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The nature of individual differences in inhibited temperament and risk for psychiatric disease: A review and meta-analysis

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ABSTRACT

What makes us different from one another? Why does one person jump out of airplanes for fun while another prefers to stay home and read? Why are some babies born with a predisposition to become anxious? Questions about individual differences in temperament have engaged the minds of scientists, psychologists, and philosophers for centuries. Recent technological advances in neuroimaging and genetics provide an unprecedented opportunity to answer these questions. Here we review the literature on the neurobiology of one of the most basic individual differences—the tendency to approach or avoid novelty. This trait, called inhibited temperament, is innate, heritable, and observed across species. Importantly, inhibited temperament also confers risk for psychiatric disease. Here, we provide a comprehensive review of inhibited temperament, including neuroimaging and genetic studies in human and non-human primates. We conducted a meta-analysis of neuroimaging findings in inhibited humans that points to alterations in a fronto-limbic-basal ganglia circuit; these findings provide the basis of a model of inhibited temperament neurocircuitry. Lesion and neuroimaging studies in non-human primate models of inhibited temperament highlight roles for the amygdala, hippocampus, orbitofrontal cortex, and dorsal prefrontal cortex. Genetic studies highlight a role for genes that regulate neurotransmitter function, such as the serotonin transporter polymorphisms (5-HTTLPR), as well as genes that regulate stress response, such as corticotropin-releasing hormone (CRH). Together these studies provide a foundation of knowledge about the genetic and neural substrates of this most basic of temperament traits. Future studies using novel imaging methods and genetic approaches promise to expand upon these biological bases of inhibited temperament and inform our understanding of risk for psychiatric disease.

Abbreviations: 5-HTTLPR, serotonin transporter-linked polymorphic region; *A1AR*, adenosine A_{1A} receptor gene; *A2AR*, adenosine A_{2A} receptor gene; ACC, anterior cingulate cortex; ACTH, adrenocorticotropic hormone; ADHD, attention-deficit hyperactivity disorder; ALE, activation likelihood estimation; ALN, alone in a new cage condition in the human intruder paradigm; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; *COMT*, catechol-O-methyltransferase gene; CRH, corticotropin-releasing hormone; *CRH*, corticotropin-releasing hormone gene; *CRHR1*, corticotropin-releasing hormone receptor 1 gene; CNTNAP2, contactin-associated protein-like 2; *DAT*, dopamine transporter gene; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; *DRD4*, dopamine D4 receptor gene; EEG, electroencephalography; ERN, error-related negativity; ERP, event-related potential; FDG, [^{18}F]-fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; *GAD*, glutamic acid decarboxylase gene; GWAS, genome-wide association study; HPA, hypothalamic–pituitary–adrenal axis; *MAOA*, monoamine oxidase A gene; MMN, mismatch negativity; MRI, magnetic resonance imaging; mRNA, messenger RNA; NEC, no eye contact condition in the human intruder paradigm; NPY, neuropeptide Y; NPY1R, neuropeptide Y receptor 1; NPY5R, neuropeptide Y receptor 5; NTRK3, neurotrophic tyrosine kinase receptor, type 3; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; *PENK*, preproenkephalin gene; *RGS2*, regulator of G protein signaling 2; *SERT*, serotonin transporter gene; SNP, single nucleotide polymorphism; ST, stare condition in the human intruder paradigm.

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Contents

1. Introduction

Why are some babies happy while others are fussy? Why do some individuals seek out new experiences while others prefer things that are familiar? What is the nature of these differences? Philosophers and scientists have been curious about these individual differences for centuries. The Greeks recognized four different temperaments—the sanguine, choleric, melancholic, and phlegmatic—and in the 5th century B.C.E., Hippocrates proposed that the behavioral differences reflected underlying differences in the bodily fluids of blood, yellow bile, black bile, and phlegm. In the modern era, we continue to be interested in describing how individuals differ and identifying the biological causes of these differences. Recent advances in neuroscience methods have provided an unprecedented ability to examine both the neural and genetic bases of temperament. In this review we will detail and integrate our current understanding of the neurobiological bases of one of the most basic individual differences—the tendency to approach or avoid new people, objects, and experiences.

Temperament is defined as innate individual differences in behavioral and emotional tendencies that appear in infancy and are relatively stable across context and time. In the past fifty years, there have been numerous theories of temperament, with each proposing different constructs to best capture individual differences in emotion and behavior. One of the most consistently included constructs is the tendency to approach or avoid novelty. This trait has been referred to as behavioral inhibition to the unfamiliar (Kagan et al., 1984; Kagan and Moss, 1962), fear and distress to novelty (Rothbart, 1981), and approach/withdrawal (Thomas and Chess, 1977). For this review we will use the general term inhibited temperament. At the extremely inhibited end of the trait are individuals who are shy, quiet, and cautious; on the other extreme are individuals who are outgoing, bold, and risk-seeking. Because novel stimuli are ubiquitous, we propose that how one reacts to new people, objects, and environments forms a person's basic behavioral pattern for interacting with the world. Finally, approach and avoidance of novelty has a clear behavioral component (approach/avoidance) that can be assessed in other species, providing the translational foundation needed to identify the shared neural and genetic substrates.

Individual differences in responses to novelty are observable very early in life (Calkins et al., 1996; Kagan et al., 1998). The