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Understanding heterogeneity in the effects of birth weight on adult cognition and wages

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ABSTRACT

A large economics literature has shown long term impacts of birth weight on adult outcomes, including IQ and earnings that are often robust to sibling or twin fixed effects. We examine potential mechanisms underlying these effects by incorporating findings from the genetics and neuroscience literatures. We use a sample of siblings combined with an "orchids and dandelions hypothesis", where the IQ of genetic dandelions is not affected by in utero nutrition variation but genetic orchids thrive under advantageous conditions and wilt in poor conditions. Indeed, using variation in three candidate genes related to neuroplasticity (*APOE*, *BDNF*, and *COMT*), we find substantial heterogeneity in the associations between birth weight and adult outcomes, where part of the population (i.e., "dandelions") is not affected by birth weight variation. Our results help uncover why birth weight affects adult outcomes.

1. Introduction

A large literature in economics and other disciplines has established the importance of the early nutrition environment, which is often measured by birth weight, on both short and long term outcomes. Short term impacts are most straightforward to motivate, where babies born with low birth weight, from having lower levels of intrauterine nutrition or are otherwise unhealthy, have been shown to have higher infant mortality and have higher medical care costs (Almond et al., 2005; Conley et al., 2006). The existence and magnitude of longer term (i.e., adult) impacts are less obvious but have been the subject of a growing body of work.[1] One motivation for this line of research is the fetal origins hypothesis by Barker (1995) who provides evidence that individuals born with low birth weight are prone to heart disease and type 2 diabetes later in life. In economics, Black et al. (2007) further test and extend this hypothesis by showing that birth weight differences between twins have lifelong impacts on IQ, labor force participation, and earnings. These findings are further supported by a number of natural experiments. A long term follow up of individuals who were in utero during the Dutch Hunger Winter (Stein et al., 1975), in which fetuses were exogenously exposed to poor intrauterine nutrition during the famine of 1944–45, have been shown to have later experienced a range of negative health and economic outcomes (de Rooij et al., 2010; Schulz, 2010). Additionally, individuals in utero during the month of Ramadan, which is associated with diurnal fasting, are shown to have reduced birth weights, leading to reduced mental performance later in life (Almond and Mazumder, 2011).

The biological mechanisms linking poor nutrition in utero and long term effects on cognition are not fully developed, but several hypotheses have been proposed. A tenant of the fetal origins hypothesis is that nutritional insults cause the body to shift resources to the brain, leaving other organ systems prone to future deficits from this critical period of under-development. Heterogeneity in the ability to shift resources as well as differences in the potential plasticity in neurodevelopment suggests there could be varying impacts on cognition as well as health across individuals born with low birth weight.

Even with these hypothesized resource shifts to protect the brain, there is also ample evidence of long term effects on cognition. Most related to the current work is the evidence of effects of early nutrition on cognitive development, particularly IQ in

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[1] See Figlio et al. (2013) and Fletcher (2011) for evidence of "medium run" impacts of birth weight between ages 5 and 18. For "longer run" impacts see Conley and Bennett (2000), Conley et al. (2003), and Hack et al. (2002).

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early adulthood.[2] A positive and statistically significant association between birth weight and IQ has been found in a number of studies and samples (see e.g., Black et al., 2007; Newcombe et al., 2007). For example Newcombe et al. (2007) finds that a kilogram increase in birth weight is associated with a 3 point increase in IQ. Furthermore, this link between birth weight and IQ is found within MZ twin pairs, decreasing the likelihood of spurious results from unmeasured family background or genetics. This has important economic consequences, as IQ has both direct and indirect impacts on lifetime earnings, schooling decisions, and criminal and risky behavior (Heckman et al., 2006; Gensowski, 2013). However, there is currently limited understanding of the mechanisms linking low birth weight with adult IQ and labor market outcomes. Physiologically, emerging evidence suggests that birth weight has a positive, linear association with regional surface area and total volume of the brain (Walhovd et al., 2012). Additional research to further uncover mechanisms could allow us to gain a better understanding of the determinants of adult IQ and productivity as well as, more speculatively, to suggest avenues to target resources at individuals most likely to be affected by low birth weight.

The main idea of the current work is to explore whether genetic variation related to neuroplasticity may be essential sources of heterogeneity in the impacts of low birth weight on adult outcomes. The framework follows that proposed by previous studies examining the moderating properties of particular genetic variants within varied environments.[3] The idea being that certain genetic variants moderate, or amplify, the effects of exposure to a treatment—and this variation in impact may then help us understand mechanisms linking low birth weight with adult outcomes.

In short, our main hypothesis is that candidate genetic variants, which have a previously shown relationship with an ability of the brain to strengthen or rewire neural connections, what we refer to broadly as neuroplasticity, moderate the negative association between low birth weight and later life cognitive performance.[4] With this understanding, we estimate a within-family multiplicative interaction between birth weight and a candidate gene neuroplasticity risk score. To preview our findings, birth weight is shown to have a strong positive association with later-life IQ only for individuals endowed with few neuroplastic variants, whereas the most plastic individuals have no statistically significant association between birth weight and IQ. Furthermore, we are able to control for common environmental conditions amongst siblings, allowing us to account for shared harmful or beneficial post-natal environments that may also influence IQ. The leveraging of the within-sibling genome also allows a quasi-experiment in genetics, as genetic variation between full biological siblings is random and has been labeled as a "genetic lottery" in prior work (Fletcher and Lehrer, 2011; Fletcher, 2011).

1.1. Neuroplasticity

Neuroplasticity refers to the ability of the brain to maintain and strengthen neural connections as well as developing new connections between neurons (Pascual-Leone et al., 2005).[5] It is a constant process of strengthening and replacing neural connections, affecting the structure and function of axons, dendrites, and synapses (Teter and Ashford, 2002). Plasticity is commonly invoked after brain injuries, or insults, such as a stroke; after which, neural networks are re-organized from damaged to undamaged areas within the brain (Frost et al., 2003; Pascual-Leone et al., 2005). Other examples of neuroplasticity are found in the increased sensitivity in touching and hearing in the blind. For our purposes, plasticity represents an ability to respond to environmental shocks—i.e., poor early life nutrition. Individuals with greater plasticity, or individuals who are more able to recover from negative cognitive shocks, should be cognitively robust to a poor in utero environment. In other words, birth weight may not be a major predictor of cognitive development, or earnings, for individuals with greater neuroplasticity.

In order to measure neuroplasticity, we will use the variation in genetic markers. The genes under consideration are *APOE*, *COMT*, and *BDNF*. All three genes are associated with neuroplasticity, both directly and in relation to one another.[6] The three genes were selected because they are the only ones available in the WLS dataset that have been shown to be related to neuroplasticity in the literature, as we document below.[7] Focusing only on these three genes allows us to reduce to concern of multiple hypothesis testing.[8] We also show below that the results are robust to a number of different ways of measuring neuroplasticity based on these three genes.

APOE (apolipoprotein E) is associated with the transportation of lipids, or fatty acids, within the brain. The gene variant under consideration for the current work is the E4 variant, which has strong associations with Alzheimer's disease.[9] *APOE4* is particularly poor at removing plaques within neural pathways, resulting in poor synaptic plasticity (Trommer et al., 2005); therefore, the E4 variant has a negative association with neuroplasticity.[10] When constructing our measure for neuroplasticity, we consider individuals who do not have the E4 variant for the *APOE* gene.

The Val66Met locus (rs6265) of the *BDNF* (brain-derived neurotrophic factor) gene has been shown to be related to neuroplasticity.[11] *BDNF* is a protein associated with nerve growth, which is influenced by both the genotype as well as by early life stress (Roceri et al., 2002; Dumman and Monteggia, 2006). The presence of this protein is positively associated with hippocampal plasticity and development (Mizuno et al., 2000; Witte et al., 2012). Therefore, the genetic variant associated with greater production of this protein, and greater robustness to early stress—the Val, or "G" variant of SNP rs6265—is considered for our measure of neuroplasticity.

[2] While differential birth weight does provide a head-start or lag in cognitive development, post-natal family and schooling environments are also associated with later life cognitive development (Cunha et al., 2006).

[3] One of the first, and most famous, papers on gene-environment interactions is by Caspi et al. (2003), in which the authors show that childhood abuse leads to more severe later-life depression for individuals containing a gene variant, or allele, for the serotonin transporter gene 5-HTT. For review, please see Rutter et al. (2006) and Caspi and Moffit (2006). Additional studies that are similar in spirit and design include Shanahan et al. (2008) and Thompson (2014).

[4] Neuroplasticity is discussed in detail in Section 1.1.

[5] Neuroplasticity is not solely a positive, or favorable, condition. Continual remapping may lead to degenerative conditions (Pascual-Leone et al., 2005; Teter and Ashford, 2002).

[6] All genetic variants under consideration are single-nucleotide polymorphisms (SNP). A SNP is a single change along a sequence of DNA. For example, "ATA" versus "ATC", where the "A" and "C" are variants for the third nucleic base in the sequence. Each SNP under consideration is assigned a reference, or "rs," number.

[7] See complete list of SNPs at http://www.ssc.wisc.edu/wlsresearch/documentation/supdoc/biomarker/cor1019b_SNPs_in_wave1_data.pdf.

[8] For example, the Health and Retirement Study has recently released over 2 million genetic variants for each of the over 12,000 respondents in the genetic sample. This would allow a nearly infinite number of ways to characterize neuroplasticity, and similarly allow a very large number of regressions to be examined, leading to multiple-comparison concerns.

[9] The four variants of the APOE gene are determined by two SNPs: rs429358 and rs7412. The E4 variant is defined as having a "C" variant for each.

[10] The negative association between the E4 variant and plasticity may be one reason for its correlation with Alzheimer's disease (Teter and Ashford, 2002).

[11] For review, please see Cheeran et al. (2009).