Genetic Factors Influencing Cognitive Function

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Abstract- It has been found that several nongenetic factors, such as age and education levels could influence cognitive function of healthy adults. Recently, investigators found that variances in COMT also have effects on cognitive functioning. However, this finding cannot be replicated by subsequent studies. Several reasons may contribute to the discrepancy. First, their sample sizes were too small. Second, they did not control for the nongenetic factors. The most recent study published on Cell in 2003 demonstrated that minor variation in brain-derived neurotrophic factor (BDNF) might also alter episodic memory in humans. The possible effects of this variation on other cognitive domains also require elucidation. Certainly, numerous other genes may influence cognitive functions too. The genes that modulate the activity of dopamine, serotonin, acetylcholine, adrenaline, noradrenaline, cannabinoid, estrogen, or glutamate deserve investigations at first.

Key Words: Cognitive function, Genetic factor, Nongenetic factors, BDNF, COMT

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INTRODUCTION

One of the most remarkable aspects of an animal's behavior is the ability to modify that behavior by learning, an ability that reaches its highest form in human beings. Learning, memory, and other cognitive functions have proven to be endlessly fascinating mental processes because they address one of the fundamental features of human activity: our ability to acquire new ideas from experience and to retain these ideas over time in memory[(1)]. Moreover, unlike other mental processes such as thought, language, and consciousness, memory and other cognitive functions seem from the outset to be readily accessible to cellular and molecular analysis.

The last decade has seen the development of cognitive neuroscience as an effort to understand how the brain represents mental events[(2)]. Progress in all of these areas has been swift and impressive, but much remains to be done to reveal the mechanisms of cognition at the local circuit and molecular levels.

BOTH NONGENETIC AND GENETIC FACTORS INFLUENCE COGNITIVE FUNCTIONS

Earlier, it has been found that several nongenetic factors, such as age, gender, and education levels could influence cognitive function of healthy adults[(3-7)].

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Recently, Thompson et al[8] found that genetic factors significantly influenced cortical structure in Broca's and Wernicke's language areas, as well as frontal brain regions. They reported on detailed three-dimensional maps revealing how brain structure is influenced by individual genetic differences. Preliminary correlations were performed suggesting that frontal gray matter differences may be linked to Spearman's g, which measures successful test performance across multiple cognitive domains[8].

Rujescu et al[9] also indicated that homozygosity for methionine at codon 129 of the prion protein is associated with white matter reduction and enlargement of CSF compartments in healthy volunteers and schizophrenic patients. This, however, being a novel finding, should warrant further investigation.

More importantly, Egan et al[10,11] suggest that genetic variances in catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) also somewhat affect certain cognitive functioning. This is the first study showing the degree to which human cognitive functions depend on our genes.

COMT

Egan et al[10] demonstrated that variances in certain genes, such as COMT, have effects on cognitive functioning. They examined the relationship of a common functional polymorphism (158-Val/Met) in the COMT gene, which accounts for a 4-fold variation in enzyme activity and dopamine catabolism, with both affecting prefrontally mediated cognition and prefrontal cortical physiology. In 175 patients with schizophrenia, 219 unaffected siblings, and 55 controls, COMT genotype was related in allele dosage fashion to performance on the Wisconsin Card Sorting Test of executive cognition and explained 4% of variance ($p=0.001$) in frequency of perseverative errors. Consistent with other evidence that dopamine enhances prefrontal neuronal function, the load of the low-activity Met allele predicted enhanced cognitive performance. These data suggest that the COMT Val allele impairs prefrontal cognition.

However, this finding was not replicated by Joober et al[12]. Several reasons may contribute to the discrepancy between two studies. First, their sample sizes were too small: 55[10] and 96[12], respectively. Second, they did not simultaneously take into account the nongenetic factors.

Moreover, current studies[10,12] on COMT genotypes in healthy adults merely focused on abstract thinking. Other domains (such as attention, problem-solving, working memory, and so on) of cognitive functions also need to be explored.

BDNF

Brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase (trk-B), play important roles in neural plasticity, long-term potentiation and memory formation[13,14]. The most recent studies published in "Cell" and "Science"[11,15] further demonstrated that minor variation in BDNF might also alter episodic memory in humans. Egan et al[11] examined the effects of a Val to Met substitution in the 5' pro-region of the human BDNF protein. In human subjects, the met allele was associated with poorer episodic memory, abnormal hippocampal activation assayed with fMRI, and lower hippocampal n-acetyl aspartate (NAA) assayed with MRI spectroscopy. Neurons transfected with met-BDNF-GFP showed lower depolarization-induced secretion, while constitutive secretion was unchanged. The Val-to-Met switch at site 66 seemed to be promising. It is a fairly common variant: Of 600 people examined, 32% had at least one copy of the oddball gene. The variation was located in the so-called ZIP code of BDNF, a sequence that directs the protein to its correct destination in the cell. Thus, the amino acid change would not alter BDNF function directly, but it could do so indirectly by causing the protein to end up at the wrong place.

These results demonstrate a role for BDNF and its Val/Met polymorphism in human memory. Certainly, the possible effects of this variation on other cognitive domains also require clarification.

NEUROTRANSMITTERS THAT MAY MODULATE COGNITIVE FUNCTIONS

In addition to the COMT and BDNF genes, as stated above, the roles of other genes that may influence activity of adrenaline[16] and noradrenaline[17,18], cannabinoid[19,20], dopamine[4,21,22], estrogen[23], glutamate[24,25], nicotine[26], and serotonin[27] also require investigation.

These neurotransmitters or endogeneous compounds may be involved in modulation of cognitive functioning.

Adrenaline and noradrenaline

The basolateral nucleus of the amygdala appears to be crucial for the formation of long-term declarative memory of emotional events[28]. Beta-adrenergic systems are implicated in long-term memory for an emotionally arousing story[29]. Noradrenaline has also been suggested to play a role in emotional memory. Hatfield and McGaugh[30] injected noradrenaline (norepinephrine) directly into the basolateral nucleus of rats, immediately after training, which resulted in a dose-dependent increase in memory performance on the stressful memory task.

1. Beta-adrenergic receptor

It has been clearly established from animal experiments that enhanced memory associated with emotional experiences involves activation of the beta-adrenergic system[16]. For example, beta-adrenergic receptor agonists infused selectively into the basolateral nucleus in rodents could enhance memory, and lesions of the basolateral nucleus or infusion of beta-adrenergic receptor antagonists into the basolateral nucleus block the memory-enhancing effects of systemically administered dexamethasone (a synthetic glucocorticoid)[31].

2. Alpha-2A noradrenergic receptor

Modulatory influences on memory consolidation also include release of norepinephrine within the amygdala[31]. Alpha-2 noradrenergic agonists improve spatial working memory in animals[32,33] and in humans[34]. Franowicz et al[18] further suggest that this cognitive improvement may be mediated by the alpha-2A receptor subtype.

Whether the genetic polymorphisms of these receptors can affect cognitive functions remains unknown.

Cannabinoid

Exogenous cannabinoids disrupt behavioral learning and impede induction of long-term potentiation (LTP) in the hippocampus; endocannabinoids, however, facilitate the induction of LTP in the hippocampus[19].

On the other hand, acquisition and storage of aversive memories is one of the basic principles of central nervous systems throughout the animal kingdom. In the absence of reinforcement, the resulting behavioural response will gradually diminish to be finally extinct. Despite the importance of extinction, its cellular mechanisms are largely unknown. Marsicano et al[20] showed that the endogenous cannabinoid system has a central function in extinction of aversive memories.

Cannabinoid receptor 1

Cannabinoid receptor 1 (CB1)-deficient mice showed strongly impaired short-term and long-term extinction in auditory fear-conditioning tests[20]. The CB1 and endocannabinoids thus are present in memory-related brain areas and modulate memory. The effects of the genetic variants of this receptor on cognitive domains are yet unclear.

Dopamine

Converging evidence suggests that dopaminergic mechanisms affect distinct aspects of cognitive performance[4,35,36]. For instance, Rihet et al[37] showed that levodopa specifically affects the stimulus preprocessing stage, which suggests that the dopaminergic system plays a role in sensory processing, possibly by acting on the level of arousal. Considerable evidence also shows that post-training administration of dopamine agonists can enhance memory through actions on consolidation processes in rodents[38,39]. Comparatively speaking, there have been fewer studies of dopaminergic involvement in memory consolidation using dopamine antagonists. Setlow and McGaugh[40] demonstrated that dopamine receptor blockade immediately post-training also enhances retention in hidden and visible platform versions of the water maze. In view of previous findings[38-40], these results highlight the complexity of dopamine involvement in memory consolidation and suggest that multiple factors, including the brain regions and receptor subtypes may need to be taken into account in explaining consolidation processes.

1. D_1 receptor

Overshadowing describes the phenomenon where less is learned about a stimulus when it is paired in compound with a more intense second stimulus, than when it

is not[41]. In a typical paradigm in the rat, two simultaneously presented stimuli (e.g. light and tone) are paired with an aversive unconditioned stimulus (e.g. mild footshock); overshadowing is observed when learning to the less salient stimulus is weaker than learning to the same stimulus when it is conditioned alone. The phenomenon of overshadowing provides an example of the stimulus selection aspect of selective attention[42], whereby particular informationally salient cues are selected for further processing, while less salient cues are, conversely, deselected. The overshadowing phenomenon therefore demonstrates one of the fundamental principles governing how animals and humans select and deselect information from arrays of environmental stimuli to direct learning.

The O'Tuathaigh and Moran study[43] indicated a modulatory role for the dopamine D_1 receptor in the expression of stimulus selection and suggested that the D_1 receptor might play a role in salience allocation aspects of learning.

Ni et al[44] suggest that D_1 receptor may play a role in the etiology of bipolar disorder. However, the possible role of its genetic variances[44] in relevant cognitive functions remains unknown.

2. D_2 receptor

Systemic administration of dopaminergic receptor agonists, such as bromocriptine or pergolide, or antagonists, such as sulpiride or haloperidol, can affect cognitive performance in healthy volunteers[45-47]. Performance on tests of visuo-spatial working memory has been shown to be improved[45,48] or unaffected[46,49] in humans given an acute dose of the D_2 receptor agonist bromocriptine. Conversely, visuo-spatial memory is impaired following administration of D_2 receptor antagonist sulpiride[47] or mixed dopamine antagonist haloperidol[45].

Mehta et al[50] therefore designed a study to test a number of hypotheses regarding the possible cognitive effects of acute administration of a low dose (1.25 mg) of D_2 receptor agonist, bromocriptine. They found that bromocriptine could improve short-term spatial memory but impair reversal learning in human volunteers. The differences between the findings of this study and some previous studies might be accounted for by various psychological, neurobiological and individual factors. Other candidate factors are the timing of drug administration relative to cognitive testing and, of course, the dose of the drugs administered to subjects. Therefore, Mehta et al[50] suggest that optimal levels of dopamine appear to be critical in performing certain cognitive tasks and the differing patterns of effects produced by dopaminergic interventions on various cognitive tasks may be understood in terms of differences in the underlying levels of dopamine function engaged by these further tasks.

Several polymorphisms on the D_2 receptor gene have been found. For example, Taq I polymorphism of the D_2 receptor gene has been reported to be associated with haloperidol response in psychotic patients[51]. The -141C Ins/Del polymorphism (in the promoter region) may be associated with anxiety or depressive symptoms[52]. Whether these genetic variances in D_2 receptors may modulate various cognitive functions deserves further studies.

3. D_3 receptor

Recently a dopamine D_2 receptor, which is associated with behavioral suppression in rodents, has been identified[53]. Rybakowski et al[54] further found that D_2 receptor gene polymorphism (9-Ser/Gly) is associated with the intensity of eye movement disturbances in schizophrenic patients and healthy subjects. Since eye movement disturbances may be related with attention[55], it will be interesting to evaluate the genetic effect of polymorphism on attention and other cognitive functions.

4. Dopamine transporter

The dopamine transporter is the primary indicator of dopaminergic tone. Mozley et al[21] investigated the relationship between cognition and dopamine transporter availability in healthy men and women. They found that dopamine transporter availability was correlated with learning performance within gender groups.

Blum et al[56] suggest that there is an association between the 480-bp VNTR 10/10 allele of the dopamine transporter gene with schizoid/avoidant behavior. The effects of this genetic factor on learning or other cognitive functions deserve investigation.

Estrogen

Whether and how the hormone estrogen affects cognitive functions has not been clear but has important implications for hormone replacement therapy in women. Current therapy involves the administration of a complex equine estrogen mixture, and its effects appear to include providing some protection against Alzheimer's disease. Estrogen receptors are expressed in the mammalian brain, but estrogen has been reported either to enhance or to impair memory.

Estrogen receptor-a and estrogen receptor-b

Mice lacking the estrogen receptor-a isoform display some types of behavioral alteration, though not as severely as mice lacking the estrogen receptor-b isoform. Rissman et al[23] reported that estrogen receptor-b knockout female mice learned to escape in a water maze just as well as wild-type females; however, when treated with physiological doses of estrogen, learning was impaired or blocked in the knockout mice. In addition, the knockout mice displayed decreased expression of estrogen receptor-a in response to estrogen treatment. Rissman et al[23] propose that estrogen receptor-b may facilitate the positive effects of estrogen on spatial learning and that its absence may increase the negative consequences of estrogen by removing a suppressive effect on estrogen receptor-a-mediated activities.

Previously, increased risk for Alzheimer's disease has been reported for polymorphism in the estrogen receptor-a gene in a Japanese cohort. However, this association has not been systematically replicated. Lambert et al[57] suggest that the risk for Alzheimer's disease may be modulated only when both estrogen receptor-a and estrogen receptor-b have particular variations in their expression and/or biological activities. Yaffe et al[58] also suggest that estrogen receptor-a polymorphism is associated with risk of developing cognitive impairment.

The relative impacts of the genetic variances of these two receptors on cognitive functions thus require systemic evaluation, particularly after adjustment for gender, age, and other variables.

Glutamate

Of all the neurotransmitter receptors in the brain, the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor has an unmatched hold on the imagination of neuroscientists. The secret of the NMDA receptor's enduring appeal is its crucial involvement in regulating changes in the strength of synapses, the regions where neurons communicate. Such changes in synaptic strength (synaptic plasticity) are believed to underlie learning and memory[59]. The NMDA receptor is a multimeric protein complex in the membranes of postsynaptic neurons. It consists of an NR1 subunit and one or more NR2 subunits, which form a channel that is permeable to calcium ions. The defining feature of the NMDA receptor is that it allows calcium ions to flow into the postsynaptic neuron when the neurotransmitter glutamate is released into the synapse. An increase in the calcium ion concentration of the postsynapatic neuron triggers a series of biochemical changes that result in modulation of synaptic strength. Despite the fact that the NMDA receptor is presumed to be a central player in synaptic plasticity, surprisingly little is known about the way in which NMDA receptor-mediated calcium influx is regulated.

1. EphB receptor

The EphB receptor tyrosine kinases are localized at the excitatory synapses where they cluster and associate with NMDA receptors. Using developing cortical neurons, Takasu et al[60] identified a mechanism whereby EphBs modulate NMDA receptor function. They indicate that EphrinB2 activation of EphB in primary cortical neurons potentiates NMDA receptor-dependent influx of calcium. Treatment of cells with ephrinB2 led to NMDA receptor tyrosine phosphorylation through activation of the Src family of tyrosine kinases. These ephrinB2-dependent events result in enhanced NMDA receptor-dependent gene expression. Their findings suggest that ephrinB2 stimulation of EphB modulates the functional consequences of NMDA receptor activation. Meanwhile, Grunwald et al[61] and Henderson et al[62] also provided in vivo evidence for the involvement of Eph receptors in synaptic plasticity.

Oba et al[63] analyzed the genomic structure of EphB2 and revealed an infrequent polymorphism (intron 2) and mutation (intron 8). Another polymorphism in exon 6, localized at nucleotide 1359 (A→G), was found to be

rather frequent in the Japanese and the Chinese, but very rare in the Caucasian.

Whether this polymorphism affect cognitive functions remain unknown.

2. NMDA receptor subunit 2B

An association between the NR2B subunit 2664-C/T polymorphism and clozapine treatment response has been suggested from the study of Hong et al[64]. In addition, Ohtsuki et al[65] screened 48 Japanese patients with schizophrenia for mutations in the coding region of the GRIN2B gene. Eight single nucleotide polymorphisms were detected. The association sample showed statistically significant excesses of homozygosity for the polymorphisms in the 3' region of the last exon in patients with schizophrenia and higher frequency of the G allele of the 366-C/G polymorphism in the patients than the controls. Studies to clarify the role of these variants on cognitive functions are warranted.

Nicotine

Nicotinic receptor systems are involved in a wide variety of behavioral functions including cognitive function[66]. Nicotinic medications may provide beneficial treatment for cognitive dysfunction in Alzheimer's disease and schizophrenia. Nicotine has been shown to improve attentional performance in these disorders[66,67]. Nicotine is also involved in memory function. Chronic nicotine administration has also been shown to significantly improve working memory[68].

Alpha 4 beta 2 and alpha 7 nicotinic receptors

Both alpha 4 beta 2 and alpha 7 nicotinic receptors in the ventral hippocampus and basolateral amygdala are involved in working memory function[69]. Working memory was impaired following local infusion of either alpha 4 beta 2 or alpha 7 antagonists[68]. Ventral hippocampal alpha 4 beta 2 blockade-induced working memory deficits are reversed by chronic systemic nicotine treatment, while ventral hippocampal alpha 7 blockade-induced working memory deficits were not reversed by the same nicotine regimen[68,69].

Whether genetic variances of these receptors may also alter other cognitions deserves elucidation.

Serotonin

The serotonergic system plays a significant role in learning and memory, in particular by interacting with the glutamatergic, dopaminergic or GABAergic system[27]. Its action is mediated via specific receptors located in the crucial brain structures involved in these functions, primarily the septo-hippocampal complex and the nucleus basalis magnocellularis (NBM)-frontal cortex .

1. 5-$HT_{1A/1B}$, 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_4 receptors

Converging evidence suggests that administration of 5-$HT_{2A/2C}$ or 5-HT_4 receptor agonists or 5-HT_{1A} or 5-HT_3 and 5-HT_{1B} receptor antagonists prevents memory impairment and facilitates learning in situations involving a high cognitive demand[27]. In contrast, antagonists for 5-$HT_{2A/2C}$ or 5-HT_4, or agonists for 5-HT_{1A} or 5-HT_3 and 5-HT_{1B} generally have opposite effects[27]. However, there are some contradictory results[70].

2. 5-HT_6 receptor

More recent studies also suggest that 5-HT6 receptor antagonists enhance retention of a water maze task in the rat[71]. The study of Meneses[72] provides further support to the notion that, 5-HT_6 receptors play a significant part in the learning consolidation under normal and dysfunctional memory conditions.

CONCLUSION

Cognitive functioning determines individuals' ability to acquire, retain, or relearn skills that are needed for real world functioning[2]. The molecular characterization of single-gene disorders or chromosomal abnormalities that result in a cognitive abnormality and of the genetic variants responsible for variation in intellectual or cognitive abilities is expected to provide new insights into the biology of human cognitive processes[73].

Earlier, genetic approaches were limited to exploring neuronal function; it thus was unclear whether they will throw light on how neuronal connections give rise to cognitive processes[73]. In short, a rapprochement between molecular and system neurosciences is required. More recently, studies to evaluate genetic effects on cognitive functions are just spurring[10,11]. However, method-

ology, subject number, variety of cognitive domains and candidate genes evaluated in the past studies still have much more space for improvement.

Further studies should simultaneously evaluate genetic and nongenetic factors that may influence cognitive functions in humans. In this way, investigators could identify a potential combination of gene polymorphisms that may provide the best predictive value of cognitive functions, particularly after control for nongenetic factors. These data may also lead to a better understanding of genetic and nongenetic modulations of various cognitive functions.

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