Neuroscience and Biobehavioral Reviews 37 (2013) 1500–1517

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

"He who sees things grow from the beginning will have the finest view of them" A systematic review of genetic studies on psychological traits in infancy☆

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ARTICLE INFO

Article history:
Received 19 January 2013
Received in revised form 10 April 2013
Accepted 24 April 2013

Keywords:
Infancy
Genetic association
Psychological phenotypes

ABSTRACT

This paper reviews the studies that have aimed to identify genes influencing psychological traits in infancy (from birth to age 12 months). The review also addresses why genetic research in infancy is worthwhile and what genetic approaches such as genome-wide association studies and next generation sequencing could offer infant genetics. The results revealed that: (a) all studies ($N = 26$) have employed a candidate gene association design; (b) existing studies have most commonly focused on the Dopamine receptor D4 (DRD4) and the Serotonin transporter promoter (5-HTTLPR) gene polymorphisms; (c) phenotypes that have been assessed are temperament, attachment, and attention. Two further studies included both temperament and electrophysiological markers; (d) among many unreplicated findings, the most promising result appeared to be an association between the long DRD4 polymorphism and several "positive" temperament characteristics from birth to 4-months of age and at 12-months of age. It is concluded that, to date, there are limited, and mixed, findings regarding the possible association of genes with psychological phenotypes in infancy.

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☆ This research was supported by the EC Marie Curie Initial Training Networks, Royal Society and the Waterloo Foundation.
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http://dx.doi.org/10.1016/j.neubiorev.2013.04.013

1. Introduction

Aristotle (384-322BC) was trying to understand "how does a chicken come out of the egg". At this time, people observed either an egg or its end product (a chicken) but they did not have a clear idea on how the chicken came out of the egg. He set out twenty eggs on a table in chronological order based on the day that the eggs were laid. As he moved down the table each egg was a day older than the previous; therefore one could see twenty different stages in the life of chicken embryo. He observed the formation of a primitive heart in two-day old eggs and later on the formation of the rest of the organism (Kiessling and Anderson, 2003). These and similar observations, drove him to the conclusion quoted in the title of this paper "*He who sees things grow from the beginning will have the finest view of them*".

Genetic research in infancy should be considered important because, first, it forms part of a larger goal of understanding the causes of individual differences in human behavior. It can test for genetic variants that might be specific to influencing infant behavioral development, as well as test whether genetic variants associated with psychological traits in later development are also associated with related phenotypes in infancy. That is, infant genetic research can be informative about genetic continuity and change across the lifespan (Ronald, 2011). Knowledge about which genes play a role in psychological development in infancy would contribute to the broader field of developmental cognitive neuroscience by providing clues about the mechanisms involved in early brain development (Johnson, 2011). Finally, because most psychological disorders appear to have their onset after infancy, knowledge about genetic risk that can be applied to infant samples has considerable potential for the identification of populations at risk of atypical development, based on genetic propensity, and thus for informing early prevention and intervention approaches.

In genetics, the search for genes associated with complex traits in older samples has been notoriously difficult (Manolio et al., 2009; Frazer et al., 2009). A hypothesis is that finding genes associated with infant psychological traits might be easier than finding genes associated with psychological traits in older age groups. The reason behind this hypothesis is that across development, multifactorial gene × environment (G × E) interactions are taking place which could make 'main effect' associations between genes and behavior more difficult to identify (Johnson and Fearon, 2011). The hypothesis is that there will be fewer cumulative gene-environment interaction effects on infant psychological phenotypes, and, as such, main effects of genetic influences will be easier to find.

The present paper systematically reviewed the literature of studies that have aimed to identify genes that influence psychological trait phenotypes in infancy (from birth to age 12 months). Longitudinal studies that have aimed to identify genes that influence psychological trait phenotypes in older ages are also reviewed where they included data on infants. While reviews of genetic research on child and adult psychological traits are available elsewhere (e.g. Frazer et al., 2009; Heard et al., 2010; Sullivan et al., 2012), this is the first review of infant genetic research. This review is restricted to the age range of birth to age 12 months because this is the typical definition of infancy (Mallina et al., 2004). Beyond 12 months, when there are some major normative shifts in behavior, such as learning to walk and to speak, is generally defined as the start of childhood (Mallina et al., 2004).

All studies in this field have employed a candidate gene association design. The candidate gene design involves searching for an association between a phenotype of interest and a known candidate gene. The gene might be chosen because of its genomic position or because it codes for the synthesis of a protein, which is hypothesized to contribute to the phenotype's causal pathway (Ronald, 2011). For psychological traits, examples of such hypotheses relate to the neurotransmitters dopamine and serotonin. Empirical data has demonstrated that the dopaminergic system mainly influences the frontal lobe and basal ganglia and acts as a strong regulator of several aspects of cognition and attention (Nieoullon, 2002). Serotoninergic neurons in mammals form the most extensive axonal arborizations of all neuronal systems and their innervations appear early in development. Converging evidence supports the hypothesis that serotonin is a neurotransmitter that plays a major role in a variety of cognitive functions (Turlejski, 1996). As such, genes that directly or indirectly influence the serotoninergic or dopaminergic systems are often included in candidate gene association studies of psychological traits; for example, the dopamine receptor D4 (DRD4) gene has been selected as a dopamine system gene that might affect frontal cortex functioning in infancy, since it is expressed in the retina and the prefrontal cortex; its polymorphisms have been associated with several phenotypes, including an increase risk of attention deficit hyperactivity disorder (ADHD), impulsivity, lower levels of response inhibition and sensation seeking in toddlers, when combined with poor parenting (Holmboe et al., 2010).

2. Method

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.co.uk/schhp?hl=en&tab=ws) and PsychINFO (http://www.apa.org/pubs/databases/psycinfo/index.aspx) databases were employed to conduct a systematic search on genetic studies in infancy. Terms "genetic study", "candidate genes", "Genome-wide association study", "DNA sequencing study" "infants", and "infancy" were used. Moreover, reference lists of the selected publications were checked for relevant publications. The last literature search was performed in April 2013.

We used the following criteria to select studies for inclusion in the literature review.

1. The participants' age did not exceed 12-months of age.
2. Longitudinal studies that have aimed to identify genes that influence psychological trait phenotypes in older ages are also reviewed if they included data on infants.
3. Studies had to include psychological phenotypes. Biological or physical phenotypes were not the subject of this review.
4. The review excluded research on known genetic syndromes (e.g., Williams Syndrome) because these represent a different genetic model where the genes associated with the phenotype have been identified. The review focused on complex traits with largely unknown genetic etiology.

3. Results

Twenty-six genetic studies on psychological phenotypes in infancy were identified. The Appendix (Table A1) lists the candidate genes that have been assessed in this literature. DRD4 and 5-HTTLPR genes were the most frequently used candidate genes; they were included in nineteen and twelve studies out of the twenty-six studies, respectively. The following psychological phenotypes were studied in these papers: *temperament* (e.g. adaptability, emotionality, self-regulatory behavior), *attachment* (between the infant and the caregiver) and *attention* (e.g. visual attention). Two studies attempted to associate genetic markers with both behavioral measures and electrophysiological markers. Sample sizes ranged from $N = 48–1136$ (Mean $N = 212$; Median $N = 90$).

Table 1 provides a quick look summary of the 26 studies. It includes the phenotypes and the genetic markers and it outlines, for each study, whether the association between the genetic marker and the phenotype was significant or non-significant based on the