THE DEVELOPMENT OF HIGH IQ: AN INTEGRATION OF BEHAVIOR GENETICAL AND COGNITIVE NEUROSCIENCE APPROACHES.

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The development of high IQ: An integration of behavior genetical
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The promotion of high intellectual ability is of huge and increasing societal interest with accelerating technological advances. Distinct trajectories of structural brain development according to IQ score are hypothesized to reflect an extended sensitive period during childhood and early adolescence in individuals of higher IQ. A thorough explanation of this question requires a synthesis of individual differences research from behavior genetics and the knowledge of species-general hallmarks of normal development from developmental cognitive neuroscience; two fields that, for the most part, have proceeded independently. This dissertation investigates this question from several angles. First, developmental structural equation modeling is applied to longitudinal twin data to examine the typical patterns of continuity and change in genetic and environmental influences on intelligence between age 1 and 16, demonstrating a pattern of increasing heritability and decreasing shared environmental influence that is not qualitatively different in individuals of higher IQ. Study 2 uses a DeFries-Fulker regression framework in a large cross-sectional study of twins and a smaller longitudinal replication sample of twins, biological siblings and adoptive siblings to examine whether the change in the magnitude of genetic and environmental influences on IQ throughout development is consistent with a sensitive period in IQ development that is extended in individuals of higher IQ, treating score as a continuous predictor of environmental sensitivity. Study 3 seeks to demonstrate this pattern for a measurable environmental variable in a longitudinal sample of Phenylketonuria

patients, and to test causal models for individual differences in sensitive period length. Finally, Study 4 outlines motivation for and considerations in designing a computational model to examine the mechanistic role of neurobiological events underlying sensitive periods in determining outcome and why an extended sensitivity to the environment may be beneficial in the development of high intelligence. Results are supportive of an extended sensitive period for cognitive development in individuals of higher IQ that is driven by actualized intellectual capacity in late childhood. These findings may have implications for the search for genetic variants underlying individual differences in intelligence and successful interventions for promoting high cognitive ability.

For Mum and Dad

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CHAPTER 1: INTRODUCTION

1.1 Overview

Higher-level reasoning skill is becoming ever more important in society. As noted by Hernstein & Murray (1994) in The Bell Curve, and by others (e.g. Gottfredson, 1997; Reich, 1991) changes in our society are increasing the value of intellectually demanding occupations. The ascendance of the "systems analyst" (Reich, 1991) is projected to progressively increase with technological advance (Hunt, 1995a; cf. Hunt, 1995b). Promoting intellectual ability is therefore an important goal for society both now and in the future. From Baby Einstein to Brain Training video games, to the many column inches in the popular press and online dedicated to "how-to" instruction and prominent lay reporting of the science of IQ, increasing intelligence is of huge and broad interest in modern America. The overarching goal of this thesis is to examine causal factors underlying high intelligence, with a particular focus on how differences in general intelligence unfold developmentally. Understanding how the balance between genetic and environmental influences affect outcome generally and what factors specifically vary between individuals of differing ability is a crucial step in the goal of nurturing intellectual excellence and in designing better curricula for remedial and gifted programs.

This Chapter will bring together previous literature from differential psychology, behavioral genetics and developmental cognitive science to argue that a synthesis of these

approaches can provide the most comprehensive understanding of the roots of inter-individual differences in intelligence and the factors that promote high intellectual ability. Previous conceptions of extremes of ability posit causal influences (both genetic and environmental) that are distinct from those evident within the normal range of ability and ignore the important role that co-activation between factors internal and external to the developing organism play. Conceptualizing development as a path to an eventual goal, as behavior genetics typically has, rather than as a dynamic process of incremental change according to immediate and shifting constraints both internal and external to the organism obscures the potential role of developmental trajectories in cognitive outcome.

To build this argument I will first describe the phenotype of intelligence and what is known about causal influences throughout development for both the full range of ability and for high IQ in particular. I will then move to describing evidence from comparative studies and human cognitive neuroscience that demonstrates clear associations between prolonged trajectories of brain development and cognitive ability. This research points to the potential of a prolonged environmental sensitive period as a contributing factor to high IQ. After describing current theorizing on the concept of the sensitive period, I will examine how the predictions of changing genetic and environmental influences throughout development resulting from this theoretical framework compare to existing knowledge and explanatory frameworks in behavior genetics, identifying apparent inconsistencies between the two fields. I will end by outlining the methods by which the current thesis attempts to integrate these disparate approaches to examine 1. whether the developmental trajectory of change in the genetic and environmental influences is consistent with the hypothesis of an extended sensitive period in the most intelligent and 2. To

start to address unanswered questions regarding the causal basis of such a pattern.

1.2 Intelligence: The heritable phenotype

General Intelligence (or *g*; Spearman, 1904) is typically measured by IQ (intelligence quotient) tests, the most popular of which are the Stanford-Binet (Terman & Merrill, 1973) and the Wechsler tests (e.g. Wechsler, 1991; 1997;1981), include many verbal and nonverbal subtests that are amalgamated into a single full-scale score. Ravens Progressive Matrices (Raven & Court, 2003) are also popular as a single, nonverbal and culture fair measure. It has been shown that the first unrotated principal component derived from scores of the subtests of these and any batteries of varied cognitive tasks typically explains around 50% of the variance and g scores are have been shown to be almost completely correlated between various different batteries (Johnson, Bouchard, Krueger, McGue & Gottesmen, 2003). g has been described as "a very general mental capacity that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly, and learn from experience." (Gottfredson, 1997 p. 13), although there isn't an exact universally accepted definition (Sternberg & Detterman, 1986). It has been shown to be predictive of social and occupational status, educational and job performance, adult health and longevity throughout the range of ability in the general population (Gottfredson, 1997; Gottfredson & Deary, 2004; Neisser *et al*, 1996; Whalley & Deary, 2001). Although of notable predictive value from early childhood, IQ scores become increasingly stable across development (Deary, Whalley, Lemmon, Crawfod & Starr, 2000), during which time the structure of causal influence is changeable.

Inter-individual differences in g are the subject of a large and increasing body of etiological, especially behavioral genetic research. It is one of the most heritable traits known. Simultaneous consideration of family, adoption and twin data puts the estimate of variance explained by additive genetic differences (heritability) at around 50 percent (Chipuer, Rovine & Plomin, 1990; Loehlin, 1989). This figure has been replicated in countries as varied as America, United Kingdom, the Netherlands, Russia, Germany, Japan and India (Plomin, DeFries, McClearn and McGuffin, 2001). However these estimates include data from both childhood and adulthood. Estimates from adult samples only are higher, perhaps up to 80 percent (Plomin and Spinath, 2004), although the figure appears to decrease in later life (Finkel, Pederson, McGue & McClearn, 1995). A recent study by Haworth and colleagues (Haworth *et al*, 2010) found a heritability of 66% for IQ in young adulthood in a sample of 3075 twin pairs from 6 separate samples collected in 4 countries. As will be discussed further below, the influence of genetics in childhood is smaller and increasing throughout development. This changing etiological pattern over the course of the lifespan is widely and consistently found - Jenson (1998) describes it as '…among the most striking and strongly substantiated findings of behavioral genetics in recent years' (p. 179).

Although the quest to find individual genetic variants that contribute to intelligence has not been fruitful (and it is likely that almost all identified variants are in fact false positives; Chabris *et al*, in press), aggregate measures using many thousands of common genome-wide variants validate heritability estimates from family studies. A 2011 study by Deary, Visscher and

colleagues (Davies *et al*, 2011) found that 40-50% of the covariation in g scores between unrelated individuals could be predicted from pairwise genetic relationship, estimated from almost 550,000 single nucleotide polymorphisms (SNPs). The additive effect of many individual variants of small effect was demonstrated by the linear relationship between chromosome size and proportion of g variance explained. A partially overlapping sample used a bivariate extension of same method to estimate the genetic correlation between g in childhood (age 11) and old age at .62 (Deary *et al*, 2012).

1.3 Developmental changes in IQ etiology

That the magnitude of genetic and environmental influence on intelligence is changeable during development has been known since the 1940s (Skodak & Skeels,1949). Heritability increases and the influence of the environment shared by family members (the shared environment) decreases between infancy and adulthood, and this pattern has been replicated in many samples (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Boomsma & Molenaar, 1987; Bouchard & McGue, 1981; Cardon, Fulker, DeFries & Plomin, 1992; Cherny & Cardon, 1994; Eaves, Long, & Heath, 1986; Fulker, Cherny, & Cardon, 1993; Humphreys & Davey, 1988; McGue, Bouchard, Iacono & Lykken, 1993). Haworth *et al* (2010) recently replicated this finding using a cross-sectional sample of almost 11,000 twin pairs of varying ages from 4-34. It was found that heritability increased linearly from 41% in childhood to 66% in adulthood, and the influence of the shared environment decreased accordingly. Non-shared environmental influences remained largely steady in magnitude at 23%.

Several studies have gone further, analyzing not only the differing magnitudes of genetic and environmental influences throughout development, but also the patterns of continuity and change in the underlying genetic and environmental constructs. Petrill *et al* (2004) examined scores from biological and adoptive siblings in the Colorado Adoption Project (CAP) at ages one through sixteen and found that the best-fitting structural equation model included an additive genetic factor influencing scores at all ages, no shared environment and only age-specific non-shared (individual-specific) environmental factors. Similar results were obtained from looking at combined data from the CAP and the Longitudinal Twin Study (LTS) by Bishop, Cherny, Corley, Plomin, DeFries and Hewitt (2003) from ages one to ten. Individual –specific (non-shared) environment contributed to phenotypic continuity from age seven through age-to-age transmission and to change (innovation) throughout development. Shared family environment contributed exclusively to continuity through an age-wide common factor and additive genetic influences were accounted for by age-to-age transmission (continuity) and, less prominently, by innovations (change) up to age nine. The conflicting results with regard to the shared environment in these studies may be accounted for by the use of only siblings in the CAP sample and the addition of twins in the Bishop *et al* sample, since twins share environments to a greater extent by virtue of being the same age.

Similar results have also been reported from the Twins Early Development Sample (TEDS) a large community sample collected in the UK. Spinath, Ronald, Harlaar, Price and Plomin (2003) found evidence for only modest genetic effects and large shared environmental effects at ages two, three and four, Davis, Arden and Plomin (2008) analyzed scores from ages seven, nine and ten, demonstrating that continuity was due to genetic and shared environmental

factors. Both genetic and shared environmental influences also contributed to differences between ages, however. Non-shared environment contributed almost entirely to differences. There was a high genetic correlation across age, test composition, and method of administration. Additionally, genetic influences were stronger and shared environmental factors more modest than in the earlier childhood study. Davis, Haworth & Plomin (2009) found that a cross-age genetic correlation of .57 and a shared environmental correlation of .65 between early and middle childhood.

It is clear from the above discussion that, for individual differences in intelligence, genetic and shared environmental influences contribute mostly to stability, whereas non-shared environment contributes mostly to change over development. Additionally, genetic contributions to IQ increase across development, due at least in part to new genetic variants becoming important, while shared environmental influences decrease.

1.4 High intelligence.

Although a causal relationship can never be demonstrated in observational studies, the gold standard for the demonstration of a predictive relationship comes from prospective longitudinal study. Such studies demonstrate a strong relationship between early high IQ and later educational and occupational achievement. The most famous and earliest demonstration of this pattern comes from Terman's Stanford study (Shurkin, 1992) but more recent data also comes from the Study of Mathematically Precocious Youth (SMPY), a 50-year longitudinal

study of more than 500 ‘gifted’ youths (Lubinski, 2009; Lubinski & Persson Benbow, 2006). Identified at age 12 by SAT results (high score on either Math or Verbal test), a SAT-M – SAT-V composite for each participant was calculated for each participant. This composite has been demonstrated to be a good approximation of general intelligence (Frey & Detterman, 2004). A statistically significant relationship was found between score quartile and measures including percentage earning a doctorate, STEM publications, literary publications, patents and income in the 95% percentile for the general population. Achievements in all measures of extraordinary educational and occupational success were substantially higher than those found in the general population.

IQ is therefore related to performance even within the higher echelons of scores (all participants had a score greater than 1 in 200 of the population, up to greater than 1 in 10,000), suggesting that extraordinary achievement is at least aided by extraordinary scores. It also suggests that it is not simply the covariation of IQ with measures of access to resources (e.g. SES) that underlie its relationship to outcome, since such measures would not be expected to distinguish individuals of extraordinarily high intellectual ability.

1.5 Causal Influences on High IQ

Compared to the attention IQ in the normal range and indeed mental retardation has received in the behavior genetics literature, the etiological basis of high intelligence is somewhat understudied. What research there is has tended to focus on whether different causal variables influence high ability. There are some reasons to expect this to be the case, both anecdotally and from psychometric study. “Einstein Syndrome” is a term used by Thomas Sowell in his 2001

book of the same name to describe exceptionally bright people who experience a developmental delay in acquiring speech. It is named after Albert Einstein but there are other famous examples (e.g. physicists Richard Feynman and Edward Teller). Children displaying Einstein syndrome also show a number of other characteristics including a precocious ability to read, highly selective interests and unusual concentration or absorption. Sowell also presents evidence that bright late talkers have a high likelihood of having close relatives in "analytical occupations". This abnormal ordering of cognitive development and potentially specific environment suggests particular causal factors for at least some high IQ individuals, although whether this is typical of high IQ children is doubtful.

Another suggestive piece of evidence comes from studies of Spearman's "law of diminishing returns" (SLODR; Spearman, 1927). As described by Spearman himself, this is a phenomena in which "The correlations [between different tests] always become smaller—showing the influence of g on any ability to grow less—in just those classes of person which, on the whole, possess this g more abundantly. The rule is, then, that the more 'energy' [i.e., g] a person has available already, the less advantage accrues to his ability from further increments of it" (p. 219). There is mixed evidence of this phenomenon in psychometric studies (e.g. Deary, Egan, Gibson, Brand & Kellaghan, 1996; Hartman & Teasdale, 2004; Jensen, 2003). If SLODR is a true phenomonon one would expect additional causal influences to be operating at the top of the score distribution to explain the variance unaccounted for by *g*.

Additionally, intelligence test scores from children with high IQs show patterns that are not typical of the general population (Sweetland, Reina and Tatti, 2006; Wilkinson, 1993). Large verbal-performance discrepancies are seen in IQ scores, as well as more idiosyncratic subtest

score scatter. The majority of children tested in these studies were third graders, which suggests an early difference in the characteristics of high IQ.

1.6 Behavior Genetic Studies of high IQ

Twin studies examining differing magnitudes of genetic and environmental influence according to IQ score have shown confusing results. Detterman, Thompson and Plomin (1990) found higher heritability and less influence of common environment at lower ability levels in a small sample of twins, as did Bailey and Revelle (1991). However, Jensen (1987) found higher heritability at higher ability levels in a much larger sample. Thompson, Detterman & Plomin (1993), in an extension to their previous investigations, found no differences in heritability across ability level in another small sample, although they note a trend towards higher heritability in the upper ranges. The majority of studies examining whether differences between causal influences on high IQ and IQ in the normal range have not found any difference in children (Cherny, Cardon, Fulker & DeFries, 1992; Horn, Loehlin & Willerman, 1982; Ronald, Spinath & Plomin, 2002; Vogler & DeFries, 1983) or adults (Sundet, Eilertsen, Tambs & Magnus, 1994).

A larger and more recent study by Haworth and colleagues (Haworth *et al*, 2009) examined the magnitude of genetic and environmental influences on IQ (defined as above the 85% percentile of ability) in a community sample of over 11,000 twin pairs of age 6-71. It was found that genetic influences explained 50% of the variance in IQ scores, while shared environmental influences explained 28%. These figures are not significantly different from those

seen for the full range of ability in the same sample, although they show a trend for lower genetic and higher shared environmental influence.

One study thus far has looked at trends in genetic and environmental influence in the development of high IQ. Petrill *et al* (1998) used data from the Longitudinal Twin Study sample at four ages during infancy. Using a cut-off of the ninetieth percentile to define high IQ, it was found that the heritability at each age was not different from that of the unselected sample. However, the proportion of shared genetic influence between ages was not compared to the rest of the sample. Additionally, the reliability of the measurement of infant IQ is relatively low meaning that a systematic effect is less likely to be found in infancy than in later childhood/adolescence.

1.7 The importance of environmental experience

As shown above, there is no consistent pattern of differing genetic and environmental influence in higher scoring individuals. Research thus far has, however, focused predominantly on whether different genetic and environmental influences operate at different levels of the spectrum of intellectual ability. The idea that trajectories of development may differ in their timing has been less examined. It is clear that developmental factors are crucial for cognitive ability. Nobody is "born" intelligent. Although genetic influences play a prominent role in the emergence of intellectual ability, it is self-evident that they can only be realized by incorporation of experience through interaction of the individual with their environment.

Acknowledgement of this process was evident in the literature as early as 1909 by Woltereck in his discussion of the "norm of reaction" (Woltereck (1909; 1928). The concept was clarified by Dobhansky in1955 to refer to the range of phenotypes produced by carriers of certain genotypes in all possible environments. Dobhansky (1955) was careful to specify that "Any height or weight or intelligence a person may have is [only] 'intrinsic' in the sense that the phenotype observed is the necessary outcome of the development brought about by a certain genotype in a certain succession of environments" (p.77). Gottesman (1963) articulated a more deterministic variation of this in his concept of the "reaction range", which has been defined as "genes set the limits, but the environment determines where within those limits the phenotype will fall." (see Platt & Sanislow, 1988). The wealth of studies of gene-environment interactions in recent years is testament to the acceptance in behavior genetics that the effect of genetic variation is realized only by environmental exposure (e.g. Turkheimer, Haley, Waldron, D'Onofrio & Gottesmen, 2003; Caspi *et al*, 2002; Moffitt, 2005).

1.8 The association between prolonged brain development and cognitive ability

Any effect of the environment on cognitive ability will happen via brain plasticity and plasticity is highest when the brain is still developing. It is known that the human brain continues to develop postnatally well into early adulthood. For example, Petanjek *et al* (2011) demonstrated, using a sample of postmortem human prefrontal cortices aged from infancy to 91, that overproduction and remodeling of synaptic spines continues into the third decade of life. The largest changes happen earlier however - dendritic spine density increases during childhood

to a peak of is 2 to 3-fold adulthood levels before decreasing during puberty. This protracted period of brain maturation allows integration of environmental information into neural networks for longer, potentially promoting our uniquely human cognitive capacities.

Evidence for the importance of prolonged development on cognitive ability can be seen from examination of differences between the brains of humans and our closest ancestors. A recent comparative gene expression study (Liu *et al*, 2012) demonstrated that the most prominent human-specific expression change compared to chimpanzees and macaques was in genes associated with synaptic functions. This was evident in the prefrontal cortex but not the cerebellum. Peak expression was shifted from <1 year in the chimps and macaques to 5 years in humans. It is additionally known that areas of the brain putatively related to IQ in humans (areas of frontal and parietal cortex; e.g. Woolgar *et al*, 2010) expand the most, mature more slowly and display the most cellular complexity when fully developed (Hill, Inder, Neil, Dierker, Harwell & Essen, 2010). This pattern is also seen in postmortem studies of synaptic density in the human brain (Huttenlocher, 1997).

Patterns of synaptogenesis and synaptic pruning can be inferred from changes in cortical thickness in the brains of developing children. Cortical thickness is a measure derived using structural magnetic resonance imaging (MRI) referring to the combined thickness of the layers of the cerebral cortex. It is usually calculated as the local or average distance between the white matter surface and the pial surface, encompassing the grey matter. Although the relative change is small, cortical thickness shows a developmental pattern that maps onto those seen by direct measures of synaptic density. That is, cortical thickness increases throughout childhood and then

decreases in adolescence. Thickness stabilizes during early adulthood. (Sowell *et al*, 2004; Gogtay *et al*, 2004; Shaw *et al*, 2008).

Cortical surface area follows a similar developmental pattern, although it has been less studied. The two determinants of cortical volume have independently genetic influences underlying inter-individual variability (Panizzon *et al*, 2009), although their similar developmental change (both in typical development and in developmental disorders; Shaw *et al*, 2011; Shaw, Malek, Watson, Sharp, Evans & Greenstein, 2012) suggests that similar factors influence postnatal change.

1.9 The relationship between cortical thickness and IQ: The importance of developmental timing

In adults, cortical thickness is positively correlated with IQ in frontal and temporal areas of the brain. Nar *et al* (2007) found significant associations with bilaterally in prefrontal (Brodmann's areas [BAs] 10/11, 47) and posterior temporal cortices (BA 36/37) and proximal regions in a same of 65 adults. (Narr *et al*, 2007). These same regions have been functionally associated with IQ. Gläscher *et al* (2010) performed a comprehensive lesion mapping study of in which they compared intelligence of patients with lesion in a particular voxel with those that don't have a lesion there. This method identifies cortical areas that have a causal relationship with intellectual ability.

This evidence suggests that synaptic density in areas of the brain that support intelligence is an important factor in determining individual differences and this finding has been subsequently replicated in several studies (Karama *et al*, 2009; Karama *et al,* 2011). Karama *et al* (2011) additionally demonstrated that adjusting for g score eliminated all associations between cortical thickness and scores on both the seven individual cognitive tests and three first-order factors representing cognitive domains.

Comparing the relative timing of development between different cortical areas demonstrates that areas of cortex associated with intelligence tend to mature the latest. Shaw *et al* (2008), using a sample that ranged in age from 3 to 33 years, found that primary sensory areas attain peak cortical thickness first, followed by secondary and association areas. Higher order cognitive areas (associated with IQ) achieve peak thickness last. Given this pattern of development and the above-mentioned prolonged brain development in humans compared to other primates, one might expect there to be a relationship between prolonged developmental trajectories and later intelligence.

This pattern was indeed found by Shaw and colleagues (2006). Using data from 307 children and adolescents, 58% of which had at least two scans, rate of change of cortical thickness in 40,962 vertices were measured and tested for an association with full-scale IQ. Developmental trajectory in large areas of the PFC was associated with IQ. To explore the interaction further, the same was split into 3 groups: Average (mean IQ 100), high (mean IQ 114) and Superior (mean IQ 120) IQ. Large areas of PFC including bilateral superior frontal gyri (expending into medial PFC), OFC and middle frontal gyrus showed IQ-related differential

developmental trajectories. In other areas the relationship was left-latererized. These included middle frontal gyrus, inferior temporal gyrus and angular gyrus. Many of these areas overlap with those in which cortical thickness was previously seen to be associated with IQ, including the relatively circumscribed temporal area. Individuals of superior IQ showed a pattern of prolonged thickening in these areas, followed by a later-starting and more rapid period of thinning. In addition, there was a age-dependent relationship between cortical thickness and IQ in these areas, with early negative correlations becoming positive in late childhood before diminishing and disappearing in adolescence/early adulthood.

1.10 Why is prolonged development beneficial?: The extended sensitive period hypothesis

This converging evidence of an association between prolonged cortical development and high intelligence raises questions of utility and causality. Why is an extended period of cortical thickening beneficial and what are the factors underlying the timing of development? Specifically, with respect to the latter, does a propensity towards higher IQ promote prolonged synaptogenesis or does prolonged synaptogenesis (perhaps via experientially-mediated processes) promote increased cognitive ability? Shaw *et al* (2006) suggest that "…the prolonged phase of prefrontal cortical gain in the most intelligent might afford an even more extended 'critical' period for the development of high-level cognitive cortical circuits." This hypothesis makes a number of assumptions. First it posits a defined critical period or (less deterministically) a sensitive period early in development within which neural networks underlying intelligence are particularly sensitive to environment input. Secondly, it posits that individuals' that develop

higher IQ are more sensitive to the environment for longer into development. Finally, it makes a tacit causality assumption: Higher IQ is presumed to be a result of prolonged environmental sensitivity, rather than early tendency towards high intelligence promoting environmental engagement and reactivity. The following discussion will outline the characteristics of critical and sensitive periods, and current thinking on factors influencing their duration.

Knudsen (2004) describes a sensitive period as a broad term for when an organism is unusually sensitive to the effects of experience on the brain. They are expressed in behavior but are in fact a property of neural circuits. Knudsen proposes a distinction between the concept of a critical period (as posited by Shaw and colleagues) and sensitive periods, with a critical period referring to a special case that results in irreversible changes in brain function e.g. imprinting or ocular dominance. However, Thomas and Johnson (2008) present evidence that critical periods are not as sharply timed and reversible as first thought, giving imprinting in chicks as an example where plasticity is extendable in the absence of appropriate sensory stimulation and reversible under certain circumstances (cf. Bolhuis, 1991). This has also been observed for ocular dominance plasticity, in which dark rearing can prolong critical period sensitivity (e.g. Cynader, 1983) and enriched environments can reopen critical periods (Baroncelli *et al*, 2010). It has been additionally shown that enriched environments can counteract the effects of dark rearing on visual acuity and critical period closure (Bartoletti, Medini, Berardi & Maffei, 2004). Enriched environments have been shown to affect other brain areas, apparently in the order of normal development (Cancedda, Putignano, Sale, Viegi, Berardi & Maffei, 2004) and different types of enriched environments have been shown to have different effects (Lambert, Fernandez & Frick, 2005).

This evidence is consistent with the idea that, instead of being clock-like, built-in or predetermined stages, sensitive periods may instead be a natural consequence of fundamental brain development (Michel & Tyler 2005). Thus, we should expect the variability in onset/ offset (timing) evident in their study and would not expect to observe (or need to posit) specific mechanisms underlying their progression. Such variations would be expected to be observed not just in timing of sensitive periods for different cognitive processes within an individual, but in timing of developmental processes between developing brains with differing genetic make-up and environmental experience. The environment in brain development includes not only experience with the external world but also how the environment is perceived and processed. It is therefore likely that later developing cognitive functions can be influenced by earlier developing systems in terms of both developmental timing and outcome. Indeed, plasticity tends to reduce in low-level sensory systems before it reduces in high-level cognitive systems, suggesting that sensitive periods for higher functions result from integration from other lower-level systems (Huttenlocher, 2002). For example, there is evidence that components of language show differential sensitive periods (Neville, 2006; Wartenburger, Heekeren, Abutalebi, Cappa, Villringer & Perani, 2003; Werker & Tees, 2005). Plasticity may show earlier reductions for phonology and syntax than it does for lexical-semantics, in which there may in fact be no age-related change.

Such considerations are important in understanding sensitive periods for intelligence as intelligence is a cognitive process of integrating experience to form flexible and abstract representations, which can be applied to unique problems. This process of abstraction may appear inconsistent with the process of progressive specialization seen in brain development for

lower-level functions (Mareschal, Sirois, Westermann & Johnson, 2007) but, as noted by Johnson and Munakata (2005), it is likely that once complementary computational routes have been achieved in the specialization of networks underlying lower-level processes, mechanisms for overall integration are required to map knowledge across, for example, modes of sensory input.

1.11 Factors affecting sensitive period length

Although it is intuitively clear that extended incorporation of experience into neural networks is beneficial for the kind of generalizable representations that contribute to high intelligence, understanding how this may arise requires consideration of the factors that underlie the marked reduction in plasticity that characterizes the end of a sensitive period.

Thomas & Johnson (2008) identified three general classes of explanation that have been proposed for the termination of sensitive periods: 1. termination of plasticity, 2. self-termination of learning and 3. stabilization of constraints on plasticity. The first option posits "fossilization" of existing connectivity patterns via endogenous factors with a fixed time course. This process would be consistent with the idea that delayed expression of these endogenous factors underlies the extended sensitive period in individuals of higher IQ in an experience-independent fashion. The second refers to how processes of learning may themselves lead to neurobiological changes that restrict further plasticity. There are several processes that could contribute to this including: Competition for computational resources from previous learning; entrenchment, which puts the system in a non-optimal state for acquiring radically new representations; and assimilation, in

which the representational context of existing knowledge reduces the ability to recognize and respond to environmental change. This explanation is consistent with an effect of the environment and the neural response to it in guiding the progression of sensitive periods.

The final class of explanation refers to the stabilization of the constraints on plasticity, without a reduction in the underlying neurobiological sensitivity to environmental change. This explanation again gives a prominent role to environmental quality in reducing plasticity but also allows for an active role of the individual in the process. Children may interact with their environments differentially depending on either genetic propensity or representations build from existing experience. For example, individuals who develop increased intellectual ability show faster habituation in infancy (e.g. Kavsek, 2004). There is some evidence from both humans and mouse models that this relationship is intimately associated with propensity for exploration (Bornstein & Sigman, 1986; Matzel *et al*, 2003). It is possible, therefore, that high IQ individuals may prolong their own environmental sensitivity by responding differentially to their environments or indeed seeking out novel experiences. These ideas correspond closely to the constructivist approach of Piaget (1955) and others who have argued for a proactive role of the child in the acquisition of knowledge, and particularly the neuroconconstructivist framework (Mareschal *et al*, 2007; Westermann, Mareschal, Johnson, Sirois, Spratling & Johnson, 2007) which stresses the importance of mutually induced changes at the neural and cognitive levels of description and interactions between constraints both intrinsic and extrinsic to the organism. Knudsen (2004) has also noted that heightened levels of attention may prolong sensitive periods.

The above discussion points to an integral role for experience in not only guiding changes

throughout a sensitive period but in affecting their timing. However, as we have seen above, genetic variation has a large and increasing role in individual differences in intelligence throughout development. The difficulty of explaining the role of genetics in a fundamentally experience-driven account of development has not been ignored (see e.g. Mareschal *et al*, 2007). In line with the interactive nature of the environmental, neural and cognitive constraints already mentioned, several theorists have conceptualized genetic influences themselves as fundamentally interactive and dynamic throughout development. Oyama (2002) rejects the notion of preformative effects of genetics and stresses the inherently reactive nature of genetic influence. She describes evidence that the cell's genetic program contains not information for its own regulation but "…an indeterminate process in time, whose regulation depends on conditions". This conception of genetic variation as another element of the linkage between biological processes and extraorganistic factors fits very well with Gottfried's (2002) notion of probabilistic epigenesis. Under this bidirectional view of structure-function relationships, development is fundamentally a result of coaction of influences at the environmental, behavioral, neural and genetic level. Gottfried stresses that genes produce proteins, not fully developed features, which necessitates incorporation of other developmental influences. Protein synthesis is known to be regulated by neural activity (e.g. Wolf & Linden, 2012). This line of thinking is consistent with the idea that gene expression, like environmental exposure, can contribute not just to the maintenance of developmental change, but importantly to its facilitation and induction.

1.12 Behavior genetics and the extended sensitive period hypothesis

Behavior genetics is a perfect way to test whether predictions resulting from developmental models of cognitive function described above are evident in developmental changes in the continuity and change in genetic and environmental influences, but such analysis has been lacking thus far. In fact, ideas about the emergence of cognitive function from developmental science (which tends to focus on species typical progressions) and those of developmental change in behavioral genetics (a field that focuses on explaining individual differences in outcome within organisms of the same species) have progressed somewhat independently.

Developmental increases in heritability and decreases in the influence of the environment have been attributed to continuous sources of influence throughout development, most prominently gene-environment correlation and genetic amplification. Genetic amplification refers to the increasing, "snowball" effect of a constant set of genetic variants throughout development due to cumulative information processing demands (Plomin, 1987). Gene-environment correlation (rGE), on the other hand, refers to the relationship between genetic propensity and the environment that the individual experiences. (Plomin, DeFries & Loehlin, 1977). Two subtypes of rGE could contribute to increases in heritability during development: Evocative rGE, in which children provoke differential reactions from others according to their genetic propensity; and active rGE, in which the individual gains increasing scope to shape their own environment throughout development, again guided by genetic propensity.

Both accounts concentrate on continuity in genetic influence, which proceeds in a unidirectional fashion, and neither explanation clearly posits a change in environmental

sensitivity, instead conceptualizing development as a progressive realization of genetic potential. One paper (Eaves *et al*, 1986) has discussed increases in ostensibly unitary constructs and the potential influence on outcome. They reference the possible influence of "individual differences in the speed and pattern of development" (p. 144) and how they might contribute to misspecifications in models of family resemblance. These issues are discussed with reference to height and blood pressure and cognitive ability, but are arguably compounded in the latter case. Although flagged as a potential important source of variation by Eaves *et al* (1986), individual differences in the developmental trajectories of genetic and environmental influence have not been examined thus far.

1.13 Outstanding questions and dissertation outline

Since the overarching goal is to understand factors contributing to high IQ, the following studies are particularly focused on whether there is an extended period of sensitivity to the environment in individuals of high IQ and what factors contribute to this. This thesis aims to integrate methodology from developmental behavior genetics, clinical genetics and biologically motivated neural network modeling to address 3 major questions.

1. Is there evidence for a prolonged influence of the environment in individuals of higher IQ in a manner consistent with an extended sensitive period for intellectual development?
2. Are any observed individual differences in sensitive period length related to genetic predisposition or does high intelligence itself prolong environmental sensitivity?
3. How do typical neurobiological changes during development support the cognitive changes that underlie the emergence of adult intelligence and the characteristics of

sensitive periods? How does this inform the question of why an extended sensitive period is beneficial to cognitive development?

These questions are addressed via four experimental studies as follows:

Chapter two presents data from a longitudinal twin sample to examine the pattern of continuity and change in genetic and environmental influence throughout development on high IQ and on IQ in the full range. Structural equation models are fit to scores in the sample as a whole and the best-fitting model was compared that for high IQ treated as a discrete phenotype. It is found that the model for the whole population provides a satisfactory fit for high IQ defined as the 85% percentile of population scores, indicating that there are not distinct genetic or environmental influences on high IQ and that the developmental pattern as a whole does not widely differ. This is evidence that high IQ is part of a normal distribution of causal influences rather than a distinct phenotype.

Chapter three extends this work, explicitly testing whether, as hypothesized by Shaw *et al* (2006) and described above, intellectual ability may be associated with a prolonged pattern of childhood causal influence in higher scoring individuals. Extensions of DeFries-Fulker regression analysis (a special case of linear regression using pairs of related individuals) are employed to analyze IQ scores in a cross-sectional sample of around 11,000 twin pairs and a smaller longitudinal sample of twins, biological siblings and adoptive siblings. Results are consistent with the existence of a sensitive period in IQ development that is extended in

individuals of higher IQ. This finding does not appear to be an artifact of confounding effects and is not easily accommodated by existing theories of the increase in heritability over childhood and adolescence.

Chapter 4 uses a longitudinal sample of individuals with the single-gene recessive disorder PKU to examine whether this extended environmental sensitivity can be observed, not only in aggregate, but also in a single measurable environmental variable. Sufferers cannot metabolize dietary phenylalanine (Phe), which builds up in the brain affecting development. If untreated (by a Phe-restricted diet) it causes severe mental retardation. However, even in treated individuals it has been demonstrated that the levels of Phe in the diet and the age at which dietary restriction is lost do affect outcome in IQ.

The relationship between Phe level and reduction in IQ at different stages of development is therefore an informative measure of environmental sensitivity in PKU sufferers and a potentially strong test of whether sensitivity is extended in higher IQ individuals. This sample can further address the question of the direction of causation in the relationship between IQ score and the length of the sensitive period. It is unclear from the study in Chapter 3 whether individuals that end up with a higher IQ are genetically predisposed to have an extended sensitivity to the environment or whether having a higher cognitive ability during development extends the influence of the environment longer into development. By comparing the predictive power of the individual's own IQ to the predictive power of the scores of their siblings or parents (a genetic "potential" score) it is possible to test whether level of IQ during development is a feedback variable in extending environmental sensitivity or if environmental sensitivity is determined by genetic influences indexed by genetic propensity.

Chapter 5 examines the mechanism by which changes in the brain might lead to development of intelligence and increases in heritability. The benefit of computational models for exploring and explaining mechanistic processes underlying sensitive periods in general and development of cognitive ability in particular has been highlighted by Thomas & Johnson (2005; 2008) and this approach is utilized to examine how individual differences in developmental changes could support varying maturational trajectories. Specifically, a biologically–based connectionist model of a simple cognitive process (representation of simple lines that are presented as combination inputs) is modeled and the level of neural inhibition is increased throughout learning to simulate normative changes in the brain throughout development. The effect of the timing of this change on performance, plasticity to changes in the input environment and on trajectory of change in "synaptic density" will be examined in the model. Additionally, different schedules of adjusting the level of inhibition will be examined, including basing rate of change on ongoing model activity to examine which method fits the data best.

Finally, chapter 6 examines what the results of these studies reveal in answer to the overarching research questions and how this improves understanding of the factors that promote high IQ. Implications of these results are discussed in terms of future directions for research in intelligence and the search for genetic and environmental that are associated with increased IQ. Finally, the utility of these results for guiding interventions aimed at promoting intelligence in at-risk or gifted children, and the population more generally is discussed.

CHAPTER 2: THE DEVELOPMENTAL ETIOLOGY OF HIGH IQ

Abstract

The genetic and environmental trends in IQ development were assessed in 483 same-sex twin pairs in the Colorado Longitudinal Twin Study using maximum-likelihood model-fitting analysis. The twins were assessed periodically from ages 1 to 16. Results show a decreasing influence of shared environment and an increasing influence of heritability across development, with large and increasing age to age stability of genetic influences. Non-shared environment contributes almost exclusively to age to age change. Similar analyses were conducted designating the top 15% of the sample as having high IQ at each age. The developmental etiology of high IQ did not significantly differ from that found for the continuous measure in this relatively novel analysis. These results demonstrate relatively early stability in etiological influences on IQ and have potential implications for gene-finding efforts, suggesting that samples selected for high IQ can be used to find genetic variation that will be applicable to the full range of the IQ distribution, although conclusive demonstration that the same genes are indeed involved was beyond the scope of this study.

Introduction

There is an extensive literature relating to the etiological basis of IQ and its development. However, the question of whether the levels of individual differences in IQ correspond to differing etiological trends is less well studied. The current investigation is the first extended longitudinal study of cognitive development in the upper end of the IQ distribution, using an etiologically informative sample (The Colorado Longitudinal Twin Study). We additionally address cognitive development from infancy to late adolescence across the full distribution of ability.

Numerous studies have shown that the genetic and environmental influences on intelligence change from age to age. This phenomenon was first noticed in a small adoption study by Skodak and Skeels in 1949. Since then, research using data from both twins and adoptive children has focused on the resulting pattern of increased heritability and decreased shared environmental effects with age and found it to be robust and widespread (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Boomsma & Molenaar, 1987; Bouchard & McGue, 1981; Cardon, Fulker, DeFries and Plomin, 1992; Cherny & Cardon, 1994; Eaves, Long, & Heath, 1986; Fulker, Cherny, & Cardon, 1993; Humphreys & Davey, 1988; McGue, Bouchard, Iacono & Lykken, 1993).

Petrill *et al.* (2004) used data from siblings who participated in the Colorado Adoption Project (CAP) at ages one through sixteen to examine these factors further. Results showed positive correlations between intelligence scores at all ages except between age one and ages nine and twelve, and a pattern of higher correlations between intelligence scores closer together in time. The best-fitting model included a common additive genetic factor, no shared environment and only time-specific non-shared environmental factors. Similar results were

obtained from looking at combined data from the CAP and the Longitudinal Twin Study (including non-twin siblings) using the same multivariate model by Bishop, Cherny, Corley, Plomin, DeFries and Hewitt (2003) from ages one to ten. Non-shared environment contributed to continuity from age seven through age-to-age transmission and to change (innovation) throughout development. Further, shared environment contributed exclusively to continuity through a common factor and additive genetic factors were accounted for by age-to-age transmission and by innovations up to age nine.

Results of behavioral genetic analyses have been reported from ages two to ten from the Twins Early Development Study (TEDS) - a sample of over 11,000 pairs of MZ and DZ twins recruited in the UK between 1994 and 1996. Spinath, Ronald, Harlaar, Price and Plomin (2003) extracted the first principal component from cognitive tasks given to the participants at ages two, three and four, finding evidence for only modest genetic influence, and a large effect of shared environment. Davis, Arden and Plomin (2008) used the same method at ages seven, nine and ten, demonstrating that continuity was due to genetic and shared environmental factors. Both genetic and shared environmental influences also contributed to differences between ages and methods. Non-shared environment contributed almost entirely to differences. There was a high genetic correlation across age, test composition, and method of administration. Additionally, genetic influences were stronger and shared environmental factors more modest than in earlier childhood.

It is clear from the above discussion that genetic and shared environmental influences can be concluded to contribute mostly to stability, whereas non-shared environment contributes mostly to change across ages. Additionally, genetic contributions to IQ increase across development, while shared environmental influences decrease. One aim of the current study was

to extend this research by fitting the simultaneous common factor, simplex and unique factor model in a systematic age-to-age twin sample to provide a more comprehensive analysis of developmental trends from infancy through late adolescence.

The second aim of the current study was to examine whether the factors outlined above apply equally across the distribution of intelligence scores, specifically to the upper levels of ability. Does the available evidence suggest a similar effect for high IQ individuals? Cherny, Cardon, Fulker and DeFries (1992) used an extension of the DeFries-Fulker multiple regression methodology and found no evidence for either linear or quadratic influences of level of cognitive ability on heritability or shared environmental effects in the Longitudinal Twin Study at ages one, two or three. This replicated the results of Horn, Loehlin and Willerman (1982) in the Texas Adoption Project and Vogler and DeFries (1983) in the Hawaii Family Study of Cognition. Sundet, Eilertsen, Tambs & Magnus (1994) found no evidence for differential heritability across the spectrum of ability in a sample of over 3000 Norwegian male young adults.

A more recent study by Ronald, Spinath and Plomin (2002) compared the pattern of etiological influences found for the full ability distribution found for a sample of 1943 preschool twin pairs to those found in a series of DF extremes analyses using increasingly stringent thresholds for proband status from the top 15 to the top 2.5 percent of the sample. Results indicated that genetic influences accounted for 20% of the variance, shared environmental factors accounted for over 70% of the variance, with around 10% attributable to unique environment. This pattern of etiology did not differ according to ability level. This study once again suggests that high cognitive ability is the quantitative extreme of the genetic factors influencing the full ability distribution, in children as well as adults.

Other studies *have* found a differential heritability estimate depending on level of cognitive ability, but with conflicting results. Specifically, Detterman, Thompson and Plomin (1990) found higher heritability and less influence of common environment at lower ability levels in a small sample of twins, as did Bailey and Revelle (1991). However, Jensen (1987) found higher heritability at higher ability levels in a much larger sample by examining the mean weighted correlations between intrapair sums and absolute differences in MZ versus DZ twins. Thompson, Detterman & Plomin (1993), in an extension to their previous investigations found no differences in heritability across ability level in another small sample from the Western Twin Project, although they note a trend towards higher heritability in the upper ranges.

Conflicting results are evident in this field, showing the need for a large-scale investigation of this question. Additionally, two descriptive studies examining intelligence test scores from 'gifted' children with IQs of 120 and above (Wilkinson, 1993) and 130 plus (Sweetland, Reina and Tatti (2006) show patterns that are not typical of the general population. Large verbal-performance discrepancies are seen in IQ scores, as well as more idiosyncratic subtest score scatter. The majority of children tested in these studies were third graders, which suggests an early difference in the characteristics of high IQ. The different characteristics of the phenotype in the upper range suggest at least the possibility of different etiological factors.

Regardless of similarity or differences in etiological influences on high ability at a specific age compared to those of the rest of the distribution, it is possible that the developmental model of stability and change of causative factors in development may vary depending on ability level. This is a theory that has some intuitive merit. For example, the existence of child prodigies suggests that, in some cases at least, high ability children reach their potential earlier, with less influence of structured educational resources, than other children. This could suggest an earlier

and stronger influence of stable genetic factors in childhood. On the other hand, some historically renowned geniuses did not stand out early in life, suggesting a quite different pattern of influence. It is possible that for such children, specific genetic influences come into play later in development, which may be related to *g* or to other characteristics, such as creativity or motivation. In this case, one may expect genetic influences on stability of high IQ to be the same as in the general population, with a strong possibility of age-specific genetic or environmental factors.

One other study, to the authors' knowledge, has examined longitudinal trends in the development of high IQ. Petrill et al (1998) used data from the Longitudinal Twin Study sample in infancy- 14, 20, 24 and 36 months. Using a cut-off of the ninetieth percentile and conducting DeFries-Fulker extremes analysis, it was found that the heritability of high IQ at each age was not different from that of the unselected sample. However, the sample used was small and the age-to-age analyses, indicating significant shared genetic influence only between the 24 and 36 month time points, were not compared to those of the unselected sample. Additionally, the reliability of the measurement of early childhood IQ is lower than that at later time points, meaning that a systematic effect is less likely to be found in infancy than in later childhood/adolescence.

One issue that arises from previous studies using truncated samples is the criterion used for selection. Previous research presented here use various approaches, but the criterion chosen for our analyses was to select as being of high IQ those twins in our community sample that scored above the 85th percentile in IQ. This criterion was applied on an age-by-age basis, so different individuals can fulfill the criterion at each age. Using this value as a threshold enabled a good balance between selection on the trait of interest and keeping the sample large enough to

maintain statistical power. It is also in accordance with the selection criteria used in the meta-analysis presented in this special journal issue, allowing the reader greater scope to compare results across studies.

Methods and Materials

Sample and Procedure

Twins participating in the Longitudinal Twin Study (LTS; Rhea et al, 2006) served as our sample for the current analyses. The LTS is an ongoing, prospective study of behavioral development conducted at the Institute for Behavioral Genetics (IBG; University of Colorado, Boulder). A total of 483 families participated and included 966 individual twins (240 male-male twin pairs and 243 female-female twin pairs). Those twins who were of the same sex and lived within 300 kilometers of the University were recruited by IBG between 1985 and 1991. At the time of enrollment into LTS, the average age of mothers and fathers was 29.65 and 31.65 years of age, respectively. Over 95% of these parents had completed high school, 50% of whom subsequently completed two or more years of college (Rhea et al, 2006). Self-reported ethnicity of the families participating in LTS was primarily Caucasian (>95%), with the remaining 5% of the sample consisting of African-American, Hispanic-American, and/or Native American. Twin zygosity status was determined using observer ratings and, subsequently, 12 molecular genetic markers as described elsewhere (Haberstick et al, 2004). The analysis presented here uses IQ information collected from the twins at seven time points from age about 1 year to age 16 years.

We obtained written consent from parents prior to their children's participation in the LTS, and/or parental or individual assent/consent (as appropriate) at each testing session. The Human

Research Committee of the University of Colorado at Boulder approved the study protocols.

Measures

IQ scores at ages 1 and 2 were calculated using the mental development component of the Bayley Scales of Infant Development (BSID; Bayley, 1969). The Stanford-Binet Intelligence Scale (Terman & Merrill, 1973) was administered at ages 3 and 4. These tests were administered in the twins' homes by separate examiners. Intelligence at age 7 was measured in person using the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1974), at age 12 also by the WISC-III ((Wechsler, 1991) and at age 16 using the Wechsler Adult Intelligence Scale-III (WAISIII; Wechsler, 1997).

Analyses

Means, standard deviations, and ANOVA results as a function of zygosity and gender and their interaction were calculated using SPSS (Version 16.2, SPSS, 2005) using one randomly selected member of each twin pair. Estimates of the skewness and kurtosis were calculated to determine whether IQ scores at each age were normally distributed. Prior to model-fitting analyses, the IQ scores were standardized within age and across zygosity and sex. Four individuals (2 pairs of twins) were excluded from the analysis and the subsequent genetic modeling due to unknown zygosity.

Genetic modeling

Univariate genetic modeling

Genetic contributions included the summed influences of many genes acting additively (A) and non-additively (referred to as 'dominance', D) in their effects. Environmental effects included those sources that are shared by both siblings of a pair and serve to make them more similar (C) and non-shared unique environmental effects (E) that include influences of child-specific experiences with their environment and measurement error. As MZ twins share 100% of their genes, while DZ twins share on average 50% of their genes identical by descent, quantitative genetic analyses of twin data assumes that: (1) MZ twins correlate perfectly for all A contributions to attention problems while DZ twins correlate 0.50, (2) an MZ twin correlation of 1.0 and a DZ twin correlation of 0.25 for D effects, (3) and that siblings experience the effects of shared environments equally regardless of zygosity status and are therefore correlated 1.0.

The magnitude of latent genetic and environmental influences on observed variation can be inferred from the extent MZ and DZ twin pairs correlate. If only additive genetic effects were involved in making a pair of twins similar, it is expected that the DZ twin correlation would be one-half that of the MZ twin correlation. Shared environmental influences are implicated when the correlation between DZ twins is more than one-half that between MZ twins. Conversely, when the correlation between DZ twins is less than one-half that between MZ twins, non-additive genetic effects are implicated. With MZ and DZ twin pairs reared in the same home, estimates of non-additive genetic and shared environmental contributions to observed variation are confounded and so only one, but not both, of these can be estimated in a given model (Jinks and Fulker, 1970).

Variation in IQ is assumed to be a function of two or more latent variables: A, E and either D or C. This baseline model is refined by equating the contribution of one or more latent variables to zero and testing the difference in model fit. In same-sex twin pairs, gender differences in the magnitude of genetic and environmental effects are tested by estimating the fit of a model that allows the latent

influences for boys and girls to differ and comparing its fit with one that constrained them to be equal. However, as variances for male and female twins were found to be equal at each age, and the covariances were also found to be equal across gender, these factors were not considered in the genetic analyses.

Univariate analyses were conducted the IQ data at each age. This analysis was additionally conducted on factor scores derived from a latent IQ factor constructed from the last three ages, using the program MPlus (Muthén & Muthén, 1998) to test the generalization of our results to individuals that scored consistently high on IQ. It was decided to use this measure rather than an aggregate over the full range of ages as the pattern of etiology has been shown to change substantially across early development, whereas the influences on IQ from age seven onwards are relatively stable.

Developmental genetic modeling

We adopted the repeated-measures design shown in Figure 1 to estimate the extent that genetic and environmental influences contributed to the correlation of IQ across multiple years (Eaves et al, 1986). This approach partitions the genetic and environmental variances at each age and the covariances across all ages into influences that can be common to all ages, age-specific, and transmitted forward into later ages. Common genetic effects are denoted as a_c, age-specific genetic effects as a_s, and age-to-age or transmitted genetic effects as j. Non-shared environmental influences are denoted as e_c, e_s, and k, respectively, with similar parameters for the shared environmental influences (not shown in the Figure.) Stability is conceptualized as resulting from two different processes. The first postulates that a common latent factor influences IQ at all ages through paths a_c

and e_c. The second postulates that genetic and environmental influences on earlier ages persist or are transmitted forward to subsequent ages through paths *j* and *k*. Because of their similarity to well known psychometric models, we refer to the model for the first process as the common factor model and the second as the simplex model (Boomsma and Molenaar, 1987; Joreskog, 1970). From our developmental model we obtained the genetic and environmental correlations that indexed the extent earlier influences overlapped with later ones.

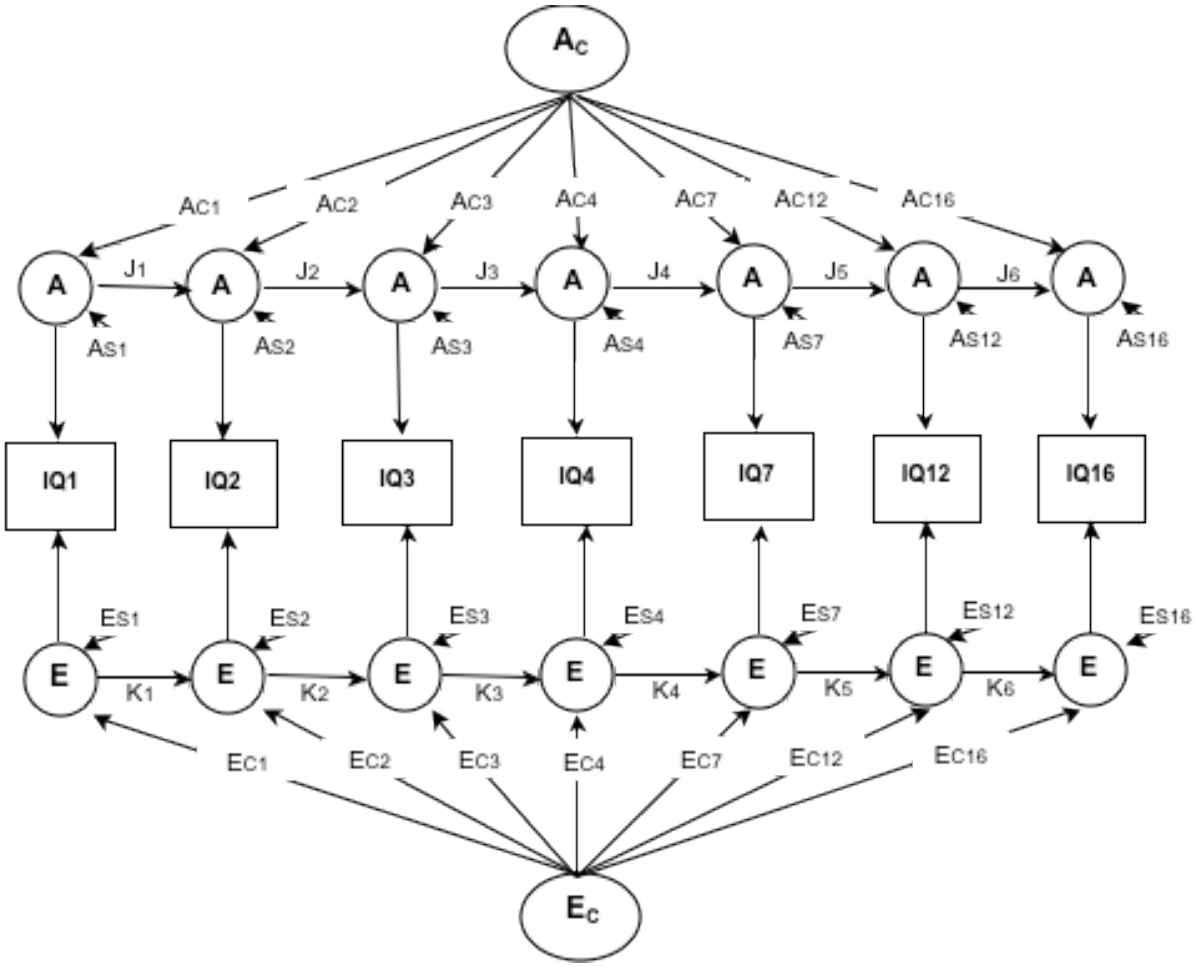

Figure 1. Developmental model. Ac, Common genetic influences, As, Age-specific genetic influences; J, Age-to-age genetic influences; E, environmental influences; Ec, Common environmental influences; Es, Age-specific environmental influences; K; Age-to-age environmental influences; IQ, IQ score at each age.

Genetic models were fit to standardized age-scaled scores, using the raw maximum-likelihood estimation option in Mx. The significance of model parameters was evaluated by a comparison of twice the log-likelihood (-2LL) for models with or without the parameters, with the difference distributed as a chi-square and the degrees of freedom being equal to the difference between the number of parameters estimated. A non-significant difference chi-square between the two models indicates that the parameters dropped from the more parsimonious model were not significantly different from zero. Classes of models were compared on the basis of the Akaike Information Criterion (AIC; Akaike, 1987), calculated by subtracting twice the difference in the degrees of freedom ($2 \cdot \Delta df$) from the difference chi-square ($\Delta\chi 2$) between any particular model and the fullest, i.e. least parsimonious model, considered. The AIC indexes the extent that a given model offers the most parsimonious, but adequate, explanation of the data.

Threshold models

The model-fitting analyses for the top 15 percent of the distribution of IQ scores proceeded in largely the same fashion as those for the full distribution. A threshold of 1.036, the z-score corresponding to the 85th percentile of a normal distribution was set, and the data file on which this analysis was made was ordinal, with '1's representing a twin whose score passed this threshold, and a '0' for a twin that did not. This criterion was applied to each age separately, so an individual could reach the threshold at one age, but not at others. The aggregate univariate analysis differed in this respect, as the individuals that were above the eighty-fifth percentile on average across the last three ages were labeled high IQ. Differences between the best-fitting models for the full IQ range and the high IQ range was tested for by compaing the fit of a freely estimated threshold model to one in

which the parameters were fixed to those derived from the continuous analysis. The developmental model was conducted by comparing the best-fitting model from the threshold analysis in which the parameters were freely estimated to the same model in which the parameter values were fixed to those from the continuous analysis. This analysis assumes a similar structure of etiological influences on the development of high IQ to the rest of the distribution, while giving a measure of whether the relative importance of certain etiological factors is different for highly intelligent individuals.

Results

Table 1 shows the mean IQs and the standard deviation around them for each age in the full sample. The mean age, standard deviation and range is also shown. The ANOVA results using data from one randomly picked twin from each pair demonstrates no significant effect of zygosity on IQ score at any age. There are sex effects on IQ observed at four ages, but the effect sizes are very small, and there are no *a priori* reasons to expect such an effect. No interactions of zygosity by sex effects are observed. Skewness and kurtosis at each age are within acceptable limits to assume a normal distribution of IQ scores at each age.

Table 1: Means (standard deviations) for age and IQ at each age, ANOVA results for IQ by age and zygosity and skewness and kurtosis results for one randomly selected member of each twin pair

Mean Age in years (SD) and Range	N		Male (N)	Female (N)	Mean IQ (SD)	Skewness (SE)	Kurtosis (SE)	ANOVA		
								Zygosity	Sex	Zygosity*Sex
One Year	MZ	DZ								
1.17 (0.07)	494	393	445	438	104.56	-0.31	0.92	p= 0.5	p= 0.04	p= 0.81
1.00-1.33					(13.80)	(0.08)	(0.16)	η^2= 0.002	η^2= 0.017	η^2< 0.001
Two Years	MZ	DZ								
2.04 (0.06)	433	366	403	392	107.44	0.07	-0.38	p= 0.4	p< 0.01	p= 0.45
1.92-2.25					(18.82)	(0.09)	(0.17)	η^2= 0.003	η^2= 0.097	η^2= 0.002
Three Years	MZ	DZ								
3.04 (0.07)	410	352	370	390	103.22	-0.06	0.08	p= 0.3	P< 0.01	p= 0.66
2.83-3.5					(17.50)	(0.09)	(0.18)	η^2= 0.005	η^2= 0.076	η^2= 0.001
Four Years	MZ	DZ								
4.01 (0.04)	405	351	387	367	103.77	0.12	0.55	p= 0.5	p= <0.01	p= 0.42
3.92-4.08					(14.12)	(0.09)	(0.18)	η^2= 0.002	η^2= 0.028	η^2= 0.003
Seven Years	MZ	DZ								
7.39 (0.36)	444	376	412	408	106.33	-0.24	0.57	p= 0.16	p= 0.76	p= 0.55
6.67-8.42					(13.40)	(0.09)	(0.17)	η^2= 0.008	η^2< 0.001	η^2= 0.001
Twelve Years	MZ	DZ								
12.43 (0.37)	390	364	370	382	103.21	-0.01	-0.39	P= 0.78	p= 0.74	p= 0.45
11.33-14.00					(12.86)	(0.09)	(0.18)	η^2 < 0.001	η^2< 0.001	η^2= 0.002
Sixteen Years	MZ	DZ								
16.55 (0.76)	427	373	384	414	102.20	0.21	0.22	p= 0.38	p= 0.59	p= 0.62
16.00-20.00					(11.47)	(0.09)	(0.17)	η^2= 0.003	η^2= 0.001	η^2= 0.001

Table 2. Within-pair and Cross-age correlations for Monozygotic and Dizygotic twins. †

	Twin 2						
Twin 1	Age 1	Age 2	Age 3	Age 4	Age 7	Age 12	Age 16
			MZ				
Age 1	.58	.39	.22	.24	.29	.18	.17
Age 2		.82	.66	.59	.52	.38	.38
Age 3			.70	.69	.48	.51	.34
Age 4				.76	.60	.53	.47
Age 7					.81	.71	.69
Age 12						.85	.80
Age 16							.84
			DZ				
Age 1	.39	.27	.15	.12	.01	-.02	.01
Age 2		.63	.44	.48	.41	.31	.25
Age 3			.51	.45	.41	.34	.31
Age 4				.50	.39	.33	.30
Age 7					.59	.50	.45
Age 12						.48	.40
Age 16							.51

Cross-twin, cross- age correlations

As can be seen in Table 2, the cross-twin correlations at all ages are higher for monozygotic than for dizygotic twins, considering the entire distribution, indicating some genetic influence at each age. The cross-age twin correlations are larger for closer ages than for those that are further away in time, suggesting at least some influence of age-to-age transmission effects. The approximate heritability estimates from simply doubling the difference between the MZ and DZ correlations range from a low of .38 at age 1 to a high of .74 at age 12.

Univariate continuous model-fitting analyses

Table 3 presents the continuous univariate analyses for the full sample distribution of IQ scores. The fit of the ACE models was compared to a saturated phenotypic model. As can be seen, the amount of variance in the sample attributable to additive genetic variance (A) increases from .3-.4 at earlier ages to just above .7 at later ages. The pattern is reversed for shared environmental (C) variance, reducing from its highest value of .46 at age 2 to just above .1 at ages 12 and 16. Non-shared environmental variance (E) does decrease somewhat over age, but not to the same extent. It should be noted that these E estimates include measurement error. As different tests were used at different ages, it is possible that the reliabilities varied, which would change the proportion of error. Examining the chi-square difference tests ($\Delta\chi^2$)and the Akaike Information Criteria (AIC) for the sub-models at each age, it appears that the full ACE model is the best-fitting at all ages, as the AIC estimate never reaches below -1, even when the $\Delta\chi^2$ indicates that the drop in fit is non-significant. It could be argued, however, that an AE model fits the best at ages 12 and 16. The aggregate IQ measure of ages 7, 12 and 16 also indicates that the ACE model provides the best fit to the data.

Table 3. Results of Univariate Model Fitting of IQ Scores at Seven Ages.

Model	Additive Genetic Variance	Shared Environmental Variance	Non-Shared Environmental Variance	Δχ2	Δ*df*	P	AIC
			AGE 1				
ACE †	0.40 (0.14 to 0.64)	0.18 (0.00 to 0.41)	0.42 (0.35 to 0.50)	1.18	3	.758	-5.18
AE	0.59 (0.52 to 0.66)	…	0.41 (0.34 to 0.48)	2.11	1	.146	0.11
CE	…	0.49 (0.42 to 0.56)	0.51 (0.44 to 0.58)	9.22	1	.002	7.22
			AGE 2				
ACE †	0.36 (0.21 to 0.54)	0.46 (0.28 to 0.60)	0.19 (0.15 to 0.23)	8.33	3	0.04	2.33
AE	0.82 (0.78 to 0.85)	…	0.18 (0.15 to 0.22)	18.7	1	.000	16.7
CE	…	0.73 (0.69 to 0.78)	0.27 (0.22 to 0.31)	23.1	1	.000	21.1
			AGE 3				
ACE †	0.30 (0.08 to 0.54)	0.39 (0.16 to 0.57)	0.32 (0.26 to 0.39)	3.04	3	0.39	-3.04
AE	0.70 (0.63 to 0.75)	…	0.30 (0.25 to 0.37)	9.69	1	.002	7.69
CE	…	0.62 (0.55 to 0.68)	0.38 (0.32 to 0.45)	7.34	1	.007	5.35
			AGE 4				
ACE †	0.51 (0.30 to 0.75)	0.26 (0.03 to 0.45)	0.23 (0.19 to 0.29)	6.80	3	0.08	0.80
AE	0.77 (0.72 to 0.81)	…	0.23 (0.19 to 0.28)	4.20	1	0.03	2.70
CE	…	0.65 (0.59 to 0.70)	0.35 (0.30 to 0.41)	25.9	1	.000	23.9
			AGE 7				
ACE †	0.48 (0.32 to 0.68)	0.34 (0.15 to 0.49)	0.18 (0.15 to 0.22)	5.55	3	.136	-1.55
AE	0.82 (0.78 to 0.85)	…	0.18 (0.15 to 0.22)	10.6	1	.001	8.56
CE	…	0.71 (0.65 to 0.75)	0.29 (0.25 to 0.35)	37.7	1	.000	35.7
			AGE 12				
ACE	0.73 (0.53 to 0.87)	0.12 (0.00 to 0.31)	0.15 (0.12 to 0.19)	9.81	3	.020	3.81
AE	0.85 (0.81 to 0.88)	…	0.15 (0.12 to 0.19)	1.09	1	0.30	-0.91
CE	…	0.67 (0.61 to 0.72)	0.33 (0.28 to 0.39)	68.8	1	.000	66.8
			AGE 16				
ACE	0.71 (0.52 to 0.87)	0.14 (0.00 to 0.32)	0.15 (0.13 to 0.19)	12.2	3	.007	6.24
AE	0.85 (0.81 to 0.87)	…	0.15 (0.13 to 0.19)	1.63	1	0.20	-0.36
CE	…	0.67 (0.62 to 0.72)	0.33 (0.28 to 0.38)	71.1	1	.000	69.1
			AGGREGATE MEASURE				
ACE	0.63(0.40 to 0.79)	0.18 (0.02 to 0.39)	0.18 (0.16 to 0.25)	53.2	3	.000	47.2
AE	0.80 (0.76 to 0.84)	…	0.20 (0.16 to 0.24)	4.58	1	0.03	2.58
CE	…	0.65 (0.58 to 0.70)	0.36 (0.30 to 0.42)	41.7	1	.000	39.7

Table 4a. Model fit statistics for developmental models of IQ. †

Model	Model specification			Model fit statistics					
	Common Factor	Age-to-Age Transmission	Age-Specific	-2LL	*Df*	$\Delta\chi^2$	Δdf	p	AIC
1. ‡	A,C,E	A,C,E	A,C,E	11758.30	5564	18.90	24	.76	-29.10
2.	A,E	A,C,E	A,C,E	11761.59	5571	3.29	7	.86	-10.71
3.	C,E	A,C,E	A,C,E	11763.41	5571	5.11	7	.65	-8.89
4.	A,C	A,C,E	A,C,E	11787.01	5571	28.72	7	.00	14.7
5.	--	A,C,E	A,C,E	11809.24	5585	50.94	21	.00	8.94
6.	A,C,E	A,E	A,C,E	11763.33	5570	5.03	6	.54	-6.97
7.	A,C,E	C,E	A,C,E	11783.01	5570	24.71	6	.00	12.7
8.	A,C,E	A,C	A,C,E	11763.33	5570	5.03	6	.54	-6.97
9	A,C,E,	--	A,C,E	11837.11	5582	78.81	18	.00	42.8
10.	**C,E**	**A**	**A,C,E**	**11772.31**	**5583**	**14.01**	**19**	**.78**	**-23.9**
11.	C	A	A,C,E	11758.30	5591	83.10	27	.00	29.1
12.	E	A	A,C,E	11811.66	5590	53.37	26	.00	1.37

Bolded indicates the best-fitting developmental model.
† Genetic analyses were performed using z-scored continuous IQ scores.
‡ Baseline developmental model vs. Saturated Model (Genetic Cholesky)
Abbreviations: A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects; AIC, Akaike Information Criteria.

Developmental continuous model-fitting analyses

Table 4a presents the model fit statistics for the developmental model shown in Figure 1 when applied to the full sample. As can be seen, the best-fitting model includes C and E common factors, an A age-to-age transmission factor, and A, C and E innovations at each age. This model gives very little reduction in fit, while reducing complexity substantially when compared to the full model. The parameter estimates yielded by the full model are presented in Figure 2, and the best-model by AIC, with parameter estimates, is presented in Figure 3.

Extensive age-to-age additive genetic transmission effects can be seen at all ages. In fact, transmission is so high from ages 7-12 and 12-16, that the simplex model is indistinguishable from a common factor. However, we included just a simplex model rather than a common factor at later ages for parsimony. There are also moderate to high levels of specific genetic influences at each age, even the highest ages, suggesting that the etiology of individual differences in cognitive development isn't completely stable even at 16 years of age. Loadings on the common environmental factor are steady and moderately high at all ages, and innovation shared environmental effects are low, suggesting that the same aspects of the family environment are important at all ages. One exception to this is the higher C innovation at age 1. The common non-shared environmental factor in the model contributes only modestly to developmental stability and primarily after age 7. This is consistent with real individual environmental influences on IQ for school age children that could include biological factors, such as poor health, or psychological or educational influences. We should remember that circumstances that have large effects for individual children, but that occur relatively infrequently among the population, will contribute only modestly to overall variance.

Age-specific E effects are at a consistent level over time. One conclusion that can be drawn from this model and from the univariate analyses is that parameter estimates from ages 7 onwards are remarkably stable. This suggests that the importance of different kinds of causal influences on intelligence does not change much once children have attained school age.

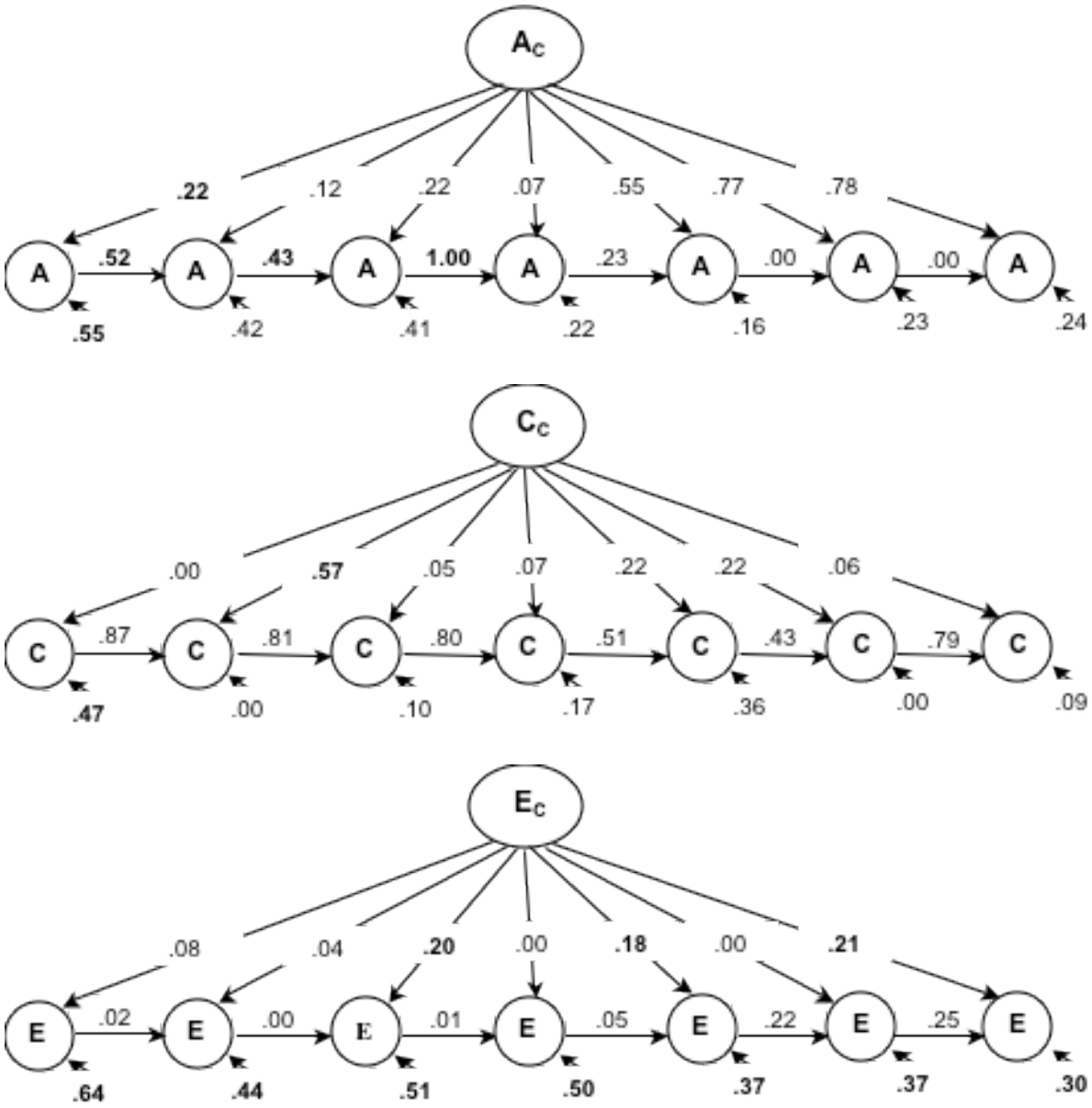

Figure 2. Standardized parameter estimates for baseline developmental model of IQ scores at seven ages during childhood and adolescence. A, additive genetic effects; A_C, common additive genetic effects; C, shared environmental effects; C_C, common shared environmental effects; E, non-shared or individual specific environmental effects; E_C, common non-shared environmental effects. Parameter estimates whose 95% confidence intervals did not include zero are **bolded**.

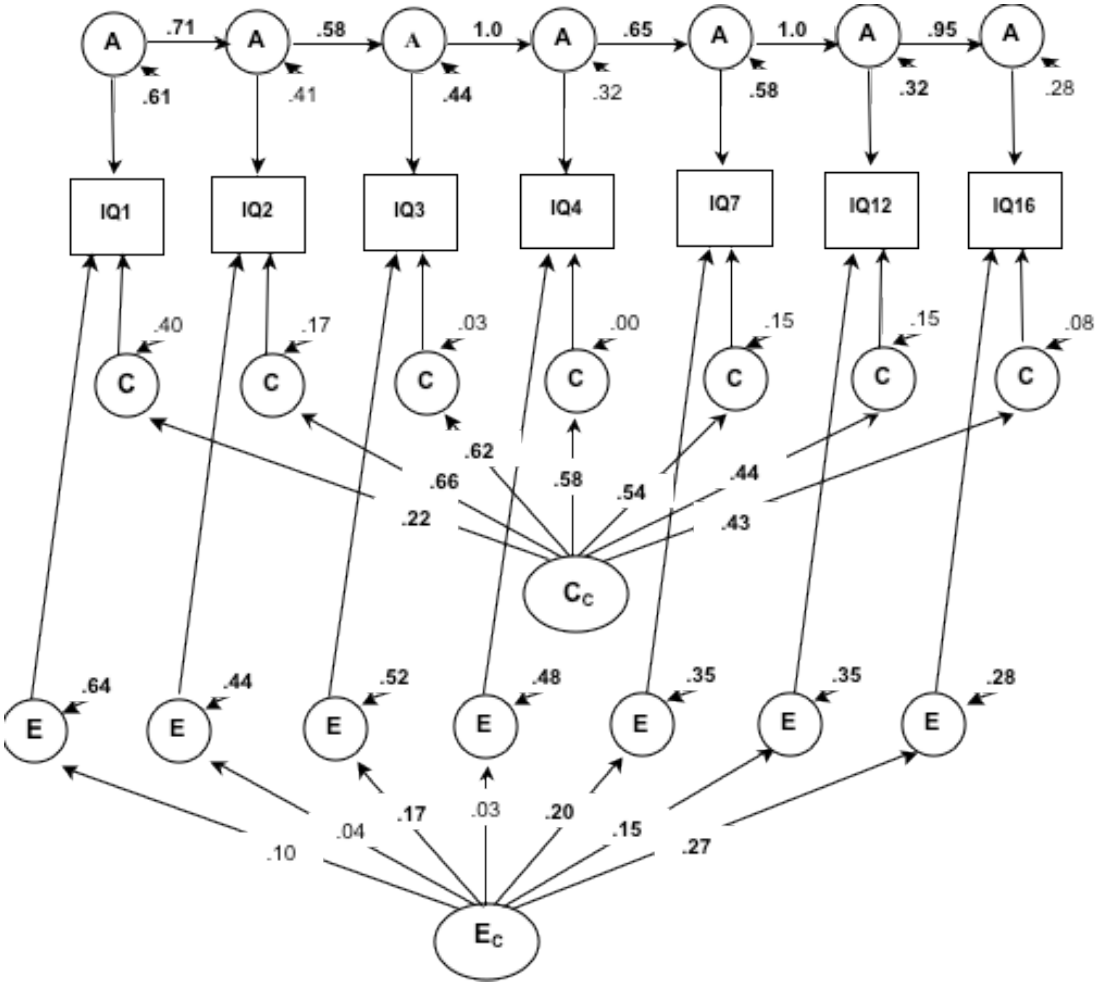

Figure 3. Best-fitting developmental model of IQ scores at seven ages during childhood and adolescence. A, additive genetic effects; C, shared environmental effects; C_C, common shared environmental effects; E, non-shared or individual specific environmental effects; E_C, common non-shared environmental effects. Parameter estimates whose 95% confidence intervals did not include zero are **bolded**.

Table 4b presents the total variance components for additive genetic, shared environment and non-shared environmental factors. These largely reflect the patterns observed in the univariate analyses of increasing genetic and decreasing environmental effects across development. It is reassuring that these estimates replicate those of the univariate analyses, and this lends credence to the results of the developmental model-fitting. Table 4b also presents age-to-age genetic and non-shared environment correlations. The shared environmental correlation approaches 1 at each age after age one because of the common factor and the low level of age-specific innovations after this time point. The genetic correlations demonstrate the increasing similarity of genetic influences over time that was seen in the larger transmission effects for ages 7 -16. The correlations are, however, high across age groups, signifying that the same genetic effects are evident from infancy to late adolescence, but that these influences increase in importance across development.

Table 4b. Variance Component Estimates and Correlations for the Best-Fitting Developmental Model of IQ at seven ages during childhood and adolescence.

	Variance Components †			Correlations ‡						
Age	Additive Genetic Variance	Shared Environmental Variance	Non-Shared Environmental Variance	1	2	3	4	7	12	16
1	0.37 (0.12 to 0.61)	0.20 (0.01 to 0.42)	0.43 (0.35 to 0.51)	**1.0**	.73	.45	.39	.23	.21	.20
2	0.35 (0.21 to 0.52)	0.46 (0.29 to 0.60)	0.19 (0.15 to 0.23)	.48	**1.0**	.62	.54	.32	.29	.27
3	0.31 (0.16 to 0.47)	0.39 (0.24 to 0.54)	0.30 (0.25 to 0.36)	.49	.97	**1.0**	.88	.52	.47	.44
4	0.43 (0.27 to 0.57)	0.33 (0.20 to 0.48)	0.24 (0.19 to 0.29)	.49	.97	.99	**1.0**	.59	.54	.51
7	0.52 (0.37 to 0.66)	0.31 (0.17 to 0.45)	0.17 (0.14 to 0.20)	.47	.93	.96	.96	**1.0**	.91	.86
12	0.64 (0.53 to 0.75)	0.22 (0.10 to 0.33)	0.14 (0.12 to 0.18)	.46	.91	.94	.94	.91	**1.0**	**.94**
16	0.66 (0.53 to 0.76)	0.19 (0.09 to 0.32)	0.15 (0.12 to 0.19)	.48	.95	.98	.98	.94	.93	**1.0**

* Parameter estimates are standardized.

† 95% Confidence intervals in parentheses.

‡ Genetic correlations are above the leading diagonal, shared environmental correlations below. Because the non-shared environmental correlations ranged between 0.01 and .10 for early ages with later ages, they are not shown. Increases in the non-shared environmental correlations were observed between ages 12 and 16, however, and ranged between 0.20 and .034.

Univariate High IQ model-fitting analyses

The threshold was set at 1.036 - the z-score corresponding to the 85th percentile of the normal distribution. The full-model results were variable, demonstrating the large drop in power from dichotomizing the data at this relatively high threshold and the resulting difficulty in estimating all parameters. Comparison of the freely estimated to the fixed-parameter models did not demonstrate a decrement of fit for any of the models from fixing the A C and E parameters to those from the continuous models. This result is concluded from insignificant chi-square values and small, largely negative AIC values. Due to the power reduction, the results from these analyses are arguably inconclusive, but are strongly suggestive of the presence of similar proportions of genetic and environmental influences at the top 15th percentile of the distribution and those found in the full range.

Developmental high IQ model-fitting analyses

Fitting the full model with all parameters freely estimated gave a -2LL of 3785.70 for df=5571. The extra seven degrees of freedom observed in this model compared to the same model estimated for the continuous data (Model 1 in Table 4) correspond to the constraining of the phenotypic variance to one at each age. The fit of the best continuous developmental model (Model 10 in Table 4: A transmission, C and E common factor and ACE innovations) to the high IQ, in which the parameters were freely estimated, yielded a -2 log- likelihood (-2LL) value of 3798.90 with 5590 degrees of freedom (df). The difference chi-square was 23.35, p =.222 and AIC = -14.65. Fixing all the parameter values to those estimated for the continuous data gives a -2LL value of 3818.21 with 5631 df. The comparison of these fit measures gives a $\Delta\chi^2(41)=19.31$, p=0.998, and AIC = -87.49 This means that, assuming the same structure of etiological influences for high IQ and

normally distributed IQ, there is no significant difference between the parameters estimated for the continuous distribution and those estimated dichotomizing the distribution for high IQ..

Discussion

The model-fitting analyses herein demonstrate developmental trends across the full spectrum of ability that largely accord with those found previously (Bishop *et al,* 2003; Davis *et al,* 2008; Petrill *et al,* 2004; Spinath *et al,* 2003). Specifically, the common shared environment factor was found to contribute to age-to-age continuity, although its influence on variance in intelligence was almost none from age twelve onwards. Genetic factors were also found to largely contribute to continuity, but the higher correlations for assessments closer together in time mean that the simplex transmission model fits the additive genetic factors best. Non-shared environmental factors contribute mainly to changes across development, although there is some age-to-age correlation of non-shared environmental effects, particularly at later time points. The great similarity of the pattern of contributing factors from between ages twelve and sixteen, and even from age seven suggests that that the etiology of individual differences in intelligence development is highly stable by early adolescence. Genetic influences increase in importance throughout development, and shared environmental influences decrease in importance.

The analysis additionally suggests that there is not only no difference between the proportion of variance attributable to genetic and environmental influence at each age for high ability individuals and the rest of the distribution, but also that the pattern of transmission, common and genetic factors from age-to-age is extremely similar for individuals scoring above

the 85th percentile at each age and that of the full normal distribution. This result is consistent with the hypothesis that the etiological influences contributing to the development of high intelligence are the same as those contributing to individual differences in the full range, but a conclusive demonstration of this were not possible in this study.

Validity of Results

The continuous developmental results relating to the full distribution can be fully accepted as the power with this sample is sufficiently high and the confidence intervals are correspondingly narrow. However, power decreases with the use of threshold models, up to 10 times with a 10 percent threshold (Neale, Eaves & Kendler, 1994). This power increases with the use of multiple measures over time (Schmitz, Cherny & Fulker, 1998), but is definitely reduced from the continuous case, also indicated by the wide confidence intervals around the estimates in the threshold model parameters. It is possible, therefore, that some correlational patterns were missed in the threshold models. However, the trend towards the same best-fitting model as the full distribution is a convincing and interesting finding.

The sample used in this study gives it strength as it is a longitudinal sample with a range of assessment periods fully representative of the course of intelligence development. The analysis is also novel in the field as it allows modeling of developmental trends in high IQ and direct comparison of the fit of this model to that found for the full distribution of ability.

As Petrill *et al* (1998) used the early data from the LTS, it is reassuring that a similar result was found using a different methodology and a less stringent threshold (85th as opposed to 90th percentile) for high IQ selection. This holds for both the univariate and the cross-age analyses. As mentioned earlier, Petrill *et al* (1998) is the only previous longitudinal and

etiologically informative study of high IQ. Others have presented cross-sectional analyses, and the current study supports those that find no difference in the relative importance of genetic, shared environmental and unique environmental influences (Cheney, *et al,* 1992; Horn *et al,* 1982; Ronald *et al*, 2002; Sundet *et al,* 1994; Vogler & DeFries, 1983). It also largely supports the specific values found, in an age-specific fashion, with the exception of the considerably higher shared environment effects found for preschool cognitive ability by Ronald *et al* (2002). These results come from a variety of twin and family studies, indicating that the finding is representative of the population, at least in the United States.

Detterman *et al* (1990) and Bailey and Revelle (1991) found increased heritability in the lower range of the ability distribution. The current investigation cannot address this issue. One study that found higher heritability for higher ability levels was that of Jensen (1987). The method used in this study, of correlating absolute difference scores with total twin scores on IQ tests, and comparing this correlation in MZ and DZ twins is quite different to that used here and could potentially pick up more subtle ability-related differences- especially if these differences are gradual and cumulative and IQ gets higher. However, one would still expect that that this cumulative effect would still be seen when a comparison was made between an upper cut-off and the general population.

The descriptive pattern of a greater verbal-performance discrepancy in 'gifted' children observed by Wilkinson (1993) and Sweetland *et al* (2006) was not addressed in our analyses. However, if correct, it does not appear to result in differential causal factors in either kind or proportion. It could be explained by less reliable measurement at the higher level of ability, or environmental, rather than heritable factors could account for the differences between performance and verbal IQ. This would accord with Cattell's (1971) idea of Fluid and

Crystallized intelligence. Under this hypothesis, verbal subtests in the Wechsler intelligence tests tap the crystallized aspect and performance subtests tap the fluid aspect of intelligence. It is hypothesized that crystallized intelligence is more amenable to the influences of the environment, and so the same aspects of the environment could account for individual differences along this dimension. This could also be the aspect of intelligence that is acted upon by gene-environment correlation, allowing a greater performance discrepancy between these factors at higher ability levels. This hypothesis is supported by the fact that the average verbal intelligence score is somewhat higher than the average performance intelligence score in the Wilkinson (1993) and Sweetland *et al* (2006) samples.

Implications

The results of this study have clear implications for gene-finding efforts in the area of intelligence. As it appears that the magnitude and possibly nature, of genetic influences on intelligence are the same for higher and average ability levels, linkage and association studies do not have to concentrate on a specific ability level when looking for genes associated with intelligence. It is likely that higher IQs result from the cumulative impact of many genes each individually increasing IQ by some small amount. If so, molecular genetics findings from high IQ individuals will be applicable to the rest of the population. As using extreme samples gives increased power in the search for specific genetic influences, this is an important finding and is indicative of a high utility in the use of high IQ individuals in gene finding efforts. Of course, the advantage of such an approach must be counter-balanced by the difficulty in ascertaining extreme samples and the resulting lack of power mentioned above.

There are also implications of the results of this study that relate to the environment. It seems that environmental influences also have similar magnitudes of impact at the higher end of the distribution. Thus it is unlikely that there are dramatic environmental influences that only highly intelligent children experience, and more likely that development of high cognitive ability comes from quantitatively better engagement with or access to, available educational materials. It is also clear that shared environmental influences are reduced after the age of seven, although several factors could contribute to this pattern.

Limitations and Further Research

The selection criteria used in the current study allowed a different subset of individuals to be included in the high IQ subsample at each age. This approach has limitations relating to sample uniformity across ages. Just fifteen percent of the sample who were above threshold at one year of age was above threshold at age sixteen, and a mere three participants met criteria at all ages. The pattern is improved when age seven to age sixteen threshold maintenance is examined; half of the participants above threshold at age seven maintained threshold status at age sixteen. This pattern reflects the strong similarity of influences on developmental from age seven onwards. There is some consistency, however. Those of greater than average intelligence at age one are 1.74 times more likely to meet threshold criteria at age sixteen. Further, those that are one s.d. above the mean at age one are 3.95 times more likely to reach threshold IQ levels at age sixteen. This issue was addressed to some extent with the aggregate univariate analysis of the IQ scores from the last three ages, although this was only a univariate analysis, yielding no information on developmental trends. Given the age to age differences observed, our future research will examine the etiological influences underlying the developmental trajectory to high adult IQ.

The 85th percentile was chosen to maintain power to detect possible differential causal influences at the higher level of ability. However, it could be argued that this is an insufficiently high selection criterion for high IQ, masking possible ability-related etiological effects. However, for a high cut-off to be viable, a much larger sample would be required to retain adequate power. Also, as mentioned earlier, our results accord with those using samples using more stringent selection, as well as those using fully continuous methods. It would, however, be interesting to see if our results replicate in a larger sample with more extreme selection. .

Overall, these analyses demonstrate a dynamic pattern of genetic and environmental influences across development that confirms and extends that of previous studies. Additionally, these findings are equally applicable to individuals with high IQ and those in the normal range. This finding has implications for gene-finding and for the search for specific environmental influences on the development of intelligence.

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CHAPTER 3: THE NATURE AND NURTURE OF HIGH IQ: AN EXTENDED SENSITIVE PERIOD FOR INTELLECTUAL DEVELOPMENT?

Abstract

IQ predicts many measures of life success, as well as trajectories of brain development. Prolonged cortical thickening observed in individuals with higher IQ might reflect an extended period of synaptogenesis and high environmental sensitivity or plasticity. We tested this hypothesis by examining the timing of changes in the magnitude of genetic and environmental influences on IQ as a function of IQ score. We find that individuals with higher IQ show high environmental influence on IQ into adolescence (resembling younger children), whereas individuals with lower IQ show high heritability of IQ in adolescence (resembling adults), consistent with an extended sensitive period for intellectual development in more intelligent individuals. These patterns hold across a cross-sectional sample of almost 11,000 twin pairs, and a longitudinal sample of twins, biological siblings, and adoptive siblings.

Introduction

Adult IQ is a measure of cognitive ability that is predictive of social and occupational status, educational and job performance, adult health and longevity (Gottfredson, 1997; Neisser *et al,* 1996; Whalley & Deary, 2001). Individuals with IQ scores at the high end of the distribution show distinct timing of postnatal structural changes in cortical regions known to support intelligence, which has been posited to reflect an extended "sensitive period" (Shaw *et al,* 2006). Specifically, change in cortical thickness in frontal and temporal regions is cubic during development, with initial thickening in childhood, followed by thinning in late childhood/adolescence that levels out in young adulthood (see also Shaw *et al,* 2008), matching the patterns of synaptogenesis and pruning observed in postmortem prefrontal tissue (Petanjek *et al*, 2011). Individuals of superior IQ (compared to average and high) show more intense and prolonged cortical thickening, followed by more rapid thinning. This distinct trajectory may reflect prolonged synaptogenesis and an extended sensitive period, during which the brain is particularly responsive to environmental input (Shaw *et al*, 2006).

Further evidence for a link between cortical thickness and IQ comes from the finding that common genes influence change in cortical thickness and IQ in adulthood (Brans et al., 2010). In addition, IQ and cortical thickness show similar patterns of change across development in the magnitude of genetic and environmental influences. Specifically, the heritability (magnitude of genetic influence) of IQ and the heritability of cortical thickness in brain regions associated with IQ both increase during childhood and adolescence, while environmental influences decrease in importance (Haworth et al., 2010; Bartels*,* Rietveld, Van Baal & Boomsma, 2002; Brant, Haberstick, Corley, Wadsworth, DeFries & Hewitt,, 2009; Lenroot *et al,* 2009).

These results are suggestive of an extended sensitive period for IQ development: cortical thickening, which is associated with IQ, occurs over an extended period for individuals with higher IQ, corresponding to prolonged sensitivity to the environment. These results are only suggestive, however, because changes in brain development do not necessarily correspond to changes in sensitivity to the environment. There is no direct evidence for individual differences in the length of a sensitive period for IQ.

We provide an empirical test of the extended sensitive-period hypothesis of high IQ, by examining changes in the magnitude of genetic and environmental influence on individual differences in IQ scores throughout development. As noted above, the magnitude of environmental influences on IQ decreases across development.We test whether these decreases in environmental influence occur later in development for individuals with higher IQ, consistent with a prolonged sensitivity to the environment. We focus on influences of the shared family environment rather than individual-specific environment, because the developmental change in environmental influence on intelligence is mainly driven by a reduction in influence of the shared family environment. Additionally, the shared family environment should arguably be the driving force behind experiential influence on IQ, because shared family environmental influences are highly correlated across different ages such that their effects can accumulate across development, while individual-specific environmental factors tend to be more age-specific and include measurement error (Brant *et al*, 2009).

We use a cross-sectional sample of 11,000 twin pairs aged from 4 -71 years, and a smaller longitudinal replication sample of twins, biological siblings and adoptive siblings tested from ages 1 to 16. Previously published investigations using the datasets examined here have

tested for differences between high IQ and IQ in the normal range. Although no difference was reported in the etiology of individual differences (Haworth *et al,* 2009; cross-sectional GHCA sample) nor in their trajectories of developmental change (Brant *et al*, 2009; Longitudinal Twin Sample), these investigations discretized IQ rather than examining continuous trends, and did not test whether the relationship between IQ score and heritiability/environmentality was specific to adolescence. Here we test this hypothesis explicitly. We predict that environmental influences should remain high for longer in higher IQ individuals, and that genetic influences conversely should remain lower for longer. IQ score should therefore be associated with magnitude of genetic and environmental influence in adolescence (but not in childhood or adulthood, where regardless of IQ, environmental influences should be high or genetic influences should be high, respectively).

Method

Participants and Measures:

Participants for the initial cross-sectional analysis were 10,897 monozygotic (MZ; identical) and dizygotic (DZ; fraternal) twin pairs amalgamated from the 6 institutions in four different countries (USA, UK, The Netherlands and Australia) that constitute the Genetics of High Cognitive Ability Consortium (GHCA). Zygosity was determined in almost all cases by analysis of DNA microsatellites, blood group polymorphisms or other genetic variants, The sample is described in detail elsewhere (Haworth *et al*, 2010) and is summarized in Table 1.

The longitudinal sample included MZ and DZ twins from the Colorado Logitudinal Twin Study (LTS) and adoptive and biological sibling pairs from the Colorado Adoption Project

(CAP), two prospective community studies of behavioral development at the Institute for Behavioral Genetics (IBG; University of Colorado at Boulder). A total of 483 same-sex twin pairs have participated in the LTS study, ascertained from local birth records (264 MZ and 219 DZ)[*]. Twin zygosity status was determined using 12 molecular genetic markers as described elsewhere (Haberstick and Smolen, 2004). In the CAP, families with an adoptive child and matched community families were ascertained in infancy. If siblings were born or adopted into the families they were included in the study. For many families, more than one sibling pair per family was available. The current analysis used the sib pair with complete IQ data at the most ages. The final sample consisted of 185 biological sibling pairs and 184 adoptive sibling pairs. Of these, 64 biological pairs were available only at age 16 and the same was true for 75 adoptive pairs. For more details on the samples see Rhea, Gross, Haberstick and Corley, 2006 (LTS) and DeFries, Plomin and Fulker, 1994 (CAP). The IQ tests administered at each of the seven measured ages are outlined in Table 2. The scores were standardized within age and across samples to maintain the slightly higher mean scores in the CAP.

Twin Methodology:

Extensions of DeFries-Fulker regression, a special case of linear regression for deriving genetic and environmental components of variance in pairs of related individuals, were employed. DeFries-Fulker regression (for details see Cherny, Cardon, Fulker & DeFries, 1992) predicts the score of one member of a sibling pair from the score of the other, the coefficient of relationship - which takes a value of 1.0 for MZ twins (100% genetic sharing), 0.5 for DZ twins and biological siblings (50% genetically related on average) and 0.0 for adoptive siblings (who are not genetically related) - and the interaction between these two variables. When the data is

[*] This total exceeds that reported in cross-sectional sample, which included only twins that had an IQ score measured at age 7 or above.

standardized, as it is here, this regression yields direct estimates of the heritability (h^2) of the measured trait and proportional influence of the family-wide environment (c^2) on differences between individuals in the sampled population. The influence of individual-specific environments (e^2) can be derived by subtraction.

The addition of other variables into the regression equation, which are allowed to interact with the existing predictors, tests whether the magnitude of either h^2 or c^2 is changeable in the population according to the variables of interest. In the current study, we were interested in whether the magnitude of h^2 or c^2 for IQ is moderated by IQ score itself, so we added a quadratic ability term (the predicting siblings' scores squared) and quadratic term x coefficient of relationahip interaction (Cherny *et al*, 1992). The significance of these interaction terms assesses whether there is a linear, contnuous relationship between IQ score and c^2 or h^2 respectively.

To directly test the extended-sensitive period hypothesis of high IQ, we were additionally interested in whether any effect of score on h^2 or c^2 was restricted to a certain age range. This was examined by estimating the coefficients for the quadratic score term separately at each measured age. In the cross-sectional GHCA sample, we were able to additionally test for signiificant differences *between* the magnitude of the ability-dependent terms at each age by adding an age covariate into the regression equation. The sensitive period hypothesis predicts that there is only a relatioship between IQ score in adolescence (i.e. the coefficient for the age term should be zero at all other times.For this reason continuous modeling of the effect of age was not possible and it was therefore decided to use discrete age categories,We split the sample into three age groups: childhood (4yrs to 12yrs; n pairs = 6044), adolescence (13-18yr; n pairs = 4304) and adulthood (18yrs +; n pairs = 549) and constructed orthogonal contrast codes based on these criteria: A linear code comparing the childhood and adulthood groups and a quadratic

code that compared these groups collectively to the adolescent group. Since our hypothesis predicts the values of h^2 and c^2 to be dependent on IQ score only in adolescence (where higher scoring participants will have a child-like etiology and lower scorers will resemble adults), we expected that the three-way interactions between the quadratic age contrast code, ability and the h^2 and c^2 terms would be significant, while the equivalent terms for the linear age code would not be (as no interactions with ability are expected in either childhood or adulthood). Although the appropriate bounderies between the age categories were somewhat ambiguous, the broad expected pattern was clear, so we chose childhood, adolescent and adulthood age boundries as typically defined.

In the longitudinal sample, we added an extra covariate, age gap in days between the siblings in each pair, into the regression (0 for all twin pairs), and all results reported from this sample are from analyses including this as an interacting variable with the c^2 and h^2 terms and the ability-dependent terms. Since maximum sharing of the family environment occurs when siblings are the same age, and the groups in our sample differ systematically not only by genetic relatedness but also by average age gap (adoptive siblings being more disparate than biological siblings and biological siblings more than twins), it is prudent to account for this confounding variable in the analysis, so as not to overestimate the magnitude of the heritability estimates.

For every analysis described, each pair appears twice in the data set, with the score of each member of a pair appearing once as a predictor and once as a dependent variable. This is routine in DeFries-Fulker regression using unselected samples because there is no *a priori* reason to favor a particular twin assignment. This procedure does, however, artificially narrow the standard errors derived from regression analysis (which assumes independence). We addressed this by bootstrapping the regression estimates in the GHCA sample by resampling first at the

family level and then at the twin assignment level, and by following the robust standard error correction outlined by Kohler and Rodgers (2001) in the longitudinal follow-up, which accounts for the fact that observations are only independent at the level of the twin pair and not the individual observations. Further explanation and details of all analyses including the regression equations can be found in the supplementary materials.

Results

Cross-sectional analysis of the GHCA sample

After describing sample characteristics and the extent of genetic and environmental influence on IQ in the sample as a whole, we examine the moderation of these values by age. As predicted by the extended sensitive period hypothesis, we find that the extent of genetic and environmental influence is dependent on IQ score, and this effect is limited to adolescence, and not present in either childhood or adulthood.

Sample characteristics and sample-wide analysis

Table 1 outlines the size and mean age of the 6 subsamples, along with the different tests used to measure IQ. The mean age of the sample is 13.06 years (with a range between 4.33 and 70.03 years). The mean age differs considerably between the subsamples, from 6 in the Western Reserve sample to almost 18 in the Netherlands twin register. There is also a considerable difference in the range between the samples, meaning that some age groups are primarily made up of particular samples. The proportion of pairs for each sub-sample and the total sample falling

into each of the three age groups is outlined in Table 1. The IQ tests used differ between samples, reflecting age- appropriate, widely-used and validated tests. For the analyses shown here, after residualization for age and sex, the IQ scores were standardized within each study to maintain the subsample structure.

For the sample as a whole, the proportional heritability (h2) was .55 (95% CI .49-.61), influence of the family environment (c2) .22 (95% CI .18-.26) and of the individual-specific environment (e2) .23 (95% CI.16-.39). This finding closely matches the results found in the same sample using different methodology (structural equation modeling; Haworth *et al*, 2010). Examining the influence of IQ score on these parameters, there was a significant effect on c^2 (β = .036, p = .026), such that the influence of c2 increased as IQ score increased. There was a slight trend for a decrease in h^2 as IQ score increased (β = -,027, bootstrapped p= .187). "Etiology" in the following section collectively refers to the estimates for c^2 and h^2. As anticipated (for reasons outlined in the introduction), there were no detectable influences of IQ score on the magnitude of e^2. For this reason we do not report results for this predictor beyond the sample-wide value.

TABLE 1: Genetics of High Cognitive Ability Consortium Sample Characteristics

Sample	Number of pairs	Mean Age (Range)	IQ measure
Ohio, USA: The Western Reserve Reading Project	292 (121MZ, 171DZ)	6.07 (4.33-7.92) 100% child	Stanford Binet Intelligence Scale (short form). Summed and standardized for age and sex.
United Kingdom: Twins Early Development Study (TEDS)	4061 (1529MZ, 2532DZ)	11.57 (10.08-12.84) 100% child	Two WISC-III verbal subtests (information and vocabulary), WISC-III picture completion, Ravens Standard and Advanced Progressive Matrices. Standarized and summed.
Minnesota, USA: The Minnesota Center for Twin and Family Research (MCTFR)	1870 (1187MZ, 683DZ)	13 (11-17) 51% child 49% adolescent	Abbreviated WISC-R or WAIS-R as age-appropriate.
Colorado, USA: Longitudinal Twin Study (LTS), Colorado Twin Study (CTS), Colorado Learning Disabilities Research Center (CLDRC)	2863 (LTS=390, CTS=696, CLDRC=1777; 1299MZ, 1564DZ).	13.12 (6-25) 47% child 45% aolescent 8% adult	WISC-R, WISC-III, WAIS-III or WAIS-R (block design & vocab. only in CTS).
Australia: The Twin Cognition Study	853 (338MZ, 515DZ)	16.00 (15-22) ~100% adolescent <1% adult	3 verbal and 2 performance subtests from the Multidimensional Aptitude Battery.
Netherlands: The Netherlands Twin Register	958 (437MZ, 521DZ)	17.99 (5.67-71.03) 54% child 19% adolescent 27% adult	Standard age-appropriate IQ tests (see Boomsma *et al,* 2008 for further details)
Total Sample	10897 (4911MZ, 5986DZ)	13.06 (4.33-71.03) 55.5% child 39.5% adolescent 5% adulthood	*g* scores standarized within each study after residualization for age and sex

note: WISC-III = Wechsler Intellegence Scales for children -Third Edition; WISC-R = Wechsler Intellegence Scales for children - Revised; WAIS-R = Wechsler Adult Intelligence Scale - Revised; WAIS-III = Wechsler Adult Intelligence Scale - Third Edition.

Age as a moderating variable

Separate analysis of the subsamples indicated variability in the strength of the relationship between IQ score and the causal influences on IQ, suggesting a moderation of this relationship by age. We therefore performed the regression analysis with age as an interacting variable, as described in the methods to test the age-dependence of the interaction between score and both heritability and family environmental effects described above. r. As expected there was no moderation by the linear age contrast on the score-etiology relationship (on separate analysis of the age groups, the score-etiology relationship in both childhood (ages 4-12) and adulthood (age 18+) was not significantly different from zero). However, the quadratic contrast code, comparing the adolescent (age 12-18) group to the childhood and adulthood groups collectively, showed that the adolescent group had a larger association between IQ and both higher environmental influence and lower genetic influence, consistent with the extended sensitive period hypothesis. Specifically, both the increase in c^2 and the decrease in h^2 as IQ score increased were significantly greater in adolescence (β = ,05, p=.04 and β = -.06, p = .04, respectively). In adolescence, IQ score predicts the pattern of genetic influence (β = -.14, p < .001) and environmental influence (β = .12, p < .001), in a manner consistent with lower IQ individuals transitioning earlier to an adult-like pattern of these influences.

Analyses removing scores below the 5th and above the 95th percentile ruled out undue influence of extreme scores on the results. We also assessed whether any of these results differed according to the sex by repeating the analysis with non sex-residualized data and adding sex as an interacting variable. Males have a slightly higher mean IQ in this sample (β_{sex} = .061, p < .001). However, no significant interactions by sex were found.

Stage-like transitions in causal influences

Figure 1 displays estimates for heritability and the influence of the shared family environment in the 4-12, 12-18 and 18+ year old participants separately estimated for the top and bottom half of the ability distribution (median split) at each age, to visualizing the relationship between age, IQ score and the etiological influences on IQ[1]. It can be seen that the estimates of both c^2 and h^2 change with age, with the magnitude of shared environmental influence decreasing and genetic influence increasing between childhood and adulthood, consistent with previous results in this sample and others (see e.g. Haworth *et al,* 2010). The magnitude of these effects is largely equal across ability for the two groups, representing a consistent beginning and end point in developmental change irrespective of ability level. However, the timing of this transition is different for the two ability groups. For the lower ability group the period of maximum change occurs between childhood and adolescence, indexed by the steeper slope of the hashed lines between these two time points. There is largely no change between adolescence and adulthood, as reflected by the relatively flat hashed lines between these points. For the higher ability group, however, a reciprical relationship exists. In this group there is largely no change between childhood and adolescence (the solid lines between these points are again nearly flat), with the change in causal influence occurring between adolescence and adulthood. This pattern is indicative of a discrete shift in influence that occurs later in development for higher IQ individuals, and highlights adolescence as an important transitional stage. This pattern further suggests that the gradual change in heritability from childhood to adulthood noted in other studies may, in fact, represent a non-linear shift with ability-dependent timing.

[1] For these analyses, a sibling pair was only double entered if both siblings met the score criteria.

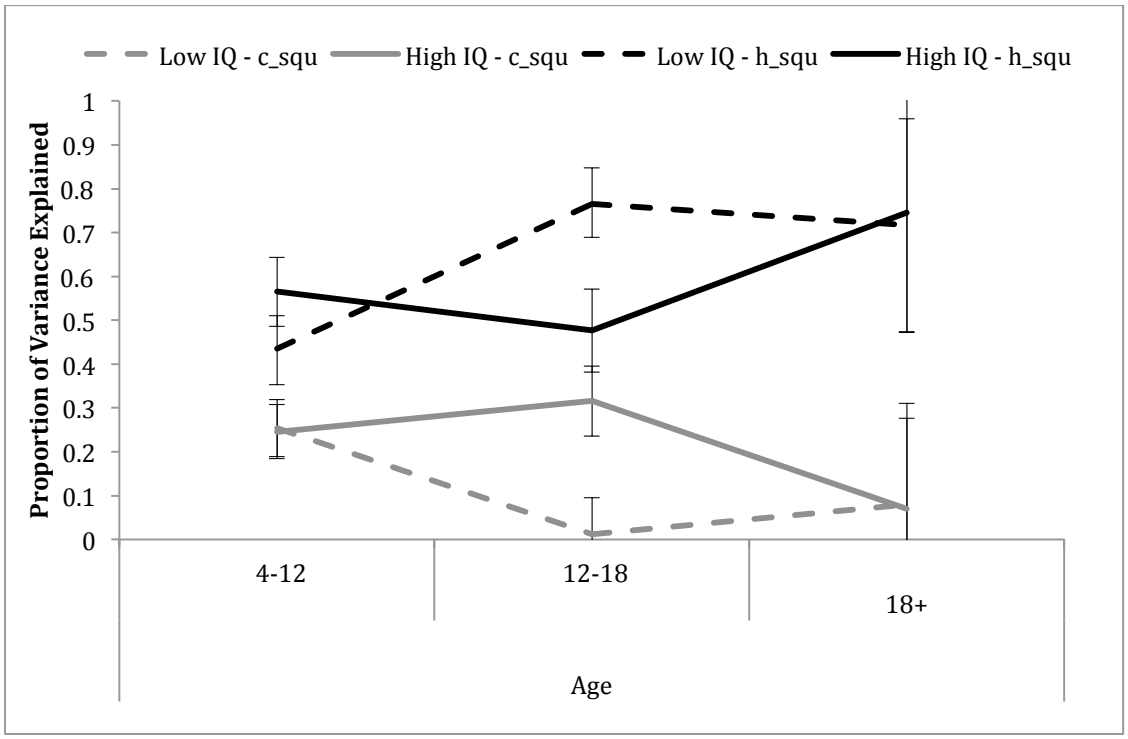

Figure 1. Ability-related differences in causal influence were observed specifically during adolescence. Notably, the lower-ability subjects underwent more age-related change before this point, as indicated by the sloped dotted lines (left side). In contrast, the higher-ability subjects underwent more age-related change after this point, as indicated by the sloped solid lines (right side). Note: High/Low IQ refers to subjects scoring above/below the median score at each age

Longitudinal sample:

Table 2 presents descriptive statistics for the longitudinal sample. The estimates of h^2 and c^2 for each of the seven testing ages (with age gap modeled) are presented in Table 3. The pattern of increasing genetic influence and decreasing influence of the shared environment corroborates that seen previously, rising from .42 at age one to .85 at age 16. The influence of the shared environment shows the opposite effect, reducing in importance from a high of .39 to a low of .01. Additionally, we confirmed the influence of IQ score on the estimates of these parameters in adolescence in the same direction as in the cross-sectional analysis (last two columns of Table 3). At age 16, the estimate of c^2 increased as ability increased and h^2 decreased in importance, with no significant influence of ability at the earlier ages. We were, however, unable to test the sample in adulthood to confirm the transience of this effect.

TABLE 2: Demographic and descriptive information for the LTS/CAP samples

Age	n pairs LTS	n pairs CAP	mean age (sd)	Test administered	mean score (sd)
1 yr	342 (245MZ,197DZ)	291 (150Bio., 141Ad.)	1.12 (.09)	BSMD	106.86 (13.83)
2 yrs	398 (215MZ, 183DZ)	270 (139Bio., 131Ad.)	2.03 (.05)	BSMD	108.00 (17.86)
3 yrs	381 (204MZ, 177DZ)	254 (130Bio. 124 Ad.)	3.03 (.06)	S. Binet Intell. Scale	104.61 (16.93)
4 yrs	378 (203MZ, 175DZ)	260 (134Bio., 126Ad.)	4.01 (.03)	S. Binet Intell. Scale	105.73 (13.94)
7 yrs	410 (222MZ, 188DZ)	262 (134Bio., 128Ad.)	7.41 (.37)	WISC-III; WISC-R	108.66 (13.43)
12 yrs	377 (195MZ, 182DZ)	267 (137Bio., 130Ad.)	12.45 (.38)	WISC-III; WISC-R	106.02 (12.95)
16 yrs	399 (213MZ, 186DZ)	352 (178Bio., 174Ad.)	16.6 (1.02)	WAIS-III; WAIS-R	103.92 (11.60)
Full	483 (264MZ, 219DZ)	384 (193Bio., 191Ad.)			

note: MZ = monozygotic twin pairs; DZ = dizygotic twin pairs, Bio. = Biological sibships, Ad. = adoptive sibships (no genetic relationship); BSMD = Bayley Scales of Mental Development, S. Binet = Stanford Binet Intelligence Scale, WISC-III = Wechsler Inelligence Scale for Children - Third Edition; WISC-R = Wechsler Intelligence Scale for Children - Revised; WAIS-III = Wechsler Adult Intelligence Scale - Third Edition; WAIS-R = Wechsler Adult Intelligence Scale - Revised

TABLE 3: Heritability and shared environmental effects in the LTS/CAP combined sample when age gap between sibling pairs is modeled as an interacting variable, with 95% confidence intervals. Rightmost two columns report the moderating effect of ability score on these estimates.

Age group	h^2 (95% c.i.s)	c^2 (95% c.i.s)	ability*h^2 (95% c.i.s)	ability*c^2 (95% c.i.s)
1 (n = 635 pairs)	0.42 (.12,.72)*	0.17 (-.07,.41)	-0.03 (-.13,.08)	0 .00 (-.07,.06)
2 (n = 583 pairs)	0.42 (.23,.62)*	0.39 (.21,.57)*	-0.01 (-.12,.09)	-0.03 (-.12, .07)
3 (n = 556 pairs)	0.33 (-.02,.67)	0.35 (.08,.62)*	-0.14 (-.36,.08)	0.05 (-.08, .18)
4 (n = 561 pairs)	0.55 (.30,.79)*	0.21 (0.00,.43)	-0.07 (-.17,.03)	0.01 (-.06,.08)
7 (n = 601 pairs)	0.54 (.33,.75)*	0.28 (.09,.47)*	-0.03 (-.10,.44)	-0.01 (-.07,.04)
12 (n = 571 pairs)	0.63 (.43,.82)*	0.20 (.02,.38)*	-0.01 (-.29,.21)	0.04 (-.15,.23)
16 (n =730 pairs)	0.85 (.67,1.03)*	0.01 (-.16,.19)	-0.08 (-.16,-.001)*	0.07 (.003, .14)*

* = significant at $P < .05$ when s.e.s are corrected for non-independence due to double entry

Discussion

We have presented evidence from two separate sets of data that supports the existence of a sensitive period in IQ development that is extended in individuals of higher IQ. Using a large-cross-sectional dataset of twins, we found a shift in causal influences on IQ between childhood and adulthood, away from environmental and towards genetic influences. Moreover, we found that the period of child-like levels of environmental influence was prolonged in higher IQ individuals, while lower IQ individuals shifted earlier to an adult-like pattern, demonstrating that higher IQ is associated with a prolonged sensitive period. This result was replicated in a longitudinal sample of twin, biological and adoptive siblings. These results were found for the influence of the family-wide environment and not the individual specific environment (including measurement error), consistent with predictions from prior longitudinal behavior genetic research showing age related changes in the relative magnitude of the former but not the latter component of variance.

Alternative explanations of these results can be ruled out (see supplementary materials for details of supporting analyses). First, assortative mating (the tendency for parents to resemble each other in cognitive ability) could artifactually increase the influence of the family-wide environment, and so could contribute to our results if assortative mating were higher in the parents of higher IQ individuals. However, we find that higher IQ parents actually show less assortative mating; the difference between parental IQ scores is positively correlated with mean parental IQ score. Thus, assortative mating could only contribute to an underestimation of the strength of the results reported here. Second, if different traits were being measured at different IQ levels, and these traits differed in their extent of genetic and environmental influences, this

could give a false impression of a single trait that varied by IQ in the extent of genetic and environmental influences. However, principal component analyses showed that the same trait was measured across IQ levels. Finally, genotype-environment interactions could contribute to our results, if the environmental variables were correlated with IQ, and estimates of environmental influence were greater for higher levels of the environmental variable. We tested for gene-environment interactions with parental education and parental IQ in the LTS twins' age 16 scores. However, no interaction was present for parental education, and heritability of IQ was higher at higher levels of parental IQ, which would cause *underestimation* of the interaction between the individual's own score and their environmental sensitivity. Moreover, all of these alternative explanations would face an additional challenge in explaining why the link between IQ and genetic and environmental influence *changes* across development.

Our findings raise the question of why a prolonged sensitive period in IQ development might be associated with higher IQ. One possibility is that protracted development is beneficial for development of higher and uniquely human cognitive functions, such as those measured by IQ tests (Rougier et al., 2005). This pattern may be supported via genetic polymorphisms in higher IQ individuals which limit the rate of developmental cellular changes. Similar arguments have been made for prolonged immaturity being beneficial for other aspects of cognitive development (Bjorkland, 1997; Newport, 1990; Thompson-Schill, 2009). *However,* individuals with an eventual high IQ show this tendency from early in development (Deary, Whalley, Lemmon, Crawford & Starr, 2000), challenging the idea that prolonged immaturity alone leads to higher IQ.

An alternative possibility is that having a higher IQ prolongs sensitivity to the

environment. For example, heightened levels of attention and arousal, as one may find in individuals of higher IQ, may allow plasticity to occur later into development (Knudsen, 2004). Relatedly, individuals of higher IQ may be more open to experience, more likely to try things and change in response to experience, whereas lower IQ individuals are less motivated as they do not get as much positive feedback from learning experiences. However, this explanation is not without its own issues. The increase in genetic influence over development comes from both an increase in importance of existing genetic influences and addition of new genetic influences (Brant *et al*, 2009). If the extension of the sensitive period is a feedback process from increased cognitive ability, it is unclear how this feedback process would lead to a delay in the introduction of new genetic influences.

The most prominent theory of developmental increases in heritability of IQ posits that individuals gain more scope throughout development to shape their own environments, based on their genetic propensities (active gene-environment correlation), which causes an increase in genetic influence over time (e.g. Haworth *et al*, 2010). Our results challenge this explanation as they show a later increase in heritability for individuals of higher IQ. To explain these results in the context of active gene-environment correlations, one would need to posit, counterintuitively, that higher IQ individuals seek out environments concordant with their genetic propensities later in development than lower IQ individuals.[2]

[2] The reason for developmental increases in heritability of IQ thus remains unclear and is debated in the field (Plomin, 1986; Plomin, DeFries & Loehlin, 1977). While resolving that debate is beyond the scope of the current work, our key contribution is in showing for the first time that the timing of the decline in the magnitude of environmental influence depends upon IQ, consistent with the extended sensitive period hypothesis.

Our results suggest that, like cortical thickness, other brain-related measures (such as functional connectivity, synaptic density, and characteristics of neurotransmitter systems) will show differing relationships to IQ across development, and that the timing of this change will be dependent on IQ score. This indicates an important new direction in the search for biological and cognitive markers of IQ, and in the study of the genetic variation and developmental processes underlying individual differences in cognitive ability.

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CHAPTER 4: INDIVIDUAL DIFFERENCES IN THE INTELLECTUAL EFFECTS OF PHENYLKETONURIA?: TESTING HYPOTHESES OF NORMATIVE DEVELOPMENT

Abstract

Prior research has suggested that there is a sensitive period in intellectual development that is extended in individuals of higher IQ. This study tested whether such a pattern was evident in a measurable phenotype with a potentially large effect on IQ, using a longitudinal sample of early-treated individuals with Phenylketonuria (PKU). PKU is an inborn metabolic disorder in which dietary phenylalanine cannot be metabolized and has a detrimental effect on IQ. We first investigated whether blood phenylalanine concentration is additive on other genetic and environmental influences by assessing IQ differences in the sample based on both parental IQ and lifetime Phe level. This analysis demonstrated that Phe concentration has largely the same effect on IQ regardless of genetic propensity, but that individuals with higher expected IQ do indeed score higher at all ages, regardless of blood phe concentration. Secondly, we used mixed linear models to demonstrate that the trajectory of change in IQ in PKU sufferers is consistent with a limited environmental influence on IQ after the age of 12. However, this trajectory is dependent on the IQ of the individual in late childhood and individuals with higher actualized IQ show a decline in IQ for longer into development. This pattern is not evident when dichotomizing for genetic propensity (mid-parental IQ) suggesting that it is intellectual ability, not genetic propensity that influences the length of the sensitive period.

Introduction

A critical period refers to a defined period of time in which certain environmental experiences must be present in order for typical development to occur. It is well established that there is a critical period in the development of primary sensory functions (e.g. Morishita & Hensch, 2008; Barkat; Polley & Hensch, 2011; Michel & Tyler, 2005) and research in recent years has examined whether the concept can be usefully extended to explain patterns of development in higher cognitive function. It has long been hypothesized that a critical period or (more likely) a number of distinct critical periods exist for language (e.g. Lenneberg, 1967; Neville, 2006) but the concept has been extended to the development of executive function and intelligence also in recent years. (Garlick, 2002; Jacobs, Harvey & Anderson, 2007; Shaw *et al*, 2006; 2008).

It appears that, instead of being distinctly timed or "fixed", critical periods may instead be variable in the timing of their onset, length and offset and appear to be precipitated, extended and even reopened by certain environmental or molecular manipulations (e.g. Bellone & Lüscher, 2012; Ciucci, Putignana, Baroncelli, Landi, Berardi & Maffei, 2007; Zhou, Panizzutti, de Villers-Sidani, Madeira & Merzenich, 2011). For this reason, the less deterministic term "sensitive period" has been adopted and will be used throughout this paper.

Various neurobiological, functional and structural changes have been observed with the closing of sensitive periods in the visual cortex. Such changes are likely to be cortex-wide (although varying in their relative importance or the extent of their expression) and therefore

open the distinct possibility that periods of enhanced plasticity operating for functions supported by other parts of the cortex share the same substrates. It additionally opens the possibility that the progression of these periods would mirror the progression of these changes in the brain, which moves broadly from posterior to anterior regions. There is much evidence that areas of the cortex that have been demonstrated to be involved in intelligence go through these developmental changes last. This has been demonstrated by examining the process of synaptogenesis and synaptic pruning in postmortem brain tissue and changes in cortical thickness using structural MRI in developing children, adolescents and young adults. It opens the possibility that variations in the timing of the sensitive period might have an effect on outcome. This is likely particularly the case for associative functions like intelligence (IQ). Initial evidence for this comes from Shaw and colleagues (2006), demonstrating a prolonged period of synaptogenesis proceeded by a more vigorous period of pruning that extends later into early adulthood in individuals of superior IQ compared to those of high or average intelligence.

Recent work in our lab has used twin-modeling techniques to examine whether the population-wide linear increase in heritability and decrease in the influence of the family-wide environment, widely reported for intelligence throughout childhood and adolescence is consistent with the existence of a defined sensitive period in intellectual development that is extended in individuals of higher IQ (Brant *et al*, under revision). We found, using a sample of almost 11,000 monozygotic and dizygotic twin pairs cross-sectionally measured at varying ages between 4 and 71 years, that the transition in the relative importance of genetic and environmental influences on intelligence between childhood and adulthood is more discrete that

previously reported, with a prolonged "child-like" pattern of enhanced environmental influence in individuals of higher IQ and an earlier shift towards the increased genetic influence that is characteristic of adulthood is observed in lower IQ individuals. This result was replicated in a longitudinal sample of twin, biological and adoptive siblings.

Our data contribute to the emerging pattern from developmental psychology and neurobiology that 1. There exists a sensitive period in the development of intelligence and 2. This sensitive period is extended in individuals of higher IQ. A stronger demonstration of this result would be to examine whether a single measurable variable that would be to examine the pattern of influence on IQ of a distinct environmental variable throughout development, in contrast to the aggregate measure of latent environmental influence employed in classical behavioral genetic study designs. This is currently a fool's errand in population samples as no environmental variable with a known influence on IQ is precisely measureable enough or varies sufficiently throughout development in the normal range to allow for age-dependent impact on intellectual ability to be assessed.

A couple of previous studies have examined whether age of the child influences or limits the effects of environmental or physical trauma. Jacobs *et al* (2007) examined the influence of focal frontal lobe lesions acquired at different ages during childhood on intelligence and executive function outcomes as compared to matched controls. Although their sample size was small, they found some evidence that the negative effect of the lesion on executive function is lowest in middle childhood and highest when it occurs prenatally or after age 10. There was a

trend towards the same pattern for IQ. Additionally, executive function deficits were more general following prenatal lesions, but more specific and adult-like after age 10. The authors interpret their results as supporting the existence of separate critical periods for different executive functions depending on the their association with different parts of the frontal cortex. Nelson and colleagues (e.g. Nelson, Zeanah, Fox, Marshall, Smyke & Guthrie, 2007; Vanderwert, Marshall, Nelson, Zeanah & Fox, 2010) have examined the effects of severe neglect in institutionalized Romanian children and the influence of being removed to supportive foster care on later cognitive and neural development. They find that intervention prior to 24 months is associated with better cognitive outcome and recovery of EEG activity.

We examine the influence of developmental phenylalanine levels on intelligence in a longitudinal sample of individuals with phenylketonuria (PKU) to extend this work by examining patterns of environmental effects on IQ throughout development according to IQ score. PKU is an inborn Mendelian metabolic disorder in which sufferers are unable to metabolize phenylalanine due to a mutation in the gene coding for the hepatic enzyme phenylalanine hydroxylase (PAH; Scriver & Kaufman, 2001). Elevated blood Phe level from a free diet causes a number of issues including severe mental retardation, seizures, physical deformity and restricted growth. These symptoms are a rarity now due to newborn screening and early adoption of phe-restricted diets, but suboptimal outcomes are still observed in diet-treated individuals (Enns, Koch, Brumm, Blakely, Suter & Jurecki, 2010), including cognitive deficits compared to siblings or matched controls. With regard to intelligence, a meta-analysis has shown around a 2-4 point reduction in IQ for each 100μmol/ml increase in lifetime phenylalanine level (Waisbren *et al*, 2007) and there is evidence that both age at diet initiation, blood phe levels and

age at loss of dietary restriction (Channon, Goodman, Zlotowitz, Mockler & Lee, 2007; Koch *et al*, 2002). Other deficits in attention and executive function have also been observed (e.g. Diamond, 2002; Huijbregts, de Sonneville, Licht, van Spronsen, Verkerk & Sergeant, 2002; .Leuzzi, *et* al, 2004).

This large effect of an environmental variable (phe level) on intellectual outcome even on early well-controlled diets, coupled with the fact that phe level is accurately measurable and variable throughout development (individuals typically lose dietary control sometime before adolescence) allows for longitudinal study of the developmental trajectory of change in IQ in relation to phe level and the age at which there is no further decline in intelligence. There is some evidence that the change in sensitivity of cognitive processes to phe level in PKU is related to timing of sensitive periods. For example, the effect of phe level on visual acuity is high in the neonatal period and steeply declines thereafter, with effects observed 13 years later (Diamond, 2002), while the relationship of current phe level to IQ persists until age 8 or 10 with highly reduced or no effect after that time (Fisch *et* al, 1995; Smith *et al*, 1991). More research is needed on the effect of phenylalanine level in adulthood, however. There is some evidence that there is some neurological effect of phe level in adulthood that is reversible with resumed dietary restriction (Thompson, Tillotson, Smith, Kendall, Moore & Brenton, 1993).

Along with bolstering the empirical evidence for a sensitive period in intellectual development, the cognitive data available on the families of the participants in our sample allow us to test conflicting hypotheses about the causal bases of individual differences in sensitive period length and why it is extended in individuals of higher IQ. As discussed in Brant *et al*

(under revision), it is possible that there is a genetic predisposition towards the delay of neurobiological changes that mark the end of the sensitive period promotes higher IQ. On the other hand, having a higher IQ may increase or prolong sensitivity to the environment. There are empirical and theoretical points in favor of both explanations and we can test both hypotheses by testing for differences in trajectories of change in IQ score depending on either genetic score (measured by mid-parent score) or actualized score at the age at which one would expect a transition from the sensitive period.

It has long been assumed that the negative effects of elevated phe in PKU are additive on top of existing genetic and environmental influences on intelligence in the general population, but this assumption has not yet been explicitly tested. This would mean that mid-parent and sibling IQ should predict IQ score at all ages. Additionally, it should be seen that the effect of phenylalanine level should be equivalent no matter the parental IQ score, meaning that the difference between scores for high versus low lifetime phenylalanine level should be equal for high vs low parental IQ (although potentially changeable for longer into development in the high parental IQ case as described above).

We find that our data is indeed consistent with an additive effect of phenylalanine on genetic background. Linear mixed models additionally suggest that developmental trajectories of change in IQ score are consistent with an extended sensitive period in higher IQ individuals, stemming from actualized IQ score rather than genetic propensity.

Method

Participants and Study Design: The United States Collaborative Study of children with phenylketonuria (PKUCS) was a prospective longitudinal study of children diagnosed early with classic PKU and placed on a phe-restricted diet. Participants were recruited from 19 treatment centers in United States and the study was conducted at these sites between 1967 and 1983. Of the infants identified, 167 met the challenge criteria for PKU and 133 remained active after 6 years, 125 up to 10 years and 98 were followed up to age 12. Children were randomized from birth until 6 years to maintain Phe concentrations in the strict (60-329 μmol) or moderate (330-600 μ mol range). At 6 years of age they were randomized to either stay on a Phe-restricted diet (ideally under 720 μmol) or terminate dietary therapy. Parents of many of the children rejected randomization (24% at age 6, 35% at age 10) but continued in study regardless. The majority of the participants discontinued the diet during adolescence. After a 15-year interval, as many subjects as possible were located and recruited for evaluation, leading to 70 original subjects participating in the follow-up study.

A large battery of physical, health, demographic, and cognitive data (along with neuroimaging of some participants in adulthood) was collected on individuals at intervals throughout the study and at adult follow-up (for further information see Azen, Koch, Friedman, Wenz and Fishler (1996) and Azen, Koch & Friedman (1991), and Koch *et al* (2002) for the adult measures). For the current study the variables of interest were: Age first treated in days; mother's and father's highest years of education; Hollingshead Socioeconomic status (Hollingshead, 1975); Mother's and Father's IQ (measured using the Wechsler Adult

Intelligence Scale; Wechsler, 1958); and age-appropriate IQ tests at ages 4,6,7,8,10,12 and adult (see table 1 for details). IQ of one sibling was also examined using the WISC (Wechsler, 1949) where possible.

Blood Phe level was monitored weekly during the first year of life and monthly after that. Assessments were made every three months after diet discontinuation. Median Phe level for a 6-month period was calculated for each child. For this study, these 6-month median values were averaged for the periods between intelligence measurements and used as the phe level modeled at each age. For the adult follow-up Blood Phe concentration was assessed at one to several times during adulthood and Phe levels were aggregated in age bins from 12-18y.o., 18-24 y.o. and 24-30 y.o. Most participants had just one measurement, but several had 2 or three measurements. For this study we averaged these scores to give one adult value for blood Phe concentration.

Parental IQ and parental education were aggregated for this study (a mean was calculated or the value for a single parent if only one was available).

Statistical Analysis*:* The analysis of this data had two goals. To establish that the effect of phenylalanine level on intellectual ability in PKU is additive on polygenic background, we examined correlations between adult IQ and both sibling and mid-parental IQ. We then examined average intelligence scores participants at each age for participants at each of the measured ages with that of the siblings. Mid-parent IQ is the most accurate measure of the genetic "potential" in the offspring and is used here to predict the score of the participants in the PKUCS sample had they not suffered the negative effects of high Phe on intellectual ability. The sibling IQ serves as a matched control for the subject's scores.

The second goal of our analysis was to model the decrease in IQ score over time and assess whether this change (particularly towards the end of development) interacts with either genetic propensity (mid-parent IQ) or actualized IQ at the point at which no further decrement on IQ from an uncontrolled diet would be expected. To do this we performed linear mixed-model regression analysis on the IQ scores, which allows multiple measurements per person to be included and within-individual variation to be controlled. It additionally allows individuals with missing values to be included in the analysis. Polynomial models for age effects were examined and a cubic model was found to fit the data best. We tested whether the relationship between IQ and age was dependent upon mid-parental IQ or IQ score of the subjects at age 10. Both these variables were tested as categorical contrast codes, using the mean score as a distinction between high and low scores. Along with age and the IQ metrics described, we also modeled age at first treatment, parental education level and parental SES, although parental education and parental SES were subsequently dropped, as they were not predictive over and above mid-parent IQ (which was included in all models). Blood Phe concentration at each age, calculated as described above, was also modeled and allowed to interact with age. (This interaction was significant for linear age). These variables were all modeled as fixed effects and random intercepts and slopes for age were both found to be significant sources of variance. Age was centered at 6 so that the intercept reflected initial values; parental IQ, phe and age at first treatment were mean-deviated. Auto-correlated within-subject errors were also modeled. The analysis was conducted using the *nlme* package in *R* (Fox, 2002).

Results

Table 1 displays descriptive statistics for IQ score at each age and average phe concentration in the developmental period immediately before each age. Several patterns are clear from this data. Firstly, there is a general pattern for IQ to decline through development to adulthood. Secondly, the estimates for IQ at age 4 are unexpectedly low. It is known that the 1972 Stanford-Binet norm procedure gave low estimates of IQ compared to other assessment measures (Thompson, 2006). Age 4 scores were therefore excluded from subsequent analysis to more accurately model the rest of the age-related change in IQ.

Table 1: Sample summary statistics

	Age 4	Age 6	Age 7	Age 8	Age 10	Age 12	Adult	Sibling	Midparent IQ	Midparent Education (yrs)	Childhood SES	Age first treated (days)
IQ Test	Stanford-Binet	Stanford-Binet	Stanford Binet	WISC	WISC	WISC-R	WAIS-R	WISC	WAIS			
Mean score	94.3 (16.5)	98.5 (15.4)	98.7 (14.0)	99.2 (12.6)	98.7 (12.8)	95.0 (14.0)	96.3 (15.0)	106.4 (10.9)	107.3 (11.5)	12.7 (2.2)	3.5 (1.1)	21 (15.1)
Mean blood Phe	511 (169)	1190 (519)	1130 (487)	1152 (488)	1249 (495)	1248 (450)	1256 (409)					
N	126	130	120	115	105	99	72	62	123	108	107	136

It can also be seen that average mid-parent IQ and sibling IQ are very similar with similar standard deviations, while the mean IQ for the probands is around 9 points lower with larger standard deviations, suggesting that excess phenylalanine has a significant negative effect on intelligence and the variability in phe concentration in the sample is an additional source of variation on top of the typical genetic and environmental influences on intelligence. It appears that the majority of the negative effect of Phe occurred before age 4. Age at first treatment is a marginally significant predictor of intelligence, which partially accounts for this. Finally, it can be seen that average phe concentration increased over time, reflecting cumulative loss of dietary control in the sample and increasing variability in dietary adherence.

The correlation between sibling and mid-parental IQ in this sample is .68 (95% c.i. = .52-.79) and between proband adult IQ and mid-parental IQ is .53 (95% c.i. = .32-.69). This suggests that mid-parent IQ is more predictive of sibling IQ, although the correlation for proband IQ is still large. This again suggests that the same genetic and environmental influences are operating in the siblings and controls, along with another unrelated source of variability. Phe level has a low to moderate correlation with parental IQ, meaning that much of the variability in phe is random with respect to parental IQ.

Figure 1 plots mean IQs at each age calculated according to a mean split on IQ and high or low lifetime phe concentration. Lifetime phe is coded high or low if it is above or below 900 μmol. This value was chosen as it is a regularly used distinction in the previous literature on PKU and is the lower-bound of diagnostic phe concentration for moderate PKU.

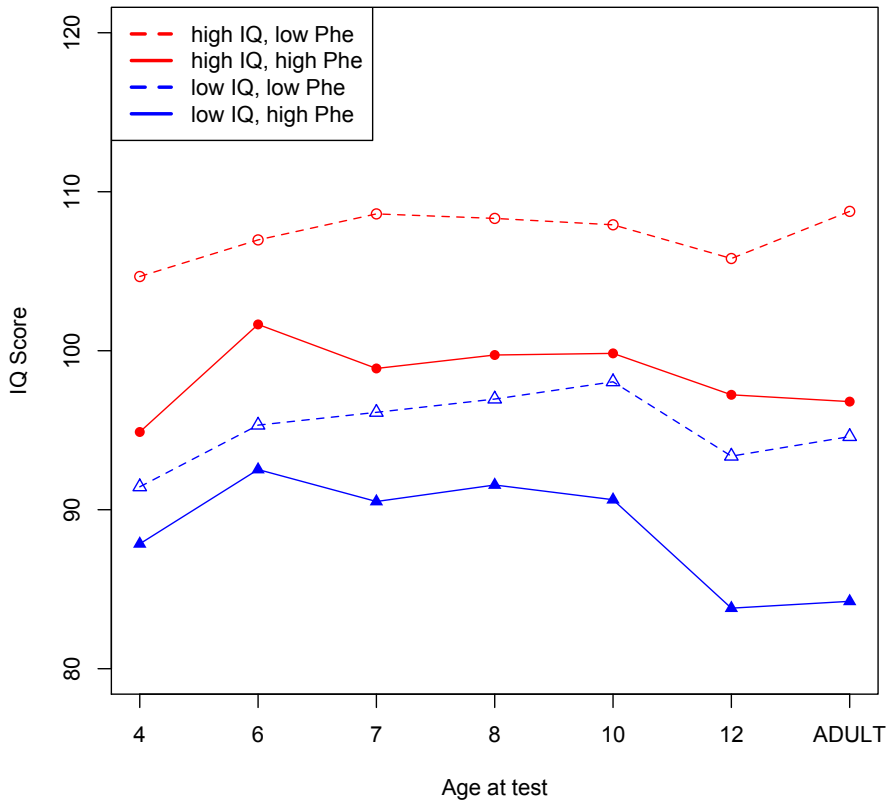


Figure 1: Mean Proband IQ at each measured age according to predicted IQ and lifetime Phe concentration (above/below 900 µmol/liter).

As suggested above, higher parental IQ translates to a higher IQ at all ages in the proband sample. It can also be seen that phe concentration has an effect on mean IQ both at the beginning of the assessment period and throughout. The trajectory of change is largely the same between low and high predicted IQ and low and high phe concentration (although the decrement is lower in those with an overall better-controlled diet). This pattern is strongly suggestive of the effect of phe being an extra environmental contributor to intellectual ability in PKU sufferers that acts proportionally with respect to existing complex genetic (and likely environmental) influences that operate in unaffected individuals. For comparison, the values for high/low mid-parental IQ are 111.9 and 100.5 respectively, this difference (11.4 points) is slightly less than that in PKU sample in adulthood (15.7) but equivalent to that at age 10 (10).

In examining whether evidence of a sensitive period is detectable in the data, it isn't immediately clear in this sample that the influence of Phe stops at any particular age.

Linear Mixed Models

Fitting linear mixed models as described earlier in Methods demonstrated a cubic effect of age on IQ in our sample. We found a significant interaction between dichotomized IQ at age 10 and both the linear and the quadratic age terms in the model ($\beta = 1.52$, $p = .002$ and $\beta = -.06$, $p = .003$ respectively) and a similar result (with larger effect sizes) is found for age 12 IQ ($\beta = 2.35$, $p = .02$, $\beta = -.1$, $p = .01$ respectively). Such an interaction was not observed for parental IQ ($ps > .9$). To examine these patterns further, we plotted the fitted values from these regressions according to the actualized IQ variables (high/low IQ at age 10 and high/low IQ at age 12)

Figures 2 and 3 present the fitted values or these models. It can be seen that the patterns are identical and it is likely that the significance of age 10 IQ comes from its high correlation with age 12 (r = .87). For those with lower actualized IQ, IQ declined increasingly between ages 6 and 12 before leveling out between age 12 and adulthood. Individuals displaying higher actualized IQ on the other hand displayed an initial gain in IQ until age 8, followed by a decline that persists until the adulthood measurements (decline between age 12 and adulthood = 2 IQ points). Figure 4 graphs the fitted values in a model that omits these interactions. Decline in IQ score is seen between ages of 7 and 12, which levels out after age 12. Across all of these models the net loss of IQ throughout the developmental period studies is 5 points.

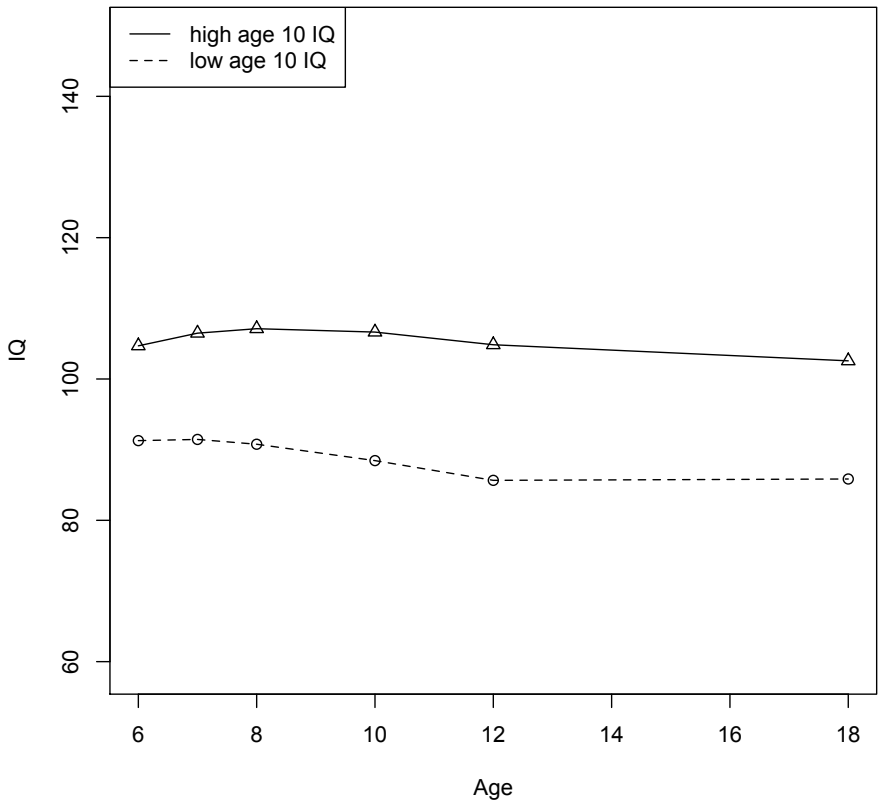


Figure 2: Fitted values for linear mixed model of age changes in IQ including actualized IQ at age 10 as a dichotomized interacting variable.

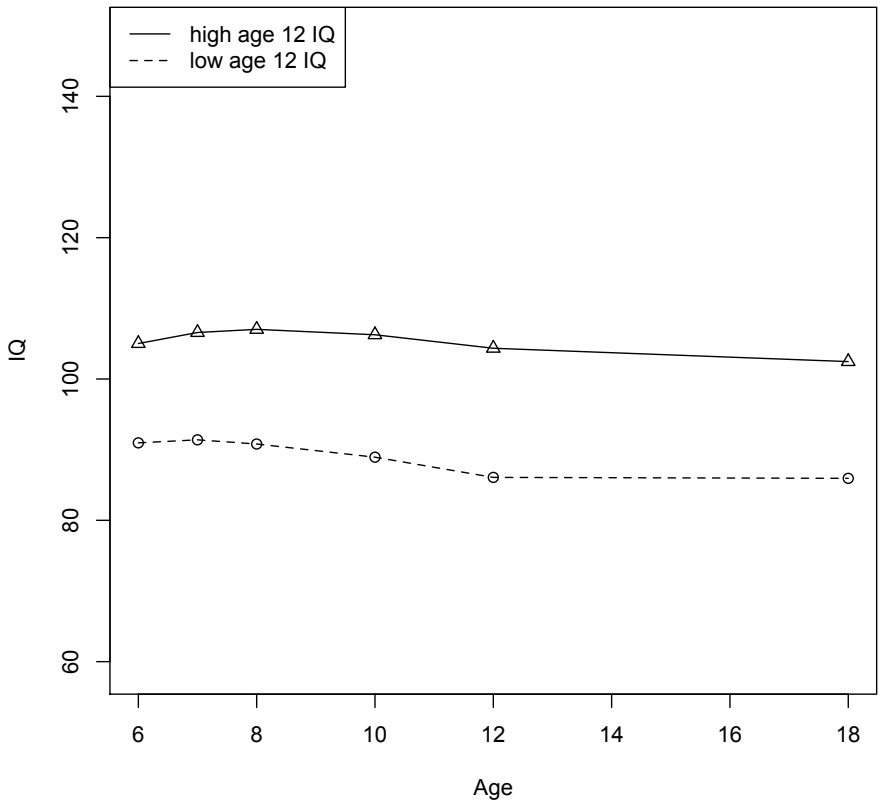


Figure 3: Fitted values for linear mixed model of age changes in IQ including actualized IQ at age 12 as a dichotomized interacting variable

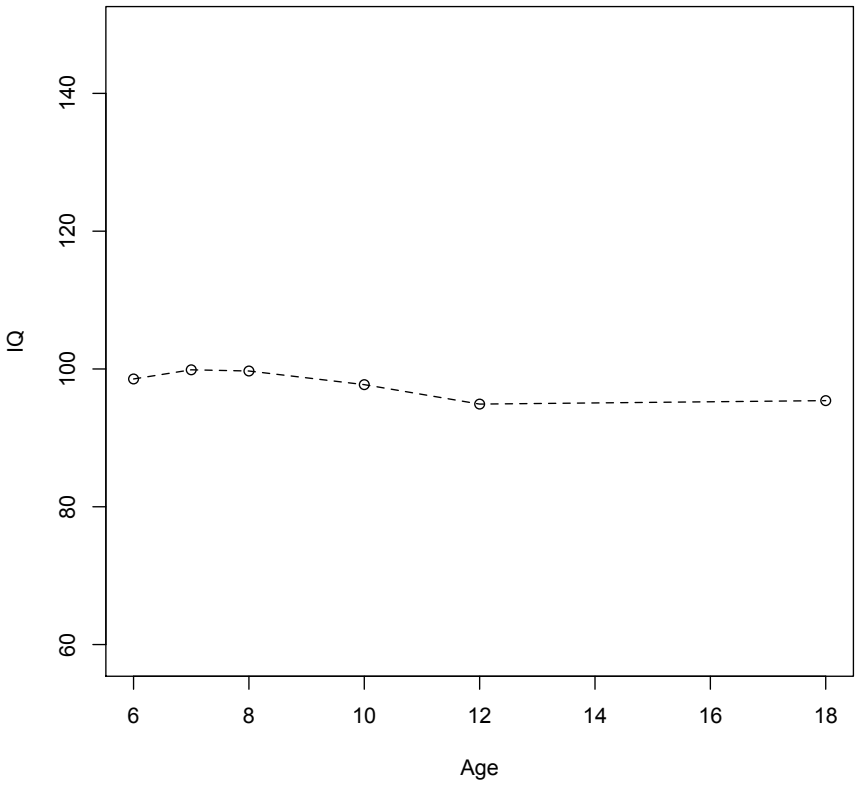


Figure 4: Fitted values for linear mixed model with no modeled IQ-age interaction

Discussion

This study has utilized a sample of individuals with PKU, a naturally occurring clinical disorder in which a single accurately measurable environmental measure has a large effect on IQ, to test hypotheses about the existence and nature of sensitive periods in intellectual development. We first established that blood phenylalanine concentration had a detrimental effect on IQ that acted additively on genetic and environmental influences that operate in unaffected individuals. We additionally found that the influence of excess Phe was largely identical no matter the genetic "potential" of the probands. These observations are important as they demonstrate that the developmental processes that underlie intellectual growth in PKU sufferers are similar to those acting in the general population and that observations made in this sample with respect to developmental changes in environmental sensitivity can inform us about normative developmental processes.

The trajectory of change in IQ from age 6 to adulthood was modeled and a cubic trajectory was found to best fit the data. There was an increasing decline in IQ until age 12, with no further decline occurring between age 12 and adulthood for the sample as a whole. This pattern is consistent with the existence of a sensitive period for the influence of PKU on intellectual ability, and for environmental influence on IQ more generally, in with line our earlier findings using behavioral genetic methodology on community samples (Brant *et al*, under revision) and with results in developmental neuroscience (e.g. Shaw *et al*, 2006).

We also examined whether this sensitive period was extended in individuals with either a genetic potential for high intellectual ability or who actually expressed higher IQ at the point in development where the closing of the sensitive period is typically seen. Testing the predictability of these two metrics allowed us to additionally test causal factors underlying individual differences in the length of sensitive periods. We found no difference in trajectories of change for IQ depending on genetic potential measured by mid-parental IQ. We did, however, find significant differences in the trajectories of change according to actualized IQ score at age 10 and at age 12, the pattern being the same for both ages but pronounced when age 12 was the metric used. Since the correlation between IQ at age 10 and IQ at age 12 is high (.87) it is likely that the interaction is being driven by the age 12 predictor and the significant interaction at age 10 is due to age 10 score being a strong predictor of age 12 score.

Specifically, we found that, compared to the higher IQ group, the group that showed a lower actualized IQ showed a steeper decline in score during development, which leveled out at age 12 and remained stable between age 12 and adulthood. This pattern closely resembled that for the full distribution of ability. Individuals with higher actualized IQ, on the other hand, showed a later, shallower decline that continued through to adulthood. This is a direct demonstration that, as predicted, there is an extended sensitivity to the environment in individuals of higher IQ and additionally suggests that this extension is driven by online IQ instead of being determined early on by inherited propensity, suggesting that having a higher IQ increases one's sensitivity to the environment, rather than length of environmental sensitivity being genetically determined. As suggested by Knudsen (2004) heightened attention, as one might find in individuals of higher IQ, could allow plasticity to occur later in development. On a

related note, individuals of higher IQ may be more open to experience, more likely to try things and change in response to experience, whereas lower IQ individuals are less motivated as they do not get as much positive feedback from learning experiences. This result should be replicated in independent samples and further research is necessary to determine how feedback from increased cognitive ability would extend the sensitive period and delay the neurobiological changes that contribute to its closing.

The causal factors behind the cognitive deficits in PKU are not well understood but three main factors are thought to contribute to functional and structural neurological effects: Overt neurotoxic effects of excess phenylalanine; competition between phe and tyrosine and tryptophan for transport proteins at the blood-brain barrier; and diminished protein synthesis in the PKU brain. Observations in support of this come from *in vitro* neuronal cultures and a mouse model of PKU, along with examination of treated and untreated human PKU brains, both postmortem and via structural imaging. Several of these overlap with normative changes during development, as will be discussed below.

Examination of the brains of untreated phenylalanine patients demonstrates severe impairments of brain architecture and retardation of maturation, including abnormal, myelination patterns, cell density and organization. Abnormalities in dendritic arborization and reductions in synaptic density have also been observed (Bauman & Kemper, 1982).

Application of phenylalanine to *in vitro* neuronal cultures has been used to more closely examine developmental effects. Primary cortical neurons treated *in vitro* with phenylalanine showed only a small increase in synaptic density between 12 and 21 days in vitro compared to the exuberant increase seen in untreated controls, suggesting a negative effect on synaptogenesis (Hörster *et al*, 2006). Ding *et al* (2008) have demonstrated using magnetic resonance imaging (MRI) that, although morphologically normal, the brains of treated PKU patients show increased cell packing density.

Perturbations in glutamatergic synaptic transmission have been demonstrated with application of Phe in ranges seen in the PKU brain, particularly in the make-up of NMDA and AMPA receptors. As reviewed by tyuk, Glushakov, Sumners, Laipis, Dennis & Seubert (2005), studies in their lab demonstrate that overall glutamatergic transmission is significantly depressed by a combination of pre and post-synaptic actions. Experiments using forebrain tissue from heterozygous and homozygous (PKU) mice demonstrate that expression of NMDA receptor subunit NR2A is significantly increased and NR2B decreased in hyperphenylalanininemic homozygotes compared to the heterozygotes. Expression of AMPA receptor subunits Glu1 and Glu2/3 is also increased.

PET studies show a reduced uptake of F-DOPA at the blood-brain barrier and reduced levels of tyrosine are seen postmortem in untreated PKU brains. Reduced concentration of catecholamines (including dopamine), serotonin and their metabolites are found in the CSF of PKU patients. Dopamine deficits are thought to be related to prefrontal deficits in PKU, although it is unclear whether the deficits come from tyrosine deficits *per se* or reduced production of

tyrosine hydroxylase caused by excess phe levels (Groot, Hoeksema, Blau, Reijngoud & von Spronsen, 2010; Martynyuk, van Spronsen & Van de Zee, 2010). Disorders of myelination, appear to be due to hypomyelination in untreated patients, but increased water content of myelin in early treated patients. These deficits appear to be reversible with adherence to a low phe diet (Anderson & Leuzzi, 2010).

Several of these neurological alterations relate to changes that occur during normal development. It is known that there is a period of exuberant synaptogenesis in childhood of variable length depending on cortical area (Huttenlocher, 1997; Petanjek *et al*, 2011; Shaw *et al*, 2006). It is known that the proportion of AMPA receptor subunits Glu2 increases during development, reduces the permeability of AMPA receptors to calcium (Kumar, Bacci, Kharzia & Huguenard, 2002). The ratio of NR2A to NR2B NMDA receptor subunits also increases through development and the varying receptor make-up is thought to contribute to patterns of synaptogenesis and synapse stabilization (Gambrill & Barria, 2011). There is evidence of changes in dopamine tone during adolescence, relative to childhood or adulthood (Wahlstrom, White & Luciana, 2010). Finally, there is a linear increase in myelination throughout development, well into the third decade of life (Westlye *et al*, 2010), which is thought to partially mediate network refinement during adolescence (Hagmann *et al*, 2010). This overlap between PKU related brain alterations and normative changes is further evidence of the additive effect of excess phenylalanine in reducing IQ on top of existing genetic and environmental influences on intellectual ability, perturbing cumulative changes that contribute to positive outcomes. It additionally suggests that the closing of the sensitive period would limit the effects of excess phe on IQ, which the results of this study demonstrate.

A potential issue with the analysis presented here is that of regression to the mean. Since the sample is dichotomized for actualized IQ at ages 10 and 12, extreme high and low scores at these ages are expected to be followed by scores that are closer the mean score (a lower subsequent score in the higher IQ case and a higher score in the lower IQ case). There are three factors that argue against this as the explanation for our results. Firstly, while the score for higher IQ individuals goes down on average, the same is not the case for lower IQ individuals. Secondly, whether choosing on age 10 IQ or age 12 IQ the same trajectory is seen, which would not be expected if regression to the mean was driving the results. Finally, as age is modeled as a random variable this should account for within-level variation and mitigate against the effects of regression to the mean appearing the coefficients of the fixed effects.

One limitation of the current study is the lack of measured IQ between the age of 12 and adulthood. This means that the strongest conclusion we can draw is that the period of sensitivity of intellectual ability to the environment in higher IQ individuals ends at some point in adolescence. Further research is needed to assess sensitivity at intervening ages to narrow down the transitionary age.

CHAPTER 5: TOWARDS A COMPUTATIONAL MODEL OF THE PROCESSES UNDERLYING INDIVIDUAL DIFFERENCES IN INTELLECTUAL DEVELOPMENT

Introduction

Studies 1-4 in this thesis have focused on examining empirical evidence for a sensitive period for intellectual development that is extended in individuals of higher IQ. The collective evidence, though not definitive, is indeed supportive of such a pattern and suggests that actualized intellectual ability in later childhood is an important factor in extending the sensitive period. What has not been addressed thus far is how neurobiological changes during development contribute towards the emergence of a sensitive period and its close and why an extended sensitive period may be beneficial in the development of high IQ. This is a challenging endeavor and requires integration over several levels of analysis: lower level neurobiological functional changes, patterns of developmental structural change (the patterns of synaptogenesis and pruning observed by Huttenlocher & Dabholkar [1997] and others and reflected in the structural MRI studies of Shaw and colleagues [2006;2008]), sensitivity of the system to environmental change and effects of cognitive change on ultimate performance. It additionally requires identification of potential sources of individual differences and an exposition of their biological and cognitive effects.

Neural network models, particularly connectionist models are a important and useful tool to examine developmental phenomena at a systems level and provide insights into mechanistic processes tying together brain and cognitive development (Munakata & McClelland, 2003; Thomas & Johnson, 2006; Thomas & Karmiloff-Smith, 2003; Westermnn, Sirois, Shultz & Mareschal, 2006). Models allow one both direct control over the conditions under which learning proceeds and unrivaled capacity to observe processes of cognition and network behavior resulting from these conditions. These factors, in combination, allow detailed exploration of the necessary and sufficient conditions for the emergence of the phenomena of interest in a fashion that follows observed developmental trajectories. It additionally allows one to gain new insights into *how* such a pattern emerges and generate new hypotheses for empirical research to falsify the model. As noted by Thomas & Johnson (2006): "Implementation forces clarity, reveals hidden assumptions and generates new candidate explanations and testable hypotheses".

One important decision that must be made when building a model is whether to rely on a static architecture and observe cognitive change resulting from the change in connection strength between nodes in the model as the network learns, or to implement structural change during learning - this latter technique has been named Connectionist Developmental Cognitive Neuroscience (CDCN; Westermann *et al*, 2008). Structural changes have been implemented using "generative" or "constructivist" models in which new units are added according to an algorithm (ordinarily units are added when network performance asymptotes; e.g. Fahlman & Lebiere, 1990; Baluja & Fahlman, 1994). The modeling of maturational change in activity dynamics within developing networks (resulting from changes in e.g. neurotransmitter systems

or receptor function) has been less of a focus of research, although it is known that such changes occur during development, as will be discussed below in the rationale for our own developmental model.

These two different approaches to developmental neural network modeling reflect two different conceptualizations of the developmental process, which are reflected in previous attempts to model the processes underlying sensitive periods in brain and cognitive development. As described by Thomas & Karmiloff-Smith (2003), a static architecture (stable number of processing units, connectivity and learning algorithm) in which development is taken to consist of changes in connection strengths between units as a result of experiential exposure (repeated training on the task of interest) reflect the inherent assumption that learning and development are qualitatively analogous. Generative models, on the other hand, assume that weight changes resulting from learning are insufficient to model developmental trajectories and alterations in network architecture are therefore necessary.

Thomas & Johnson (2006; 2008) describe three broad explanations for reductions in plasticity that accompany the end of sensitive periods and how previous computational models have simulated sensitive period effects in several cognitive domains:
Self-terminating learning is consistent with the development as learning framework described above and was demonstrated by O'Reilly & Johnson (1994). Their model of imprinting in chicks demonstrates that extended exposure to one set of stimuli can prevent learning about new inputs, successfully capturing the critical period characteristics of this infant behavior. Stabilization of constraints can refer to stabilization in inputs or a change in the organism that prevents new

inputs from being interpreted as different (e.g. due to representations developed from prior environmental exposure). McClelland, Thomas, McCandliss & Fiess (1999) demonstrated that the loss of distinction between /r/ and /l/ in native Japanese speakers can be the result of exposure to insufficiently distinct early experiences of the phonemes resulting in overlapping activation patterns that limit subsequent learning. Finally, implementing endogenous maturational changes acknowledges the potential importance of these modifications in observed developmental patterns. This was implemented by Thomas & Karmiloff-Smith (2002) by pruning a percentage of connections with low strength after an initial period of learning. This modification proved to be an important factor in the ability of their model to simulate patterns of acquisition of the English past tense and age effects in recovery from damage. This imposed change in connectivity was also shown to interact with model characteristics reflecting the above-mentioned learning effects in limiting plasticity in static networks, along with competition for computational resources.

A further consideration is how to model individual differences. The initial parameter settings in models in terms of initial connection strengths, characteristics of the learning algorithm and the activation function of neurons are variable and set by the modeler at the beginning of training. Manipulating any of these features will potentially lead to individual differences in network behavior, plasticity and performance. Adding endogenous maturational changes to a model adds another source of individual differences, namely the rate of endogenous change. For example, in the Thomas & Karmiloff-Smith past tense model, either the probability of pruning or the threshold for low connection strength could be systematically varied.

Taking these computational considerations into account, as well as the specific cognitive considerations in constructing a developmental model of the domain general capacity of intelligence and the extant literature on the neurobiological changes that underlie and accompany sensitive or critical period plasticity, we have designed a model framework to investigate relationship between maturational events, structural and cognitive change and behavioral outcome. The key decisions that need to be made are outlined as well as our decisions on how to tackle these questions. We end with a summary of results so far and a plan for further research.

Considerations in a modeling framework for intellectual development

What is the most appropriate task to simulate the development of intelligence

Choosing a model to simulate the development of intelligence differs slightly from the typical aims of connectionist models, which concentrate on modeling a specific task. For the purposes of our investigation, we were interested in modeling a basic characteristic of cognitive processing that underlies the varied cognitive tasks that make up an IQ test. An additional consideration was the fact that individual differences in IQ, although variable throughout development, show some significant early stability (Deary, Whalley, Lemmon, Crawford & Starr, 2000), suggesting that an early emerging cognitive function is an important determining factor in later intellectual ability.

Our chosen task requires pulling out statistical regularities in the inputs from the training environment using a Hebbian, self-organizing form of learning. It is known that efficient infant habituation (Kavsek, 2004), recognition memory (McCall & Carriger, 1993) and representational competence (Rose, Feldman, Jankowski & Van Rossem, in press) is related to IQ, suggesting that the ability to detect statistical regularities in the environment is an early and enduring component of intelligence. One important feature of intelligence is the domain general nature, which may seen inconsistent with progressive task specialization of typical connectionist models. However, if one conceptualizes intelligence as integration across varying modes of sensory input (Johnson and Munakata, 2005) and inputs to our self-organizing model as pre-processed inputs from sensory areas, the model can be thought one of integration and flexible abstract representations.

The model is illustrated in Figure 1 (adapted from O'Reilly & Munakata, 2000). It is a simple feed-forward 2 layer network: A 5x5 unit input layer and an interconnected 5x4 hidden layer. There is no output and therefore no overt performance metric. The Inputs to the network consist of vertical and horizontal lines (see Figure 2, panel a.), which are presented two at a time during training. We inject random noise into the inputs to simulate the fact that statistical regularities in inputs to the brain are presented in the context of other, irrelevant input (This is also necessary for other important aspects of the model, see below). Each network starts with randomized connection strength (weights) between the input and hidden units and learns via self-organizing learning. As every line is presented in combination with every other line, the network is exposed to the full range of co-occurrences within the model environment. The objective is to extract the underlying statistical regularity that these lines exist as reliable collections of pixels,

and to encode the environment in terms of the lines, instead of individual pixels. Performance is assessed by the distinctness of representations in the hidden layer assessed via a testing (non-learning) phase at the end of each training epoch in which the network is presented with each line individually. As the network is exposed to the environment and adjusts its weights accordingly, it should develop representations for each line that are increasingly distinct. Examining a matrix of pairwise distances between the hidden activation patterns assesses the distinctness of representations and both a sum of the distances across the hidden layer and a count of the number of line representations that are unique (applying a threshold for distance to be considered unique) are calculated.

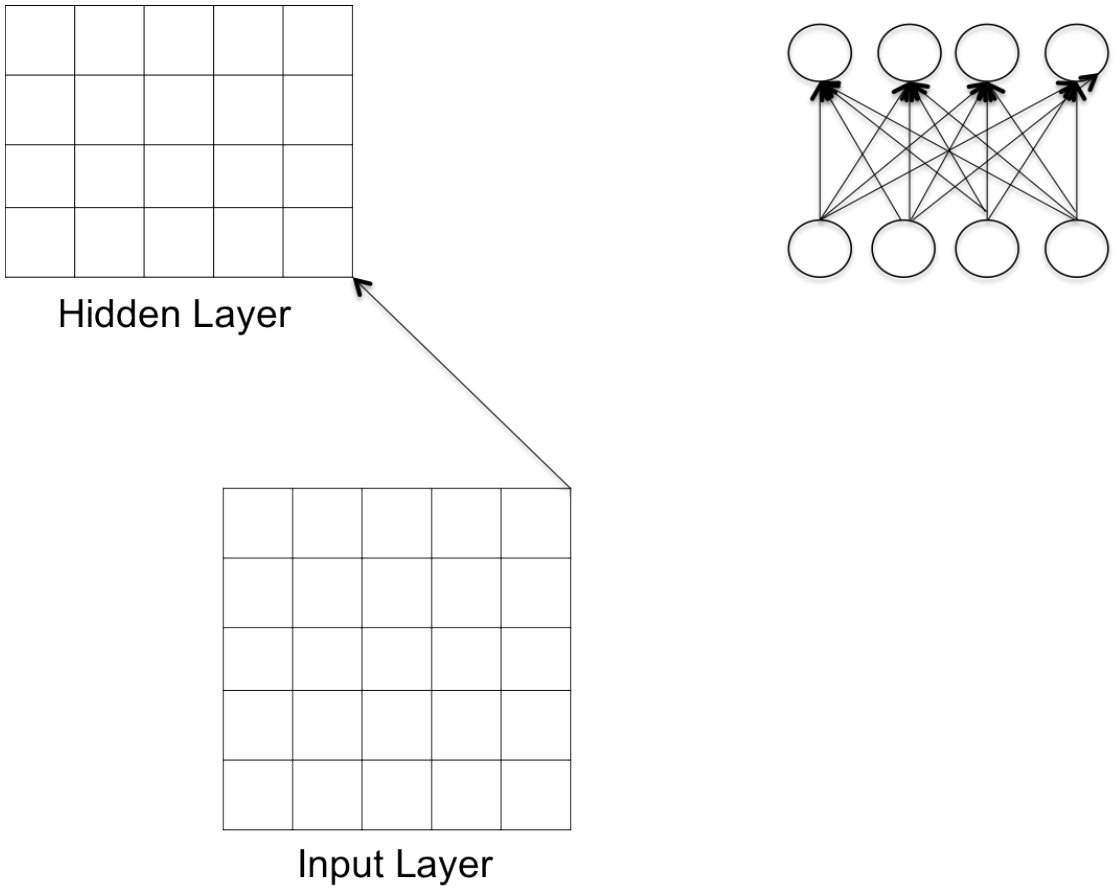
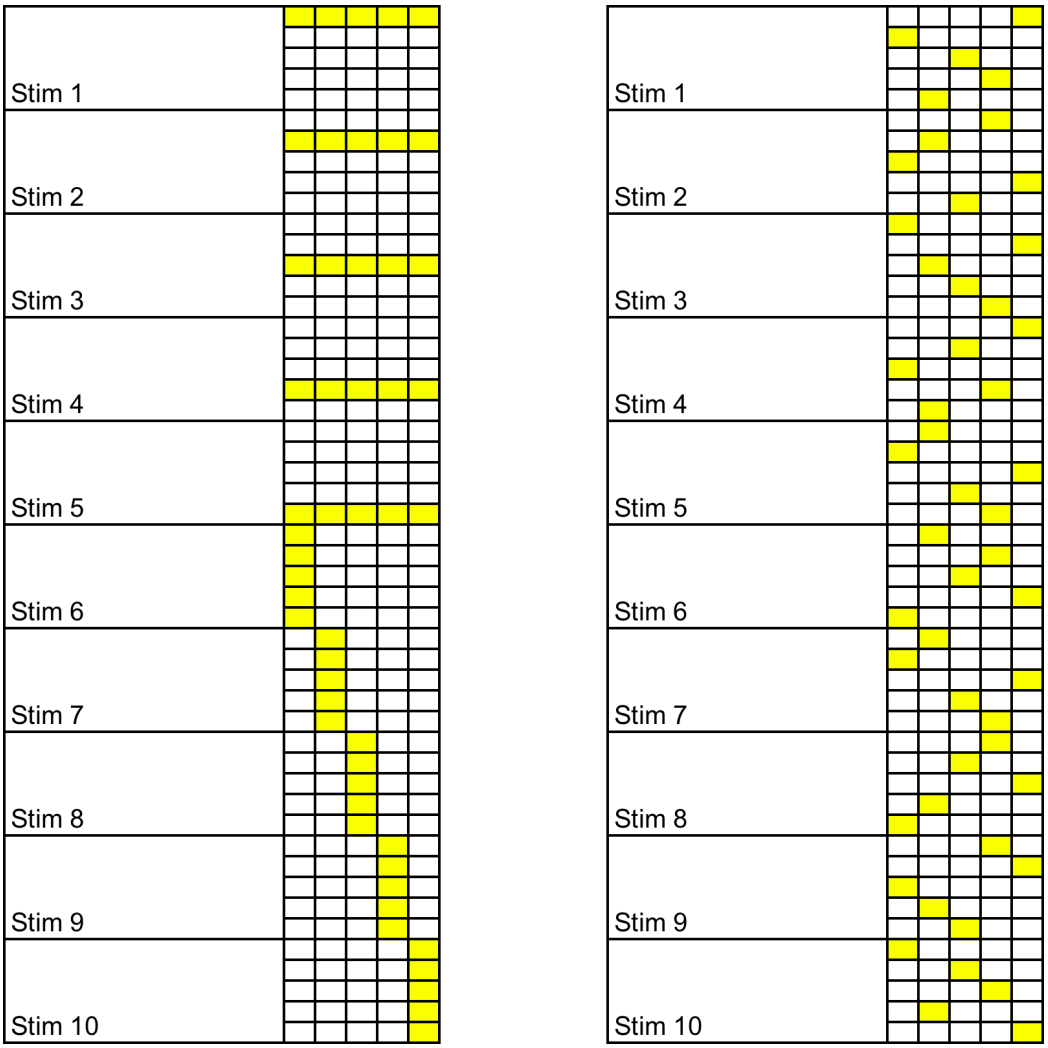


Figure 1: Model Architecture

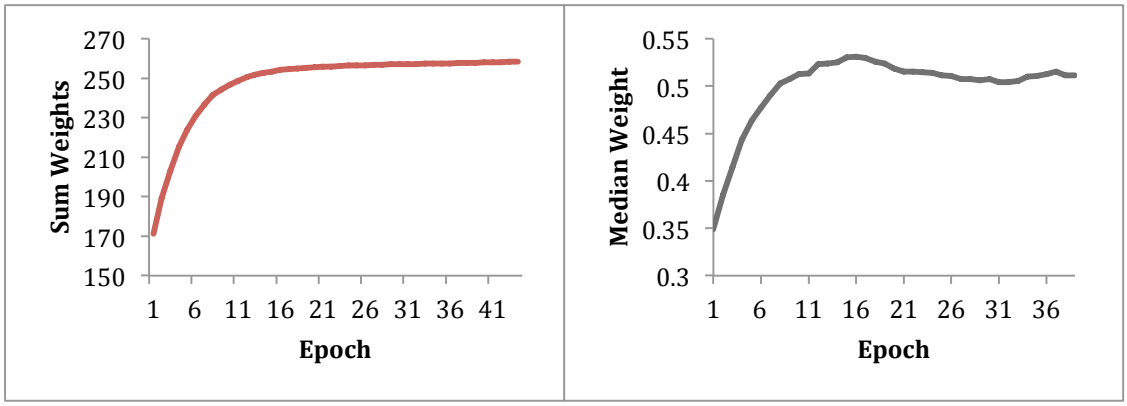


a. **b.**

Figure 2: Model Inputs. a. Initial environment of horizontal and vertical lines and b. new uncorrelated environment presented after a variable number of epochs to assess plasticity to the environment. Stimuli are presented 2 at a time in all combinations during training and one at a time during testing to assess the distinctness of hidden layer representations.

What metric in the model is an appropriate proxy for cortical thickness?

In order to assess whether the structural changes in the model throughout development match those seen during typical development and whether individual differences in sensitivity and performance coincide with patterns of developmental structural change, we examined a proxy measure of cortical thickness in the model. Change in cortical thickness over development coincides with and is thought to reflect an initial period of exuberant synaptogenesis followed by pruning (Huttenlocher, 1997; Shaw *et al*, 2008; Petanjek *et al*, 2011). This increase is followed by a decrease in synaptic connections to be thought of as analogous to connection strength in our model. Figure 3 presents example results from our model for sum of weights and median of weights by epoch. When inhibitory competition is initially low and random noise is injected into the training inputs we see that for the median weight at each age shows an initial increase before decreasing and slightly and the asymptote-ing (which may be due to the lack of explicit pruning in our model). The sum of all the weights displays the same increase but asymptotes rather than decreases. Both the random noise and the initially low inhibitory competition are necessary for this pattern to be displayed.



a. **b.**

Figure 3: Patterns of change in a. the sum of connection strengths and b. the median connection strength in the model to examine proxy measures of cortical thickness.

What individual differences are likely involved and how should these be modeled?: Inhibition/Excitation Balance

Evidence suggests that several changing neurobiological factors show developmental change in expression in a way that is related to critical period plasticity: They are changeable throughout development; absence maintains juvenile levels of plasticity; absence of appropriate experience prevents the changes and altering expression can reinstate critical period plasticity. Much of this evidence comes from examining critical period plasticity in primary visual areas, particularly V1, but it is likely that this processes apply more generally throughout cortex . These include changes in NoGo receptor expression (McGee, Yang, Fischer, Daw & Strittmatter, 2005), increases in cholinergic function (Hensch, 2004), perineuronal nets (particularly CSPGs; Pizzorusso, Medini, Berardi, Chierzi & Fawcett, 2002) and the subunit composition of NMDA receptors (Gambrill & Barria, 2010; Hensch, 2005)

There is converging evidence that the most important plasticity-limiting functional result of these maturational changes is an increase in the inhibition-excitation balance (Hensch, 2005). GABA switches from initial excitatory to mature inhibitory effects on neural transmission early in development in a self-controlled fashion (see Ben-Ari, 2002; Leitch, Coaker, Young, Mehta & Sernagor, 2005), and then increases throughout development (Cui, Wang, Wang & Xiang, 2010). There is a 2- to 3-fold increase in the number of GABAergic synapses in rodent visual cortex from eye opening to puberty (Chattopadhyaya et al., 2004, Huang et al., 1999, Morales, Choi & Kirkwood., 2002). Similar developmental increases have been documented in other sensory cortices and species (Gao, Newman, Wormington & Pallas, 1999, Micheva and Beaulieu, 1995).

This increase appears to be triggered by sensory experience (e.g. Chattopadhyaya et al., 2004, Huang et al., 1999). Dark rearing rodents prevents the typical increase in inhibition (Morales *et al*, 2002) but critical period plasticity can be stimulated in the absence of visual experience, and in mice that lack the ability to produce GABA, by application of diazepam (GAD-65 knockout mice; Iwai, Fagiolini, Obata & Hensch, 2003). Critical period plasticity can be reinstated by reducing inhibitory activity either by environmental exposure or pharmacological reduction of inhibitory activity (Vetencourt *et al*, 2008; Zhou, Panizzutti, de Villers-Sidani, Madeira & Merzanich, 2011). For a detailed review of the evidence for the role of inhibition and the molecular and genetic pathways underlying this effect (particularly the relationship between BDNF, IGF—1 and GABA transmission) see Hensch (2005) & Maya-Vetencourt & Origlia (2012).

For this reason we have decided to examine the importance of increasing inhibition in sensitive period plasticity and test if it is sufficient in itself to account for the structural and behavioral patterns and the observed individual differences.

Inhibitory competition is implemented in the network by the k-winner-takes-all (kwta) function. As shown in figure 4 (taken from O'Reilly, Munakata, Frank, Hazy & Contributors, 2012), ktwa is an approximation of the effects of inhibition in restricting activation in a layer. The inhibitory conductance in the activation function (g_I) is set for all units in the layer such that only the k most units can become active at one time. (for further details see O'Reilly *et al,* 2012). To simulate the increase in inhibition across development we start training with a high k (allowing many hidden units to become active at once) and then reduce it throughout training. Manipulating both initial level of inhibition and rate of increase simulates individual differences

in levels of inhibition. We plan to systematically vary these parameters and examine their effect on plasticity to the environment, change in “cortical thickness” and performance.

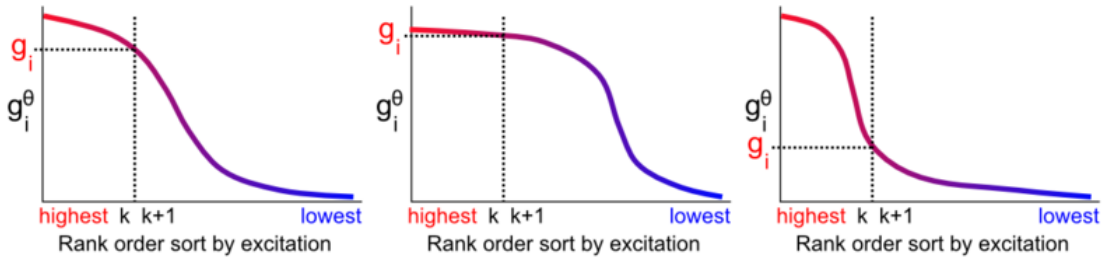


Figure 4: k-winner-takes-all approximation for inhibitory competition in the model (taken from O'Reilly *et al* 2012)

What is the best method for examining environmental sensitivity?

In order to examine the sensitivity of the network to environmental change throughout training, we will introduce new, uncorrelated stimuli (figure 2 panal b.) at varying points during training and examine the network's ability to learn about the new environmental structure. To maximize the capability of the network to adapt to the new stimuli it is necessary that 1. It is uncorrelated with the original inputs and 2. The net input for each stimulus matches that in the original environment (Thomas & Johnson, 2006).

This procedure involves training the model with the same initialized weights and switching to the new stimuli after different epochs of training to assess when the ability to learn the new stimuli is lost or reduced. Comparing this result to the pattern of cortical change and performance (distance between hidden representations) from complete training on the original stimuli allows examination of the full relationship between individual differences in inhibitory development, structural change and behavioral outcome.

This procedure requires automation to allow 1. The same initial random weights to be run several times with different parameters and stimuli 2. New stimuli to be introduced at varying stages of training. 3. Results to be collected and collated for each network and 4. The initial level of inhibition and rate of increase to be systematically varied.

Future directions

So far we have found that reducing inhibition more slowly appears to result in more distinct hidden layer representations, but whether the patterns of cortical thickness change and environmental sensitivity are consistent with this pattern remains to be seen.

Future work in this vein would conduct the systematic modeling and analyses outlined above and start to examine the change in the representational properties of the model throughout development to generate hypotheses about why the pattern of increase in inhibition and the resulting structural patterns are beneficial for cognitive development. Other parameters in the model would be examined to test for the specificity of this effect to changes to inhibitory neurotransmission. The effect of other observed developmental neurobiological changes such as changes in response to excitatory activity and cholinergic neurotransmission would also be examined to assess their importance in cognitive development. Should the change in inhibitory transmission be dependent on changes in these factors, for example? Finally, should differing experiences be the mediator of functional change and differing sensitive period length (after the results from chapter 4 suggest)? If so, how do we simulate individual differences in experience? These are all exciting questions for future research.

CHAPTER 6: SUMMARY AND CONCLUSIONS

6.1 Introduction

This thesis has sought to examine genetic and environmental influences on intelligence, particularly high intelligence and to consider the contribution of variation in the developmental trajectories of change in genetic and environmental influence might contribute to positive intellectual outcomes. The extant behavior genetics literature largely explains the increase in heritability of intelligence throughout development (and the corresponding decrease in the magnitude of the influence of the shared family environment) by reference to an increasing influence of active gene-environment correlation and no qualitative differences between the influences on high IQ and IQ in the normal range. Evidence from developmental neuroscience is, however, indicative of a sensitive period in intellectual development that is extended in individuals of higher IQ. This thesis aims to integrate theory and methods from behavior genetics and cognitive neuroscience to answer the following questions:

1. Is there evidence for a prolonged influence of the environment in individuals of higher IQ in a manner consistent with an extended sensitive period for intellectual development?
2. Are any observed individual differences in sensitive period length related to genetic predisposition or does high intelligence itself prolong environmental sensitivity?
3. How do typical neurobiological changes during development support the cognitive changes that underlie the emergence of adult intelligence and the characteristics of

sensitive periods? How does this inform the question of why an extended sensitive period is beneficial to cognitive development?

6.2 Empirical Findings

The main empirical findings were summarized in chapters 2-5. This section will synthesize these findings in order to answer the main research questions.

1. Is there evidence for a prolonged influence of the environment in individuals of higher IQ in a manner consistent with an extended sensitive period for intellectual development?

a. The influence of the family environment is prolonged in individuals of higher IQ in a pattern that is consistent with an extended sensitive period.

b. The decline in IQ score throughout development observed in Phenylketonuria sufferers levels off in late childhood but is extended in individuals of higher IQ.

2. Are any observed individual differences in sensitive period length related to genetic predisposition or does high intelligence itself prolong environmental sensitivity?

a. The length of the sensitive period in intellectual development is related to actualized IQ in late childhood rather than a genetic "predicted" score based on mid-parent IQ.

3. How do typical neurobiological changes during development support the cognitive changes that underlie the emergence of adult intelligence and the characteristics of sensitive periods? How does this inform the question of why an extended sensitive period is beneficial to cognitive development?

a. The extant neuroscience literature suggests that change in the excitation/inhibition

balance is instrumental in controlling sensitive period plasticity. A computational model was proposed to examine the relationship between length of environmental sensitivity, changes in cortical thickness and intellectual outcome, initially examining whether increases in inhibition are sufficient to explain the relationship between these 3 factors.

6.3 Theoretical Implications

Our results are supportive of the extended sensitive period hypothesis of Shaw and colleagues (2006; 2008). This is a potentially important finding in that it ties together results from individual differences psychology (particularly behavior genetics) and those from developmental science in ways that have not typically been attempted before. It also pieces together what may seem somewhat conflicting findings in the respective fields: that intelligence is a trait that requires learning about the world and develops cumulatively on the one hand, and on the other hand that there is a large genetic component to intelligence. These apparently paradoxical factors can be squared if one posits a sensitive period for brain organization, which is limited, by neurobiological changes and expression of new genetic influences. This focus on synaptic changes and neural plasticity as the basis of intelligence also gives a framework within which to conceptualize the genetic influences on IQ that are observable from the beginning of development: Plasticity requires protein expression, inter-individual variation in which will be supported by genetic variation and will accumulate in effect throughout development.

Other researchers that have suggested a role for sensitive periods in the development of intelligence include Michael Thomas (e.g. Thomas & Johnson, 2008; Thomas & Karmiloff-

Smith, 2003) and Dennis Garlick (2002; 2003), although this thesis is the first attempt to directly test this by examining environmental influence on intelligence throughout development. We additionally further theoretical thinking about the causal basis of individual differences in sensitive period length by providing preliminary evidence that high intelligence itself prolongs environmental sensitivity rather than genetic propensity providing a "blueprint" for rate of maturational change. This observation is consistent with theorizing by Knudsen (2004) that characteristics of the most intelligent, such as heightened attention may delay neurobiological changes that limit plasticity at the end of a sensitive period.

The conclusion of this thesis stands in contrast to current thinking in behavior genetics on the reasons for the increase in the heritability of IQ during development. The most widely accepted explanation for this is active gene-environment correlation, in which individuals gain increasing scope to construct their own environments throughout development according to their genetic propensities. Although we do not rule this out as a contributing factor towards increasing heritability, there are several conflicts that our framework presents to this explanation. Firstly, as outlined in chapter 3, a prolonged influence of the shared environment in individuals of high IQ would necessitate that, counter-intuitively, more gifted individuals would seek out supportive environments later in development than less intelligent children. Secondly, it suggests a conceptual understanding of intelligence as a fixed capacity that is expressed throughout development via selection of an environmental niche, whereas the sensitive period framework suggests that intelligence emerges throughout development and that is malleable via plasticity to the environment. Finally, it suggests that heritability should increase gradually through development with gradually increasing self-structuring of the environment, whereas our data is

more consistent with a definite end to the scope of plasticity in adolescence, with more superficial and transient variation occurring after this point.

6.4 Practical Implications

Our work has practical implications in the search for intermediate cognitive phenotypes (endophenotypes) of intelligence and genetic variants that contribute to individual differences in intelligence. It additionally has the potential to aid in the design of environmental interventions and teaching strategies aimed at either promoting high intelligence or correcting intellectual deficits.

The delineation of developmental stages suggests that many brain measures will show a changeable association with IQ over development, suggesting that differing cognitive characteristics will be associated with individual differences in intelligence throughout childhood and adolescence. The computational model described in chapter 5 has exciting potential to inform this work by generating hypotheses on how maturational change affects the nature of representations and patterns of behavior. That individual differences in the rate of maturational change are related to cognitive outcome additionally suggests that genetic variants coding for the substrates of important functional and structural changes will have a greater or lesser relationship to IQ depending on age of the sample. This difference will be even more pronounced if gene expression is examined. This suggests that examining the association of certain genes with

intelligence will be a more powerful method of identifying specific genetic variants, and existing knowledge of critical period changes could inform network-based analysis. Rates of maturational change in e.g. cortical thickness are additionally likely to be a promising phenotype to study instead of cross-sectional measures, pointing to the importance of longitudinal samples in molecular genetic studies of intelligence.

In considering implications of the findings presented here for the design of environmental interventions for promoting intelligence, our work points to several promising avenues, several of which have been previously discussed by Thomas & Knowland (2009). Firstly it suggests that, contrary to popular thinking, intelligence is likely to be sensitive to environmental support well past early childhood up until adolescence. One caveat to this, however, is that teaching may be optimized towards certain skills at differing stages of development, paralleling the trajectory of maturational change in the brain. A related possibility, given the apparent benefit of a prolonged period of "immaturity" in brain development is that accelerated curricula for gifted children may not be the most effective way to foster intellectual excellence. The benefits of prolonged cortical and cognitive immaturity have been posited by several researchers (Bjorkland, 1997; Newport, 1990; Thompson-Schill, 2009).

One final observation in relation to promoting high intelligence and alleviating intellectual deficit is that sensitive periods appear to be extendable or even reversible under certain conditions, both experiential and pharmacological, and our finding that high IQ itself appears to prolong environmental sensitivity. This suggests that particular pharmacological and

environmental interventions could be harnessed to improve cognitive ability even in adults (see Bardin, 2012; Baroncelli, Braschi, Spolidoro, Begenisic, Sale & Maffei, 2010).

Our work will also impact developmental and cognitive scientists more generally, by providing formal support for the existence of critical periods in the developmental trajectory of high-level cognition; critical periods have heretofore been demonstrated to exist only in lower-level processes (such as sensory perception) and in language acquisition. There is some promising preliminary evidence that aberrations in the timing of sensitive period plasticity may be involved in disorders such as autism (LeBlanc & Fagiolini, 2011) and ADHD (Shaw *et al*, 2007). More broadly, our findings are of importance to all those who are interested in the developmental origins of superior cognitive and reasoning abilities.

6.5 Limitations

Some limitations of the studies presented herein should be acknowledged. We cannot unequivocally demonstrate that a sensitive period underlies our results. It is possible that other factors, such as dissipating influence of prior experience that is delayed in individuals of higher IQ explain our results rather than a limitation of plasticity at the end of a sensitive period *per se*. There is, however, no conceptual framework that would predict such an effect as far as we are aware. Secondly, it is not clear why the influence of the shared environment decreases at the end of the sensitive period (as observed in chapters 2 and 3). It may be expected that experience would get "locked in" at the end of a sensitive period, resulting in an enduring level of

environmental influence rather than the decrease we observe. This confusing data point is a lingering uncertainty to be addressed in future research.

Our data and analysis approach did not allow us to assess the exact age at which a sensitive period for intellectual development may typically end, given, for example, the gap in data points between age 12 and adulthood in the PKU sample utilized in chapter 4. Similarly the genetically informative data presented in chapter 3 only allowed us to conclude that the influence of the shared environment decreases at some point during adolescence, and that this shift occurs later for individuals of higher IQ. Future research with longitudinal samples in which more data points are available during adolescence into adulthood will allow a more precise examination of this aspect of our thesis.

Finally, we have yet to investigate whether increases in inhibition are sufficient to explain developmental changes in plasticity and the intermediate representational changes that relate neurobiological maturation to intellectual outcome. Elucidating the answers to these questions is an exciting prospect of our ongoing research plans.

6.6 Conclusions

The problem of how brain maturation supports the emergence of cognitive abilities, particularly the uniquely human capacities tapped by IQ tests, is complex and spans several levels of analysis. The theoretical and empirical work presented herein contributes to efforts to attack this seemingly impenetrable research question by demonstrating how individual differences in behavioral outcome may be related to varying patterns of maturation. In doing so it

points to important directions in understanding the combined contributions of genetic and environmental influences to cognitive ability and disability and how such knowledge can be harnessed to develop strategies to understand and promote cognitive excellence.

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APPENDIX I. SUPPLEMENTARY INFORMATION FOR CHAPTER 3

Supplementary Appendix 1

Below is a fuller outline of the analysis techniques used in the main text, including the regression equations, bootstrap methods and correction of s.e. for double entry of the data.

Twin Methodology and DeFries-Fulker Regression: DeFries-Fulker regression analysis (LaBuda, DeFries and Fulker, 1986) uses monozygotic (MZ; genetically identical) and dizygotic (DZ or fraternal; sharing 50% of genetic variation on average) twin pairs, regressing twin two's score (C) on twin one's scores (P) and the coefficient of relationship (R; 1 for MZ and .5 for DZ pairs). A third term estimating the interaction between the P and R, yields direct estimates the heritability (proportion of sample variance accounted for by genetic influences; h^2) and the proportion of variance accounted for by family-wide environmental influences (c^2). All twin pairs were double-entered, with the twin assignment reversed in the second entry (i.e. twin 1 becomes twin 2 and *vice versa*). In equation 1, β_1 estimates c^2 and β_3 estimates h^2 when the data are suitably transformed. *K* is a constant:

$$C = \beta_1 P + \beta_2 R + \beta_3 PR + K \quad (1)$$

Further extensions to this equation can test changes in the estimations of h^2 and c^2 according to IQ score:

$$C = \beta_1 P + \beta_2 R + \beta_3 PR + \beta_4 P^2 + \beta_5 P^2 R + K \quad (2)$$

In equation 2, β_4 measures the linear relationship between twin 1's IQ score and the predictability of twin 2's IQ score from twin 1's, independent of genetic relationship. This tests for the linear change in c^2 as twin 1's score increases. β_5 measures how this variable differs as a function of the relationship between twin 1 and twin 2 and is the corresponding test for linear change in h^2 (Cherny, Cardon, Fulker &DeFries, 1992). In the cross-sectional GHCA sample, we first applied equation 1 and 2 to the full sample collectively then extended the analysis to examine the effect of age on the estimates derived. The sample was split into 3 age groups, childhood (aged 4-12; n pairs = 6044), adolescence (aged 12-18; n pairs = 4304) and adulthood (ages 18+; n pairs = 549) and orthogonal linear and quadratic contrast codes (*age_lin* and *age_quad*) were constructed and allowed to interact with all the terms in equation 2. In such a regression, $\beta_9 P^2 * age\_lin$ and $\beta_{10} P^2R * age\_lin$ test for a difference between the child and adult age groups on the relationship between ability and the estimate of c^2 and h^2 respectively. β_{16} $P^2 * age\_quad$ and $\beta_{17} P^2R * age\_quad$ compare the estimates for these groups collectively to those for the adolescent group . Applying equation 2 separately for each age group provided estimates for the ability-dependent terms at each age. Additionally, splitting the sample into 6 groups by median splitting each age group on IQ score and applying equation 1 separately for each of these subsamples gave estimates of c^2 and h^2 for the top and bottom halves of the ability distribution in each age goup separately. For this analysis pairs were only double entered if both twins met criteria for the ability cut-off. All reported *p* values for the GHCA sample are derived by bootstrapping the regression estimates in the following way: Twin pairs were sampled at random, with replacement, from a single entered dataset and twin assignment was randomized for each pair. All regressions described were performed on the resulting data and the coefficents

saved. This process was repeated 10,000 times. The standard deviations of the resulting betas were used as s.e.s of the estimates and *p* values we derived by centring the distribution around zero and calculating twice the proportion of the estimates that exceeded the observed value.

In the longitudinal sample, the coefficient of relationship (R) took on the value of 1.0 for MZ and .5 for DZ twin pairs as before. For biological siblings the value of .5 for also used, as they are genetically as similar as DZ pairs. Adoptive sibling pairs took a value of 0.0, as they are not genetically related. An extra variable, the age gap between siblings in days (0 for all twin pairs), was added to equations 1 and 2 and allowed to interact with the estimates of c^2 and h^2: All reported parameters are derived from regressions with age gap included as a moderator. This better enabled comparison of estimates between this sample and the cross-sectional twin study presented above (the estimates for when age gap = 0 to be to most accurate estimate of the maximum effect of shared environmental factors, the influence of which will diminish as age gap increases). If this difference is not modeled the smaller age gap between all biologically related pairs compared to the adoptive siblings will overestimate heritability as the increased correlation, which can reasonably be attributed to both increased environmental sharing in the biological siblings and to genetic influence, will be attributed in the regression purely to genetic influence. Standard errors of the regression estimates are calculated using the method outlined by Koehler and Rodgers (Kohler & Rodgers, 2001) by altering the robust cluster command in STATA (StataCorp., 2007) to give robust standard errors using *n* instead of *n - k -1* as a multiplier (for details see http://www.ssc.upenn.edu/~hpkohler/data-and-programs/twdfeff/twdfeffprograms.html#x1-130005). This method of calculation accounts for the fact that the double entered data are only independent at the level of the twin pair.

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Supplementary Appendix 2

These supplementary materials outline the tests of validity performed on the LTS study sample in an attempt to ensure that the apparent prolonged critical period found in both our samples could not be readily explained by any confounding variables.

Assortative mating in parents of the LTS twins: We tested for patterns of assortative mating for IQ in the parents of the LTS twins. Assortative mating increases between-family variability and therefore manifests as c^2 in the twin design. If assortative mating was higher among higher IQ parents, then this would be a potential explanation for the increased c^2 seen in higher IQ individuals at age 16.

Full-scale WISC-R IQ scores were assessed in parents at the time of intake of the family into either the Twin Infant Project (TIP) or the Longitudinal Twin Study (between 3 and 14 months post partum; the two studies were amalgamated to construct the current LTS). In the event that this information was given twice during this period, the responses were averaged

within parent. If information was available from just one parent, this value was used alone. In total, data was available for 400 fathers and 447 mothers, for a total of 399 families with complete parental information. The mean IQ score for mothers was 104.91 (sd = 12.37) and for fathers 107.50 (sd = 12.89). The correlation between parental scores was $r(399) = .388$, $p < .001$. This demonstrates a moderate amount of assortative mating for IQ in the parents of the LTS twins, which could account for some of the variance attributed to c2. In order to assess whether the extent of assortative mating was different depending on the ability level of the parents, we correlated mean parental IQ and absolute difference between parental scores. The average difference was 11.26 points (sd = 8.68). The correlation between mean parental score and the this difference score was $r(399) = .155$, $p = .002$. This suggests that assortative mating was significantly *less* strong as mean parental IQ score increased. For this reason, patterns of assortative mating cannot account for our results.

Measurement variance in the IQ scale: The second test we conducted was to examine the factor structure of the first unrotated principal component of the intercorrelations among the subtests of the WAIS-III assessed at age 16 in the LTS sample. If the factor structure differs according the ability level then it follows that the measure of full-scale IQ is actually measuring something different depending on the ability of the individual being assessed. This could potentially be a confounding factor in assessing differences in etiological influences depending on IQ score. This has been demonstrated inconsistently in tests of Spearman's Law of Diminishing Returns(Spearman, 1927), which posits that "*The correlations [between different tests] always become smaller—showing the influence of g on any ability to grow less—in just those classes of person which, on the whole, possess this g more abundantly. The rule is, then, that the more 'energy' [i.e., g] a person has available already, the less advantage accrues to his*

ability from further increments of it" (p. 219). To test this hypothesis we followed the methods outlined by Jensen (2003). First we extracted the first unrotated principal component from the 11 subtests for the entre LTS sample measured at age 16 and then successively for those in the sample with IQs measured to be above and below 100 (the population average). Table S1 demonstrates the factor loadings derived from this analysis as well as the proportion of variance explained.

TABLE S1: Factor loadings for the 11 subtests of the WISC-III for the full sample and for the two ability subsamples

Age 16 WAIS-III sub-test	**loading on first principal component**	**Loading full-scale IQ >100**	**loading full-scale IQ < 100**
Vocabulary	.84	.78	.81
Similarities	.71	.58	.65
Arithmetic	.71	.53	.52
Digit Span	.38	.09	.22
Information	.82	.77	.72
Comprehension	.78	.68	.74
Picture Completion	.39	.06	.00
Digit Symbol	.42	.20	.17
Block Design	.65	.34	.19
Picture Arrangement	.35	-.06	.07
Object Assembly	.52	.20	.13
Variance explained by first principal component:	38.80%	22.68%	23.37%

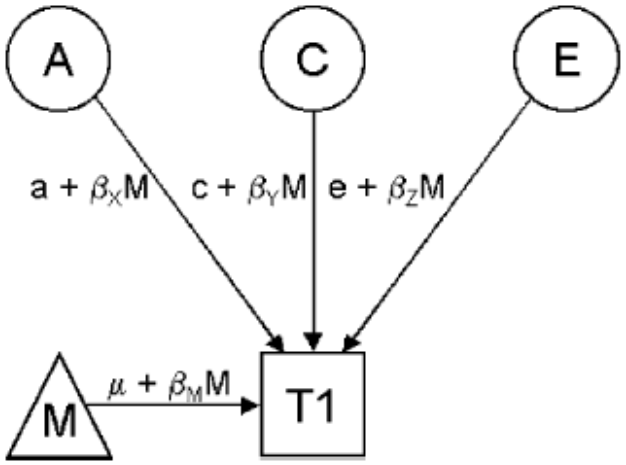
It can be seen that, although all the factor loadings across groups follow the same pattern, the loading and the variance explained are lower overall for the two truncated groups. This is due to the restricted range in the scores resulting from selecting on full-scale IQ score. To compare the factor structure between the two ability groups, we calculated the average intercorrelation for each group using Kaiser's (1968) formula in which the eigenvalue of the first principal component -1 is divided by the number of variables -1 The values were .14 and .16 for above a below 100 respectively. We then used Fisher's (1915) r-to-z transformation to test for a

significant difference between the two values. For this contrast z' = -.20, p = .83. There is therefore no evidence that the proportion of variance captured by the principal component differs between ability levels. Additionally, the congruence coefficient between the factors for the two subsamples was found to be .99, demonstrating the extreme similarity between the factor loadings.

Gene x Environment Interactions: Finally we wanted to rule out unmeasured gene x measured environment interactions as an explanation for our results. Previous studies have shown that the heritability of IQ is moderated by both years of parental education and socioeconomic status (Rowe, Jacobson, Van den Oord, 1999; Turkheimer, Haley, Waldron, D'Onofrio& Gottesman, 2003). In the LTS sample we were able to test the moderating effect of both parental education and parental IQ score on the etiology of age sixteen IQ (both are predictors of socio-economic status). The method of analysis used was the moderated paths variance components model outlined in Purcell (2002) (Figure S1). In traditional biometric models, variance is partitioned into proportion explained by additive genetic (a^2), shared environmental (c^2) and unique environmental influences (e^2), modeling the expected covariance between twins. The moderated paths model adds a continuous moderation of these proportions by an environmental variable. The mean of the trait of also moderated by the environmental variable, which removes the shared variance between the moderator and the trait from the covariance model, meaning that any detected interaction will be between the moderator and variance specific to the trait. This removes any confounding effect of gene-environment correlations (shared genetic influences between the trait and the moderator). In the resulting model the expected mean of the trait T in

twin *i* is $\mu + \beta MM_i$ and the expected trait variance is $Var(T_i) = (a + \beta_x M_i)^2 + (c + \beta_Y M_i)^2 + (e + \beta_Z M_i)^2$.

FIGURE S1: Path diagram for one twin in the GxE interaction model. a, c, e = unmoderated



additive genetic, shared environmental and unique environmental influences. β_x; β_Y and β_Z = moderated components of a, c and e, respectively. β_M = main effect of moderator; M = moderator; μ = grand mean.

Seven variables are therefore estimated in the model: the unmoderated components a,c and e, moderated components β_x, β_Y and β_Z and main effect β_M. Parameters can be dropped successively from the model and -2 log likelihoods (-2LL) can be compared to that of the full model to determine the best-fitting model (the difference between the -2LL has a χ^2 distribution with degrees of freedom being Δdf between the two models).

Years of education was self-reported by parents at the time of entry of the families into the study and information was available for both parents in the majority of families (n = 452). For some families, data for reported more than once at different times and in these cases the

mean of the two scores was used. To construct the variable used in our analyses maternal and paternal years of education was calculated, or if information was only available from one parent this one data point was used (n = 12). Resulting scores were standardized. Mean maternal years of education was 14.26 years (sd = 2.29) and paternal was 14.58 years (sd = 2.52). Full-scale WISC-R scores were used as the moderating IQ variables (details above) which were also standardized. The correlation between twin one's age 16 IQ and parental education was .40 and between twin one's age 16 IQ and parental IQ was .51. Twin correlations above and below the median on parental IQ and parental years of education for both raw age 16 IQ scores and residuals from regressing the parental variables predictors on age 16 IQ.

TABLE S2: MZ and DZ twin intra-class correlations for age 16 IQ in the LTS as a function of parental environmental variables, with and without residualization for shared variance between the two variables

	parental education		parental IQ		parental education (residualized)		parental IQ (residualized)	
cut-off	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ
above median	0.82	0.43	0.78	0.41	0.8	0.39	0.74	0.4
below median	0.8	0.52	0.78	0.41	0.78	0.48	0.76	0.2
total sample	0.84	0.51	0.83	0.5	0.79	0.43	0.75	0.34

Table S3 reports model fit statistics using parental education as a moderator of age 16 IQ etiology. It can be seen that the moderation of the estimates of a2, c2 and e2 by a parental education can be dropped from the model with no decrement in fit. The mean moderation, however, cannot be dropped. The final model gives estimates of $a^2 = .72$, $c^2 = .07$ and $e^2 = .21$.

TABLE S3: Model fit statistics for the moderation model of parental education on age 16 IQ etiology

model	-2LL	df	$\Delta\chi^2$	Δdf	p	AIC
full ACE-XYZ-M	1831.7	392				
drop XYZ	1832.33		0.63	3	0.89	-5.373
drop M	1911.97		80.97	1	<.001	78.973

Table S4 reports model fit statistics using parental IQ as a moderator of age 16 IQ. We found that moderation of c2 and e2 by parental IQ score could be dropped from the model without a decrement in fit, but moderation of the mean of age 16 IQ and moderation of a2 could not. The estimates for etiological influences as a function of standardized parental IQ score are displayed in figure S2.

Table S4: Model fit statistics for the moderation model of parental IQ on age 16 IQ etiology

model	-2LL	df	$\Delta\chi^2$	Δdf	p	AIC
full ACE-XYZ-M	1693.21	378				
drop XYZ	1706		12.79	3	<.001	6.793
drop Y and Z	1693.61		0.4	2	0.818	-3.6
drop M	1825.06		131.85	1	<.001	129.8

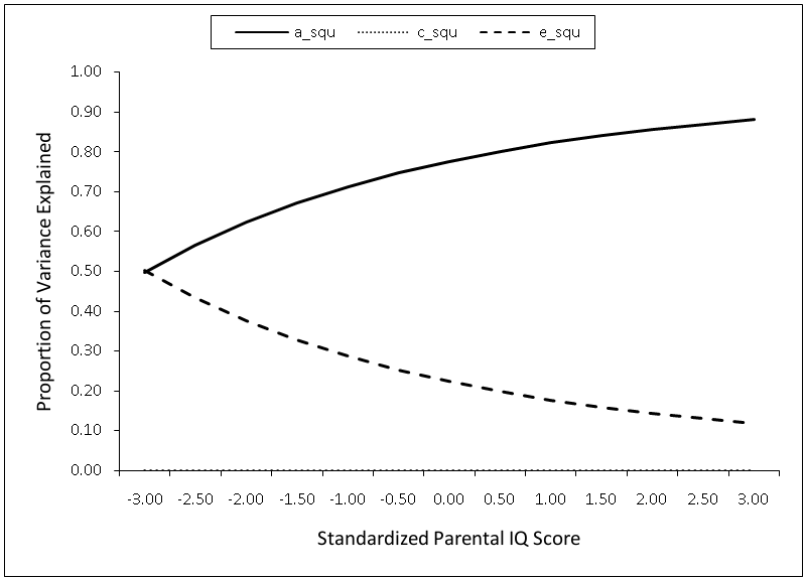


FIGURE S2: Etiological influences on age 16 IQ as a function of parental IQ score

It can be seen that the magnitude of additive genetic influences increases as parental IQ increases, with the relative influence of the unique family environment decreasing. When the shared variance between parental IQ and age 16 IQ is controlled for, there is no influence of the shared family environment at any level of parental education. Importantly, the influence of parental IQ on heritability is in the *opposite* direction to that of the cotwin's IQ score, in which heritability decreases as score increases, and so cannot account for that result.

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