

# Imaging genetic influences in human brain function

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The association between genes and brain function using functional brain imaging techniques is an emerging and promising area of research that will help to better characterize the influence of genes on cognition and behavior as well as the link between genetic susceptibility and neuropsychiatric disorders. Neurophysiological imaging provides information regarding the effect of genes on brain function at the level of information processing, and neurochemical imaging provides information on the intrinsic mechanisms on how these genes affect the brain response. In this review, we highlight recent studies that have begun to explore the influence of genetic mutations on brain function with these techniques. The results, even from these few studies, illustrate the potential of these techniques to provide a more sensitive assay than behavioral measures used alone. The results also show that neuroimaging techniques can elucidate the influence of genes on brain function in relatively small sample populations, sometimes even in the absence of significant differences in behavioral measures.

## Addresses

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## Abbreviations

<b>5-HT</b>	serotonin
<b>5-HTT</b>	serotonin transporter
<b>AD</b>	Alzheimer's disease
<b>APOE</b>	apolipoprotein E
<b>BDNF</b>	brain derived neurotrophic factor
<b>BOLD fMRI</b>	blood oxygenation level dependent functional magnetic resonance imaging
<b>COMT</b>	catechol-O-methyl transferase
<b>DA</b>	dopamine
<b>DRD4</b>	dopamine D4 receptor
<b>MAO A</b>	monoamine oxidase A
<b>met</b>	methionine
<b>PET</b>	positron emission tomography
<b>PFC</b>	prefrontal cortex
<b>SPECT</b>	single photon emission computerized tomography
<b>val</b>	valine

## Introduction

Scientists and philosophers alike have debated for years about the role of 'nature versus nurture' in human cognition and behavior. It is now well accepted that both genes and environmental factors contribute to individual differences in brain function and behavior [1]. Although it is not clear to what degree each of these factors contributes to variations in brain information processing, it is likely that genes contribute a significant proportion of the variance. With the recent completion of the working draft of the human genome sequence it is now possible to attempt to explore which of the numerous genes expressed in the brain specifically affect cognition and behavior, and to what degree. It is likely that a significant number of the 30 000 genes expressed in the brain have variations in their sequence that impact upon their function (functional polymorphisms) resulting in differences in expression, activity or binding of proteins. These genetic polymorphisms are thought to result in individual differences in how the brain processes information.

Until recently, indirect measures such as neuropsychological batteries and personality inventories were the primary methods used to assess the impact of genetic polymorphisms on human cognition and behavior [2]. However, results from these approaches have been weak and inconsistent, most likely because of the subjectivity and substantial individual non-genetic variability of such measures. Critically small effect sizes of genes involved in complex phenotypes have necessitated collection of data in very large samples, often in the hundreds, to identify such effects [3].

Recently, researchers have started to apply brain-imaging techniques in this quest. Technological advances in brain-imaging techniques during past decade now allow us to non-invasively assay brain function. They can be broadly divided into those that allow measurement of regional brain activity, that is, neurophysiological imaging with blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI), positron emission tomography (PET), magnetoencephalography, and electroencephalography, and those that allow measurement of the expression and function of specific proteins and metabolites, that is, neurochemical imaging with magnetic resonance spectroscopic imaging (MRSI), PET and single photon emission computerized tomography (SPECT). Because of their capability to non-invasively measure brain function *in vivo*, these techniques are uniquely situated to elucidate functional genomics in the brain. In recent years investigators have begun to successfully implement these techniques to characterize

gene effects on brain function in relatively small sample sizes [4,5<sup>\*</sup>]. The advantage of these methods over traditional neuropsychological tests and personality inventories is their direct measurement of the impact of the gene at the level of information processing within discrete brain regions and/or networks supposed to be engaged by the tasks. By contrast, the traditional behavioral measures can be affected by the use of alternative task strategies, the level of cooperation, and various other factors that can mask potential gene effects on the underlying neural substrates meant to be engaged by the tests.

Recent advances in magnetic resonance technology also now allow superior spatial resolution in imaging, which enables the measurement of individual differences in neuroanatomy, including grey and white matter volumes with voxel based morphometry [6] and the direction and integrity of white matter tracts using diffusion tensor imaging [7]. While studies are under way with these techniques to explore the impact of genes on neural development and its impact on brain function, to our knowledge, there are no peer reviewed published reports as yet.

The scope of this review is limited to recent functional imaging studies that have focused on common gene variants that affect cognitive and behavioral processes within the normal range. Some of these studies targeted genes with clearly defined functional polymorphisms associated with specific physiological effects at the cellular level in distinct brain circuits (e.g. catechol-O-methyl transferase [COMT], serotonin transporter [5-HTT] and brain derived neurotrophic factor [BDNF], see below), whereas others, in the absence of detailed functional variants, targeted genes with identified single nucleotide polymorphisms (SNP) or allelic variants with likely functional polymorphisms that involve circumscribed neuroanatomical systems (e.g. monoamine oxidase A [MAO A], dopamine D4 receptor [DRD4], and apolipoprotein E [APOE], see below). Disease specific mutations (e.g. polyglutamine repeats in Huntington's disease, presenilins in Alzheimer's disease, and synuclein in Parkinson's disease) and rare mutations that cause mental retardation syndromes are not covered here.

### Imaging the influence of genes that affect catecholaminergic signaling in the brain

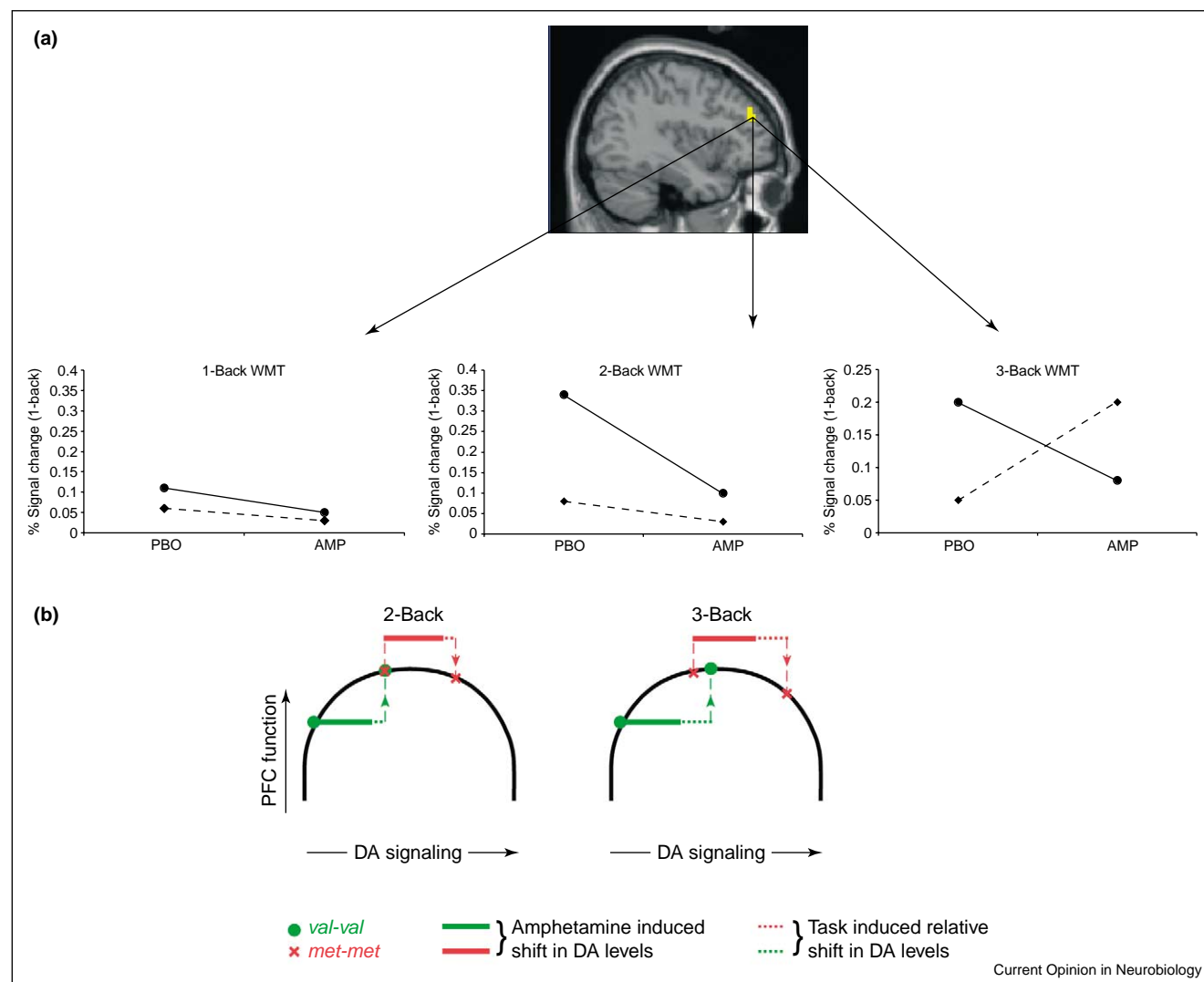
Converging evidence indicates that dopamine (DA), a crucial neurotransmitter in several brain regions including the prefrontal cortex (PFC), focuses and stabilizes the prefrontal cortical network by modulating N-methyl-D-aspartate (NMDA), non-NMDA and  $\gamma$ -aminobutyric acid (GABA)ergic currents [8,9]. Evidence also indicates an inverted 'U' relationship, whereby excessive as well as insufficient dopaminergic activity in the PFC impairs cognition, whereas levels in the moderate range result in optimal prefrontal function [10]. Recent evidence suggests that COMT, an enzyme that inactivates released

dopamine through enzymatic conversion to 3-methoxytyramine, could play a unique role in regulating DA flux in the PFC, because of the low abundance and minimal role of DA transporters in this brain region [11–13]. In humans, a functional polymorphism in the gene for COMT has been identified; an evolutionarily recent methionine (*met*) for valine (*val*) substitution at codon 108/158 results in a thermolabile protein with 3–4 times lower activity [14]. Consistent with the functional polymorphism in the COMT gene and with the evidence that COMT is important in PFC DA flux, Egan *et al.* [15] demonstrated that *met* allele carriers had superior performance on an executive cognition task. In addition, using fMRI during a working memory task, they found that *val* allele carriers consistently demonstrated a less efficient physiological response in the PFC for a fixed level of task performance (i.e. greater PFC activity) than subjects with the *met* allele. This effect of the COMT *val-met* genotype on prefrontal cognition has since been replicated by others [16–18].

Recent imaging studies also reveal that the more efficient working memory and frontal lobe information processing associated with the *met* allele could come at a price, such as adverse response to stimulants like amphetamine and heightened sensitivity to pain [19<sup>\*\*</sup>,20<sup>\*\*</sup>]. Using a double-blind crossover design and BOLD fMRI, Mattay *et al.* [19<sup>\*\*</sup>] monitored PFC activity while healthy subjects performed a working memory task. Regardless of the difficulty of the task, homozygous *val* carriers showed a more efficient frontal lobe response on amphetamine, that is, they showed a more focused PFC activation pattern on amphetamine relative to placebo while maintaining the same level of performance. By contrast, in individuals homozygous for the *met* allele, the efficiency of prefrontal response as well as accuracy and reaction time diminished significantly relative to the placebo condition at the most difficult task level, which suggests that information processing in these individuals was compromised. This is likely to be because the combined effects of amphetamine and high working memory load 'push' DA levels in these individuals beyond the optimal range on the inverted 'U' through activation of inhibitory mechanisms, including inactivation of N-type Ca<sup>2+</sup> channels [21], activation of GABAergic interneurons [22], and pre- and postsynaptic reduction of glutamate mediated synaptic responses [23]. These data extend the basic evidence of an inverted 'U' functional response curve in increasing DA signaling in PFC to suggest that individuals with the *met*<sup>158</sup>-*met* COMT genotype, although more efficient than the *val* carriers in PFC function, appear to be at increased risk of an adverse response to amphetamine (Figure 1).

Zubieta *et al.* [20<sup>\*\*</sup>] reported another negative aspect of the *met* allele. Using PET  $\mu$ -opioid imaging with C<sup>11</sup> carfentanil in concert with questionnaires that assess

Figure 1



Effect of COMT *val*<sup>158</sup>-*met* genotype on the brain response to amphetamine. **(a)** Mattay *et al.* [19\*\*], using BOLD fMRI, demonstrate a complex drug  $\times$  COMT genotype interaction in the left PFC during the N-back working memory task. N-back refers to the number of previous stimuli that the subjects had to recall. The stimuli consisted of numbers (1–4) shown in random order at approximately 2 second intervals. For example, in 3-back the subjects had to recall the number that was shown three stimuli previously. Although the *val* homozygotes (●—●) show a more efficient PFC response on amphetamine (i.e. greater PFC activity on placebo than on amphetamine) irrespective of task difficulty, *met* homozygotes (◆- - ◆) become inefficient on amphetamine at the highest working memory demand (i.e. they show more PFC activity on amphetamine than on placebo during the 3-back working memory task [WMT]). This paradoxical decrease in efficiency at 3-back in the *met* homozygotes was associated with a significant decrement in performance (decreased accuracy and increased RT). The authors suggest that the combined effects of amphetamine and high working memory load push PFC dopamine levels in these individuals beyond the critical threshold at which compensation can be made. **(b)** To illustrate these points, the authors propose a theoretical model that accounts for the variable effects of COMT genotype, working memory load, and amphetamine on dopamine signaling and PFC function. According to this model, at baseline, individuals homozygous for the *val* allele (who have relatively poorer prefrontal function, greater COMT activity and presumably less dopaminergic tone) are located on the up slope of the normal range, whereas individuals homozygous for the *met* allele are located near the peak. In *val* homozygotes, amphetamine improves PFC function as dopamine signaling is shifted to more optimal levels at all load conditions. By contrast, in individuals homozygous for the *met* allele, amphetamine shifts dopamine levels onto the down slope of the inverted 'U' curve, which has no effect or a deleterious effect depending on the magnitude of additional changes in dopamine levels associated with increasing processing demands. These data extend the basic evidence of an inverted 'U' functional response curve to increasing DA signaling in PFC (Reproduced with permission, copyright 2003 from National Academy of Sciences, USA).

pain-related sensory and affective qualities (to link the neurochemical response with the subjects' physical and psychological experience to painful stimuli), they examined the hypothesis that the different levels of COMT

activity conferred by *val-met* polymorphism might have an influence on other functions regulated by catecholamines, including the  $\mu$ -opioid system responses to noxious stimuli. They reported that, in contrast to heterozygous

individuals, individuals homozygous for the *met* allele show a diminished  $\mu$ -opioid response in the thalamus and amygdala together with higher sensory and affective ratings of pain, and a negative internal state. Individuals homozygous for the *val* allele, on the other hand, showed the opposite response. These results show that the COMT *val-met* polymorphism confers a variable response to pain across individuals by a downstream effect on regional  $\mu$ -opioid transmission through interactions with dopaminergic and/or nor-adrenergic terminals. This study not only illustrates a potential mechanism that drives the variable response to pain across individuals but it also shows that the so-called efficient allele (*met* allele) confers a lower threshold for pain tolerance.

Dopamine, along with norepinephrine, has also been implicated in attentional processes. Fan *et al.* [24<sup>\*</sup>] recently tested the hypothesis that polymorphisms linked with variability in aminergic signaling could explain the variation in the efficiency of the brain response to manage incongruent or conflicting stimuli across individuals. Using BOLD fMRI they demonstrated an effect of a polymorphism in the DRD4 receptor gene (an insertion/deletion SNP in the 5' region with unknown functional effects) and a polymorphism in the promoter region of the MAO A gene on the response of the anterior cingulate, a region thought to be crucial for conflict monitoring or conflict resolution in cortical information processing [24<sup>\*</sup>]. More efficient behavior reflected as a shorter reaction time was associated with greater cingulate activation. The insertion class group in the DRD4 polymorphism and four repeat group in MAO A polymorphism (the latter genotype linked with relatively lower catecholaminergic signaling as based on expression studies) demonstrated less conflict (in terms of reaction time [RT] ratio) and greater cingulate activity when compared to the deletion class group in the DRD4 polymorphism and the three repeat group in the MAO A polymorphism. They concluded that greater regional activity implies greater cortical efficiency, although in regard to MAO A the finding was presumably related to lower dopaminergic/noradrenergic signaling. This warrants further clarification, as it is somewhat counterintuitive. Additionally, other neuroimaging studies on the effects of the COMT *val*<sup>158</sup>*met* polymorphism (see above [15,19<sup>\*\*</sup>]) as well as studies in healthy elderly controls [25] and those in patients with Parkinson's disease [26] have shown that increased cortical activity can be associated with prolonged reaction time. This finding is thought to reflect cortical inefficiency secondary to decreased dopaminergic tone. However, it should be noted that these findings were observed in the PFC in the context of working memory performance.

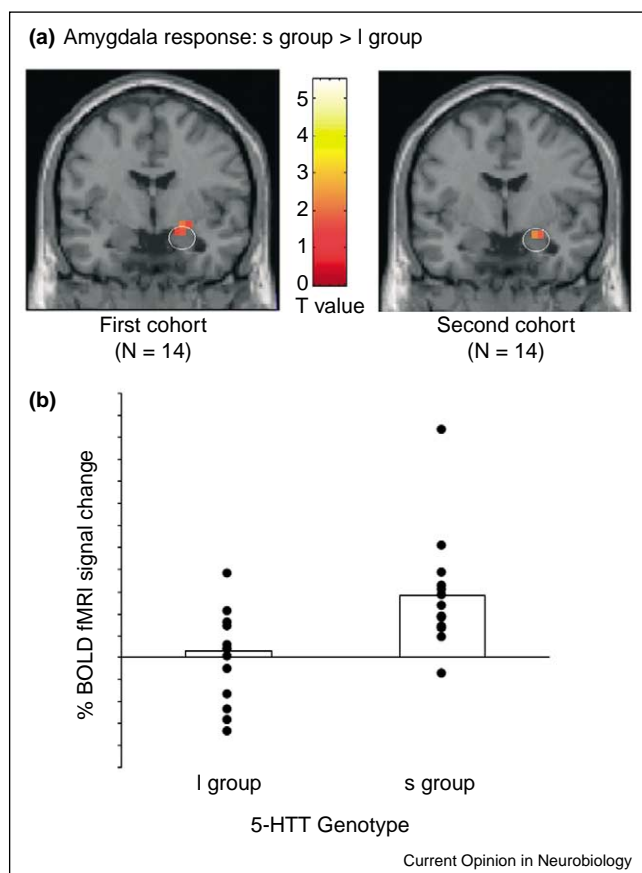
### Imaging the influence of genes that affect serotonergic signaling in the brain

The amygdala plays a crucial part in the generation and regulation of emotional behavior. Several lines of

evidence suggest that serotonin plays a crucial part in the generation and regulation of emotional behavior (for a review see Hariri and Weinberger [27]). A polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been linked to alterations in 5-HTT transcription as well as 5-HT uptake. Individuals homozygous for the long (*l*) promoter allelic variant have a higher concentration of the serotonin transporter mRNA and thereby greater serotonin uptake in comparison to individuals homozygous for the short (*s*) promoter allelic variant, who have a relatively lower concentration of the transporter and thereby relatively greater synaptic serotonin levels. Behavioral studies have suggested a relationship between the less efficient *s* allele and abnormal levels of anxiety, fear and increased incidence of affective disorders. These findings, however, have not been uniform, possibly reflecting the vagueness and subjectivity of the behavioral measurements [28–33]. With the notion that the response within the amygdala might be more reliable than measures derived from behavioral scales, Hariri *et al.* [34<sup>\*\*</sup>] demonstrated using BOLD fMRI that subjects carrying the less efficient *s* allele had an exaggerated amygdala response to fearful stimuli relative to individuals homozygous for the *l* allele (Figure 2). On the basis of these findings, the authors suggested that the increased anxiety and fear associated with individuals possessing the *s* allele might be a reflection of hyper-responsiveness of the amygdala to environmental stimuli. Studies such as this promise to provide insight into the neurobiological mechanisms of abnormal mood and affect associated with variation in 5-HT signaling.

Whereas *in vitro* studies in lymphoblast cell lines [35,36] have consistently shown that the promoter activity of the 5-HTT gene is dependent on 5-HTTLPR allelic variants — that is, the transcriptional activity of the *l* allele was greater than two times that of the *s* allele — the results from SPECT imaging in the human brain using I<sup>123</sup>  $\beta$  CIT (2beta-carbomethoxy-3beta-[4-(123)I-iodophenyl]tropine) as a radioligand have been inconclusive [33,37,38]. Recently, Shioe *et al.* [39] posited that the inconclusive nature of the SPECT studies is probably related to insensitivity of this technique to reliably assay from deep brain structures as well as to the non-selective nature of B-CIT, which binds to both serotonin and dopamine transporters. However, even with the more sensitive PET technique and a ligand with selective high affinity for 5-HTT, C<sup>11</sup>-labelled McN5652, they report no significant difference of 5-HTT binding *in vivo* across the three genotypes (*ll*, *ls* and *ss*). Given the positive results of a functional effect of this polymorphism in *in vitro* [35,36] and human fMRI studies [34<sup>\*\*</sup>], further studies are warranted to reliably characterize the association between the serotonin transporter linked polymorphisms and the 5-HTT binding.

Figure 2



Effect of 5-HTT genetic variation on the response of the human amygdala to threatening stimuli. Hariri *et al.* [34\*\*], using BOLD fMRI, demonstrate that *s* carriers of the serotonin transporter gene with presumably greater synaptic serotonin levels exhibit greater amygdala neuronal activity to threatening stimuli when compared with the activity levels in individuals homozygous for the *l* allele who presumably have lower synaptic serotonin levels. This genetically driven differential excitability of the amygdala might contribute to the increased fear and anxiety typically associated with the *s* allele (Reproduced with permission from Science).

### Imaging the influence of the gene that affects transcription of brain derived neurotrophic factor in the human brain

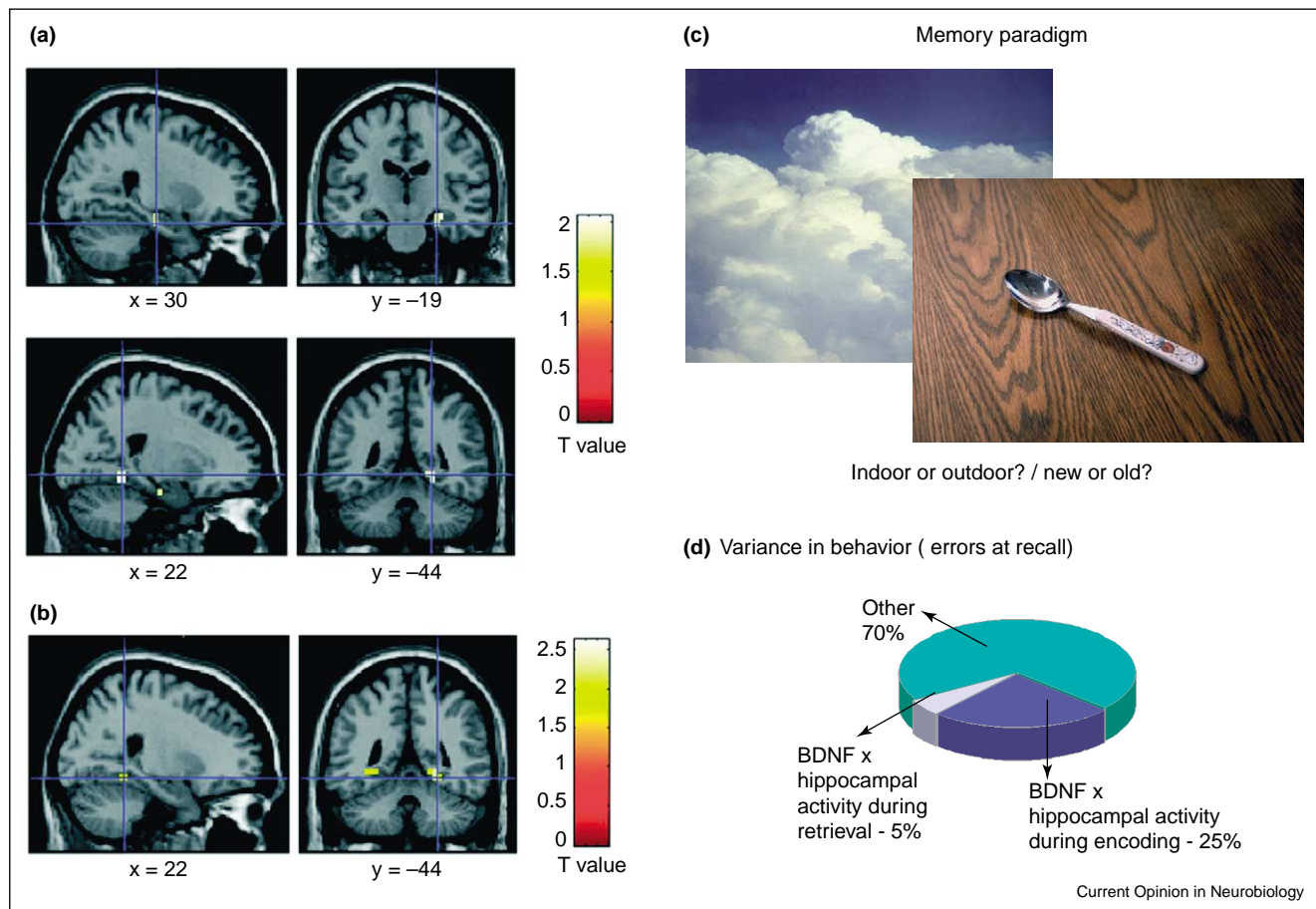
Studies in slice preparations and experimental animals have shown that BDNF plays a crucial part in hippocampal long-term potentiation associated with learning and memory [40]. Recently, a frequent polymorphism resulting in a nonconservative *val* to *met* substitution at codon 66 in the human BDNF gene has been identified by Egan *et al.* [41\*\*]. They showed that the mechanism by which the BDNF polymorphism produces a differential effect on hippocampal function relates to an alteration in intracellular trafficking and activity dependent secretion of BDNF. Using MRSI, they also showed that the *met* allele is associated with both relatively lower levels of N-acetyl aspartate, a putative marker of neuronal integrity and

synaptic abundance, and behavioral deficits in episodic memory (during a test in which subjects were asked to recall a story) when compared to subjects homozygous for the *val* allele. To explore directly the impact of this polymorphism on memory-related hippocampal activity, Hariri *et al.* [5\*] performed an experiment using BOLD fMRI in healthy human subjects during encoding and subsequent retrieval of complex novel scenes. They found that *met* carriers exhibited relatively diminished hippocampal activity during both encoding and retrieval processes in comparison to *val* homozygotes (Figure 3). Importantly, they demonstrated that the interaction between the BDNF *val-met* genotype and the hippocampal activity (as measured by the BOLD response) during encoding accounted for 25% of the total variance in recognition accuracy. Taken together, these two studies from the same group illustrate the potential of a systems level approach using *in vitro*, *in vivo* (functional brain imaging) and behavioral measures to successfully delineate the impact of a gene, BDNF in this case, on brain function.

### Imaging the influence of the apolipoprotein allele on brain function

APOE is thought to have a role in cell maintenance and repair, including amyloid clearance, perhaps on the basis of its role in cholesterol metabolism. It is now well established that the APOE  $\epsilon 4$  allele is associated with increased risk for Alzheimer's disease (AD) in a dose-dependent manner [42,43]. If the deposition of  $\beta$  amyloid (assumed to be pathogenic in AD) is a chronic and lifelong process that is either accelerated or not ameliorated by APOE  $\epsilon 4$ , then it stands to reason that individuals with APOE  $\epsilon 4$  genotypes might have increasingly evident cognitive abnormalities over their lifespan. Alternatively, a threshold effect for the impact of  $\beta$  amyloid on information processing (such that it becomes apparent only after it exceeds some limit) cannot be ruled out. Functional brain imaging studies have consistently shown APOE  $\epsilon 4$  effects in otherwise normal individuals. Early resting studies also found widespread reductions in glucose metabolism in otherwise normal APOE  $\epsilon 4$  carriers [44,45]. Using fMRI, Smith *et al.* [46] showed a reduced BOLD response in APOE  $\epsilon 4$  carriers in the inferotemporal region during fluency and object recognition. Bookheimer *et al.* [47], on the other hand, showed increased activity in response to memory tasks in subjects carrying the epsilon4 allele compared to those without this allele, and interpreted it to reflect a compensatory response through the recruitment of additional cognitive resources in the face of greater task demands. More recently, other groups replicated this phenomenon of compensatory increased activity in other brain circuits as well [48,49]. Using BOLD fMRI during a working memory task in healthy non-demented elderly individuals, Petrella *et al.* [48] demonstrated greater extent and magnitude of activation in the PFC in the  $\epsilon 4$  carriers relative to the  $\epsilon 3$  carriers. Burggren *et al.* [49], on the other hand, examined the

Figure 3



Effect of BDNF *val*<sup>66</sup>*met* polymorphism on human memory-related hippocampal activity and performance. Hariri *et al.* [5\*], using BOLD fMRI, demonstrate greater hippocampal activity during (a) encoding and (b) retrieval of (c) novel visual stimuli in *val* homozygotes of the BDNF gene when compared to the *met* carriers. (d) Of note, this interaction between the BDNF *val*<sup>66</sup>*met* genotype and the hippocampal BOLD response during encoding accounted for almost 25% of the variance in recognition memory performance (Reproduced with permission, copyright 2002 from The Society for Neuroscience).

specificity of these findings; were these differences specific to memory tasks only or could they be generalized to any difficult cognitive task? Using fMRI and a modified digit-span task with varying difficulty in carriers and non-carriers of the APOE  $\epsilon$ 4 allele, they report no significant difference in activation patterns at the most difficult task level. The authors suggest that additional cognitive effort in persons at genetic risk of AD is specific to episodic encoding and is not a reflection of task difficulty per se. Most importantly, Bookheimer *et al.* [47] also demonstrated that greater baseline brain activation correlated with subsequent verbal memory decline. When 'decline' begins is a key issue, although a recent study by Reiman *et al.* [50] indicates that it might be discernible in individuals in the 20 to 40 year old age range on [(18)F] fluorodeoxyglucose (FDG) PET.

Given that APOE  $\epsilon$ 4 confers increased susceptibility to age-related memory problems and that cholinergic sys-

tem abnormalities are associated with memory problems in the elderly and AD patients, Cohen *et al.* [51] used <sup>18</sup>F FP-TZTP (<sup>18</sup>F labeled muscarinic - 2 selective agonist) to measure directly the effect of APOE  $\epsilon$ 4 on the muscarinic component of the cholinergic system. They found increased distribution volumes of the tracer in APOE  $\epsilon$ 4 carrying older individuals relative to the non-carriers and this correlated inversely with cerebral blood flow. The authors postulate that this observation reflects an increase in the number of unoccupied muscarinic-2 receptors, probably caused by the lower synaptic acetylcholine concentration in the APOE  $\epsilon$ 4 carriers.

Taken together, data from these functional neuroimaging studies (see above) support the notion that the effects of the APOE  $\epsilon$ 4 allele can be discerned well before clinical presentation of disease and that elderly subjects with this allele are possibly more susceptible for future cognitive decline. Recent advances also show promise for *in vivo*

mapping of amyloid plaque density and neurofibrillary tangles in the human brain [52,53]. Specifically, Shoghi-Jadid *et al.* [53] reported that greater accumulation and clearance in amyloid plaque and neurofibrillary tangle rich brain areas correlated with lower performance scores not only in patients with AD but also in controls. Therefore, complemented with genetic information these *in vivo* techniques have the potential to unravel further the relationship among APOE  $\epsilon 4$  allele load affect, amyloid plaque and neurofibrillary tangle density, and susceptibility to future cognitive decline and Alzheimer's disease.

## Conclusions

Human cognition, behavior, and psychiatric disorders involve complex and polygenic modes of inheritance in which each gene might have only a small effect. To date, only the effects of single genetic polymorphisms on brain function have been explored with neuroimaging techniques. Whereas the effects of the COMT $val^{158}met$  polymorphism and the APOE  $\epsilon 4$  allele on brain function have been consistently shown across many studies, the effects of 5HTT and BDNF polymorphisms, although well supported by evidence from experimental *in vitro* studies, need replication in independent samples. The effects of MAO A and DRD4 genotypes are less clear and warrant further study. Most importantly, the functional interactions between multiple gene variants and environment, and their collective impact on brain function are yet to be explored.

Overall, the results of some of the studies reviewed in this article are striking, and they illustrate the promise of brain imaging techniques to unravel the role of genetic polymorphisms in altering brain function as well as in conferring susceptibility to illness. They also underscore the advantage of a systems level approach; that is, integrating genetic information with an endophenotype (i.e. regional neurophysiological, neurochemical and neuroanatomical measures obtained through neuroimaging techniques) and a phenotypic trait (e.g. cognitive and behavioral measures) to successfully delineate the influence of genes on brain function.

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- In this study, the authors explore the neural underpinnings related to individual differences in the brain response to stimulants like amphetamine. To this end, they investigate the effects of the COMT *val*-*met* polymorphism on the actions of amphetamine in prefrontal cortex. Subjects were given either amphetamine or placebo and imaged with BOLD fMRI while performing a task with increasing working memory load in a

double-blind counter balanced study. Consistent with basic evidence that dopamine impacts prefrontal function in an inverted 'U' shaped curve, they demonstrate that amphetamine improves the efficiency of prefrontal function in individuals homozygous for the *val* allele (who presumably have lower dopaminergic tone at baseline). On the other hand, they illustrate a detriment in the efficiency of PFC function in individuals homozygous for the *met* allele (who presumably have a higher dopaminergic tone at baseline relative to the *val* homozygotes) only at higher working memory loads. This probably reflects increased dopaminergic signaling from the combined effects of amphetamine and increased stress (for example, in situations requiring higher cognitive demands), that pushes these individuals beyond a critical threshold on the inverted 'U' curve of dopamine at which compensation can be made.

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Using PET and C<sup>11</sup> carfentanil, a  $\mu$ -opioid receptor selective radiotracer, the authors demonstrate that varying levels of catecholamine metabolism conferred by the COMT *val-met* polymorphism are associated with downstream alterations in the functional responses of the  $\mu$ -opioid neurotransmitter system and compensatory changes in  $\mu$ -opioid receptor binding in the striatopallidal circuits, the thalamus, the amygdala and the anterior cingulate. Specifically, they observed that *met* homozygotes showed a diminished  $\mu$ -opioid response in these regions to pain when compared to the *val-met* heterozygotes.

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