clinical Observations and Experimental Findings

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Abstract

The original concept of the critical period of thyroid hormone (TH) action on brain development was proposed to identify the postnatal period during which TH supplement must be provided to a child with congenital hypothyroidism to prevent mental retardation. As neuropsychological tools have become more sensitive, it has become apparent that even mild TH insufficiency in humans can produce measurable deficits in very specific neuropsychological functions, and that the specific consequences of TH deficiency depends on the precise developmental timing of the deficiency. Models of maternal hypothyroidism, hypothyroxinaemia and congential hyperthyroidism have provided these insights. If the TH deficiency occurs early in pregnancy, the offspring display problems in visual attention, visual processing (i.e. acuity and strabismus) and gross motor skills. If it occurs later in pregnancy, children are at additional risk of subnormal visual (i.e. contrast sensitivity) and visuospatial skills, as well as slower response speeds and fine motor deficits. Finally, if TH insufficiency occurs after birth, language and memory skills are most predominantly affected. Although the experimental literature lags behind clinical studies in providing a mechanistic explanation for each of these observations, recent studies confirm that the specific action of TH on brain development depends upon developmental timing, and studies informing us about molecular mechanisms of TH action are generating hypotheses concerning possible mechanisms to account for these pleiotropic actions.

Clinical and experimental studies demonstrate thyroid hormone (TH) is essential for normal brain development. This was documented initially in children with congenital hypothyroidism (1–5), followed by animal studies focused on cerebellar development, which occurs largely postnatally (6–9). However, recent observations in humans (10–13) provide important new evidence that TH is also important in early (foetal) brain development, and that the timing and severity of TH insufficiency predicts the type and severity of the neurological deficits. Because these deficits presumably reflect the impact of a loss of TH on different aspects of brain development, this clinical research provides clues as to when and where TH exerts its actions in developing brain.

Animal models of developmental TH insufficiency are beginning to provide mechanistic explanations for these observations in humans. The use of genetic models of TH insufficiency, of TH receptor deletion and mutation, and of cofactor deletion (14–17), are showing us how different brain regions may exhibit different sensitivity to TH during development. Moreover, these studies show that TH exerts different effects in different brain areas at different times during development. However, despite advances in our understanding of TH action, the specific developmental events affected by TH remain poorly understood. Several recent comprehensive reviews on TH actions in brain development have appeared (6, 7, 14). Thus, our goal here is to describe the clinical studies leading to the proposition that the timing of TH insufficiency produces differential effects on neuropsychological outcome, and to review the experimental studies that provide some mechanistic insight into these issues.

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Timing of TH action in the developing human brain

The feotal thyroid does not become functional until the 12th week of gestation (18–20); therefore, the foetus must depend entirely on TH of maternal origin during the first trimester and assume an increasingly greater role in producing TH as gestation progresses. Conditions involving a reduced maternal TH supply include maternal hypothyroidism, which typically begins during the first trimester, or premature birth, which severs the foetus from maternal TH early during the third trimester. A condition that produces TH insufficiency in the foetus still later in development is congenital hypothyroidism. Each of these conditions is associated with impaired neurodevelopment.

Maternal hypothyroidism

Nearly 3% of pregnant women have low normal (to low) circulating levels of T_4 (11, 12, 20–23). Most of these women are not aware of their biochemical insufficiency, and most likely attribute their mild symptoms to pregnancy. Because foetuses of women with undiagnosed hypothyroxinaemia are exposed to reduced TH, these children experience TH insufficiency, the severity of which is dependent upon the severity of the mother's TH insufficiency (20). Many women with pre-existing hypothyroidism are diagnosed and treated with supplemental T_4, but the majority of these women tend to be under-treated because their T_4 doses are not increased to match the normal physiological demands for TH during pregnancy (24). Thus, studies of women with known hypothyroidism, and screening studies of large populations of the offspring of women with abnormal thyroid function during pregnancy, represent two important approaches to understand the specific consequences of intrauterine TH insufficiency.

Case studies have identified suboptimal neurological outcome in offspring of hypothyroid women, including diminished perceptual and motor ability (25), as well as a markedly short attention span (26). In a survey of 23 families involving maternal hypothyroidism treated during pregnancy, Matsuura and Konishi (27) found that, in five pregnancies involving severe hypothyroidism, four children were developmentally delayed. Smit *et al.* reported (21) that the offspring of hypothyroid women did not differ in neurophysiological or motor development, but exhibited significantly lower mental development indices at 6 and 12 months. We have been following infants of women identified with hypothyroidism before or during pregnancy and have found effects on specific cognitive abilities such as poorer attention, slower and more variable reaction times to visual stimuli and visual processing deficits (28). Our findings also suggest that different types of visual deficits occur in response to TH insufficiency at different times during pregnancy (29).

In the 1960s, Man (30) found that the first 12–29 weeks of pregnancy is a critical period, when the neural substrates of some abilities that depend on the visual system, and also some aspects of the motor system that also depend on vision, are particularly vulnerable to TH insufficiency. A more recent series of studies by Pop *et al.* (12, 13, 31) demonstrate the critical need for TH early in pregnancy by finding that levels of free T_4 and the presence of circulating antibodies for thyroid peroxidase were strong predictors of infant mental development/children's IQ. Studies by Haddow *et al.* (11) determined that the children of women with low normal serum T_4 had a higher incidence of IQ levels in the subnormal range (i.e. < 1 SD below normal) compared to matched control children. Moreover, these children scored lower than controls on multiple aspects of cognitive functioning including auditory and visual attention, reading, visuomotor ability and word discrimination. The results suggest that fine and graphomotor skills and reading abilities are sensitive to TH insufficiency after 16 weeks' gestation, whereas visual attention abilities are sensitive to TH insufficiency before 16 weeks (32, 33).

Infants born prematurely also provide a model of foetal TH insufficiency because they lose maternal TH before their own glands are fully functional (34). Typically, these children exhibit low TH levels at birth and their TH levels decline in the interval between birth and projected term (34–36). Hypothyroxinaemia associated with premature birth is most evident in infants born extremely early (37–41) and with very low birth weights (42, 43) and neonatal illness (e.g, bronchopulmonary dysplasia, intraventricular haemorrhage, or periventricular leukomalacia) (44–47) (i.e. high risk births). However, it is also seen in preterm infants who are considered to be low-risk, namely those born between 30 and 33 weeks' gestation (48). High-risk preterm infants generally exhibit severe deficits that are attributed to their neonatal disease as well as their very early births (49–57). However, in the low-risk preterm population, which constitutes the bulk (85%) of preterm infants, as many as 50% of infants exhibit mild neurocognitive impairment (58). Particularly affected are their visuospatial and fine motor skills (49–53), selective attention and memory abilities (54–57, 59–61), math competency and contrast sensitivity (29).

Studies evaluating the consequences of hypothyroxinaemia of prematurity have reported an increased incidence of cerebral palsy (62), reduced intelligence (40, 63–66) and poor psychomotor abilities (67) in children whose TH levels were low at birth. We have further observed an inverse correlation between declining T_4 levels in the third trimester of pregnancy and motor and attention skills in young preterm infants born at low risk (68).

To determine whether hypothyroxinaemia of prematurity can be corrected by exogenous administration of thyroxine, van Wassenaer and colleagues gave high-risk preterm newborns a 6-week trial of T_4 (69, 70). These children were evaluated at 6 months to 5.5 years of age (78). Although the treated group showed significantly higher levels of serum T_4, neurophysiological functioning (71, 72) or cognitive abilities were not improved (71, 73, 74). However, when children were stratified by gestation age, a marked benefit of TH therapy was observed for early neuromotor skills and later cognitive abilities in children born before 27 weeks (72) whereas children born at 28 or 29 weeks showed the opposite effect, performing worse than controls. This dissociation has been attributed to developmental changes between 25 and 30 weeks in the availability of deiodinase enzymes required to convert T_4 (in the medication) to T_3 (75). To test this hypothesis, Van Wassenaer *et al.* (70) gave preterm infants

past 27 weeks a single dose of T_3 12 h after birth and found increased plasma T_3 levels for as long as 8 weeks with no clinical side-effects and this therapy was associated with improved outcome.

Congenital hypothyroidism represents a model of TH insufficiency that takes place somewhat later than the two previous conditions. Despite the success of neonatal screening programmes to identify and treat congenital hypothyroidism in newborns (76, 77), these children still exhibit impairments (78). Their IQ levels average approximately 6 points below expectation (79) and they also show selective deficits on visuospatial, motor, language, memory and attention tests (80–85). Approximately 20% of cases also have a mild sensorineural hearing loss (86, 87), which contributes to difficulties in initially learning to read.

A wide degree of variability in TH levels exists among individual children with congenital hypothyroidism. This variability reflects a number of factors associated with both the disease (endogenous factors) and its treatment (exogenous factors) (34). Children with athyreosis typically have the lowest serum T_4 and the poorest outcome, attaining the lowest IQ scores (88), have more impaired nonverbal visuospatial and arithmetic functioning than the other aetiologic groups (89), and show a basic visual deficit involving poor contrast sensitivity (90). Factors associated with treatment (initial dose of T_4 and serum T_4 levels maintained) show that, in general, a delay in the initiation of treatment is associated with poorer outcome (2), but the effects of this delay is specific to visuomotor and language skills (84). Following the advent of newborn screening, recommended starting dose levels have increased over the years, although the issue of the optimum starting dose has yet to be resolved. Abilities most affected by a low starting dose level are children's memory and fine motor skills (91). In addition, with the longer time that it takes to normalize TH levels following the initiation of treatment, the weaker language, fine motor and auditory processing discrimination abilities (84), as well as increased selective attention and memory deficits (92, 93), suggest that these abilities are sensitive to postnatal TH insufficiencies.

To summarize across conditions, TH is necessary for adequate development of a number of neuropsychological abilities whereas the type of deficit depends on the timing of TH deficiency. Generally, a prenatal TH loss contributes to difficulties in visual processing, motor (including oromotor), and visuomotor abilities whereas an early neonatal TH insufficiency is associated with impaired visuospatial abilities. A TH insufficiency somewhat later in postnatal development is associated with sensorimotor and language deficits whereas hypothyroidism that extends even further in infancy is associated with poorer language, fine motor, auditory processing, attention and memory skills. Children who are treated quite late in infancy additionally show deficits in executive processing that is not normally affected in this population.

To summarize across abilities, aspects of visual processing appear to depend on an adequate intrauterine and perinatal TH supply with more basic visual processes (contrast sensitivity) exhibiting TH-dependence earlier than higher-order visual processing (visuospatial abilities). Similarly, neural substrates supporting gross motor skills tend to require adequate TH before those requiring fine motor skills, whereas language and memory skills appear to be TH-dependent postnatally.

Experimental studies on the mechanisms of TH action in developing brain

Few experimental studies have focused on identifying the developmental windows of TH action in the developing brain, or on identifying the changing patterns of TH action across brain regions during development. By contrast, experimental animals are usually made severely hypothyroid throughout pregnancy and the progeny are further treated throughout postnatal development. Although these experiments are important, and have provided us with information about the role of TH in brain development, they do not provide insight into the developmental timing of TH action on specific brain areas that may underlie the observations in humans. Because this literature has been recently reviewed (6, 7, 14), we will focus on the issue of the developmental timing of TH action.

Prenatal TH insufficiency appears to affect adult behaviours differently than postnatal TH insufficiency. Friedhoff *et al.* (94) used an experimental paradigm in which female rats were made hypothyroid before mating and the progeny were cross-fostered to dams with normal thyroid function at the time of birth. They found that, on postnatal day 80, there was a gender difference in the effects of prenatal hypothyroidism on learning, with females being more sensitive to TH insufficiency than males. The treated animals exhibited learning deficits and 'hyperactivity'. This finding differs from those of studies in which animals are exposed to TH insufficiency throughout the perinatal period in that the latter animals exhibit reduced motor activity (95–97). Therefore, in rats as in humans, the timing of TH insufficiency appears to produce different behavioural effects, with prenatal TH insufficiency producing attention deficit and hyperactivity, but postnatal TH insufficiency producing reduced motor activity.

Many studies have characterized the neuroanatomical consequences of developmental hypothyroidism. Early work by Eayrs demonstrated that perinatal hypothyroidism could alter the density and size of neuronal perikarya within specific brain areas, as well as fibre density and orientation within adult cortical layers (98–100). More recently, Berbel *et al.* (101–104) have published a series of studies characterizing the effect of developmental hypothyroidism on a variety of anatomical features, including spine density of pyramidal neurones in the cerebral cortex, the organization of callosal connections, and other features. These studies have shown that hypothyroidism produces changes in callosally projecting neurones, which may be due to the maintenance of a juvenile pattern of projections.

Two recent studies focus on the role of maternal TH in foetal brain development. Lavado-Autric *et al.* (105) took advantage of the fact that cortical neurones occupying different lamina are born at different times. Specifically, neurones born late in the process of cortical development migrate past earlier-born cells to occupy more superficial layers of the cortex (106, 107). Using timed exposure to

bromodeoxyuracil (BrdU), the authors were able to track the final destination of cells born at a specific time and determine whether they occupied the proper layer in adulthood. They found a significant proportion of BrdU + cells in the cortex of pups derived from mildy hypothyroid dams did not migrate far enough. Because cells born early in the process of cortical histogenesis take up residence in deep layers of the cortex, some of these cells (neurones) were even found in the subcortical white matter. A second study (108) found similar effects in pups whose mothers had been treated with the goitrogen methimazole for only 3 days during pregnancy. The dams experienced only a transient, 30% reduction in serum total T_4, which was not associated with an increase in serum thyroid-stimulating hormone. Thus, maternal hypothyroxinaemia can produce migration defects in the foetal cortex and, although there is little information about the consequences on functioning of the adult rat brain, it is very clear that migration defects in the human brain are associated with neurological deficits (109).

Thyroid hormone increases proliferation of cerebellar granule cells (110, 111). Using morphometric measures, Madeira *et al*. (112) showed that TH affects the volume and packing density of cells in the dentate gyrus in a manner consistent with effects on cell proliferation. However, because TH is known to affect apoptosis (at least in cerebellar granule cells) (113), it is possible that TH affects dentate morphology as much by affecting apoptosis as by affecting proliferation. Hadj-Sahraoui *et al*. (114) recently evaluated the effect of TH on cell proliferation in the olfactory bulb, subventricular zone of the cerebral cortex, hippocampus and cerebellum in the postnatal mouse using BrdU labelling and observed site-specific effects. In particular, hypothyroidism increased BrdU labelling in the olfactory bulb and cerebellar cortex but decreased BrdU labelling in the subventricular zone of the neocortex and had no effect on the hippocampus.

Thyroid hormone in culture can increase or decrease proliferation, depending on the culture system and conditions. Thyroid hormone suppresses proliferation of oligodendrocytes purified from neonatal rat brain (115). This observation is consistent with the finding that T_3 leads to a sustained down-regulation of c-*myc* in N2a-β cells, and an increase in the expression of the cyclin-dependent kinase inhibitor $p27^{Kip1}$ (116). By contrast, TH increases proliferation of GC cells (a rat pituitary cell line with functional TH receptors) in culture at least in part by a rapid suppression of Wnt pathway-associated genes (encoding β-catenin, TCF4, Dishevelled-1, Frizzled, axin and APC) (117). This observation is consistent with TH effects on cerebellar granule cell proliferation *in vivo*, although it is not known if the mechanism is the same.

Although these studies provide information about the effects of TH on developmental processes in the rodent brain, they do not inform us about the specific timing of TH effects. One of the best examples of temporal changes in the sensitivity to TH during brain development is that of the cerebellum. The rodent cerebellum undergoes a period of rapid growth during the first two postnatal weeks (118). During this period, the population of granule cells expands in the external granule layer (EGL) causing this layer to thicken. As granule cells migrate inwardly to form the internal granule layer (IGL), the EGL shrinks, ultimately disappearing, and the IGL expands. These transient changes in thickness of the EGL and IGL follow a reproducible temporal pattern.

Hypothyroid rats exhibit a persistent EGL, reduced proliferation of granule cells in the EGL (111) and slowed migration of granule cells into the IGL (110, 119). In normal animals, granule cells in the IGL undergo a period of apoptosis, reaching a peak at postnatal day 8, and ending by postnatal day 22 (113). However, hypothyroidism increases the incidence of apoptosis in the IGL on postnatal day 8 and extends the period of apoptosis beyond postnatal day 22, resulting in a thinner IGL in adulthood. These observations demonstrate that TH plays a role in proliferation of granule cells in the EGL, migration of these cells to the IGL and apoptosis in the IGL during a developmental period that approximately extends from birth to weaning.

The temporal pattern of TH responsiveness in the cerebellum extends to the regulation of individual genes. Myelin basic protein (MBP) is an essential protein involved in myelination (120). The gene encoding MBP is regulated directly by TH (121). Ibarrola and Rodriguez-Pena (122) demonstrated that hypothyroidism reduces MBP expression in the perinatal brain whereas Schwartz *et al*. (123) found that MBP expression was not sensitive to TH in the late gestational fetus. Thus, there is a 'critical period' of TH action on MBP expression that coincides with the period of active myelination for a specific brain region. However, it does not appear that the developing brain undergoes a single critical period of TH responsiveness. TH may affect a developmental process in all brain areas but, because that process does not occur simultaneously in all brain areas, the critical period of TH responsiveness is temporally shifted accordingly. Likewise, there is no *a priori* reason to postulate that TH exerts effects on the same developmental process in all brain areas. Several aspects of the molecular mechanisms of TH action provide a variety of possibilities to explain the pleiotropic effects of TH on the developing brain.

Different TR isoforms may mediate some cell-specific effects

It is possible that cell- or developmental time-specific gene regulation by TH is attributable, at least in part, to the differential expression of thyroid hormone receptor (TR) isoforms (124). TRα2 does not bind to TH; it appears to be a constitutive repressor, and may be a repressor of TRα1/TRβ1 activation (125). Thus, its expression could represent a mechanism by which TH regulation of gene expression is abrogated. Although the binding characteristics of TRα1 for T_3 are not different from those of TRβ1, these two receptors may target different response genes for regulation (124, 126). TRα1, TRβ1 and TRβ2 can also dimerize with members of the broader family of nuclear proteins, including RARs and RXRs. This interaction can influence the regulatory element to which the heterodimer binds and thus provides target gene specificity (126–128). This may be an important mechanism by which the same TR isoform can mediate effects of TH on the expression of different genes in different cells.

Empirical evidence for the concept that different TR isoforms mediate TH effects on different cells is derived from recent work from the Bernal laboratory in Madrid. They have

demonstrated that TRα1 selectively mediates cerebellar granule cell migration from the EGL to the IGL (8), but that TRβ1 regulates the expression of Purkinje cell-specific protein-2 (PCP-2) in cerebellar Purkinje cells and is involved in Purkinje cells growth (129). This conclusion is based on the observation that hypothyroid mice exhibit defects in granule cell migration and Purkinje cell growth, that TH replacement can ameliorate both of these effects of hypothyroidism, and that the TRβ1-selective agonist has no effect on granule cells but partially restores Purkinje cell growth (129). This conclusion is based on the observation that hypothyroid mice exhibit defects in granule cell migration and Purkinje cell growth, that TH replacement can ameliorate both of these effects of hypothroidism, but that the TRβ1-selective agonist has no effect on granule cells but partially restores Purkinje cell number and morphological features (129).

TH-dependent gene activation by TRs is mediated by one of a number of cofactors: corepressors or coactivators. These proteins appear to provide a physical link between the hormone receptor and the transcriptional machinery. A variety of methods indicate that many proteins, including the Brg (SWI/SNF) complex, CBP/p300, p160 factors, P/CAF and the TRIP/DRIP/ARC complexes, are critical coregulators for at least some nuclear hormone receptors (130). Some factors harbour nucleosome remodelling activities, including histone acetyltransferase/deacetylase activities (126, 131–133). For TRs, there is an exchange of cofactors such that the unliganded TR is bound to DNA and recruits a corepressor such as N-CoR or SMRT (134–136). Following T_3 binding to the TR, the corepressor is released and a coactivator, such as SRC-1, is recruited (137–139). These conclusions, based on work performed *in vitro,* explain a number of important observations made *in vivo*. Specifically, targeted deletion of TRs (both alpha- or beta- TRs) does not produce a phenotype similar to that of hypothyroidism (17). By contrast, mice carrying a mutant TRβ1 that does not bind to thyroid hormone produces severe neurological defects similar to that of hypothyroidism (140). Thus, it is the unliganded TR, consititutively bound to the corepressor, that mediates the deleterious effects of hypothyroidism.

Thyroid hormone modulates developmentally important genes in the foetal cortex

Considering that TRs are ligand-dependent transcription factors, we recently initiated a series of studies to determine whether TH of maternal origin could selectively regulate gene expression in the fetal brain. Using a very limited combination of primers in a mRNA differential display paradigm, several TH-responsive genes were identified in the E16 foetal cortex, including Neuroendocrine Specific Protein-A (NSP-A), Oct-1, and RC3/Neurogranin (141–143). Identification of these genes as TH-responsive in the foetal cortex before the onset of fetal thyroid function represents important evidence that maternal TH can directly affect brain development.

All of these genes are selectively expressed in the ventricular zone of the E16 cortex (141, 143). Because the TRβ1 transcript is selectively expressed in the E16 ventricular zone, it is possible that these genes are regulated directly by TRβ1. Cells in the ventricular zone undergo proliferation before committing to a specific fate (106, 144–146). Therefore, we tested whether TH affects cell proliferation in the ventricular zone using BrdU. We found that manipulation of maternal thyroid status did not alter the number of BrdU-labelled cells in the ventricular zone on E16 (Iannacone EA, Zoeller RT, unpublished data); nor did it alter the expression or number of cells labelled with proliferating cell nuclear antigen (unpublished data). These findings indicate that TH does not affect proliferation of cortical neurones at a period of peak neurogenesis. By contrast, our data indicate that TH exerts effects on fate specification of these early neuroblasts in the ventricular zone of the fetal cortex.

Specifically, we found that TH increases the expression of the basic HLH gene Hes-1 (147), a gene regulated by the Notch receptor. Originally identified in *Drosophila*, the Notch receptor is a membrane-bound protein whose extracellular domain can bind to a ligand such as Delta or Jagged, proteins that also are membrane-bound (148). Upon ligand binding, the Notch receptor is cleaved by a gamma-secretase, liberating the Notch intracellular domain to translocate to the nucleus and regulate the expression of Hes-1 (149). Hes-1 (*Hairy-enhancer of Split*) (150) inhibits neurogenesis and favour gliogenesis (151–154); we are currently pursuing the working hypothesis that TH of maternal origin is involved in controlling the balance in production of neurones and glia in the ventricular zone of the early cerebral cortex. This hypothesized role of TH in fate specification of neural stem cells is similar to the role of TH in the control of oligodendrocyte differentiation (155, 156). Moreover, Johe *et al*. (157) reported that neural progenitors isolated in culture from E16 cortex would produce oligodendrocytes at the expense of neurones when provided with T_3.

Taken together, our studies demonstrate first that TH of maternal origin can selectively affect gene expression in the foetal cortex. Although this is an important observation, it does not, in itself, help us to understand the developmental events influenced by TH during brain development. The observation that TH affects Hes-1 expression in the ventricular zone of the E16 cortex indicates that TH may be affecting fate specification of neural progenitor cells (158). Interestingly, Notch signalling appears to be important in cortical neurite outgrowth (159). Considering that TH also affects neurite outgrowth (160), it is possible that TH affects neurite outgrowth by influencing Notch signalling later in development, as well as in cells before their terminal differentiation.

Conclusions

Thyroid hormone exerts effects on the brain throughout development, but the specific effects are different as development proceeds (Fig. 1). The studies of three clinical thyroid disorders show that TH is essential for adequate development of very specific neuropsychological functions and, when TH is insufficient, these functions are impaired. Across conditions, the findings suggest that the developmental timing of TH insufficiency is critical to the type of neurological deficit that occurs, and the source of TH insufficiency can be maternal, fetal or infant in origin. Experimental work lags behind the clinical work as it relates to the effects of modest TH

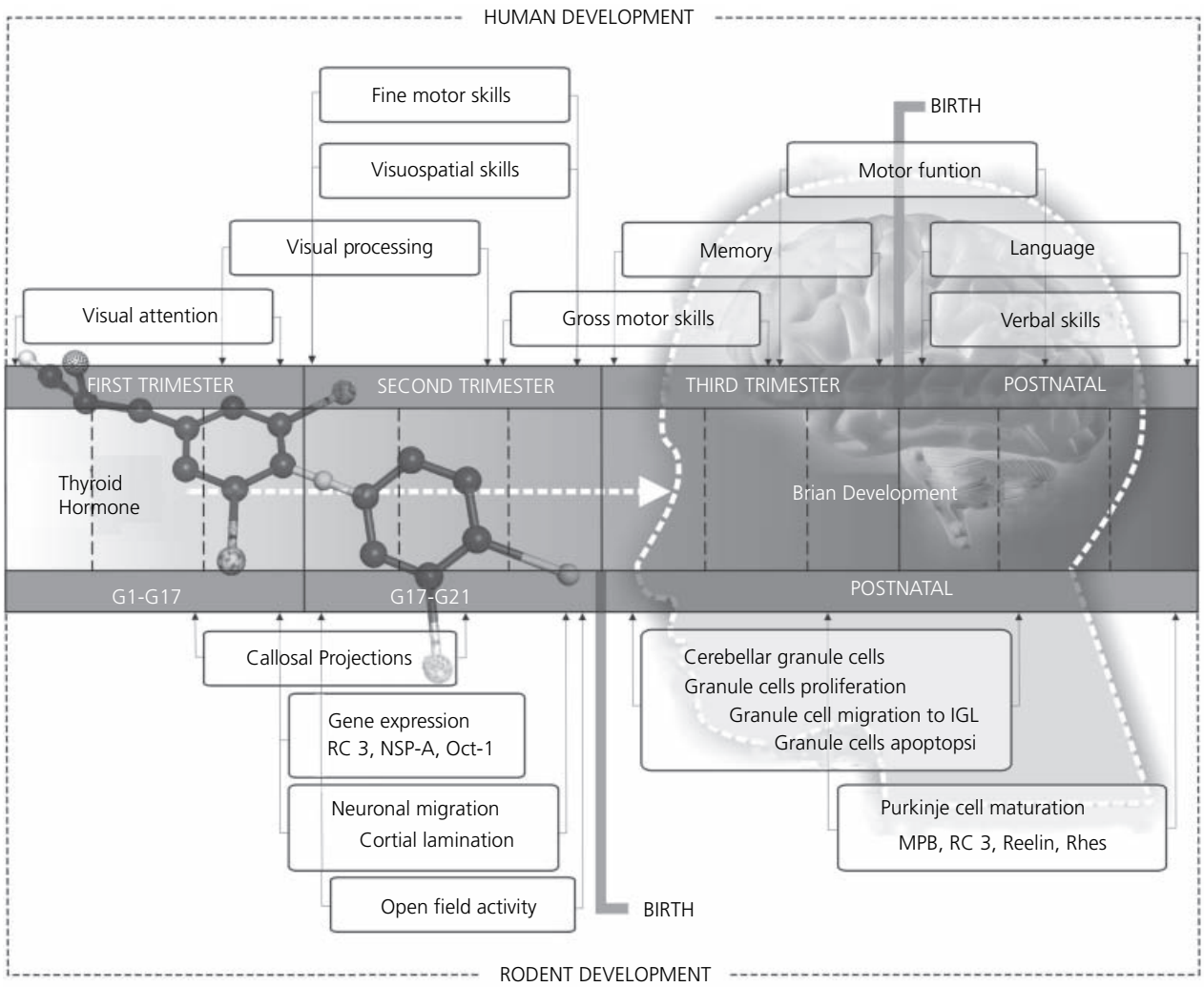

FIG. 1. The timing of thyroid hormone (TH) insufficiency produces different effects in humans (upper panel) and rodents (lower panel). Based on studies of TH insufficiency in humans limited to the early prenatal (maternal hypothyroidism), late prenatal (premature birth) and early postnatal (congenital hypothyroidism), a concept is emerging that thyroid hormone exerts effects on different brain regions as development proceeds. Although there are fewer studies in animals, this concept is gaining support. TH insufficiency during fetal development exerts effects on cortical cortical development, but postnatal hypothyroidism exerts effects on cerebellar development.

insufficiency and the precise timing of those deficits on brain development. However, the experimental literature clearly supports the concept that TH is important throughout brain development, but that its effects at any one time will be restricted to a subset of developmental events occurring at that time. Conversely, clinical work is dependent on tests that are impure measures of specific abilities and only grossly map onto specific brain regions lags. This work therefore lags behind the experimental in terms of specificity of TH action.

Recent work is beginning to focus on the molecular and cellular mechanisms underlying TH effects on specific developmental events and this will lead to better insight into clinical findings. Furthermore, the potential for neuroimaging studies of clinical populations will increase our understanding of the specificity of TH loss on the developing human brain. Information concerning the mechanisms of TH action provides ample evidence for the regulatory flexibility of this important endocrine system that may be employed to selectively regulate specific aspects of brain development. It will be important to capitalize on our understanding of the molecular mechanisms of TH action to define the mechanisms by which TH affects specific developmental processes in the mammalian brain.

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