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# Startle response related genes

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ABSTRACT

The startle reaction (also known as the startle response, the startle reflex, or the alarm reaction) is the psychological and physiological response to a sudden unexpected stimulus, such as a flash of light, a loud noise (acoustic startle reflex), or a quick movement near the face. Abnormalities of startle response have been observed in many stress-related mental disorders, such as schizophrenia and post-traumatic stress disorder (PTSD). However, the molecular mechanisms of startle in stress-associated conditions – for example, whether the startle reaction is associated with any gene variance – is still unknown. In this paper, we will carry out a systematic review by retrieving, assessing, and combining, when applicable, individual studies investigating association of the molecular variation of candidate gene with the startle response. The systematic review is based on the search for numerous publications using the keywords "startle gene" on September 15, 2010 using PubMed, which comprises more than 20 million citations for biomedical literature from MEDLINE and life science journals. A total of 486 publications regarding genes associated with startle have been obtained and reviewed here. There are fewer than 20 publications associating genes with the startle response between 1979, when the first valuable paper was published, and 1999. However, publications have dramatically increase from 2001 and reaches over 70 in 2009. We have characterized them into three categories: startle-associated gene studies in humans, in animals, as well as in both human and animals. This review of research strategy may provide the information for identifying a biomarker for startle response, with the objective of translating research into clinical utility: diagnosis and treatment of stress-induced mental disorders.

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## Introduction

An exaggerated startle response, considered as a critical characteristic in certain mental disorders, such as PTSD and schizophrenia, has been avidly studied in psychiatry. Research seeking the molecular mechanism of the startle response has consistently increased over last 10 years. One such area of research is the study of genes associated with the startle response. The published articles about startle response associated genes have been significantly increased yearly. As a phenotype, the startle response exhibits a consistent physiological pattern including physical movement away from a given stimulus, a contraction of the muscles of the arms and legs, blinking, and changes of blood pressure, respiration, and breathing rate. The muscle reactions generally resolve themselves in a matter of seconds, while other responses may take longer. The pathway for this response was largely elucidated in rats in the 1980s [1].

The basic neuroanatomy, which is demonstrated by experiments with rats using a variety of lesion and electrical stimulation procedures, is relatively simple for startle responses. The signals are conducted to the central nervous system. The output end of the startle circuitry goes through the reticulospinal tract and the lower motor neurons of the spinal cord. For example, the pathway for acoustic startle is from the ear up to the nucleus of the lateral lemniscus (LLN) from where it then activates a motor center in the reticular formation. LLN sends descending projections to lower motor neurons of the limbs. The whole reflex takes place in less than 10 ms [2]. Accordingly, the human startle response can be measured reliably. For example, it can be measured by the amplitude of eye blinking in response to a sudden abrupt auditory stimulus [3]. Besides the above control circuitry, the startle circuit is regulated by several brain regions, such as the prefrontal cortex and amygdala, which influence the tone of startle and the processing of information related to conditional fear [4], respectively.

There are two typical examples for regulation of the startle response. First, is prepulse inhibition (PPI). PPI is a neurological phenomenon in which a weaker pre-stimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse) [5]. The reduction of the amplitude of startle reflects that the nervous system temporarily adapts to a strong sensory stimulus when a preceding weaker warning signal is given. PPI deficits are noted in patients with schizophrenia [6–9] and Alzheimer's disease, and in people under the influence of drugs, surgical manipulations, or gene mutations.

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The second example for regulation of the startle response is startle habituation. Startle response can be decremented by repeated presentation of the same, initially novel stimulus [10]. This regulatory mechanism can be inhibited. Schizophrenia patients exhibit impairment of startle habituation. In general, exaggerated startle reactivity can become a chronic condition to lasting for 30, 40, or more years [11].

If human behavioral traits result from the interplay of genes and environment, exaggerated startle response may have a complex genetic basis. Although it is not necessarily inherited in strict Mendelian fashion, the transmission of hereditary characteristics does pass from parents to offspring. Factors such as incomplete penetrance – (carriers of the disease allele not becoming ill or having a later onset), pleiotropy (multiple effects of a single gene), heterogeneity (similar phenotype from different genotypes), epistasis (interaction of multiple alleles in the same subject) and epigenetics among others, must be accounted for. Since startle is a peculiar behavioral response to stimuli, it represents an excellent model for studying the mechanism of interaction of gene and environment. We hypothesize that startle is an endophenotype (a concept which divides behavioral symptoms into stable phenotypes with a clear genetic connection – seen in mental disorders, such as schizophrenia and PTSD). It is possible to identify a gene, which is associated with startle response in a specific environment, for example, in subjects who experiences the Iraq war and in a restrictive population, such as military subjects. Those environmental factors, such as war exposure and subjects, can be defined. The determination of which genes are associated with startle response is a challenge.

There are 486 publications regarding gene and startle response. Fewer than 20 of these were published between 1979 and 1999. The total numbers of publications have increased markedly since 2001, reaching over 70 publications in 2009. Depending on the research subjects, they can be categorized into: studies in human subjects (Table 1), studies in animals (Table 2) and studies in both human and animals. There are 13 genes which are associated with startle response in human studies. Four genes have been studied in both human and animals, including COMT, GLRA1, GlyT2, and NRG1 dehydrogenase. Here we briefly discuss several genes which are associated with startle response in both humans and animals, and in psychiatric researches.

## The 5-HT transporter (5-HTT) and startle response

There are studies regarding 5-HTTLPR (serotonin-transporter-linked promoter region) and startle-related topics. 5-HTTLPR is a degenerate repeat polymorphic region in *SLC6A4*, the gene that codes for the serotonin transporter [30,31] and is associated with many neuropsychiatric disorders [32]. The 5-HT transporter (5-HTT) influences on neural circuits processing fear and anxiety are discussed [33]. 5-HTTLPR, a functional polymorphism of the 5′-flanking region of the 5-HTT gene is involved in several neuropsychiatric phenotypes [34]). 5-HTTLPR is an insertion/deletion polymorphism with a long (L) variant comprising 16 copies of a 20–23 bp repeat sequence and a short (S) variant comprising 14 copies. Among Caucasians, the frequencies of the L and S alleles are about 0.60, and 0.40, respectively [35]. An association study regarding 5-HTT, especially the S allele with anxiety, fear and startle response has been studied in human subjects (Table 1). The S allele is associated not only with increased scores in measures of negative emotionality including anxiety [36–38], but also with lower transcriptional efficiency of the 5-HTT gene and lower levels of 5-HT uptake [30,35]. S allele carriers show stronger amygdala activity in response to fear stimuli than L/L homozygotes [33] and increased anxiety [39,40]. The S allele is also specifically associated with stronger overall startle responses than L/L homozygotes [41]. S allele carriers were not only more sensitive to the effects of stressful life events than L/L homozygotes, but also were more likely to develop depressive symptoms [42–47]. S allele carriers with low social support had an increased risk for behavioral inhibition, indicating that in the early years of life before maturation of prefrontal regulatory circuits, stress could produce stronger response to fearful stimuli. In addition, stressful life events may have cumulative effects [42,45]. However, there is a negative result in the study of the relation of 5-HTTLPR with fear and anxiety [45]. No interaction of 5-HTTLPR and stressful life events was found on the risk for generalized anxiety disorder in adults, although the positive results demonstrated an interaction of 5-HTTLPR and environment on fear and anxiety in children.

## COMT genetic variation and startle response

One of the promising, well-studied candidates for the association of gene with startle is the gene for catechol-O-methyltransferase (COMT), the catabolic enzyme for dopamine, norepinephrine, and epinephrine. COMT is the major clearing step for dopamine in the prefrontal cortex [48,49] and expressed in many brain regions synaptically [50,51] and subcortically [52]. The COMT gene contains a common functional polymorphism resulting from a non synonymous G to A base pair substitution in the coding sequence of the gene, producing a valine to methionine substitution at position 158 of the membrane bound allozyme that predominates in the brain (MB-COMT); soluble allozyme S-COMT [53]. Since the

**Table 1**
Startle associated gene studies in human subjects.

| Gene | Location | Polymorphism | Phenotype | References |
|---|---|---|---|---|
| 5-HT(2A)R | 13q14-q21 | A-1438 G and T102C | PPI | [12,13] |
| | | T102C | PPI | [14] |
| AVPR1a | 12q14-15 | VNTR (RS1 and RS3) | PPI | [15] |
| AADC | 7p12.2 | 1303 C > T<br>1367ins A | Startle | [16,17] |
| COMT* | 22q11.21 | Val158Met | PPI | [18] |
| CSF1-R* | 5q32 | D5S209, and D5S119 | Hyperekplexia | [19,20] |
| DRD3 | 3q13.3 | Ser9Gly | PPI | [21] |
| DRD4 | 11p15.5 | 7-folds repeat | Startle | [22] |
| GLRA1* | 5q32 | Arginine271proline | Hyperekplexia | [23] |
| GlyT2* | 11p15.1 | Arg271Pro | Hyperekplexia | [20] |
| | | 910A>C/Lys304Gln | Hyperekplexia | [24] |
| HTTLPR | 17q11.2 | S/L | Startle | [25,26] |
| NRG1* | 8p12 | rs3924999/rs10503929 | PPI | [27] |
| PRODH | 22q11.21 | 1945T/C, 1766A/G, 1852G/A | PPI | [28] |
| TPH2 | 11p15.3-p14 | −703G/T | Startle | [29] |

* Study in both human and animals. COMT, catechol-O-methyl-transferase; HTTLPR, serotonin-transporter-linked promoter region; TPH2, tryptophan hydroxylase 2.

**Table 2**
Startle associated gene studies in animals.

| Gene | Phenotype | Species | References |
|---|---|---|---|
| 5-HT(1A) receptor | PPI/Acoustic startle | Rats | [88] |
| 5-HT(1B) receptor | PPI/Acoustic startle | KO mice | [89] |
| COMT* | PPI | Transgenic mice | [90] |
| D1/D2 | Startle/PPI | Rats | [91,92] |
| FGFR-3 | PPI/Acoustic startle | $Fgfr3^{-/-}$ null mutant mice | [93] |
| Glr-1 | Startle | Spasmodic recessive mouse | [94] |
| GLP-1 | Startle | KO mice | [95] |
| GLRA1* | Startle | Mutant mice | [96–99] |
| GlyT2* | Hyperekplexia | GlyT2 deficient mice | [100] |
| Histamine H1 | PPI | KO mice | [101] |
| Huntington's disease gene | PPI | Transgenic mice | [102] |
| mGluR5 | PPI | KO mice | [103] |
| Nicotinic receptors with beta3 subunit | PPI | Mice with null mutation | [104] |
| NMDA receptor | PPI/Acoustic startle | Rearing rat in isolation | [105] |
| NRG1* | PPI | $NRG1^{+/-}$ mice | [106] |
| NPY | Acoustic startle/PPI | KO mice | [107,108] |
| | PPI | Male Wistar rat-pups | |
| Oxytocin (Oxt) | PPI | Oxt KO mice | [109] |

* Animal + Human study

158Met form is less thermo-stable than the Val158 form, it has lower activity at physiologically relevant temperatures in the brain [54]. Met158 homozygotes have an approximate one-third diminution in activity compared with Val158 homozygotes [55]. Lowered COMT activity, resulting in higher concentrations of dopamine [49], may have a salutary effect on cortical function. For instance, the Val158 (higher activity) allele is associated with prefrontal inefficiency during working memory and cognitive control [56–59], with relatively poorer performance on prefrontally mediated tasks [60–62]. Furthermore, the Val158 allele is associated with schizophrenia – particularly in interaction with other schizophrenia risk genes [53,63]. However, as both alleles are maintained at high levels in populations worldwide, it has been proposed that each confers an environment-specific selective advantage – representing a trade-off between cognitive efficiency and emotional resiliency [64]. The Met158 allele is linked to poor emotion regulation, anxiety disorders [65–70], anxiety-related traits including high neuroticism and low sensation seeking and extraversion [71–74], obsessive–compulsive disorder [75], and increased pain sensitivity [76]. However, the results of such associations are not entirely consistent.

COMT Val158Met genotype affects functional activation and connectivity within critical neural circuits for affective arousal and regulation. Smolka et al. [77] found that the Met158 allele was associated in an allele dose-dependent manner with exaggerated limbic and prefrontal engagement in response to aversively valenced pictures. An additive interaction was also found between genotypes at the COMT Val158Met locus [78]. The Met158 allele is also associated with increased hippocampal and ventrolateral prefrontal activation while viewing angry and fearful facial expressions; these brain regions showed augmented functional connectivity in Met158 homozygotes, the magnitude of which negatively predicted scores on a temperamental measure of flexibility [79]. Study of COMT in relation to the startle response demonstrated that COMT genotype significantly affected startle reflex modulation by aversive stimuli. Met158 homozygotes show a markedly potentiated startle reflex compared with Val158 carriers. A trait measure of anxiety [80] was also associated with acoustic affective startle reflex modulation.

## Glycine receptor subunit alpha 1(GLRA1) mutation associated with startle response in an atypical hyperekplexia?

Individuals with hyperekplexia have an excessive startle reaction to sudden unexpected noise, movement, or touch, suggesting defects in glycinergic neurotransmission. A GLRA1 mutation associated with startle response was discovered in subjects with hyperekplexia, a rare neurological disorder characterized by an exaggerated startle response, infantile hypertonia and hyperreflexia without spasticity, a hesitant gait that usually improves by 3 years of age, and nocturnal myoclonus. Familial hyperekplexia is usually autosomal dominant, with the mutated inhibitory GLRA1 gene being on chromosome 5q. Three generations of a family have been identified with progressively more severe phenotypes of hyperekplexia. All affected family members were found to be heterozygous for a novel arginine 271proline mutation in GLRA1. Affected members of the third generation, now aged 6 and 7 years, exhibited enhanced startle responses [26].

Within the hyperekplexia, there are two clinical forms. The major form exhibits continuous generalized stiffness in the first year of life and an exaggerated startle reflex, accompanied by temporary generalized stiffness and falls, whereas the minor form only shows excessive startle and hypnic jerks. The GLRA1 mutations are responsible for the major form of hyperekplexia. However, genetic analysis of the GLRA1 gene of two English families in which both forms of hyperekplexia were present revealed no genetic defect in the GLRA1 gene [81].

More recently, missense, nonsense and frame-shift mutations have also been identified in the glycine transporter GlyT2 gene, SLC6A5, demonstrating a presynaptic component to this disease. Further mutations, albeit rare, have been identified in the genes encoding the GlyR β subunit (GLRB), collybistin (ARHGEF9) and gephyrin (GPHN) – all of which are postsynaptic proteins involved in orchestrating glycinergic neurotransmission. Whether these genes are also associated with exaggerated startle response in stress-related disorders is still unknown.

## Is p11 (S100A10) associated with startle response?

Previous studies have reported that p11 is associated with both depression [82] and PTSD [83,84]. P11 mRNA was down-regulated in the brain of patients with depression, but up-regulated in the brain of those with PTSD. P11 is a member of the S100 family of proteins containing two DF-hand calcium-binding motifs, which are localized in the cytoplasm and/or nucleus in a wide range of cells [85]. P11 regulates a number of cellular processes such as cell cycle progression and differentiation, is implicated in exocytosis and endocytosis by reorganization of F-actin, and interacts with and transports the 5-HT1B receptor from the cytoplasm to the membrane [82]. This suggests that p11's regulation of the 5-HT1B

receptor is critical to mental status. P11 knock-out mice showed behavioral changes similar to depression. Because of dysregulation of 5-HT1B receptor trafficking, p11 knock-out mice respond more poorly to antidepressant medication than did wild type [82]. Antidepressant medication increased expression levels of p11 and reversed the depressive behavior [82]. A recent study demonstrated that p11 mRNA expression levels are lower in the stress-related brain regions of suicide subjects [86,87]. Peripheral blood mononucleocyte p11 mRNA levels were significantly lower in suicide attempters and higher in suicide non-attempters, when compared to normal controls [87]. This data suggest that p11 mRNA levels may be a potential adjunctive biomarker for the assessment of suicide risk in mental disorders. However, there is a study demonstrating no association of p11 polymorphism with major depression. Therefore, it would be worthwhile to examine the influence of the p11 polymorphism and the role of p11 on the overall startle response.

## BDNF and startle

Brain-derived neurotrophic factor, also known as BDNF, is a member of the "neurotrophin" family of growth factors, which are related to the canonical "Nerve Growth Factor", NGF. Neurotrophic factors are found in the brain and the periphery [110]. The BDNF gene is located on chromosome 11 [111,112]. BDNF protein is synthesized as a glycosylated precursor (proBDNF) and is then converted intracellulary to mature BDNF protein, which is released upon cell stimulation [113]. Several studies demonstrated that BDNF is associated with depression [110–112,114].

Exposure to stress and the stress hormone corticosterone has been shown to decrease the expression of BDNF in rats [115]. In addition, rats bred to be heterozygous for BDNF, therefore reducing its expression, have been observed to exhibit hippocampal atrophy, suggesting that an etiological link exists between the development of depression and BDNF. Supporting this link, the excitatory neurotransmitter glutamate, voluntary exercise [116], caloric restriction, intellectual stimulation, curcumin [117], antidepressants [118], electroconvulsive therapy [119], and sleep deprivation [120] increase expression of BDNF in the brain. Some of these treatments, such as drugs and electroconvulsive therapy [121], have been shown to protect or reverse hippocampal atrophy, which is seen in PTSD.

Although the results are not always in the same direction, a common single-nucleotide polymorphism in the BDNF gene – a methionine (Met) substitution for valine (Val) at codon 66 (Val66-Met) – is associated with alterations in brain anatomy and memory. Positive associations of the BDNF Val66Met have been reported with specific symptoms of depressive disorders [122]. Egan and co-workers found a functional relevance of this substitution and of the lower activity-dependent secretion of BDNF which is associated with the Met allele as compared to the Val allele [123,124]. There is an effect of genotype on memory and cognitive performances [123] and an effect of the Val66Met polymorphism of BDNF gene on brain morphology, with Met carriers having a reduced volume of different brain structures, including hippocampus, parahippocampal gyrus and prefrontal cortex [125,126].

A variant BDNF mouse (BDNFMet/Met) reproduces the phenotypic hallmarks in humans with the variant allele. In the mouse, BDNFMet was expressed in brain at normal levels. However, when mouse were exposed to stressful conditions, BDNFMet/Met mice exhibited increased anxiety-related behaviors that were not normalized by the antidepressant and fluoxetine. That suggests that a variant BDNF may play a key role in genetic predispositions to anxiety and depressive disorders [127]. As of 2008, Val66Met is probably the most investigated SNP of the BDNF gene [123,128]. But there are other SNPs in the gene, including C270T, rs7103411, rs2030324, rs2203877, rs2049045, and rs7124442. Recently, it was reported that the BDNFMet polymorphism contributes to abnormalities in memory extinction. This abnormality in extinction learning may be explained by alterations in neuronal morphology, as well as decreased neural activity in the specific brain region, the ventromedial prefrontal cortex [129].

Furthermore, the Val66Met polymorphism has also been widely investigated as a genetic susceptibility risk factor for a large spectrum of neuropsychiatric disorders, in particular those with a neurodevelopmental origin [130–132]. For example, Met carriers (Val/Met and Met/Met) had a significant BDNF protein level reduction in Amniotic Fluid (AF) comparing to non-carriers (Val/Val), suggesting that AF BDNF levels could be indicative of fetal CNS development [133] and supporting the involvement of this polymorphism in behavioral and functional brain individual differences in adulthood. Since BDNF and its receptor TrkB mRNA increased in the paraventricular nucleus after acoustic challenge and prelimbic BDNF is critical for consolidation of learned fear memories [134], the role of BDNF in startle is suggested. Gatt et al. [135] demonstrated a significant interaction of BDNF with early life stress; BDNF Met carriers exposed to stress early in life have smaller hippocampal and amygdala volumes, heart rate elevations and a decline in working memory. The interaction of BDNF Met–stress in early life also predicted elevated neuroticism and higher depression and anxiety by elevations in body arousal. In contrast, the combination of BDNF Val/Val genotype and early life stress predicted increases in gray matter of the amygdala and associated medial prefrontal cortex, which in turn predicted startle-elicited heart rate variability and higher anxiety. Overall, these findings may aid establishing an evidence base for BDNF and startle research.

## Conclusions

There are studies with human subjects demonstrating the association between a list of candidate genes, including COMT, GLRA1, GlyT2, and 5HTTLPR and startle response. These association studies in humans were at least partially supported by results of animal studies. In addition, the information from the animal studies indicates a list of candidate genes that warrant human studies. This review provides a framework for identifying a biomarker for exaggerated startle response. Despite some issues that remain to be resolved, the startle response and genotyping appear to provide a valuable endophenotype for underlying gene and environment interaction in startle, a hallmark of PTSD.

## Conflict of interest

The authors declare no conflict of interest.

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