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Serotonin transporter polymorphisms (5-HTTLPR) in emotion processing
Implications from current neurobiology

R. Jonassen *, N.I. Landrø

Clinical Neuroscience Research Group, Department of Psychology, Oslo, Norway

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ABSTRACT

The candidate gene approach directly tests the effects of genetic variation within a potentially contributing gene in an association study. However, the candidate gene approach is limited by how much is known about the biology of the disease being investigated. The serotonin transporter gene *SLC6A4* has been studied more than any other single candidate gene in the field of neurobiology. Transcription of the serotonin transporter gene is modulated by a polymorphic region, 5-HTTLPR, near the promoter. 5-HTTLPR genotype has been associated with individual variation in emotion processing, brain structure, and brain function. We present an updated review of the biological literature on the serotonin transporter polymorphism. Recent imaging and behavioral studies of the role of 5-HTTLPR genotype in emotion processing are discussed in light of new biological findings related to 5-HTTLPR variation. We also examine the clinical implications of discoveries about the role of serotonin and 5-HTTLPR genotype in neural plasticity and behavioral malleability.

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1. Introduction

As early as the middle of the 19th century, it was discovered that after blood clots a factor in the resulting serum constricts vascular smooth muscle so as to increase vascular tone. This factor was later isolated and identified in blood platelets as 5-hydroxytryptamine (5-HT, also called serotonin). Simultaneously a similar substance was found within the gastrointestinal tract, where it also constricted smooth muscles (Hensler, 2012). Serotonin is a hydrophilic

Abbreviations: MDD, major depressiv disorder; 5-HTTLPR, serotonin-transporter-linked polymorphic region; 5-HTT, 5-hydroxytryptophan transporter; 5-HT, 5-hydroxytryptophan; mRNA, messenger ribonucleic acid; SLC6A4, serotonin transporter gene; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; SERT, serotonin transporter; PET, positron emission tomography; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; SNP, singel nucleotide polymorphism; CpG site, cytosine and guanine separated by only one phosphate; BOLD, blood-oxygen-level dependent.

* Corresponding author. Tel.: +47 22845391.
E-mail address: rune.jonassen@psykologi.uio.no (R. Jonassen).

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substance and therefore does not easily cross the lipophilic blood–brain barrier. Today, we know that 5-HT is also produced by nine serotonergic clusters of cells along the midline of the brain stem. The axons from these core raphe nuclei innervate nearly every area of the central nervous system. Ascending serotonergic projections to the cerebral cortex mainly come from the dorsal raphe, the median raphe and one of its extensions. Understanding the neuroanatomical organization of these neurons has provided insight into the functions of serotonin as a neurotransmitter, as well as its possible roles in mental processes and psychiatric disorders. The idea that serotonin has important behavioral effects arose from various theories that linked dysfunctions in serotonergic pathways to psychological disorders, particularly to symptoms characteristic of schizophrenia and depression. Pharmacotherapies that are effective in depression, anxiety and schizophrenia have potent, and in some cases selective, effects on serotonergic neurons in the brain. Individual differences, such as genetic variation, associated with serotonin function can strongly affect robustness, vulnerability and malleability during the development and treatment of mental disorders. Thus, studies on basal mechanisms in serotonin transmission may help explain complex phenomenology, such as clinical syndrome diagnoses. A neuroscientist tends to explore the relationship between behavior, brain systems, cells and genes. In this particular context, we are interested in uncovering intermediate phenotypes (endophenotypes), or behavioral phenotypes which are associated with variation in genes involved in serotonin function. Endophenotypes include indicators such as biological markers, imaging phenotypes and cognitive traits that are less complex than top-level phenotypes such as psychiatric disorders. Variation in these phenotypes may reflect vulnerability or resistance to the development of symptoms characteristic of psychological disorders, such as major depressive disorder (MDD). Serotonin-mediated functional and structural properties in the human brain could strongly affect a person's ability to adaptively process emotion. Therefore, one of the most fruitful approaches in cognitive and affective neuroscience has been the combination of neurobiology and psychology with the ultimate goal of improving clinical decision-making and treatment of psychological disorders.

The candidate gene approach is a commonly used technique to identify genetic risk factors for complex disorders such as major depressive disorder. In this method, a candidate gene is selected for study based on prior knowledge of its functional relationship to the trait of interest. In a pioneering study, Caspi et al. (2003) investigated the role of 5-HTTLPR, a functional variant near the promoter of the gene encoding the serotonin transporter protein, 5-HTT. They concluded that individuals with the short (S) variant of 5-HTTLPR, when compared to individuals with the long (L) variant, were more often diagnosed with major depression, had higher subjective ratings of depressive symptomatology, were rated higher on informant reports of depression and had more suicide ideation and attempts. Importantly, this association was stronger among individuals who had experienced several traumatic life stressors. Thus, the study provides evidence for a gene-environment interaction, in which an individual's response to environmental insults is moderated by the individual's genetic make-up. Although the picture is not completely consistent (see McGuffin et al., 2011), the bulk of evidence supports an association between the S allele of 5-HTTLPR and major depressive disorder (for a comprehensive review, see Uher and McGuffin, 2010). These studies have motivated neuroscientists to explore the mechanisms that may underlie the association between 5-HTTLPR genotype, negative life events, and MDD. In particular, the known role of the amygdala in the perception of emotional valence has led to a series of studies to determine the role of 5-HTTLPR variation in processing emotionally salient information (Munafo et al., 2008). Despite some controversy about the magnitude of this effect, a recent meta-analysis concluded that there is a real effect of 5-HTTLPR genotype on amygdala reactivity, but it is smaller than earlier thought (Murphy et al., 2012). Carriers of the S allele (genotype S/S or L/S) show highly significant reduction of amygdala-anterior cingulate cortex connectivity in comparison to L homozygotes (genotype L/L) (Pezawas et al., 2005). Short allele carriers also show more functional coupling between the amygdala and the ventromedial prefrontal cortex, compared to L carriers (Heinz et al., 2005). Recently, several studies have reported an effect of 5-HTTLPR variation on brain circuitry associated with cognitive control of emotion (Beevers et al., 2010b; Canli and Lesch, 2007; Jonassen et al., 2012a,b; Selvaraj et al., 2011). Thus, 5-HTTLPR genotype may have a wider role in emotion processing than previously thought.

Candidate gene studies rely heavily on preconceptions about the functional neurobiological differences associated with genetic variation. Herein, recent imaging studies and behavioral studies of 5-HTTLPR are discussed in light of new biological findings. The role of 5-HTTLPR genotype in emotion processing is discussed in the context of neural plasticity, gender differences, basal cognitive functioning and, importantly, implications for clinical decision-making and practice. This update on biological and methodological aspects of studies of 5-HTTLPR illustrates many of the limitations and advantages of the use of the candidate gene approach in general.

2. The biology of 5-HTTLPR variation

Serotonin activity in the brain is regulated by the serotonin transporter 5-HTT, a sodium/chloride-dependent transporter located in the plasma membrane of the cell. When serotonin is released into the synaptic gap, the presynaptically located 5-HTT returns serotonin to the cell for recycling and metabolic decomposition under normal physiological circumstances. The major purpose of 5-HTT is the efficient removal of serotonin from extracellular areas. Abnormal or manipulated 5-HTT function will alter the duration and intensity of 5-HT communication with postsynaptic receptors and targets located in limbic structures, mediating emotional processing, or in presynaptic receptors mediating inhibitory control of the 5-HT neuron itself. Seven distinct families of 5-HT receptors have been identified (5-HT1 through 5-HT7), and at least 15 subpopulations have been described for some of these (Glennon et al., 1998). Decreased 5-HTT gene function increases serotonin levels and leads to reduced receptor binding to receptors 5-HT_{1A} and 5-HT_{1B}, but increased 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptor mRNA levels and/or ligand binding. The 5-HT_{1A} acts as both the somatodendritic autoreceptor and a postsynaptic receptor. The 5-HT_{1B} is an autoreceptor in presynaptic terminal fields and is also a postsynaptic receptor. The 5-HT_{1A} and 5-HT_{1B} receptor inhibits the enzyme adenylyl cyclase, but only 5-HT_{1A} opens K^+ channels. The 5-HT_{2A} and 5-HT_{2C} effector mechanism is stimulation of adenylyl cyclase while the 5-HT_3 is a ligand-gated cation channel (Hensler, 2012). Messenger RNA, carrying the genetic code for the receptor protein, is adaptive to extracellular 5-HT levels. This means that 5-HTT can have both excitatory and inhibitory effects on the postsynaptic cell due a variety of post-translational and epigenetic mechanisms. Thus, both the frequency and the order of postsynaptic excitation and inhibition will decide whether the postsynaptic cell will reach its action potential for further cellular communication. If we imagine that the presynaptic cell is a raphe nucleus efferent and the postsynaptic cell is coupled to limbic structures involved in emotion processing, the net effect of functional variation in the 5-HT transporter and 5-HT receptor transmission will be a spectrum of neurodynamical responses to serotonin.