Université de Montréal

The Predictive Value of Head Circumference Growth during the First Year of Life on Child Traits in Early Childhood

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Résumé

Une croissance atypique du périmètre crânien (PC) durant la première année de vie a été associée à certains troubles du neurodéveloppement, notamment l’autisme. Cependant, l'impact d'une croissance du PC atypique durant la période néonatale sur le développement de l'enfant n'est pas bien connu. Ainsi, ce mémoire s'intéresse à la croissance néonatale du PC comme biomarqueur du développement socioémotionel, cognitif et moteur durant l'enfance. Plus précisément, l'apport prédictif de la croissance du PC de 0 à 12 mois sur le tempérament (contrôle volontaire, extraversion et affectivité négative), les habiletés cognitives et les habiletés motrices (grossières et fines) à 24 mois a été évalué au sein d'un échantillon d'enfants sains (N = 756) provenant de l'étude longitudinale 3D du Réseau intégré de recherche en périnatalogie du Québec et de l'Est de l'Ontario (IRNPQEO). Les résultats indiquent que la croissance néonatale du PC prédit inversement le contrôle volontaire et l’extraversion, mais prédit directement les compétences motrices grossières chez les garçons. Les comparaisons de groupe indiquent que les garçons ayant une croissance du PC plus lente montre un contrôle volontaire significativement plus élevé et des compétences motrices grossières inférieures à ceux ayant une croissance normale ou plus rapide du PC. Cette étude est la première à démontrer une relation entre la croissance néonatale du PC et des aspects spécifiques du fonctionnement de l'enfant dans une population saine. Les résultats confirment la validité de la croissance du PC en tant que potentiel biomarqueur du développement normal et anormal de l'enfant. Des études subséquentes sont cependant nécessaires pour mieux comprendre les mécanismes de la croissance du PC et confirmer l’importance clinique des résultats.

Mots-clés : Périmètre crânien, développement cérébral, tempérament, cognition, motricité

Abstract

Atypical head circumference (HC) growth during the first year of life has been associated with neurodevelopmental disorders, notably autism spectrum disorders. However, its association with socioemotional, cognitive and motor development in early childhood in the normal population is unknown. The objective of this master's thesis was to assess the predictive value of head circumference growth as an early biomarker of toddlers' outcomes. More precisely, it investigated the relationship between HC growth from 0 to 12 months, temperament (effortful control, surgency/extraversion and negative affect), cognitive skills and motor skills (fine motor and gross motor) at 24 months in a healthy subsample of children (N=756) from the large-scale longitudinal 3D cohort study of the Integrated Research Network in Perinatalogy of Quebec and Eastern Ontario (IRNPQEO). Results indicate that postnatal HC growth inversely predicts effortful control and surgency/extraversion, but directly predicts gross motor skills in boys. Group comparisons reveal that boys with less postnatal HC growth showed significantly higher effortful control and lower gross motor skills compared to those with normal and faster head growth. This study is the first to demonstrate a relation between postnatal HC growth and specific aspects of child functioning in a healthy population. The results stress the importance of assessing neonatal HC growth and confirm the validity of HC growth as a potential biomarker of normal and abnormal early child development. Nevertheless, further research is warranted to reveal the underlying mechanisms of the relationships and support clinical importance of the findings.

Keywords: Head circumference, brain development, temperament, cognitive skills, motor skills

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ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
ECBQ	Early Childhood Behavior Questionnaire
HC	Head circumference

It always seems impossible until it's done.

- Nelson Mandela

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Malgré que tout le reste de ce mémoire soit en anglais, mes remerciements doivent se faire en français. Si pour moi l'anglais est la langue des sciences, le français est celle du cœur.

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General Introduction

Adequate socioemotional, cognitive and motor abilities during early childhood are usually representative of healthy child development (Berk & Meyer, 2016). Developmental problems in these abilities are important indicators of potential psychosocial maladjustment later in life (Cairney, Veldhuizen, & Szatmari, 2010; Hughes & Ensor, 2011) and have been found in neurodevelopmental disorders (Baranek et al., 2013; Dyck & Piek, 2012; Jones, Gliga, Bedford, Charman, & Johnson, 2014). Identifying early factors influencing normal and abnormal development of theses abilities is thus crucial for a better understanding of early child functioning. Brain development arises as a potential critical element underlying socioemotional, cognitive and motor development during early childhood. Although there is a wide range of neuroimaging techniques that can be used to assess brain growth during infancy, most of them, such as magnetic resonance imaging, are very invasive and require expensive equipment. Hence, researchers and clinicians are turning towards at a more global, but nonetheless informative approach to assess brain development: head circumference measurement (HC). During early childhood, HC is closely correlated with intracranial volume, which in turn reflects overall brain volume (Adams et al., 2016). HC measurement, which is a routine step in postnatal pediatric follow-ups, has long been used to identify infants exhibiting potentially atypical brain growth, such as microcephaly and macrocephaly. Atypical HC growth during the first year of life has also been associated with neurodevelopmental disorders, notably autism spectrum disorders (Courchesne, Carper, & Akshoomoff, 2003a). However, the impact of atypical neonatal HC growth on socioemotional, cognitive and motor development in early childhood in the normal population has not yet been investigated.

Hence, the first part of this master's thesis highlights the need to identify factors underlying developmental problems, stresses the importance of early child functioning on developmental outcomes, and positions HC as potential early biomarker of child development. The second part presents a scientific article focusing on the predictive value of neonatal HC growth during the first year of life on socio-emotional, cognitive and motor development at two years of age in a healthy population. Finally, the third part draws a general conclusion and addresses prospects for future research.

Developmental Problems

In clinical practice, "developmental problem" is an umbrella term used to designate any ongoing delay or problem in meeting age-specific developmental milestones. Developmental problems mostly become apparent at the beginning of early childhood (around 2 years of age), and are usually categorized into three different broad types: socioemotional, cognitive, and motor problems (Rosenberg, Zhang, & Robinson, 2008; Simpson, Colpe, & Greenspan, 2003). Although developmental problems do not constitute disorders per se, they are often part of the complex phenotype of various neurodevelopmental disorders diagnosed in later childhood, around 4 years of age (Baranek et al., 2013; Dyck & Piek, 2012; Jones et al., 2014; Mayes & Calhoun, 2007). Neurodevelopmental disorders usually combine several, sometimes all, types of developmental problems (Gillberg, 2010; Hillemeier, Farkas, Morgan, Martin, & Maczuga, 2009; Yeargin-Allsopp & Boyle, 2002). However, the etiology and severity of problems and symptoms varies wildly from one disorder to another. For instance, socioemotional problems in attention deficit hyperactivity disorders (ADHD) can include overreacting to certain situations, interrupting conversations or having trouble taking turns (Wåhlstedt, Thorell, & Bohlin, 2008). In autism spectrum disorders (ASD), socioemotional problems can manifest by failure to initiate and respond to social interactions, abnormalities in eye contact and body language, and deficits in developing, maintaining, and understanding relationships (American Psychological Association, 2013).

Hence, developmental problems, whether they occur independently or within a developmental disorder, have serious consequences on child functioning. Early detection and intervention could significantly reduce adverse outcomes in child functioning. Unfortunately, early markers of developmental problems and overall child functioning are currently lacking. As mentioned, identifying such markers is very challenging due to significant heterogeneity in phenotypes. So far, extensive work has focused on identifying isolated markers that predict specific developmental disorders. This strategy requires that the child has already developed elaborate socioemotional, cognitive and motor skills, thereby prohibiting identification of reliable markers earlier in development. Thus, early markers (during the first year of life) of child functioning in early childhood are urgently needed to inform targeted interventions and have a better understanding of general child development.

Early Child Functioning

Early childhood is a salient period for child development (Eisenberg, Fabes, & Spinrad, 2006; Goswami, 2008). Research shows that children’s socioemotional, cognitive and motor abilities during this period are important indicators of psychosocial adjustment later in life (Cairney et al., 2010; Dewey, Kaplan, Crawford, & Wilson, 2002; Hughes & Ensor, 2011; Sanson et al., 2009; Zalewski, Lengua, Wilson, Trancik, & Bazinet, 2011). Although socioemotional abilities in early childhood consists of several abilities, studies have often focused on the assessment of temperament, as it can be easily measured at an early age. As for cognitive and motor skills in toddlers, they are often evaluated concurrently, since many behaviors in early childhood can inform clinicians on both capacities (e.g. visual and tactile exploration, object assembly).

Temperament. Temperament is an early emerging affective and motivational component of socioemotional development. It has been shown to be genetically and environmentally mediated (Lemery-Chalfant, Kao, Swann, & Goldsmith, 2013). Twin studies have demonstrated an influence of genetic factors on a variety of temperament dimensions such as emotionality, shyness, effortful control, inhibitory control, positive affect and negative affect (Cyphers, Phillips, Fulker, & Mrazek, 1990; Gagne & Saudino, 2010; Saudino, Cherny, & Plomin, 2012). There are a number of ways to measure temperament in early childhood. One of the most well-established, reliable and valid measure is the Early Childhood Behavioral Questionnaire (ECBQ; Putnam, Gartstein & Rothbart, 2006). It has been proven useful for screening and detecting the more salient aspects of temperament and those related to psychopathology. The ECBQ allows for characterization of early child temperament using three broad subscales: surgency/extraversion, which refers to the tendency to act with impulsive and active behavior including positive affect; effortful control, which involves self-regulation, including voluntary regulation of attention and behavior; and negative affect, which is characterized by the predisposition to experience negative feelings and difficulty being soothed (Rothbart, Ahadi, Hershey, & Fisher, 2001). These three broad temperamental traits have consistently been identified in factor analyses of early childhood temperament (Ahadi, Rothbart, & Ye, 1993; Goldsmith, Buss, & Lemery, 1997; Kochanska, Devet, Goldman, Murray, & Putnam, 1994; Rothbart et al.,2001).

Cognitive and Motor Skills. Cognitive skills in early childhood involve the progressive building of learning skills, such as attention, memory and thinking (Goswami, 2008). In toddlers, they can be assessed by examining visual and tactile exploration, object assembly, reaction to situations involving object permanence and many other interactions involving sensorimotor integration. Early motor skills are divided into gross and fine motor skills (Berk & Meyer, 2016). Gross motor skills include the larger movements of arms, legs, feet and the entire body, such as locomotion, balance, and coordination. Fine motor skills reflect smaller actions, such as prehension, object manipulation and tactile response. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006) is currently one of the most widely used assessment tools of cognitive and motor skills in toddlers. It is being employed extensively in both clinical and research paradigms to diagnose developmental delays.

While socioemotional, cognitive and motor capacities reflect seemingly distinct aspects of child functioning, impairments in these domains have been shown to be related to similar outcomes, such as deficits in learning, executive control and functions, and intelligence in later childhood and adolescence (Burman, 2016; Oberer, Gashaj, & Roebers, 2017; Smits-Engelsman & Hill, 2012). Moreover, poor cognitive skills, poor motor skills and socioemotional problems (such as low self-regulation and withdrawal tendencies) have all been identified as risk factors for neurodevelopmental disorders (Martin, Piek, Baynam, Levy, & Hay, 2010; Rapp, 2015; Rothbart, Posner, & Hershey, 2006), suggesting that the development of these abilities might share common etiology. Environmental factors, such as socioeconomic status and parental care (Bradley & Corwyn, 2002; Englund, Luckner, Whaley, & Egeland, 2004; Landry, Smith, Swank, Assel, & Vellet, 2001; NICHD, 2002), have been studied as possible common causes of developmental problems and individual differences in early child functioning. However, careful examination of these external factors reveals they might also influence and be influenced by another internal factor, which is nowadays increasingly considered central to the development of socioemotional, cognitive and motor abilities: the brain development.

Brain Development

Advances in neuroscience suggest the biology of the brain is the foundation for behavior and that individual differences in developmental abilities could in part come from individual differences in brain development (Anderson, 2015; Barrett & Satpute, 2013; Bressler & Menon, 2010). Human brain development is a complex, long-lasting process that begins in the early embryonic state and continues well into adolescence, and even throughout adulthood (Singer, 1995; Stiles & Jernigan, 2010). However, brain development does not exhibit a linear growth pattern, especially during the postnatal months where a particularly intense magnitude and velocity of change can be witnessed. The brain develops at a phenomenal rate during the first two years of life, doubling in size during the first year and reaching almost adult size by the second year (Knickmeyer et al., 2008; Pfefferbaum et al., 1994). Specifically, Knickmeyer et al. (2008) found that total brain volume increases by approximately 100% in the first year o life and by only 15% in the second year. They also showed the cerebellum is the structure with the most striking growth during the first year of life, increasing in volume by about 240%. This rapid postnatal brain development arises from multiple factors, including migration of neurons out of the ventricular zone, synaptogenesis, dendritic and axonal growth, differentiation and proliferation of glia, and white matter myelination by oligodendrocytes (Holland et al., 2014). By the end of the second year of life, gray matter growth reaches its lifetime maximum, and adult white matter patterns can already be observed (Matsuzawa et al., 2001; Sampaio & Truwit, 2001; Shi et al., 2011). The early postnatal period is characterized by a particularly robust growth of cortical gray matter compared with white matter, with occipital regions growing much faster than prefrontal regions (Gilmore et al., 2011). Thus, during the first few months of life, gray matter is maturing faster in the sensory and motor regions than in the prefrontal regions, reflecting the rapid maturation of visual and motor functions relative to the executive functions of the prefrontal cortex (Kagan & Herschkowitz, 2006). A similar posterior to anterior maturation of cortical white matter can be observed later in development, with the occipital regions myelinating before the frontotemporal regions (Sampaio & Truwit, 2001). The regional differences in gray matter growth coincide with a rapid burst of synapse formation in the occipital cortex, peaking around four months of age, and a much slower synaptogenesis in the prefrontal cortex, peaking around five years of age (Huttenlocher & Dabholkar, 1997; Parker, 1998). Similarly, primary visual and motor-sensory networks emerge as adult-like during the first year of life, while higher-order networks are still topologically incomplete and mature more slowly (Gao, Alcauter, Smith, Gilmore, & Lin, 2015). Hence, although changes in brain architecture and circuitry can be observed throughout the lifespan, most of brain growth happens during the first year of life. The early postnatal period, thus emerges as a potential pivotal period for adequate structural and functional development of the brain, which in turn is likely to influence child functioning later in life. Tracking changes in growth during that period appears particularly important and could benefit pediatric health care practices. Unfortunately, research assessing the relationship between neonatal brain development and child functioning is still scarce. This could partially be due to the difficulty of measuring brain growth longitudinally during infancy.

Assessing Brain Development During Infancy

The depiction of the rapid changes in brain development during the neonatal period is based on years of cumulative evidences from cross-sectional neuroimaging studies. However, the imaging techniques available to date make it difficult to assess brain development longitudinally during the first few years of life (Raschle et al., 2012). For example, magnetic resonance imaging, one of the most commonly used technique, often requires infants to be sedated to stay still, and is usually not recommended for small children unless it is required for clinical purposes (Edwards & Arthurs, 2011). Cranial ultrasound, another technique available, is much less invasive than magnetic resonance imaging. Unfortunately, it can only be used until approximately nine months of age, since it requires the fontanelle to still be open in order to acquire clear images (Daneman, Epelman, Blaser, & Jarrin, 2006). Moreover, both of these techniques require expensive equipment, and can only be conducted in specific settings. Hence, even if these techniques are powerful tools to explore brain development at specific points in time, they cannot serve as systematic clinical tool to track brain growth longitudinally. Researchers and clinicians are therefore aiming their attention at a more global, but nonetheless informative approach to assess brain development: head circumference measurement.

Head Circumference Measurement

The American Pediatrics Association and the College of Family Physicians of Canada strongly recommend head circumference (HC) to be measured at birth and repeatedly throughout infancy and early childhood (Fraser et al., 2016; Sniderman, 2010). It is deemed the most simple, inexpensive and quick available tool to assess brain development and identify neonates with abnormal brain growth patterns (Garcia-Alix, Saenz-de Pipaon, Martinez, Salas-Hernandez, & Quero, 2004). The particularly intense brain growth happening during the first postnatal months is paralleled by an equally intense increase of HC, by about fourteen centimeters during the two first postnatal years, followed by only seven centimeters until adulthood (World Health Organization, 2009). Although HC measures skull size, genetic studies have shown it is highly correlated with intracranial volume, which closely reflects brain volume during infancy (Adams et al., 2016). Head circumference is a highly heritable trait (Smit et al., 2012) and several rare genetic mutations that have effects on head size have been identified. For example, Brunetti-Pierri et al. (2008) identifies features of microcephaly in individuals with 1q21.1 microdeletion and features of macrocephaly in individuals with microduplications. Qureshi et al. (2014) found increased head size in deletion carriers and reduced size in duplication carriers of the 16p11.2. (Qureshi et al., 2014). Moreover, Angelman and Rett syndromes patients typically show microcephaly (Bird, 2014; Chahrour & Zoghbi, 2007), whereas PTEN-related disorders and Tuberous Sclerosis Complex patients tend to show macrocephaly (Fidler, Bailey, & Smalley, 2000; McBride et al., 2010). These genetic mutations not only often result in extreme head size patterns (either microcephaly or macrocephaly), but have also been linked with developmental delays, learning disabilities, autistic and attention deficit/hyperactivity traits (Shinawi et al., 2009; van Dyck & Morrow, 2017; Williams, Dagli, & Battaglia, 2008).

Hence, HC is currently used in clinical practice to identify neonates exhibiting extreme brain growth patterns, either microcephaly or macrocephaly. Microcephaly (HC<2SD) has been associated with a range of neurological problems including developmental delays, intellectual delays and epilepsy (Baxter, Rigby, Rotsaert, & Wright, 2009; Gordon-Lipkin, Gentner, German, & Leppert, 2017; von der Hagen et al., 2014; Watemberg, Silver, Harel, & Lerman-Sagie, 2002). Several brain abnormalities often resulting in abnormal brain functioning, such as cerebral atrophy, cortical dysplasia, myelination delay and white matter hypoplasia, have been found in children with microcephaly (Custer et al., 2000). In the case of macrocephaly (HC>2SD HC), a cranial ultrasound evaluation is routinely performed to exclude hydrocephaly, but in the majority of cases, images are normal (Jeong, Kim, & Han, 2014). Macrocephaly is associated with reduced long-distance connectivity in the brain and with greater conduction delays of neural responses (Changizi & Shimojo, 2005; Karbowski, 2003). This might be explained by the enlargement of brain structures and peculiarities in distance between them, affecting connectivity efficiency, which have been found in children with increased head growth (Lewis, Theilmann, Townsend, & Evans, 2013). Moreover, macrocephaly, especial in early childhood, is thought to be a biomarker of autism spectrum disorder (ASD), as it is found in 20% of ASD patients (Courchesne et al., 2003a; Hazlett et al., 2005; Sacco, Gabriele, & Persico, 2015), although the specificity of this relationship is still controversial (Dinstein, Haar, Atsmon, & Schtaerman, 2017). Interestingly, studies have found atypical head circumference specifically during the first year of life to be related to ASD, but also to other neurodevelopmental psychiatric disorders such as attention deficit/hyperactivity disorder, intellectual disability and schizophrenia (Gurevitz, Geva, Varon, & Leitner, 2014; McKeague et al., 2015; Rommelse et al., 2011; Ward, Friedman, Wise, & Schulz, 1996). These findings highlight the importance of closely monitoring HC growth during the first years of life.

Since adequate brain development during the neonatal period seems to provide the scaffolding for later structural and functional development, it appears likely to influence cognitive, motor and socioemotional development. However, studies assessing brain development longitudinally during the first year of life are scarce, partly due to technical constraints of investigating the neonatal brain. As a result, researchers and clinicians alike recognize the importance of HC measurement in assessing early brain development. However, most studies have focused on clinical population and extreme growth patterns. Therefore, how HC growth variations outside of extreme values in healthy children relates to specific changes in behavior and functioning in later development remains poorly understood. Assessing functioning in children after the rapid and intense neonatal brain growth period might elucidate how brain growth impacts child development, and may guide early intervention that may prove more efficacious than later in development.

Scientific Article

Objective. The objective of the scientific article included in this Master's thesis was to assess the predictive value of head circumference growth in the first year of life as an early biomarker of child functioning in a healthy population. More precisely, it looked at the link between HC and socioemotional, cognitive and motor development in early childhood, which is deemed a crucial period for child development.

Contribution. The scientific article included in this Masters's thesis describes the research project that was conducted by Caroline Dupont in the framework of her Master's degree, based on an initial idea from her supervisor Sarah Lippé. This research project is a substudy of the large-scale longitudinal 3D (Design, Develop, Discover) cohort study of the Integrated Research Network in Perinatalogy of Quebec and Eastern Ontario (IRNPQEO) which aimed to collect data on child development and parental health. It is also part of the research on brain development in healthy children and infants conducted in the Neuroscience of Early Development (NED) lab. As the first author of the scientific article, Caroline Dupont devised the research problem, conducted most of the statistical analyses with the help of Natalie Castellanos Ryan and wrote the article. Sarah Lippé helped and guided her throughout the whole process. The article is currently under final review by co-authors before submission. It is expected to be submitted to the *Proceedings of the National Academy of Sciences* by the end of the year.

Scientific article

The Predictive Value of Head Circumference Growth during the First Year of Life on Early Child Traits

The Predictive Value of Head Circumference Growth during the First Year of Life on Early Child Traits

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Abstract

The objective of the study was to assess the predictive value of head circumference growth as an early biomarker of socioemotional, cognitive and motor development in early childhood. More precisely, it investigated the relationship between postnatal HC growth from 0 to 12 months, temperament (reflecting socioemotional development) and neurodevelopment (cognitive, fine motor and gross motor skills) at 24 months in a healthy population. A healthy subsample of children (N=756) was drawn from the large-scale longitudinal 3D (Design, Develop, Discover) cohort study of the Integrated Research Network in Perinatalogy of Quebec and Eastern Ontario (IRNPQEO). Neonatal HC growth was modeled with latent growth curve analysis. Temperament, cognitive, fine motor and gross motor skills were examined as outcomes in the model. Results indicate that postnatal HC growth directly predicts gross motor skills, while it inversely predicts temperamental effortful control and surgency/extraversion in early childhood in boys. Group comparisons indicated that boys with less postnatal HC growth showed significantly higher effortful control and lower gross motor skills compared to those with normal and faster head growth. No significant effect of HC growth was found in girls, and HC at birth did not predict any temperamental and neurodevelopmental outcomes, both in boys and in girls. This study is the first to demonstrate a relation between postnatal HC growth and specific aspects of child functioning in a healthy population. The results stress the importance of assessing neonatal HC growth and confirm the validity of HC growth as a potential simple, yet reliable, biomarker of normal and abnormal early child development

Keywords: Head circumference, brain development, temperament, cognitive skills, motor skills

The Predictive Value of Head Circumference Growth during the First Year of Life on Early Child Traits

Anomalies in the development of brain structures and functions have been associated with characteristics of certain neurodevelopmental disorders and impairments in child functioning (Baglio et al., 2014; Fairchild et al., 2011; Nickl-Jockschat et al., 2012; Seidman, Valera, & Makris, 2005). Genetic and biological mechanisms determine prenatal and postnatal brain growth (van Dyck & Morrow, 2017). Genetic disruptions can hinder important biological mechanisms involved in brain growth, resulting in microcephaly or macrocephaly. A number of genetic syndromes involving learning disabilities, autistic and attention deficit or hyperactivity traits are associated with abnormal brain growth. Whereas the Angelman and Rett syndromes patients typically show a microcephaly (Bird, 2014; Chahrour & Zoghbi, 2007), PTEN-related disorders and Tuberous Sclerosis Complex patients tend to show macrocephaly (Fidler, Bailey, & Smalley, 2000; McBride et al., 2010). Moreover, abnormal brain volume and growth have been controversially reported in children with autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), two frequent neurodevelopmental disorders(Dinstein, Haar, Atsmon, & Schtaerman, 2017; Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007). Research has shown that the mean brain volume of children with ASD is greater than that of neurotypical children during childhood (Courchesne, Carper, & Akshoomoff, 2003; Hazlett et al., 2005). Similarly, head circumference (HC), a commonly used surrogate measure for brain volume, is significantly larger in autistic compared to neurotypical individuals, and even more so in early childhood (R. Sacco, Gabriele, & Persico, 2015). Retrospective studies of infants who later developed ADHD have shown slower increase in head circumference (Gurevitz, Geva, Varon, & Leitner, 2014) and smaller head circumferences persisting as far as eighteen months of age (Heinonen et al., 2011). To note, Raghuram et al. (2017) also found that, in pre-term infants, lower HC growth is related to higher neurodevelopmental impairments, specifically cognitive and motor delays. Hence, abnormally slow or fast head size growth has been underlined in neurodevelopmental disorders involving socio-emotional, cognitive and motor impairments. However, how brain growth relates to child's socio-emotional, cognitive and motor development in the general population is unknown.

Brain volume more than doubles during the first year of life and reaches almost adult size by 2 years of age (Gennatas et al., 2017; Knickmeyer et al., 2008; Pfefferbaum et al., 1994). This corresponds with an increase in overall gray matter volumes to a lifetime maximum around two years of age (Gilmore et al., 2011). Concurrent with the rapid development of the brain during that period, is an equally rapid development of a wide range of socio-emotional, cognitive and motor functions (Kagan & Herschkowitz, 2006). Considering early postnatal years are the most dynamic and important phase of brain development, abnormal growth may be most prominent during that period and may be more associated with child functioning that can be measured more robustly later on.

Although there is a wide range of methods available to assess brain growth in infancy, head circumference is most commonly used as a proxy measure of early brain size maturation. Clinicians and researcher alike agree that HC measurement is the most simple, inexpensive and quick available tool to assess brain size and identify neonates with abnormal brain growth patterns (Garcia-Alix, Saenz-de Pipaon, Martinez, Salas-Hernandez, & Quero, 2004; Harris, 2015). More knowledge on if and how deviations in HC growth trajectory impact on child development may improve pediatric health care.

Early childhood functioning domains most commonly include the evaluation of socio-emotional, cognitive, and motor development. Although socio-emotional adjustment in early childhood can be conceptualized in several ways, studies have often focused on the assessment of temperament. Temperament is an early emerging affective and motivational component of behavior associated with later social relationships, academic competences and psychopathology (Sanson et al., 2009; Whittle, Allen, Lubman, & Yücel, 2006; Zalewski, Lengua, Wilson, Trancik, & Bazinet, 2011). Temperament has been demonstrated to be genetically and environmentally mediated (Lemery-Chalfant, Kao, Swann, & Goldsmith, 2013). Core dimensions of highly heritable childhood temperament include effortful control, negative affectivity, and extraversion/surgency (Mary K. Rothbart & Bates, 2007; Saudino, 2005). Whereas low effortful control and high negative affectivity have been shown to confer risk for behavioral problems, affective disorders, and neurodevelopmental disorders later in life (Muris & Ollendick, 2005; Nigg, 2006; Mary K Rothbart, Posner, & Hershey, 2006), studies pertaining to surgency show less consistent results. More specifically, children with low self-regulation are at increased risk for the development of externalizing disorders and problems related to attention, while withdrawal and tendency towards negative affectivity are thought to be related to anxiety disorders and problems in social competence (Auerbach et al., 2008; Hankin et al., 2017; Mary K Rothbart et al., 2006). While moderate level of surgency/extraversion positively predicts infants' communication development and children's conversational skills (DeThorne, Deater-Deckard, Mahurin-Smith, Coletto, & Petrill, 2011; Peterson et al., 2017), some studies show that very high surgency/extraversion in toddlers could predict aggression in preschool and early childhood (Berdan, Keane, & Calkins, 2008; Gunnar, Sebanc, Tout, Donzella, & van Dulmen, 2003). In ASD toddlers, surgency and effortful control domains have been shown to be significantly reduced during infancy, childhood and adolescence (Macari, Koller, Campbell, & Chawarska, 2017; Schwartz et al., 2009). Finally, literature on early childhood functioning has also consistently identified poor cognitive and motor abilities in young children as a shared risk factor in a plethora of neurodevelopmental disorders (Martin, Piek, Baynam, Levy, & Hay, 2010; Rapp, 2015). Hence, temperament, cognitive and motor skills are important and easily available indicators to track milestones and identify early problems in child development. It is therefore crucial to have a better understanding of the factors influencing these aspects of early child functioning. If brain size is a relevant biomarker of neurodevelopment in clinical populations, variations of brain size in a healthy general population should further be indicative of symptomatic traits.

The objective of this study is to investigate the predictive value of head circumference growth trajectory in the first year of life on early childhood functioning at 24 months in a healthy population.

More specifically, temperament and neurodevelopment (cognitive and motor skills) at 24 months will be assessed since they offer a global and comprehensive overview of child functioning at that age. Based on the literature reviewed, it was expected that there would be an association between abnormal head circumference growth (either more rapid or slower) and child functioning at 24 months.

Method

Participants

3D Cohort. A subsample of participants (N=756) were drawn from the large-scale longitudinal 3D (Design, Develop, Discover) cohort study (Fraser et al., 2016), which includes prospectively-collected data, and aims to address prenatal and early-life determinants of perinatal health and child development. Participants were recruited at nine urban clinical centers in three metropolitan areas in the province of Quebec (Canada), accounting for more than half of the population of Quebec. 2366 pregnant women, between 18 and 45 years of age, participated in the study (Figure 1). They were recruited during the first trimester of pregnancy (6 to 14 gestational weeks), seen during the second (20 to 24 gestational weeks) and third trimester (32 to 35 gestational weeks), and followed along with their child at birth and at 3, 12 and 24 months postpartum (see Fraser et al., 2016 for more details on the recruitment process). The study was approved by the CHU Sainte-Justine Research Ethics Board and by the ethics board of each participating study center.

Study subsample. A subsample was selected from the 3D cohort study (Figure 1) to conduct analyses. Participants for whom data on child behavior, temperament, cognitive skills and motor skills were not collected at the 24-month infant follow-up visit (n = 1360) and those for whom no HC measures were available at any time point were excluded (n=160). Since the aim of the study was to investigate HC growth and general child development in a non-clinical population, infants with serious health conditions, neurological insults or known risk factors that could affect normal development were excluded from the study subsample. Thus, infants whose mother used drugs during pregnancy (n = 8) and infants born before 34 weeks of gestational age (n = 12), who suffered from respiratory distress at birth (n = 48), who had a history of concussion and head trauma (n = 5) or a diagnosis of congenital abnormalities (n = 17) were excluded. This resulted in a final study subsample size of 756 that was subsequently divided in two subsamples based on infant sex (male, n = 375; female n = 381) for analyses, as norms for HC and HC growth show differentiated development for girls and boys (Health, 2009).

Measures

Mothers completed questionnaires prenatally (at each trimester) and postnatally regarding socio-demographic information and medical history of their child. Follow-ups of 3D infants were performed at 3, 12, and 24 months of age. All measures used in the current study were drawn from the questionnaires completed prenatally and postnally by the mother regarding sociodemographic information, medical history and child temperament, as well as the evaluation of the infant cognitive and motor abilities conducted by a qualified health professional at 24 months postpartum. Information regarding head circumference measurements were drawn from the medical history questionnaires completed at birth, 3 months and 12 months postpartum.

Child temperament. Child temperament was assessed at 24 months using the Very Short Form of the Early Childhood Behavior Questionnaire (ECBQ; Putnam, Gartstein & Rothbart, 2006). The ECBQ is a well-established, reliable, and valid measure of child temperament (Putnam & Stifter, 2008). Its very short form, comprising thirty-six items rated on a scale of 1 (extremely untrue of your child) to 7 (extremely true of your child), has been proven useful for screening and detecting the more salient aspects of temperament and those related to psychopathology. It allows for characterization of early child temperament using three broad subscales: Surgency/Extraversion(SE), which refers to the tendency to act with impulsive and active behavior including positive affect; Effortful Control (EC) which involves self-regulation, including voluntary regulation of attention and behavior; and Negative Affect (NA) which is characterized by the predisposition to experience negative feelings and difficulty being soothed (Mary K Rothbart, Ahadi, Hershey, & Fisher, 2001). These three broad temperaments traits have consistently been identified in factor analyses of early childhood temperament (Ahadi, Rothbart, & Ye, 1993; Goldsmith, Buss, & Lemery, 1997; Kochanska, Devet, Goldman, Murray, & Putnam, 1994; Rothbart et al.,2001).

Child neurodevelopment. Infant cognitive and motor abilities were evaluated using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006). The Bayley-III is designed to measure the developmental functioning of infants and toddlers and identify possible developmental delay. The Cognitive scale of the Bayley-III contains 91 items assessing information processing, conceptual resources and perceptual skills. The Motor scale of the Bayley-III consists of the Fine Motor and the Gross Motor subtests. The Fine Motor subtest contains 66 items measuring skills associated with eye movements, perceptual-motor integration, motor planning, and motor speed. The Gross Motor subtest contains 72 items assessing movements of the limbs and torso. In addition to the Bayley-III, the Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) was also completed. The M-CHAT is a screening tool designed to identify children showing possible early signs of autism spectrum disorder (ASD) or developmental delay. In the present study, it is used as a complement to the assessment of child neurodevelopment through cognitive and motor abilities.

Covariates. Family income status and level of education of the mother, which are commonly used as indicators of socioeconomical status (SES), as well as infant gestational age at birth (GA) were used as covariates in all analyses. SES is a well known factor influencing child development and GA has been shown to influence both head circumference at birth and child development.

Statistical Analyses

Preliminary Analyses and Descriptive statistics. Analyses were carried out using IBM SPSS for Windows, Version 22.0. The amount of partial missing data ranged from 3% to 41% (Bayley-III cognitive and motor development at 24 months follow-up). When separating the sample by sex, the amount of missing data was similar for both boys and girls. Descriptive analyses were performed separately for boys (n = 375) and girls (n = 381) subsamples.

Unconditional Latent Growth Curve Models. Analyses were carried out with latent growth curve and path analyses using Mplus version 7 for Windows. Maximum likelihood with robust standard errors (MLR) estimation was used in all analyses and full information maximum likelihood (FIML) was used to account for missing data. First, several unconditional latent-growth curve models (LGCM) were conducted to assess HC development during the first year of life, modeling both the intercept (HC at birth) and slope (HC growth from 0 to 12 months). LGCM methodology is substantially more flexible than traditional analysis of variance for the assessment of longitudinal data, as it allows examining intra-individual change and inter-individual differences in change across time (Nesselroade, McArdle, Aggen, & Meyers, 2002) using all data available.

All models were run separately for girls (n=381) and boys (n=375), as multigroup models, in Mplus. A model assuming linear growth in HC across the first year of life (time score loadings constrained at 0, 1 and 2) for both boys and girls did not fit the data well (X2 (2, 756) = 25.43 (boys=20.45; girls=4.98), CFI=0.88, TLI=0.63, RMSEA=0.176, SRMR=0.18). Thus, a second model was constructed in which the loading for the last time point was freed for boys and girls. In order to identify the model (having at least 1 degree of freedom), the residual variance for the first time-point was constrained to be equal across infant sex. This was deemed justified as the residual variance for the first-time point was comparable for boys (1.30, p<.001) and girls (1.16, p<.001). This model fit the data very well (X2 (1, 756) = 0.005 (boys=0.003; girls=0.002), CFI=1.00, TLI=1.03, RMSEA=0.00, SRMR=0.01), and showed that the mean HC at birth was slightly larger for boys (34.57 cm, p<.001) than for girls (34.16 cm, p<.001) and average overall growth in HC from birth to 12 months was larger in boys (slope mean=6.55, p<.001) than girls (slope mean=5.92, p<.001). The freely estimated loading for the last time point indicated that growth slowed down slightly more for boys (time score loading at 12 months (last time point) of 1.88) than for girls (time score loading at 12 months of 1.95, which approximates a loading indicating linear growth, i.e., a loading of two) from 3 to 12 months of age (see Figure 2). Results also showed that the variance for the intercept and slope factors of HC was significant in both boys (intercept: 1.06, p<.001; slope: 0.33, p=.001) and girls (intercept: 0.96, p<.001; slope: 0.19, p=.017), indicating that there was significant individual variability in HC at birth and in HC growth over the first 12 months of life in this sample. Finally, HC at birth was negatively associated with growth in HC from birth to 12 months (boys: r=-.31, p=.052; girls: r=-.32, p=.011).

Path Models Testing Associations Between HC Factors and Child Development Outcomes at 24 months. Once head circumference development was modeled, the LGCM factors for HC (HC at birth and HC growth during the first year of life) together with covariates (GA, family income and maternal education) were included into one multivariate path model to test the relationship between HC development and child development outcomes at 24 months (temperament, cognitive and motor).

Results

Preliminary Analyses and Descriptive Statistics

Table 1 presents zero- order correlations among all main variables. Table 2 presents the means and standard deviations of each continuous variable used to describe the boys and girls subsamples. In the sample, 49% of infants were male. The mean GA at birth was 39.0 weeks (SD = 1.4) for boys and 39.2 weeks (SD = 1.3) for girls. The mean maternal education level were 17.3 years (SD = 3.0) and 16.9 years (SD = 2.7), for the boy and girl subsamples respectively. Furthermore, 9.3% of participants in the boys subsample and 9.4% in the girls subsample had a before-tax household income below Statistics Canada's before-tax low-income cut-off for their family size, which is a little lower than the 2010 Canadian norm of 13.7%. The mean HC at all 3 time points (birth, 3 months, 12 months) was similar to established norms (Organization, 2009). Child development outcomes (ECBQ, Bayley and M-CHAT scores) tended to cluster around normal values in both sex subsamples. Screening of variable distributions revealed normal or near-normal distributions (all kurtosis and skewness indices ≤ 2.5).

Path Models Testing Associations Between HC Factors and Child Development Outcomes at 24 months

The univariate latent growth model for HC was included in a model with child development outcomes at 24 months (temperament, cognitive development, fine and gross motor development and M-Chat) to test the relationship between both HC at birth (intercept) and HC growth during the first year of life (slope), and child development, controlling for GA and SES (family income and maternal education). Thus, regression paths from the intercept and slope latent factors for HC to these outcome variables were included in this model. Table 3 shows regression coefficients from HC at birth and HC growth during the first year of life to child development outcomes at 24 months. Results indicate that, controlling for covariates, HC growth during the first year of life significantly predicted the temperamental traits of surgency and effortful control, as well as gross motor skills in boys, but failed to predict cognitive development, fine motor skills and M-CHAT scores. Furthermore, HC growth during the first year of life failed to significantly predict any outcomes in girls. HC at birth did not predict child development outcomes at 24 months, neither in boys, nor in girls. None of the covariates

(GA, family income and maternal education) significantly predicted child development outcomes at 24 months.

Discussion

We studied, for the first time in the general population, how head growth during the first year of life can predict infants' temperamental and neurodevelopmental outcomes. Our results provide evidence that postnatal HC growth significantly predicts temperamental and neurodevelopmental outcomes in early childhood. This predictive value was exhibited for boys only. Results suggest that HC growth from 0 to 12 months negatively predicts temperamental effortful control and surgency/extraversion, and positively predicts gross motor skills at two years old. In other words, a more rapid increase in brain volume in infancy would be related to lower self-regulation and lower tendency for outgoing behaviors, positive affect and interactions later in development. Whereas our results suggest that HC growth during the first year of life would not be related to general cognition, increased in HC growth is seemingly related to better motor skills.

Temperament refers to individual differences in reactivity and regulation that are thought to be neurobiologically based and to serve as the foundation for subsequent personality (Goldsmith et al., 1987; M. K. Rothbart & Ahadi, 1994). Surgency, which includes high-level of energy and positive approach behaviors, is related with better language and communicative skills in toddlers, and with extraversion in childhood (Muris, Meesters, & Blijlevens, 2007). Given the existing, yet controversial, literature on the association between increased brain growth and ASD (Chaste et al., 2013; Courchesne & Pierce, 2005; Dementieva, Vance, & Donnelly, 2005; Dinstein et al., 2017), our results are well in accordance with the temperamental profile found in toddlers later diagnosed with ASD, which includes less positive anticipation (Garon et al., 2009; Zwaigenbaum et al., 2005), less enjoyment in play (Clifford et al., 2013) and less surgency (Macari et al., 2017). Lower effortful control, which includes self-regulation of attention and behavior, is significantly associated with psychopathology and neurodevelopmental disorders involving internalizing and externalizing symptoms (Muris & Ollendick, 2005; Neumann et al., 2016). Lack of effortful control is associated with later ADHD of both types (Einziger et al., 2017) and is often present in other neurodevelopmental disorders, including ASD (Macari et al., 2017). Here we report that increases in HC growth, which has been reported in ASD populations, predicts two temperamental traits typical of ASD (reduced surgency/extraversion and effortful control). Hence, our findings in the general population are in accordance with expectations based reports from clinical populations.

Several factors, including genetic and environmental factors, may account for this relationship in the clinical as well as in the general population. First, mechanisms responsible for brain growth are also involved in establishing synaptic functions, circuitry and brain networks (van Dyck & Morrow, 2017). As such, the underlying biological mechanisms involved in brain growth dysregulation may also interfere with attentional and socio-emotional brain networks functions at the molecular and network levels. Second, increased in brain size may hamper network integration, hindering their functions. In an infant brain where structural connections of myelinated white matter are slowly maturing (Paus et al., 2001; Sampaio & Truwit, 2001), increased distance between brain regions may further impact the brain network, leaving the network to segregate regions rather than promote integration (Lewis, Theilmann, Townsend, & Evans, 2013; Vakorin, Lippé, & McIntosh, 2011). Furthermore, brain regions associated with higher order functions such as attention, executive control and emotional regulation exhibit a more protracted developmental timetable (Casey, Tottenham, Liston, & Durston, 2005; N. Gogtay et al., 2004). For example, effortful control includes the ability to inhibit dominant responses to perform subdominant responses (Mary K Rothbart et al., 2001). This temperamental dimension is thought to be closely related to underlying brain networks of executive attention in the anterior cingulate and other frontal areas (Gerardi-Caulton, 2000; Mary K Rothbart, Sheese, & Posner, 2007). Slower brain growth and volumes seem beneficial for these brain networks, as it might allow their underlying brain structures to more optimally integrate. Hence, brain regions with more long-lasting development would be more strongly and adversely affected by volume upregulation in infancy, potentially leading to maldevelopment of large integrative networks, which could lead, in particular, to abnormal top-down control signaling and complex behavior initiation (Courchesne & Pierce, 2005).

HC growth did not predict cognitive skills at 24 months of age. This is more surprising, since cognitive skills in young children are often associated with the temperament construct effortful control, and both have been linked with overlapping neural networks (Casey et al., 2005; Mary K. Rothbart, Ellis, Rosario Rueda, & Posner, 2003). Moreover, general cognition has been repeatedly reported as being affected by microcephaly (Baxter, Rigby, Rotsaert, & Wright, 2009; Gordon-Lipkin, Gentner, German, & Leppert, 2017; Watemberg, Silver, Harel, & Lerman-Sagie, 2002). It could be that the tool used to measure cognitive skills in our study (Bayley-III) provides a too broad assessment of this neurodevelopmental construct to draw a relationship with early brain development. Scales or tests targeting more specific cognitive skills in young children, such as attention, memory or learning, might yield different results. However, faster HC growth predicted greater gross motor skills, such as motor coordination, motor planning and balance. Brain correlates of these motor functions, namely sensorimotor cortex and cerebellum, typically undergo striking development in infancy (Bastian & Thach, 2002; Holland et al., 2014; Knickmeyer et al., 2008). Moreover, the motor and sensorimotor network (somatosensory, motor and visual cortices) is the fastest to myelinate, facilitating integration in this particular network (Deoni, Dean, Remer, Dirks, & O'Muircheartaigh, 2015). Of course, the proposed frameworks for the explanation of our results are speculative, since HC measuring unfortunately does not allow for quantification of specific brain volumes nor network integration measures. They nonetheless contribute to the growing body of evidence on the mechanisms that might be at play in early postnatal brain development and their influence on later child development.

Interestingly, our results suggest a differentiation based on sex of the predictive value of general HC growth during the first year of life on temperamental and neurodevelopmental outcomes in early childhood. Indeed, overall HC growth from 0 to 12 months predicts temperamental surgency and effortful control, as well as gross motor skills at 24 months in boys, but do not predict any temperamental or neurodevelopmental outcomes in girls. An explanation for this difference could come from the sexual dimorphism observed in brain structure and brain growth during infancy. Research has shown that there is a widening separation in brain sizes with age between male and female infants, with males growing faster than females (Holland et al., 2014) and that males have larger total brain volume than females in infancy (Giedd, Raznahan, Mills, & Lenroot, 2012; Gilmore et al., 2011). Hence, this more rapid brain growth in boys may potentiate its effect on brain functions and behavior. Atypical brain growth during that period might thus be more susceptible of influencing later outcomes in boys than in girls. Research on the sex bias in neurodevelopmental disorders might also provide an alternative explanation for the sex differences in current results. Indeed, a higher male prevalence has been repeatedly reported in a number of neurodevelopmental disorders involving attentional difficulties and withdrawal (Hill, Zuckerman, & Fombonne, 2015; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), and emerging evidence suggests a "female protective model" as an explanation for the lower female prevalence (Jacquemont et al., 2014; Polyak, Rosenfeld, & Girirajan, 2015). This model suggests that a complex mix of genetic factors specific to females might influence neurobehavioral development and act as protective factor, even in the presence of adverse outcomes, such as high familial risk for neurodevelopmental disorders. Hence, it could be that brain growth during the first year of life is less of biomarker in girls due to these potential protective genetic factors.

Our study did not provide support for HC growth during the first year of life as a predictor of negative affect. The amygdala and hippocampus have consistently been demonstrated to underlie this temperamental construct (Liberzon, Phan, Decker, & Taylor, 2003; Whittle et al., 2006). These subcortical structures mostly develop in late childhood, with especially substantial increases in volume from 4 to 9 years old, which offers an explanation as to why brain volume growth variations in the first year of life do not seem to particularly influence negative affect (Lenroot & Giedd, 2006; Uematsu et al., 2012). An analogous reason might explain why brain growth from 0 to 12 months could not predict fine motor skills, which comprises perceptual-motor integration, motor planning and motor speed. Indeed, motor cortical regions subserving these fine motor skills, such as the premotor cortex and the dorsolateral prefrontal cortex, also mostly develop and mature in later childhood and adolescence (Gerván, Soltész, Filep, Berencsi, & Kovács, 2017; Willingham, 1999). This probably makes HC growth during the neonatal period less of a biomarker for fine motor skills, as opposed to gross motor skills whose associated brain structures mature and develop very early.

Lastly, HC growth during the neonatal period did not predict risk for ASD and developmental delay. We anticipated that result, since when constituting our cohort subsample, we removed children with most of the confounding factors for neurodevelopmental delays to investigate a seemingly healthy population. In fact, most of the children in our subsamples scored very low on the M-CHAT questionnaire. Nevertheless, this absence of results support recent findings suggesting that significant low levels of surgency in ASD toddlers did not predict ASD severity levels (Macari et al., 2017). Hence, the temperamental surgency domain may be more predictive of long-term social adaptation such as friendship and employability rather than a clinical constituent of the ASD diagnosis. Brain growth upregulation during the first year of life may be a relevant biomarker of such trait in the general population, but also in clinical populations, proposing a specific phenotypic profile within a broad spectrum.

On a final note, it is important to mention that, as opposed to postnatal HC growth, HC at birth does not appear to be a significant predictor of early child functioning, neither in boys, nor in girls. This is not surprising, since it has been demonstrated that it is not the brain size at a fixed time point that is informative, but rather the evolution between two or more time points that gives a better view on ongoing processes, even more so in infancy where changes are rapid (Nitin Gogtay et al., 2004; Holland et al., 2014). Noteworthy, our sample is representative of a healthy population, thus HC at birth in clinical samples may be relevant to later outcomes (Cheong et al., 2008; Raghuram et al., 2017).

Limits of the substudy

An important strength of this study was our ability to examine associations between postnatal HC growth and child functioning in early childhood within the context of a prospective longitudinal study. Nevertheless, a frequent limit in epidemiological longitudinal studies is both selection and recall bias. In the 3D cohort study, mothers declining to participate, withdrawing and or not completing follow-ups with their infants might be due to personality and environmental factors. Unfortunately, demographic characteristics of these women were not compiled, making such factors impossible to assess. These factors could partly explain why the 3D study and our subsamples have a higher SES (i.e. family income and education level) than the general population, which limits the generalizability of our findings. Similarly, the amount of missing data differed between time points and was greater in mothers with lower SES. The generalizability to rural populations might also be limited, since the 3D cohort was recruited in large metropolitan areas. Finally, mothers from the 3D cohort study and both our subsamples were older, more frequently married and more frequently born outside of Canada compared to Canadian births overall (Fraser et al., 2016).

Another important strength of our study is the assessment of HC growth specifically during the first year of life. However, we assessed this growth using the available HC measurements that were taken at only three time points during the study (i.e birth, 3 months and 12 months). This might not make it possible to draw a detailed portrait of the accelerated head and brain growth happening in the first year of life. For future studies, more measurements times are warranted, thus even possibly making it feasible to pinpoint specific critical period of growth within the first year of life for later child functioning. It is also important to underline that HC measurement can only estimate intracranial and overall brain volume. It would thus be important to assess HC during the postnatal period concurrently with measurement of brain volume to have a better understanding of how the different cortical and subcortical brain structures influence HC growth and potentially child functioning in later development.

Conclusion

In conclusion, our study is the first to demonstrate a relation between postnatal HC growth and specific aspects of child functioning in a healthy population. We have shown in a large subsample drawn from a longitudinal cohort that HC growth during the first year of life predicts specific aspects of temperament, effortful control and surgency/extraversion, and gross motor skills in healthy boys at two years of age, strengthening the existing evidence that HC is a useful tool to assess child development. Although there are factors limiting the generalizability of our findings, the results nonetheless stress the importance of investigating HC growth during the neonatal period as a biomarker of later child development. Nevertheless, further research is warranted to reveal the underlying mechanisms of the relationships and to support the clinical importance of the findings.

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Declaration of interests

None of the authors has any conflict of interest to disclose.

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Table 1

Zero-Order Correlations Among all Main Variables

	1	2	3	4	5	6	7	8	9	10
1. Gestational Age	---	-0.06	0.05	-0.02	-0.03	0.01	0.02	0.13*	0.03	-0.03
2. Family income status		---	-0.13*	0.07	0.09*	0.02	-0.01	-0.02	-0.09*	0.10*
3. Maternal Education			---	-0.02	-0.04	0.06	-0.06	0.06	-0.02	0.01
4. Surgency/Extraversion				---	0.12	-0.02	-0.03	-0.06	-0.06	0.02
5. Negative Affect					---	-0.13*	-0.02	-0..03	-0.06	-0.07
6. Effortful control						---	0.01	0.02	-0.01	-0.09*
7. Cognitive skills							---	0.48*	0.31*	-0.09*
8. Fine motor skills								---	0.37*	-0.02
9. Gross motor skills									---	-0.01
10. M-CHAT										---

Note. *$p < 0.05$.

Table 2

Means and standard deviations (SD) of head circumference measures and outcome variables for both subsamples.

	Boys (N = 375)		Girls (N = 381)	
	n	Mean (SD)	n	Mean (SD)
HC measures (cm)				
Birth	363	34.6 (1.5)	371	34.2 (1.4)
3 months	338	41.1 (1.4)	355	40.1 (1.2)
12 months	335	46.9 (1.3)	358	45.6 (1.2)
Outcome variables at 24 months				
Temperament				
Surgency/Extraversion	330	4.0 (1.0)	327	3.6 (1.0)
Negative Affect	330	2.2 (0.6)	327	2.3 (0.7)
Effortful control	330	4.9 (0.7)	327	5.0 (0.7)
Neurodevelopment				
Cognitive skills	237	9.9 (2.0)	235	10.0 (2.1)
Fine motor skills	223	11.4 (2.6)	222	11.7 (2.9)
Gross motor skills	223	8.8 (2.1)	222	9.3 (2.6)
M-CHAT	330	0.8 (1.0)	327	0.8 (1.0)

Note. HC = head circumference

Table 3

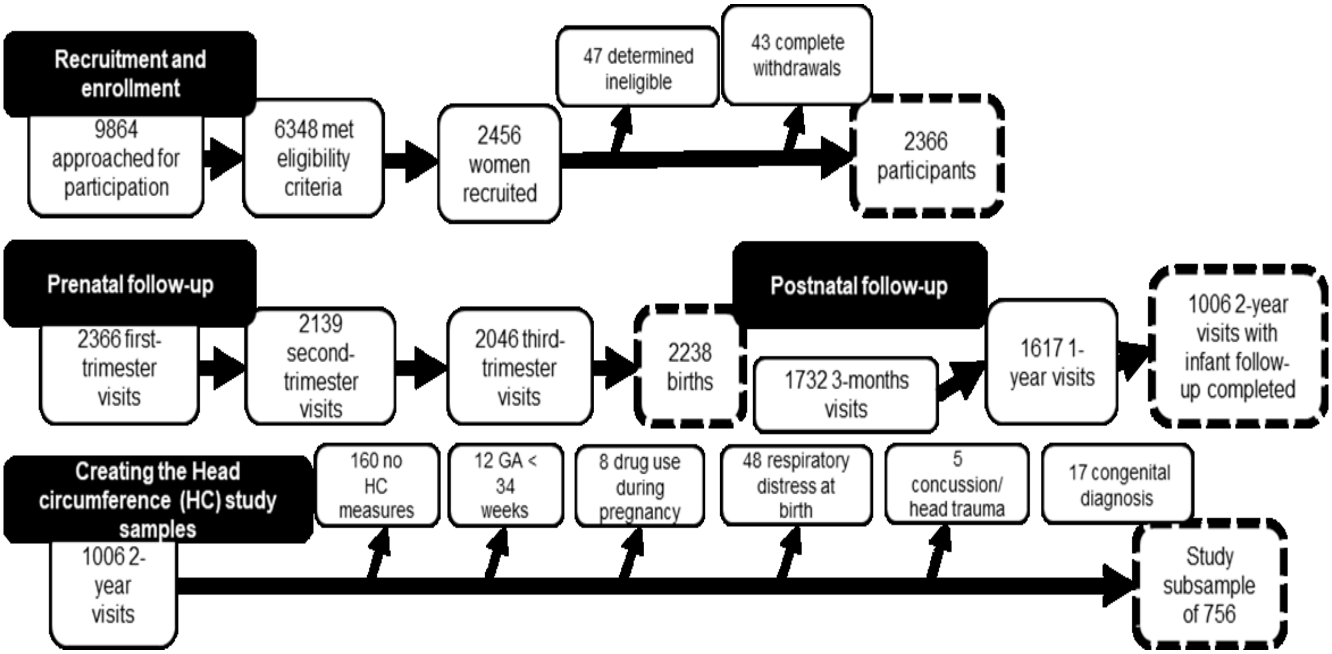
Head circumference predicting child functioning at 24 months

	Temperament						Neurodevelopment							
	Surgency		Effortful Control		Negative Affect		Cognitive skills		Gross motor skills		Fine motor skills		M-CHAT	
	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β	B (SE)	β
Boys														
HC at birth	0,04 (0,10)	0.01	0,13 (0,11)	0.18	-0,01 (0,06)	-0.021	-0,17 (0,22)	-0.09	-0,11 (0,28)	-0.04	-0,23 (0,36)	-0.07	0,04 (0,10)	0.04
HC growth 0-12 months	-0,44 (0,22)	**-0.23***	-0,37 (0,19)	**-0.27***	0,04 (0,11)	0.036	0,43 (0,44)	0.12	1,05 (0,52)	**0.24***	0,84 (0,83)	0.14	-0,05 (0,20)	-0.03
Girls														
HC at birth	-0,03 (0,10)	-0.03	0,13 (0,08)	0.17	-0,04 (0,06)	-0.055	0,14 (0,21)	0.06	-0,38 (0,37)	-0.11	-0,86 (0,47)	-0.20	-0,04 (0,09)	-0.03
HC growth 0-12 months	0,19 (0,26)	0.10	-0,31 (0,24)	-0.19	0,27 (0,21)	0.176	0,14 (0,61)	0.03	1,83 (1,26)	0.26	1,85 (1,51)	0.19	-0,12 (0,23)	-0.05

Note: *p<0.05; HC=Head Circumference; Model fit for a) the model predicting temperament: X2 (13, 756)=21.83 (boys=16.62; girls=5.20); CFI=.99; TLI=.92; RMSEA= .04; SRMR= .06; b) the model predicting Bayley's and M-CHAT scores: X2 (15, 756)=20.54 (boys=15.29; girls=5.26); CFI=.99; TLI=.99; RMSEA= .03; SRMR= .06.

Figure 1

Recruitment and Follow-up in the 3D Study, and Creating the Head Circumference Subsample



General Conclusion

Summary - Objectives and Results of the Scientific Article

The objective of the scientific article included in this Master's thesis was to assess the predictive value of head circumference growth, a surrogate measure for brain growth during infancy, as an early biomarker of socioemotional, cognitive and motor development in early childhood, a crucial period for child development. More precisely, it investigated the relationship between postnatal HC growth from 0 to 12 months, temperament (reflecting socioemotional development) and neurodevelopment (cognitive, fine motor and gross motor skills) at 24 months in a healthy subsample of a large longitudinal study cohort. Based on the literature reviewed, it was expected that there would be an association between atypical HC growth (either more rapid or slower) and child functioning at 24 months. Results provided evidence that postnatal HC growth significantly predicts temperamental and neurodevelopmental outcomes in early childhood in boys. This predictive value exhibits a dual pattern: HC growth from 0 to 12 months directly predicts gross motor skills, while it inversely predicts temperamental effortful control and surgency/extraversion. Further group comparisons indicated that boys with less postnatal HC growth showed significantly higher effortful control and lower gross motor skills compared to those with normal and faster head growth. No significant effect of HC growth was found in girls, and HC at birth did not predict any temperamental and neurodevelopmental outcomes, both in boys and in girls.

Contribution

This Master's thesis is embedded within the framework of neurodevelopment research and general child development research. It contributes to the literature of both domains in several ways.

This Master's thesis investigates two particularly sensitive period for child neural and general development: infancy and early childhood. Infancy has been demonstrated to be a prominent period for brain development. The striking structural development of cortical regions during that period is thought to pave the way for the complex development of basic and higher-order cerebral functions later on (Grayson & Fair, 2017; Knickmeyer et al., 2008; Stiles & Jernigan, 2010). By demonstrating that postnatal HC growth in boys significantly predicts certain aspects of temperament and neurodevelopment, but not others, this Master's thesis contributes to a better understanding of how typical and atypical brain growth during the first year of life might specifically affect the development of certain functions in healthy children. Interestingly, results show that increases in HC growth, which has been reported in ASD populations (Chaste et al., 2013; Courchesne, Carper, & Akshoomoff, 2003b), predicts two temperamental traits typical of ASD, namely reduced surgency/extraversion and effortful control (Clifford et al., 2013; Macari, Koller, Campbell, & Chawarska, 2017). Hence, our findings in the general population are in accordance with expectations based on reports from clinical populations. Moreover, the lack of predictive value of HC growth in girls hints that genes related to HC growth might also be at play in the complex mix of genetic factors thought to be responsible of the "female protective model" for neurodevelopmental disorders, althought more research on the subject is warranted (Jacquemont et al., 2014; Polyak, Rosenfeld, & Girirajan, 2015). Hence, this Master's thesis puts forward the validity of HC growth as a potential simple, yet reliable, biomarker of normal and abnormal early child development. These findings are particularly important, since socioemotional, cognitive and motor impairments in early childhood have been associated with deficits in learning, executive control and functions, and intelligence in later childhood and adolescence (Burman, 2016; Oberer, Gashaj, & Roebers, 2017; Smits-Engelsman & Hill, 2012). Results of the study described in the scientific article thus contribute to the identification of crucial factors influencing early childhood functioning and subsequent adequate psychosocial and cognitive adjustment in later life.

An innovative aspect of this Master's thesis is its methodological strength. The study uses a longitudinal research design, which allows for a stronger confidence in the direction of observed relationships between variables, as opposed to a cross-sectional design, which relies on concomitant measures. Furthermore, measures of neurodevelopmental outcomes at 24 months come from structured observational assessments carried out by research nurses and research assistants trained in developmental psychometrics. Observational measures by a neutral individual confer greater reliability, since they are more objective than self-reported measures (in this case measures reported by the mother). Lastly, this study puts forward a multimodal approach of early child development evaluation, whilst other studies on the subject often measure only one aspect of child functioning. As mentioned before, by assessing three dimensions (temperament, cognitive and motor) of child development, the study made it possible to highlight that certain dimensions, namely temperamental effortful control, temperamental surgency/extraversion and gross motor skills, seem more affected by neonatal brain development than others (temperamental negative affect, cognitive and fine motor skills).

Limitations

This Master's thesis has some limitations. The use of a correlational design does not allow for causal inference between the variables of the study. Hence, results could be due to uncorrelated factors, such as genetic or environmental factors (i.e SES, parental care). Our subsample for the study had a higher SES (i.e. family income and education level) than the general population and mostly came from large urban areas, which limits the generalizability of our findings.

An important strength of the study is the longitudinal assessment of HC growth. Nevertheless, a minor methodological shortcoming of the study is the limited available HC measurements (three time points only), which might not encompass precisely enough the striking HC growth, and brain growth, happening during the first year of life. Another potential shortcoming of the study could come from the fact that we did not include height and weight as covariates in our analyses, even though they are thought to closely correlate with HC. However, the additive value of these variables is still controversial. Several studies suggest they mediate the relationship between HC and developmental outcomes (Chaste et al., 2013; Chawarska et al., 2011), whereas others suggest they vary independently from HC and thus do not need to be taken into account in analyses (Lainhart et al., 2006; Miles, Hadden, Takahashi, & Hillman, 2000). It is also important to note that results are inferential in nature, since HC is closely correlated with overall brain volume, but does not provide a direct measurement of it.

Future Directions

This Master's thesis raises a number of question for future research. Are environmental and genetic factors mediating the relationship between postnatal HC growth and early socioemotional, cognitive and motor abilities? Do certain cortical and subcortical regions more strongly influence HC growth and overall brain volume and if so, are they related to specific aspect of child functioning? Could neonatal cerebral activity and HC growth combined make a stronger biomarker of early socioemotional, cognitive and motor outcomes?

The subsample of this study mostly comprised families with a higher SES (i.e. family income and education level) than the general population and young children with mostly normal temperamental and neurodevelopmental outcomes. Although it is essential to study this population, which represents the majority of families in our society, the results obtained cannot be generalized to higher risk populations. Family income, the psychological functioning of the mother, and the quality of the home environment, which are particularly important in predicting child development and cerebral development, may well vary from one population to another (Carlson & Corcoran, 2001; Dawson, Frey, Panagiotides, Osterling, & HessI, 1997; Lupien, McEwen, Gunnar, & Heim, 2009; Walker et al., 2007). Similarly, studies in at risk populations and healthy population have demonstrated that genetic factors influence both brain development and child development (Adams et al., 2016; Johnson et al., 2016). Therefore, it would be appropriate to replicate this study among higher risk populations and to see if, and how, these genetic and environmental factors mediate to the relationship between postnatal brain development and early child functioning.

Moreover, assessing cortical and subcortical brain volumes variations concurrently with HC growth during the neonatal period might enlighten us on how the development of specific cerebral regions differentially influence early socioemotional, cognitive and motor abilities. A longitudinal research project in Sarah Lippé's lab is underway to characterize typical and atypical brain volume in infants using non invasive three dimensional cranial ultrasound technology. In the same study, neonatal cerebral activity and child functioning will be assessed. Evaluating cerebral activity in infancy provides a novel approach for a better understanding of the neural mechanisms at play during the striking postnatal brain growth. Specifically, Lippé's lab is interested in investigating predictive coding, a core brain function essential for normal cognitive development that underlies perceptive, attentional and learning processes (Hsu, Hamalainen, & Waszak, 2014; Saffran, Aslin, & Newport, 1996). Predictive coding involves both local circuits and large-scale brain networks, including fronto-striatal-sensory cortex loops(Lafontaine, Théoret, Gosselin, & Lippé, 2013; Schwartze, Tavano, Schroger, & Kotz, 2012). It can be assessed in very young infants using well-established neuroimaging paradigms, such as repetition suppression (RS) and oddball, with electroencephalography(Basirat, Dehaene, & Dehaene-Lambertz, 2014). The EEG signatures (RS and oddball) of predictive coding have been found to be abnormal in neurodevelopmental disorders (Bomba & Pang, 2004; Jeste et al., 2015). Although predictive coding exists in early phases of development, it has never been used as a marker of neurocognitive development trajectories. Hence, the combination of cerebral activity underlying cognitive processes with HC growth and brain volumes could provide a more powerful biomarker of early child functioning than each independent variable on its own.

Implications for Clinical Practice

Results of the study demonstrate the importance of HC measurement in infancy, not only to identify potentially abnormal brain development patterns, but also to relate them with potential later problems in child functioning. This has important implications for pediatric health care. Since HC measuring is easy, quick and non invasive, it is a useful tool for clinical settings. It only requires a measuring tape and some basic anatomic knowledge to be able to measure it accurately. Hence, anyone from research assistant to nurses to family physician and even parents can closely monitor HC growth (although not as precisely as with sophisticated statistical analyses) making it a biomarker of choice for clinical practice. Results of the study suggest HC might inform clinicians on infants at risk for behavioral and neurodevelopmental problems and lead to more appropriate and timely interventions during infancy and early childhood.

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