

Genome-Wide Analyses of Working-Memory Ability: A Review

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Abstract Working memory, a theoretical construct from the field of cognitive psychology, is crucial to everyday life. It refers to the ability to temporarily store and manipulate task-relevant information. The identification of genes for working memory might shed light on the molecular mechanisms of this important cognitive ability and—given the genetic overlap between, for example, schizophrenia risk and working-memory ability—might also reveal important candidate genes for psychiatric illness. A number of genome-wide searches for genes that influence working memory have been conducted in recent years. Interestingly, the results of those searches converge on the mediating role of neuronal excitability in working-memory performance, such that the role of each gene highlighted by genome-wide methods plays a part in ion channel formation and/or dopaminergic signaling in the brain, with either direct or indirect influence on dopamine levels in the prefrontal cortex. This result dovetails with animal models of working memory that highlight the role of dynamic network connectivity, as mediated by dopaminergic signaling, in the dorsolateral prefrontal cortex. Future work, which aims to characterize functional variants influencing working-memory ability, might choose to focus on those genes highlighted in the

present review and also those networks in which the genes fall. Confirming gene associations and highlighting functional characterization of those associations might have implications for the understanding of normal variation in working-memory ability and also for the development of drugs for mental illness.

Keywords Working memory · Genomics · Cognition · GWA · Dynamic network connectivity

Introduction

Working memory is crucial to everyday life; it plays a key role in everyday tasks—following spoken directions, reading a magazine article, calculating a tip in a restaurant—that require information to be temporarily stored and manipulated [1, 2]. It has been described as being core to reasoning and judgment in humans; in other words, working memory is crucial to other important aspects of cognitive performance, such as attention and executive functioning [3, 4], and is a determinant of an individual's level of intelligence [5, 6]. As a consequence, working memory is one of the most studied concepts in cognitive neuroscience [7]. In addition, working memory is impaired in psychiatric and neurodegenerative illnesses such as schizophrenia and Alzheimer's disease [8, 9]. Moreover, there is thought to be a substantial genetic overlap between those genes that mediate illness risk and those that influence working-memory ability [10, 11]. The importance of working memory to cognition in general, combined with the key role that working memory plays in the symptomatology of certain illnesses, behooves the research community to provide insights into the molecular underpinnings of working-memory ability. The field of behavior genetics is ideally suited to fulfill this task and, to date, several genome-wide searches for genes influencing working memory have been conducted. The present manuscript provides a qualitative review of this literature.

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The work reviewed here converges on the role of neuronal excitability in working-memory ability, with a focus on dopaminergic signaling, which is in line with the work of Goldman-Rakic and colleagues and, more recently, Arnsten and colleagues [12–14, 15•, 16].

A Definition of Working Memory

Working memory is a theoretical construct from the field of cognitive psychology. The term was coined by Miller et al. [17] to refer to the ability to temporarily store and manipulate task-relevant information. As a concrete example, imagine that someone asks you to solve a difficult multiplication problem without using a pen and paper (e.g., “What is 8 times 35?”). It is unlikely that you could simply recall the answer from your long-term memory—instead, you would probably need to split the problem into several easier multiplications (e.g., 8×5 and $8 \times 3 \times 10$) and then sum together those answers. Working memory is needed to choose which smaller multiplications to perform, to remember the answers before summing them (40 and 240), and to remember the final answer before saying it out loud (280). A critical feature of this definition of working memory is that it includes both *storage* and *manipulation*. Working memory is not just a synonym for short-term memory; rather, it subsumes many functions that allow the retrieval, integration, transformation, and disposal of stored information (for a review, see Baddeley [7]).

It is easy to see how working memory would play a role in most everyday tasks, and empirical work supports this intuition: working memory is believed to constrain other aspects of cognition, such that the better an individual’s working memory, the better their attentional control and executive functioning [3, 4, 18, 19]. Moreover, measures of working memory usually correlate with general intellectual ability better than almost all other cognitive measures [5, 6]. Thus, working memory ubiquitously influences cognition.

Heritability of Working Memory

Heritability (h^2) is a measure of effect size that describes the amount of phenotypic variance that is due to genetic differences between individuals. It is bounded between 0 (indicating no genetic influence) and 1 (complete genetic influence), and is estimated using the correlations between relatives in the phenotype of interest [20]. Estimates of h^2 for working memory range between 0.32 and 0.66—indicating moderate to high heritability—in both healthy individuals [21–26, 27•] and clinical samples [28–31].

Multivariate analyses have demonstrated that the strong correlations between measures of working memory and general intelligence can be almost entirely attributed to shared

genetic influences. In other words, the majority (~95 %) of the genes that influence working memory also influence general intelligence [26, 27•]. Although there is this substantial genetic overlap, there is utility in focusing on working memory rather than on general intelligence when attempting to isolate genetic effects on cognitive ability. Compared with broad abilities, specific cognitive measures are associated with relatively distinct brain circuits [32]. For example, the neural systems that support different aspects of working memory are consistently linked to portions of the dorsolateral and ventrolateral prefrontal cortex, the medial posterior parietal cortex, and regions of the medial temporal cortex, depending on the particular task used [33–40]. While it is unlikely that brain regions are rigidly specialized for domain-specific cognitive processing, there is clear evidence for differential engagement of particular brain networks for classes of information processing [41]. To the extent that genes are uniquely expressed in anatomic regions of the adult brain [42], it is possible that specific genes or gene networks may have relatively more control on domain-specific cognitive processing associated with those regions. This line of thought suggests that identifying genes that influence distinct cognitive domains may be more tractable than finding genes for general intelligence [43]. Some might argue that because heritability estimates for intelligence are higher than those for working memory (between 0.50 and 0.80 [44]), gene-finding efforts should focus on intelligence. However, heritability estimates reflect the overall cumulative genetic effect on a trait but do not reveal the subtle complexities therein or the specific composition, architecture, and number of the underlying causal genes [45]; therefore, the strength of a heritability estimate is not necessarily predictive of the ease with which genes will be detected.

The Molecular Basis of Working Memory

Because working memory is a collection of largely transient processes, the underlying neural circuitry and molecular mechanisms must be well suited to moment-to-moment processing [16, 46]. By contrast, it is known that long-term memory is governed by long-lasting architectural changes induced by long-term potentiation in brain regions, including the hippocampus [47, 48]. Previous work has shown that layer III of the dorsolateral prefrontal cortex (DLPFC) is particularly important in working memory, where synaptic connections are found on long, thin dendritic spines ideally suited to dynamic processing [12, 49]. Research in primates has revealed that networks of DLPFC neurons are persistently active during the execution of a visual delayed response task (an archetypal measure of working memory) and become inactive upon task completion [50, 51]. The same type of neuron has also been found in other brain areas associated with working

memory, including the inferior temporal cortex, hippocampus, posterior parietal cortex, and entorhinal cortex [52–56].

It has been consistently shown that dopamine levels in the DLPFC influence performance on working-memory tasks [57–60]. Modulation of neurons in the DLPFC is thought to take place, broadly speaking, by dopaminergic signaling, which acts in concert with excitatory glutamatergic and inhibitory GABAergic systems [61]. In more detail, the binding of dopamine to its receptor (D_1) allows stimulatory G-protein (G_s) to increase adenylyl cyclase (AC) activity. AC enhances intracellular cyclic adenosine monophosphate (cAMP) concentrations, and cAMP in turn activates protein kinase A (PKA), resulting in the opening of ion channels HCN (hyperpolarization-activated channels) and KCNQ [61]. The opening of potassium (K^+) KCNQ channels decreases firing and results in rapid weakening of the network of neurons that are otherwise active during a working-memory task. Conversely, the binding of norepinephrine to its receptor (α_2A) strengthens the network by inhibiting the release of cAMP [16]. Arnsten and colleagues coined the term “dynamic network connectivity” to describe the mediating role of these neurotransmitters on the neural activity associated with working memory [15••]. A schematic of this process is shown in Fig. 1 where, on the left (green) side, the inhibition of cAMP results in strengthened network connections and fast cognitive operations and, on the right (red) side, the increase in cAMP results in the slowing down of cognition. Thus, the strength of the network underlying working-memory ability is reliant on cAMP mediation of ion channels and, specifically, the transfer of positive ions (or cations) across voltage-gated channels, both independently and also via activation of PKA [16, 62, 63].

Genes Contributing to Healthy Variation in Working Memory

Identifying genes for working memory in humans might further elucidate the underlying molecular mechanisms by confirming and possibly extending those that have already been discovered via animal research [16]. Many genetic associations have been identified for cognition and, more specifically, for working memory, under the candidate-gene approach [64]. However, attempts to replicate those associations have failed [65]. Even associations that were considered to be robust—for example, with *COMT* [66]—have been revealed to be false positives when tested in large samples of healthy individuals [67]. Consequently, the present review focuses on genome-wide approaches. The majority of candidate-gene documented variants for working memory are common, and consequently those same associations should be amenable to detection by genome-wide association (GWA), an approach that focuses on common variation [68]. Upon reviewing the

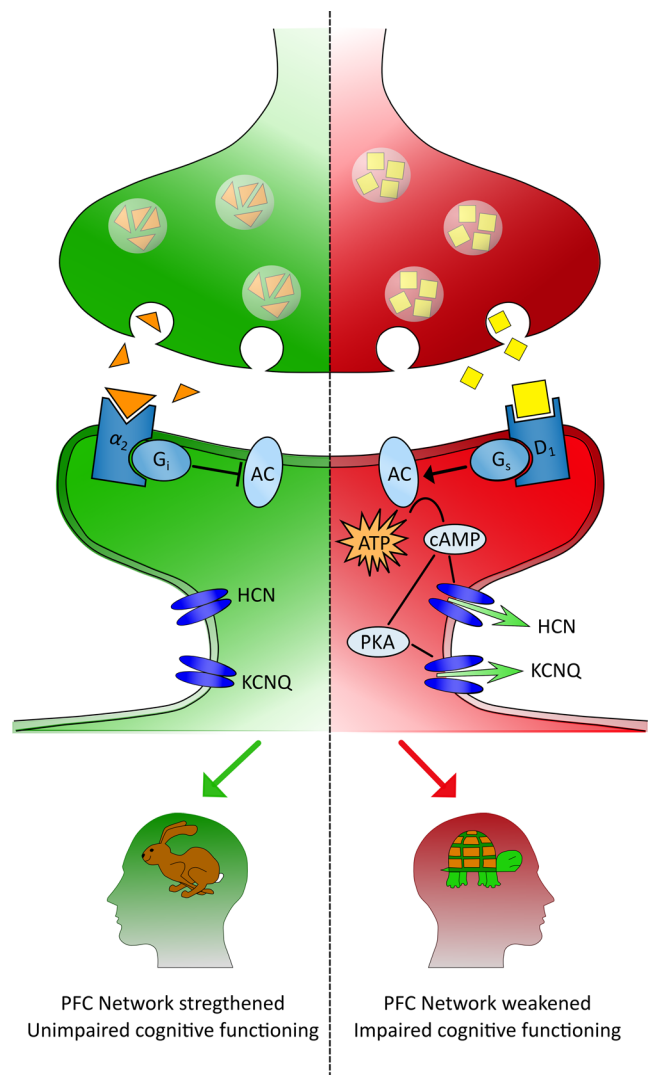


Fig. 1 Dynamic network connectivity in the dorsolateral prefrontal cortex (PFC) [adapted from Arnsten and colleagues [15••]]. The neuromodulators norepinephrine and dopamine mediate the strength of the network, residing in the dorsolateral PFC, that underlies working-memory ability. On the left (green) side of the figure, the binding of norepinephrine (represented by the orange triangles) to its receptor (α_2A) strengthens the network by inhibiting the release of cyclic adenosine monophosphate (cAMP), which results in uninterrupted cognitive function. Conversely, on the right (red) side of the figure, the binding of dopamine to its receptor (D_1) results in increased adenylyl cyclase (AC) activity via the activation of stimulatory G-protein (G_s). Increased AC activity results in enhanced cAMP concentration, and this results in the opening of sodium and potassium ion channels (HCN and KCNQ, the latter via the activation of protein kinase A [PKA]). The opening of ion channels results in depolarization of the neuron and, consequently, weakening of the network and impaired cognitive function. ATP adenosine triphosphate, G_i inhibitory G-protein

genome-wide searches of working memory carried out in recent years, it becomes evident that the results of most studies appear to converge on the role of neuronal excitability via voltage-gated ion channels—a key feature of the experimental work carried out in animals by Arnsten and colleagues [16].

Genome-Wide Association Studies of Working Memory

Cirulli and colleagues conducted a GWA study principally focused on executive function in 1,086 healthy individuals of mixed ethnicity. Additional cognitive tests, including some that indexed working memory, were conducted in a subsample of 514 individuals [69•]. No individual test yielded any genome-wide significant results. The top result was for digit-span backward ($p=6.3 \times 10^{-8}$; another classic measure of working memory), but this result was intergenic. The second-best hit for the same test was located in the gene *KIAA1217* ($p=3.9 \times 10^{-7}$). KIAA genes are a group of novel human genes identified by the cDNA project, and the functional characterization of many of these genes remains unknown [70–72].

Cirulli and colleagues also found suggestively significant hits for animal fluency and the trail-making test, both of which measure aspects of working-memory ability. The animal fluency task requires participants to name as many animals as possible in 60 seconds and necessarily relies on working memory to retain and inhibit already uttered responses and to implement memory retrieval strategies [73]. The top hit for animal fluency ($p=6.41 \times 10^{-7}$) was located in an intron of the gene *KCNB2*, which encodes a type of voltage-gated potassium channel called Kv2.2 [74]. *KCNB2* contributes to the maintenance of overall excitability of neurons, such that neuronal networks can be disrupted if there is disruption in the placement or functionality of voltage-gated ion channels [75, 76]. Kv2.2 channels are preferentially expressed in the basal forebrain and particularly in GABAergic neurons [77]. Research in rats suggests that these neurons contribute to working-memory performance, possibly via modulation of ascending dopaminergic projections to the frontal cortex [78, 79].

The other suggestively significant result from Cirulli and colleagues was for the trail-making test part A (TMT-A); this test is primarily considered a measure of visuomotor processing, cognitive flexibility, and attention, but it also includes a strong working-memory component [80, 81]. Participants must consecutively connect numbered circles on a work sheet, without lifting the pen, as quickly as possible [82]. The top hit for TMT-A ($p=2.55 \times 10^{-7}$) was located in an intron of the gene *ATL1* (or *SPG3A*), which encodes the alastin-1 protein [83]. This gene is associated with hereditary spastic paraplegia, a group of disorders characterized by movement disorder and cognitive impairment, and which, on the basis of evidence from case studies, may be related to Parkinson's disease; the two illness types are thought to have shared etiologies, possibly within nigrostriatal dopamine projections [84–87]. Research using *Drosophila* with a disrupted *ATL1*-homolog exhibits age-related degeneration of dopaminergic neurons—degeneration that can be restored by the administration of a D₁ receptor agonist [88]. Lee and colleagues maintain that this

finding might have treatment implications for spastic paraplegia sufferers, although this has not been found to be the case in the small number of patients tested to date [89]. The full story is not yet clear, but the *ATL1* gene may indirectly mediate prefrontal dopamine levels, which underlie working-memory performance.

Need and colleagues conducted a GWA study of the Cambridge Neuropsychological Test Automated Battery (CANTAB). They calculated heritability estimates of each test by comparing correlations in 100 monozygotic and 100 dizygotic twin pairs, and then conducted association analysis in a sample comprising one member of each twin pair plus additional unrelated subjects, totaling ~700 individuals [90•]. No genome-wide significant variants were identified. However, the top-ranked variant ($p=6.03 \times 10^{-6}$) for working-memory strategy, a score that indexes the efficiency of the search strategy employed in a spatial working-memory task ($h^2=0.53$), was located 1.5 kb upstream of the gene *FXYD2*, which encodes a membrane protein (Na⁺, K⁺-ATPase gamma subunit) that regulates sodium and potassium ion transportation; this protein is phosphorylated by PKA [91, 92]. Dopamine inhibits this particular membrane protein by increasing cAMP via binding to D₁ receptors [93–97]. Thus, the gene *FXYD2* plays a part in maintaining the excitability of neurons that might be crucial to the completion of a working-memory task.

Papassotiropoulos and colleagues conducted a multiphase GWA study and found that a variant within the gene *SCN1A*, which mediates the construction of a type of sodium (Na⁺) channel (Nav1.1), was associated with working-memory performance at a genome-wide significant level [98•]. The study was conducted in multiple phases, from discovery through to replication in several additional samples, totaling 2,032 individuals. The neuropsychological task was immediate recall performance, a type of short-term memory storage that is essential to working memory. Moreover, the authors also showed an association between the same variant and brain activation associated with the performance of an n-back task, a classic measure of working memory [98•]. Sodium channels for which *SCN1A* is responsible control the flow of sodium into a cell and therefore play a crucial role in neuronal excitability [99, 100]. Indeed, mutations in *SCN1A* are thought to contribute to the neuronal excitability that leads to epilepsy [101, 102]. GABAergic neurotransmission is impaired in *SCN1A* mutant mice, for whom there is a 50 % reduction in the proportion of Nav1.1 sodium channels in the prefrontal cortex [103]. This is a particularly interesting result, because the role of GABAergic neurons in the prefrontal cortex is thought to involve fine-tuning of activated neuronal networks, such that said activity can be focused onto task-relevant items [104]. GABAergic hypofunction in the prefrontal cortex makes up one theory of cognitive impairment in schizophrenia, of which one of the primary deficits is in working memory [8, 105, 106].

Seshadri and colleagues conducted a GWA study of a cognitive test battery in a sample of 694 individuals taken from families that make up the Framingham extended-pedigree study [107•]. The top hit for any cognitive test ($p=3.2\times 10^{-6}$) was for an index of abstract reasoning. This is a relevant finding because working memory and reasoning ability are similar constructs [5]. The variant was located within an intron of *SORLI*, which encodes a low-density lipoprotein receptor (LDLR). LDLR is thought to be involved in endocytosis of amyloid precursor protein (APP) [108]. Specifically, *SORLI* activity modulates APP processing, such that down-regulation of the gene results in increased APP sorting into amyloid- β ($A\beta$) [109–111]. Alzheimer's disease is associated with an accumulation of $A\beta$ protein in the brain [112]. Indeed, *SORLI* has been found to mediate Alzheimer's disease risk [113–116], and levels of *SORLI* are decreased in the frontal cortex and lymphoblasts of patients with Alzheimer's disease [117]. An association between cognitive impairment and *SPOR1* has also been shown [118]. Moreover, an association has been shown between hippocampal volume and *SPOR1* in a sample of healthy adults [119]. It is thought that elevated $A\beta$ destabilizes those neuronal networks that underlie cognition by suppressing excitatory activity at the postsynaptic level [112]. Specifically, increased levels of $A\beta$ decrease the number of N-methyl-D-aspartate (NMDA) receptors, a subclass of glutamate-gated ion channels [60, 89].

Knowles and colleagues conducted a genome-wide linkage analysis of factor models of genetically clustered cognitive traits, followed by quantitative trait locus (QTL) region-specific association analyses in a sample of 1,269 Mexican American individuals from extended pedigrees [27•]. This study is distinct from the other studies discussed so far because rather than relying on an individual neuropsychological measure to index working memory, detailed phenotypic models were built. More specifically, the authors built a three-tier hierarchical model of cognition, which included a “g” (general intelligence) factor that subsumed several correlated cognitive domains onto which loaded the individual neuropsychological tasks. In this way, the working-memory phenotype in this study might be said to more reliably reflect the underlying construct than those from previous studies. By definition, a latent variable reflects the shared variance between the multiple tasks that load upon it and thus, rather than reflecting the version of working memory indexed by a particular neuropsychological task, the domain reflects the overlapping working-memory portion of each task in a single score [120]. Two genome-wide significant QTLs were revealed for working memory on chromosome 8 (8q21.11–13 and 8q24.22), and each exhibited pleiotropy with the other cognitive domains in the model. Post hoc association analysis in the region beneath the linkage peak at 8q21.13 revealed two common variants that were associated with working memory near the *HEY1* gene. *HEY1* is a transcription target of Notch

and makes up part of the hairy and enhancer of split (HES) and hairy/enhancer-of-split-related with YRPW-like motif (HEY, also named HERP) gene families. Notch is associated with the formation of long-term memories [121]. Furthermore, *HEY1* binds to *DAT1*, the dopamine transporter gene, such that deficits in the *HEY1* gene result in enhanced expression of *DAT1* and in turn increase expression of *D1* receptor genes [122]. *HEY1* knockout mice exhibit impaired performance on the Y-maze test, a measure of working memory in rodents [123, 124]. The same type of knockout mice also exhibit enhanced prepulse inhibition due to altered dopamine sensitivity [125]. The full story is not clear, but it seems likely that *HEY1* has a mediating role in dopamine activity related to successful working-memory performance. Two genome-wide significant QTLs were also observed for the spatial-memory domain, for which a contributing measure was a spatial working-memory task, on chromosome 17 (17q22–24.2 and 17q25.1–3). For the first QTL, post hoc association analysis highlighted two variants as being peak-wide significant. Several genes were highlighted in post hoc analysis as being implicated in spatial-memory ability, including *BCAS3*, *MGAT5B*, and also *APPBP2*. *APPBP2*, which is functionally associated with the production of $A\beta$, is particularly interesting given previous research highlighting the importance of $A\beta$ in Alzheimer's disease, and also given the results from the GWA study by Seshadri and colleagues outlined above [107•].

Taken together, each GWA study of working memory has a top-ranked gene that is implicated in neuronal excitability via ion-gated channels, and/or prefrontal dopamine expression (Table 1). Cirulli and colleagues found a role for *KCNB2*, which encodes a type of voltage-gated potassium channel [69•]. Need and colleagues highlighted the involvement of *FXDY2*, which encodes a membrane protein that regulates sodium and potassium ion transportation [90•]. Papassotiropoulos and colleagues emphasized the gene *SCN1A*, which is responsible for control of the flow of sodium into a cell [98•]. Seshadri and colleagues noted the importance of *SORLI*, which increases $A\beta$ and consequently destabilizes neuronal networks by suppressing excitatory activity [107•], and Knowles and colleagues further underscored the role of *APPBP2*, which is functionally associated with the production of $A\beta$ [27•]. Knowles and colleagues also highlighted the gene *HEY1*, which results in enhanced expression of the *DAT1* and *D1* receptor genes [27•]. Neuronal excitability appears to be key to working-memory performance across samples and neuropsychological tasks. It is difficult, upon reviewing this literature, not to be struck by the way in which the majority of the results highlight genes with a moderating role in neuronal excitability, which fits in neatly with the dynamic network connectivity model of working memory [15••].

Table 1 Summary of the top-ranked variants, taken from genome-wide searches, for working-memory ability

Authors	N	Measure	Variant	<i>p</i> value	Gene; gene function
Seshadri et al. (2007) [107•]	694	Abstract reasoning	rs1131497	3.2×10^{-6}	<i>SORL1</i> ; encodes an LDLR that modulates APP processing into A β , which can suppress excitatory neuronal activity
Need et al. (2009) [90•]	721	Working-memory strategy	rs4472969	6.03×10^{-6}	<i>FXRD2</i> ; encodes a membrane protein (Na ⁺ , K ⁺ -ATPase gamma subunit) that regulates sodium and potassium ion transportation
Cirulli et al. (2010) [69•]	514	Animal fluency	rs2247572	6.41×10^{-7}	<i>KCNB2</i> ; encodes a type of voltage-gated potassium channel (Kv2.2) that mediates potassium ion transportation
		TMT-A	rs17122693	2.55×10^{-7}	<i>ATL1</i> ; encodes alastin-1 protein. Disrupted <i>ATL1</i> results in age-related degeneration of dopaminergic neurons in <i>Drosophila</i>
Papassotiropoulos et al. (2011) [98•]	333 _{discovery} 1,699 _{replication}	Immediate recall	rs10930201	3.0×10^{-4} ^a	<i>SCN1A</i> ; mediates the construction of a type of sodium (Na ⁺) channel (Nav1.1)
Knowles et al. (2014) [27•]	1,269	Factor score	rs2467774	1.1×10^{-5} ^b	<i>HEY1</i> ; encodes a protein belonging to the HES and HEY gene families

A β amyloid- β , *APP* amyloid precursor protein, *FDR* false discovery rate, *HES* hairy and enhancer of split, *HEY* hairy/enhancer-of-split-related with YRPW-like motif, *LDLR* low-density lipoprotein receptor, *TMT-A* trail-making test part A

^a FDR corrected

^b Linkage peak-wide corrected

Enrichment Studies of Working Memory

Heck and colleagues recently published cohesive evidence for a link between neuronal excitability and working memory, using enrichment analysis [126••]. While GWA studies have been successful in isolating genes for working memory, many of the results discussed in the present review failed to meet genome-wide significance. This might be because GWA, which focuses on single variants, has limited power to identify genetic influences on a complex trait because of the vast number of tests conducted and the associated necessity for multiple-testing correction [127]. Enrichment analysis, on the other hand, uses a more powerful approach whereby the association of biologically related gene sets is tested with a trait [128].

Heck and colleagues conducted gene-set enrichment of analysis of working memory using an n-back task, first in a discovery sample and then in two replication samples, totaling 2,824 individuals [126••]. They found that the voltage-gated cation channel activity gene set was significantly associated with working memory in the discovery sample and in one of the replication samples, and was the top-ranked gene set in the remaining sample. The authors extended this finding to show that alleles from the gene set correlated with working-memory-associated brain activation in brain regions previously shown to be important for working-memory performance.

Voltage-gated cation channel activity refers to the transfer of a positively charged ion (for example, calcium, sodium, or potassium) across a cell membrane via ion channels, the permeability of which is mediated by the membrane potential of the cell. Thus, neuronal excitability, which is underlain by the proper functioning of ion channels, was again shown to be crucial for working-memory performance in this study.

Conclusion

Genetic studies have the potential to provide key insights into the molecular mechanisms that underlie working memory. The work of Arnsten and colleagues highlights the role of dynamic networks of neurons, the activity of which is mediated by dopaminergic signaling, such that non-optimal levels of dopamine result in rapid weakening of the network via cAMP-mediated depolarization of neurons [15••]. Genome-wide studies of working memory confirm and extend this work. The associations documented to date converge on the role of neuronal excitability, which fits in neatly with the dynamic network connectivity model of working memory [15••]. Each result highlights the role of genes with a functional role in voltage-gated ion channels and/or prefrontal dopamine expression. These findings represent QTLs, not true functional gene localizations, but nonetheless they provide an

interesting starting point. Future work that aims to characterize functional variants influencing working-memory ability might choose to focus on those genes highlighted in the present review and also those networks in which the genes fall. Those networks should relate to voltage-gated ion channel activity and neuronal excitability. This will expand upon the work discussed here and, in so doing, will shed light on working memory, a construct thought to be extremely important for normal variation in general cognitive ability, as well as in psychiatric and neurodegenerative illness. Confirming gene associations and highlighting functional characterization of those associations might have implications for the development of treatments for mental illness.

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Compliance with Ethics Guidelines

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- Of importance
- Of major importance

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