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Genetic Architecture Of Declarative Memory: Implications for Complex Illnesses

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Abstract

Why do memory abilities vary so greatly across individuals and cognitive domains? Although memory functions are highly heritable, what exactly is being genetically transmitted? Here we review evidence for the contribution of both common and partially independent inheritance of distinct aspects of memory function. We begin by discussing the assessment of long-term memory and its underlying neural and molecular basis. We then consider evidence for both specialist and generalist genes underlying individual variability in memory, indicating that carving memory into distinct subcomponents may yield important information regarding its genetic architecture. And finally we review evidence from both complex and single-gene disorders, which provide insight into the molecular mechanisms underlying the genetic basis of human memory function.

Keywords

heritability; declarative memory; schizophrenia; Alzheimer's Disease; Neurofibromatosis I

Introduction

Human memory is a genetically complex trait that likely involves epistasis as well as interactions between genes and experience-dependent (environmental) factors. Throughout human history, survival has depended on accurate representations of remembered knowledge: for the food-gathering human, remembering – for example-spatial locations of food sources, or whether a particular kind of berry is poisonous. Thus, from an evolutionary standpoint it is clearly advantageous for memory to be a highly heritable cognitive trait (Manns and Eichenbaum, 2006). Accordingly, the anatomy and functional role of the critical neural circuitry underlying declarative memory – namely, the hippocampus and adjacent entorhinal and parahippocampal cortices- are largely conserved across species, despite considerable diversity in other brain regions (Manns and Eichenbaum, 2006). Furthermore, while the type of information processed by cortical areas may vary among species, intrinsic computations of the hippocampal system may not (Manns and Eichenbaum, 2006). Yet,

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despite evidence for evolutionary conservation and heritability in humans, the specific genes and genetic networks that influence memory are largely unknown.

Many neurological and psychiatric illnesses associated with memory dysfunction (e.g., Alzheimer's Disease (AD) and other forms of dementia, schizophrenia, and multiple sclerosis) are at least partially under genetic control. As such, a more complete understanding of the genetic architecture and neural underpinnings of long-term memory could provide clues about the biological pathways that influence these disorders. To the extent that declarative memory is sensitive to the function of genes that also predispose to these illnesses, quantitative indices of memory function could be used, either independently or in conjunction with clinical diagnostic information, in order to identify genes that confer disease risk. This approach is referred to as an endophenotype strategy (Bearden and Freimer, 2006; Gottesman and Gould, 2003). This strategy has been successfully employed in the investigation of non-psychiatric complex diseases. For example, asthma is characterized by the production of high levels of immunoglobulin E (IgE) in response to common allergens. Total serum IgE has a heritability of 40–50%, and has been successfully used as a quantitative trait to map susceptibility genes for asthma. Heart disease provides another compelling example of the value of genetic studies of normal variation in quantitative traits (Kathiresan et al., 2009). Recent studies of lipid variation localized quantitative trait loci that later were confirmed to influence risk of heart disease (Teslovich et al., 2010; Waterworth et al., 2010). Thus, the use of a quantitative allied phenotype or endophenotype – such as performance on a memory task – holds promise for gene identification for brain-related illnesses.

In this review, we consider evidence for the heritability of declarative memory, and focus on empirical evidence for both common and partially independent inheritance of distinct aspects of memory function. Next we highlight some genetic studies that have used declarative memory as an endophenotype, along with findings regarding memory deficits in disease states, which collectively suggest that genetic variation – in the form of both common variants and rare mutations – may independently impact similar components of hippocampal circuitry, resulting in partially overlapping deficits that emerge from unique genetic roots. Although there are likely multiple genes that influence human memory – exactly how many is not yet known – we will focus here on a few key examples, for which the molecular mechanisms are relatively well understood. It is likely that many additional genes that influence memory function have yet to be discovered; these genes may leverage their effects via common molecular pathways.

Cognitive components of memory

Declarative, long-term memory (LTM) involves memories that can last as little as a few days or as long as decades. It differs structurally and functionally from working or short-term memory, which stores items for time frames on the order of seconds. Short-term memory involves a temporary potentiation of neural connections that can become long-term memory via rehearsal and meaningful association. LTM is typically divided into two categories: declarative (or explicit) memory and implicit (or procedural) memory (see Figure 1). Declarative (explicit) memory refers to memories that can be consciously recalled, such as factual knowledge and events. Declarative memory also has two major subdivisions, episodic and semantic memory (Tulving, 1972). Episodic memory refers to memory for specific events in time and is uniquely different from other memory systems, as it enables human beings to remember past experiences (Tulving, 2002). Semantic memory (also known as conceptual knowledge or conceptual memory) refers to general knowledge of facts, word meanings, objects and people without connection to a particular event. While

memory for episodic events tends to be specific to an individual, conceptual knowledge is largely shared across people within a given culture.

Implicit or procedural memory (also known as non-declarative memory) refers to unconscious memories for skills involving the use of objects or movements of the body, such as how to ride a bicycle. This type of memory involves neural circuitry that is dissociable from that involved in declarative memory, as it is associated with the basal gangli rather than the temporal lobe (Gabrieli, 1998). There is relatively little evidence regarding heritability of procedural memory; while the learning of motor skills is highly heritable (Fox et al., 1996; Francks et al., 2003), heritability of other forms of skills and habits has not been previously reported. These sub-types of memory can be differently affected across disorders, providing further evidence that while they may interact, they are least to some extent independent. For example, in AD, procedural memory abilities are relatively spared, because these abilities are less dependent on prefrontal and hippocampal brain regions, which are most compromised with disease progression (Poldrack and Gabrieli, 1997).

Assessment of memory

Most of the tasks used to measure LTM involve the assessment of declarative rather than procedural memory. As with all cognitive domains, the memory literature represents a combination of standardized neuropsychological tests often employed as a part of clinical assessments, and experimental tasks designed to address theoretical questions about memory function. Neuropsychological tasks have the advantage of being standardized, so that they are comparable across study groups and populations, but often the constructs they test are more general. Experimental tasks have the benefit of being able to probe more refined questions about components of memory function, but are not easily comparable across sites or studies (Barch and Carter, 2008). Standard neuropsychological tests of declarative memory generally involve a delay between the encoding and retrieval (or recollection from memory stores) of information. In the verbal domain, list-learning tasks involving both an immediate and delayed condition are commonly used. Tasks of visual memory typically involve presentation of drawings or designs, which the subject must draw immediately and after a brief (approximately 20 minute) delay. Because such tasks also require intact graphomotor skills, typically a ‘copy’ condition – which does not require memory – is also included, in order to determine whether impaired performance represents a primary memory impairment or basic visuo-perceptual deficit. In order to disentangle difficulties with encoding versus retrieval, memory tests typically include both a free recall (i.e., freely retrieving the information from memory) and a recognition component (i.e., responding yes or no when presented with a particular item). In general, recognition is easier (less effortful) than free recall.

Neural underpinnings of memory

A crucial step in outlining the role of genetic influences on memory is to understand the functional neuroanatomy of the memory system. Neural systems supporting declarative memory involve a set of interconnected neural networks linking neocortex, parahippocampal regions (including both perirhinal cortex and more posterior parahippocampal cortex), and the hippocampus (see Figure 2). Lesions to this region result in global amnesia characterized by an inability to form new memories and a temporally graded loss of previously acquired memories. The predominant contemporary view of the functioning of this system highlights the role of more ventral regions of neocortex, and closely-connected perirhinal cortical regions that they project to, in the immediate representation of stimulus features and maintenance of those representations over brief delays (Eichenbaum, 2000; Ranganath,

2010; Wang and Morris, 2010). More dorsal regions of neocortex, and closely-connected parahippocampal cortex, participate in the representation and maintenance of stimulus context. Both of these constituents of the greater parahippocampal region cooperate to help representation persist, buffering them against interference, and providing a venue for an initial phase of feature binding across information modalities and brief time intervals. The hippocampus in turn provides an additional degree of association-building, linking representations across longer spans of time, binding items into the context of a particular learning episode (Ranganath, 2010), and allowing generalization (and inference) between related learning episodes (Eichenbaum, 2000). Critically, once these assemblies of neocortical representations and their relationships are encoded, reactivation of any part of the assembly triggers activation of the entire, bound set of representations, allowing for retrieval of complex memories based on only partial cues (Wheeler and Buckner, 2004). The role of the neocortex is not restricted to sensory regions subserving stimulus feature representation, however. Heteromodal regions such as prefrontal and parietal cortices also contribute to the conscious, effortful organization of information to be encoded, as well as to conscious recollection of learned information (while suppressing irrelevant information) and judgments based on the retrieved information (Ranganath, 2010).

Positioned at the highest level of this associative hierarchy, the hippocampus displays a heterogeneous organization that facilitates its role in declarative memory functioning. Information generally flows from perirhinal and parahippocampal cortices, as noted above, to entorhinal cortex, which projects axons into the dentate gyrus, entering the hippocampus proper (see Figure 3). The dentate, in turn, projects excitatory links to area CA3, which excites area CA1. CA1 then sends inputs to deeper, out-going lamina of the entorhinal cortex, via the subiculum (Amaral and Lavenex, 2006). Both intrinsic and extrinsic inhibitory connections innervate all levels of this system. Wang and colleagues (Wang and Morris, 2010) have proposed that the projections into CA1 provide information establishing spatial context for stimuli to be remembered, while separate inputs into CA3, and then into CA1, are critical for indexing the stimuli themselves. Building of associations within CA1 is therefore fundamental for binding together objects and context information into the complex representation of a learning episode (Wang and Morris, 2010).

In light of this highly associative nature of the process by which declarative memories are constructed and reconstructed, the creation, stabilization/consolidation, modulation, and reactivation of these associations is critical. Each of these phases, and each component of the circuitry they rely on, represents a point of vulnerability. Disruption of any of these components could result in a memory deficit, and a fine-tuned cognitive dissection of the deficit is needed to determine precisely which aspects of the process are impaired. As discussed in relation to memory deficits associated with neuropsychiatric disease, below, genetic influences on any one of these processes could all result in a final common pathway of poor performance on a memory task, albeit through distinct mechanisms.

Molecular basis of memory

At the neuronal level, modification of the strength and efficiency of synaptic connections by synchronous activity in pre- and post-synaptic neurons – what Hebb famously postulated to be the cellular basis of memory (Hebb, 1949) – provides a model of the type of experience-dependent neural plasticity that would be required of a physiological substrate of long-term memory. Although this modification can occur through a number of mechanisms (Bliss and Collingridge, 1993; Malenka and Bear, 2004), the most intensively studied example is long-term potentiation (LTP), or persistent enhancement of post-synaptic signaling triggered by a specific pattern of activity during the initial learning episode (Bliss and Collingridge, 1993).

Perhaps the most widely-studied example of LTP involves enhancement of CA1 pyramidal neuron activity after stimulation of presynaptic CA3 neurons – a phenomenon mediated by glutamatergic N-methyl-D-aspartate (NMDA) receptors on the post-synaptic neuron. Briefly, the presynaptic neuron releases glutamate into the synapse, and it binds to post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, triggering an excitatory post-synaptic potential. Intense, repeated stimulation unblocks post-synaptic NMDA receptors and initiates a number of intracellular signaling cascades (Blitzer et al., 2005). These modifications of AMPA receptor capabilities are sufficient to enhance the amplitude of subsequent post-synaptic responses over relatively short periods of time (e.g., hours). However, stable, LTM formation requires additional steps, including gene transcription and protein synthesis (Blitzer et al., 2005).

Despite parallels between certain properties of molecular mechanisms of LTP and behavioral observations of fundamental aspects of long-term memory (e.g., fast initial encoding/modification, persistence over a year or more, stability amidst interference), proving definitively that synaptic plasticity is necessary and sufficient for long-term memory functioning has been difficult (Neves et al., 2008). Nevertheless, progress is ongoing as investigators strive to understand the molecular and cellular underpinnings of remembered experience.

Heritability of memory

Twin and family studies

Heritability provides an index of the extent of genetic control over a trait. Heritability estimates (h^2) range between zero, indicating no genetic contribution to trait variance, to 1, suggesting that the trait is completely under genetic control. Heritability is typically assessed through twin, family, and pedigree studies, in which the relationship between genetic proximity and similarity in cognitive performance can index the degree to which a trait is associated with genetic or environmental factors. These designs have been frequently employed to assess the heritability of general cognitive abilities (Plomin and Kosslyn, 2001). However, it is important to note that heritability estimates reflect the magnitude of the overall genetic effect on a trait, but do not indicate either the total number of genes that might be involved, or the relative contributions of those genes (Almasy, 2003). Thus, while higher heritability estimates suggest that a trait is more strongly influenced by genetic factors, it does not provide information about the genetic architecture of the trait (e.g., whether trait variance is influenced by many genes of small effect, or a single gene of large effect).

Recent studies of genetic influences on cognitive abilities have highlighted the role of *g*, or general intelligence, based on findings of genetic correlations across different cognitive domains that are present even in cognitive disorders. The heritabilities of individual cognitive traits, including components of LTM, have been investigated, although not to the same extent as general intellectual function (IQ). There is evidence that episodic memory performance in young to middle aged adult samples is moderately heritable, with estimates falling around 50% (Alarcon et al., 1998; Finkel and McGue, 1993; Finkel et al., 1995a; Swan et al., 1999; Volk et al., 2006), suggesting that half of all between-subject variation in memory performance is due to genetic factors. However, various component processes of memory may have different genetic determinants. For instance, in a study of female twins, Volk and colleagues (Volk et al., 2006) found that free recall of semantically unrelated words was more highly heritable (h^2: 0.55) than free and cued recall of categorized words (h^2: 0.38 and 0.37, respectively). Additionally, covarying for verbal intelligence (h^2: 0.77) indicated substantial shared variance between IQ and categorized word recall, but not between IQ and recall of unrelated words. These findings suggest that recall of unrelated and

categorized words is at least partially influenced by different genetic and environmental factors. Furthermore, a recent study of middle-aged twins showed evidence for shared genetic influences on learning ability and retrieval (h^2: 0.36), as well as unique genetic influences on learning ability, likely reflecting unique genetic contributions to information acquisition (Panizzon et al., 2011).

There is also evidence that heritability estimates for episodic memory are heavily task-dependent, further supporting the notion that heritability patterns may be more nuanced (Finkel et al., 1995a; Thapar et al., 1994). For instance, strategy use is genetically influenced, and may mediate the heritability of episodic memory performance (Nandagopal et al., 2010). In other words, differences in heritability estimates between memory measures may be related, to some extent, to the degree to which the measure is amenable to strategy use. Factors such as processing speed may also account for some of the genetic influence on episodic memory, particularly as related to heritability of age-associated changes (Finkel et al., 2009). Thus, heritability findings may be influenced by processing speed constraints that can limit the ability to perform memory tasks. In addition to the observed heritability of behavioral assays of memory, twin and family studies have shown the neuroanatomic structures associated with these cognitive functions to be heritable as well (generally with higher heritability estimates than behavioral measures of memory). For instance, volumes of temporal regions have heritabilities in the range of 50–80% (see Tables 1 and 2).

Specialist vs generalist genes: the case for faces

While many genes are likely to contribute to common pathways that affect memory performance, there may also be specialist genes that contribute predominantly to genetic variance for particular types of memories. Evidence for such ‘specialist genes’ comes from two recent studies of face recognition or face memory abilities, suggesting that face memory is both substantially heritable (Wilmer et al., 2010; Zhu et al., 2010) and may be qualitatively distinct from other kinds of visual memory. In a large study of healthy adult twins, additive genetic factors accounted for 68% of the total variation in face recognition performance and 100% of the familial resemblance; task performance was only modestly correlated with other visual and memory abilities, suggesting that both face recognition ability itself and its genetic underpinnings are largely domain-specific (Wilmer et al., 2010). These findings nicely complement those of Zhu and colleagues (Zhu et al., 2010), who found significant heritability for standard face recognition, but that heritability was near 0 for recognition of both houses and inverted faces. Data from singleton adults also demonstrated independence of upright face memory from both general cognitive ability (verbal paired associate memory and IQ), and from non-face visual recognition for abstract art. Additionally, evidence from prosopagnosia studies indicates that severe face recognition deficits can run in families, independent of IQ (Duchaine et al., 2007) sometimes with normal recognition for non-face objects (Lee et al., 2010). These findings provide compelling evidence that a specific cognitive ability – face memory- is heritable independent of *g* (McKone and Palermo, 2010). The neural mechanisms underlying face recognition – involving bilateral midfusiform gyrus – are well established, in both humans and non-human primates (Kanwisher, 2006). As such, cognitive neuroscience studies may guide genetic investigations of this socially advantageous trait.

Age-associated changes in heritability of memory functions

It is unknown if the memory and brain-related changes associated with normal aging reflect a process of ‘damage accumulation’ with increasing age, or are intrinsically programmed (Charlesworth, 2000; Holliday, 2006; Medawar, 1952). Yet, as heritability estimates tend to increase with increasing age (McArdle and Plassman, 2009; Reynolds et al., 2002), genes likely play an important role. Although there are considerable individual differences in

normal age-related changes in neurocognition and neuroanatomy (Creasey and Rapoport, 1985), these changes appear to be non-linear and domain-specific. While cognitive domains like memory, executive functioning and processing speed decline with normal aging (Craik et al., 1994; Park, 2002; Park et al., 1996; Salthouse and Ferrer-Caja, 2003), other areas of cognition like short-term memory, autobiographical memory, semantic knowledge and emotional processing are often relatively preserved, as shown in Figure 4 (Carstensen and Lockenhoff, 2003; Fromholt et al., 2003; Happe et al., 1998; Hedden and Park, 2003; Jacoby, 1999; La Voie and Light, 1994; Shimamura, 1995). Cross-sectional data from the Seattle Longitudinal Study (Schaie, 1996) showed a near linear decline in cognitive processing speed from age 20 to age 80. However, the longitudinal data from this seminal study that followed 7 age cohorts over 35 years indicated almost no age-related changes between 20–60 years, with declines after the age of 60 similar to those observed in the cross-sectional data (Hultsch, 1998; Schaie, 1996; Zelinski and Burnight, 1997). Differences between the cross-sectional and longitudinal results may reflect cohort differences, such as educational opportunity, cultural factors and socioeconomic status (Hofer and Sliwinski, 2001). The high heritability estimates for long-term memory in elder twins over (Johansson et al., 1999; McGue and Christensen, 2001), suggests that at least a portion of normal age-related decline is under genetic control. However, relatively little is currently known about specific genes that influence healthy normal aging.

Progressive gray matter loss beginning in the sixth decade appears to closely parallel declines in cognitive function over this time period (Haug and Eggers, 1991; Resnick et al., 2003; Walhovd, 2005). These volumetric declines appear to result from reduced synaptic density rather than cell death (Terry, 2000), being closely associated with neurotransmitter depletion, particularly prefrontal levels of dopamine, noradrenaline and serotonin (Sheline et al., 2002; Volkow et al., 2000; Volkow et al., 1996). MRI-based neuroanatomic studies consistently indicate that age-related declines are pronounced in frontal and parietal cortices, with the temporal and occipital lobe showing relatively less volume loss in normal aging (Raz et al., 1997; Raz et al., 2004a; Raz and Rodrigue, 2006; Raz et al., 2004b; Resnick et al., 2003; Salat et al., 2004). Volumetric changes in subcortical regions show a pattern that is structurally specific (Allen et al., 2005; Raz et al., 2004a; Walhovd et al., 2005; Walhovd, 2005). In the absence of Alzheimer's dementia, volumes of the hippocampus and the parahippocampal gyrus decrease by 2–3% per decade (Jack et al., 1998; Raz et al., 2004b). Unfortunately, at present very little is known about the genes that may influence these changes.

Genes contributing to normal variability in memory function

Behavior genetics studies have been informative regarding the relatively large contribution of genetic factors to memory function, but cannot inform us about the specific genes involved. In the past decade, increasingly high-density genotyping platforms have afforded an opportunity to examine the genetic basis of human memory on a genome-wide level. In a genome-wide screen (Papassotiropoulos et al., 2006) found that a locus encoding the WW and C2 domain-containing protein KIBRA (Kremerskothen et al., 2003) was significantly associated with performance on a verbal learning and memory test in a Swiss cohort of 351 healthy young adults. This finding was subsequently validated, using two slightly different verbal memory tasks, in a sample of outbred, cognitively normal adults from the United States. There were no allele-dependent differences in performance on control tasks of executive function, attention or working memory, suggesting that the action of the KIBRA gene is specific to hippocampal-dependent memory. This finding was replicated in a second Swiss cohort, using a visual episodic memory task. The investigators further bolstered the association findings by fine-mapping the genomic region harboring KIBRA and the flanking genes, to ensure that the observed association was not due to linkage disequilibrium with

surrounding genes. Next, they determined expression levels of KIBRA in the hippocampal formation and dentate gyrus, two key brain regions involved in memory, in both human and murine brain tissue, finding that expression levels of the truncated KIBRA protein were higher in these structures than in other, non-memory related brain structures. Finally, functional magnetic resonance imaging (fMRI) studies of an associative memory task were conducted in a subset of Swiss participants. Although there were no allele-dependent differences in encoding, nor in behavioral performance, during the retrieval phase those without the T allele showed significantly increased neural activity compared with T allele carries in the medial temporal lobe and frontal cortex, suggesting that individuals without the T allele require more activation in memory-related brain structures to achieve comparable performance.

The KIBRA protein is known to act as a binding partner for dendrin, a putative modulator of synaptic plasticity, and also to interact with multiple proteins involved in vesicular transport and neuronal plasticity (Schneider et al., 2010). Although subsequent studies in other populations have not been able to replicate this association (Need et al., 2008), this study is unique in its multi-level investigation of how the KIBRA gene may actually be involved in the neurobiology of memory. Recent studies have investigated the role of this gene in Alzheimer's disease, suggesting a modest role for this gene's involvement in memory and AD risk (Corneveaux et al., 2010).

Genes contributing to memory deficits in disease states

Disturbances of memory are a central feature of a number of psychiatric and neurological illnesses and in many cases, these disturbances appear to be genetically mediated, often serving as endophenotypes for the disorders (see Figure 5). One line of evidence for the role of genetics comes from family studies demonstrating the presence of deficits in unaffected relatives who carry some risk genes, but do not suffer from the clinically manifest disorder. Alzheimer's disease (AD) and schizophrenia represent two salient examples.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder that affects approximately 3% of the population (Smalley et al., 1992). Examining heritability of memory phenotypes in the context of cognitive disorders becomes more complex, as both genetic and disease-associated factors are involved. As a result, there may be less familial resemblance in the memory phenotype (i.e., low sibling correlations) if a major gene with non-shared environmental influences underlies the phenotype (Smalley et al., 1992). For instance, it has been found that heritability of episodic memory performance among unaffected family members of AD patients was 0.62, slightly above the range typically reported in younger healthy individuals (Wilson et al., 2011), and that unaffected siblings show memory deficits relative to healthy age-matched controls (Rice et al., 2003), particularly when the ill sibling has an early onset form of AD (La Rue et al., 1992). However, asymptomatic adult children of AD probands showed little evidence of similarity (i.e., low intraclass sibling correlations with heritabilities around 0) on memory tasks sensitive to Alzheimer's symptomatology, as compared to other, non-memory tasks that showed heritabilities ranging between 0.24–0.52 (Smalley et al., 1992),. However, a subgroup of siblings had markedly lower memory performance, with that subgroup putatively representing a prodromal AD group. So, the degree to which siblings resemble their affected relatives may not just depend on overall genetic proximity, but on the mode of genetic inheritance, and which particular genes are shared. In support of this, there is evidence that AD is genetically heterogeneous, involving not just additive genetic risk based on genes of small effect, but a few genes of large effect, such as apolipoprotein E (APOE), which has been strongly and unequivocally associated with increased risk for AD, as discussed below.

In addition to behavioral studies of memory, neuroanatomic phenotypes have also been examined in AD families. Studies assessing AD patients and their unaffected siblings have shown that MRI phenotypes, such as cerebral atrophy, medial temporal atrophy, white matter hyperintensities, and indices of cerebrovascular disease are heritable and may be useful endophenotypes for genetic studies of AD (Cuenco et al., 2008; Kochunov et al., 2009; Kochunov et al., 2008; Lunetta et al., 2007). Heritability remained significant after covarying for APOE genotype, implying that a substantial proportion of the additive genetic variance in these brain phenotypes is explained by other genes (Lunetta et al., 2007). In addition, healthy adults with a maternal history of AD showed brain metabolic changes in temporal, parietal, and frontal regions that resembled those observed in the prodromal stages of the disorder (Mosconi et al., 2007).

The APOE gene on chromosome 19 likely represents the most well-validated common genetic variant identified to date that is relevant to memory function. There are three possible allelic variations of APOE, 2, 3, and 4, being the 3 the most frequent (Eisenberg et al., 2010). The APOE-4 allele has been strongly associated with risk for AD (Bertram et al., 2007; Saunders et al., 1993), and the risk conferred is gene dose-dependent, with those individuals carrying two APOE-4 alleles having the highest risk for developing the disease (Tsai et al., 1994). In addition to its role in AD, APOE-4 genotype is associated with a number of memory related phenotypes. For instance, asymptomatic APOE-4 carriers have smaller hippocampal volume than do non-carriers, as well as lower functional activation during memory tasks, and thinning in medial temporal regions (Donix et al., 2010). Other studies have also reported that episodic memory declines in APOE-4 carriers prior to symptomatic presentation of mild cognitive impairment (MCI; (Caselli et al., 2004).

Mechanistically, the apolipoprotein E is involved in lipid metabolism. The APOE-4 genotype results in lower levels of APOE and consequently higher concentrations of circulating cholesterol (Takeda et al., 2010). In addition, APOE-4 genotype is also associated with gene dose-dependent decreases in dendritic spine density in post-mortem brains (Ji et al., 2003). Relevant to AD neuropathology, the APOE-4 protein may be associated with tau and amyloid production, although not necessarily neurofibrillary tangles except in older subjects (Takeda et al., 2010). In patients with AD, the APOE-4 genotype is associated with a worsened course of the disorder, as well as more profound neural changes such as increased hippocampal atrophy, as shown in Figure 6 (Mori et al., 2002; Pievani et al., 2010).

Schizophrenia

As a broad phenotype, long-term, declarative memory deficits also present in schizophrenia and predict much of the disorder's characteristic functional impairment (Green et al., 2000). However, more fine-grained analysis demonstrates important differences in the cognitive profiles of schizophrenia versus AD. In particular, the severity of the mnemonic impairment in AD tends to be greater than in schizophrenia, and it also tends to involve impairment in both the encoding of novel information and the retrieval of well-learned information (i.e., "forgetting") (Ting et al., 2010). Schizophrenic patients, in contrast, tend to show slowed, inefficient learning of novel information, but can generally retrieve that information once it has been consolidated (Cirillo and Seidman, 2003). Additionally, while AD tends to emerge later in life and show a degenerative course, schizophrenia is a distinctly neurodevelopmental disorder with cognitive impairments observable long before the emergence of frank psychotic symptoms (Reichenberg et al., 2010), reflecting latent illness vulnerability.

Declarative memory deficits have also been seen in high-risk adolescents (Brewer et al., 2005; Cosway et al., 2000) and non-psychotic relatives of schizophrenia patients (Cannon et

al., 1994; Faraone et al., 1999), further suggesting that this cognitive phenotype derives at least in part from an inherited genotype. However, because these memory deficits are more pronounced in patients compared with their own healthy monozygotic co-twins, non-genetic, disease-related factors must also be involved (Cannon et al., 2003). Specifying the genetic basis of memory deficits in schizophrenia could help to elucidate the molecular pathogenesis of the disorder, and to develop treatments that target this area of substantial cognitive deficit.

As in AD, computational brain-mapping approaches have revealed underlying neural correlates of schizophrenia patients' verbal learning and memory deficits, demonstrating both genetic liability and disease-specific effects on hippocampal volume (van Erp et al., 2004). Studies comparing monozygotic (MZ) and dizygotic (DZ) twins have also allowed the distinction between unique environmental and unique genetic effects on endophenotypes of interest. Specifically, in a population sample of Finnish twins concordant and discordant for schizophrenia, hippocampal volume varied in a dose-dependent fashion with the genetic loading for schizophrenia (see Figure 7). However, the intraclass correlations (ICCs) for hippocampal volumes among healthy MZ pairs were larger than those among healthy DZ pairs, but the ICCs for hippocampal volumes among discordant MZ and DZ pairs were equivalent. Together, these findings indicate that while hippocampal volume in healthy subjects is under substantial genetic control, hippocampal volume in schizophrenia patients and their relatives appears to be influenced to a greater extent by unique and shared environmental factors (van Erp et al., 2004). Furthermore, intra-pair differences between patients and their non-affected co-twins in hippocampal volume and declarative memory performance were highly positively correlated, indicating that these neural abnormalities are strongly tied to the behavioral phenotype (van Erp et al., 2008). Functional neuroimaging of declarative memory performance among non-psychotic, non-twin relatives of schizophrenia patients offers additional evidence suggestive of abnormal prefrontal and temporal lobe activity associated with memory recollection, presumably reflecting genetic vulnerability (MacDonald et al., 2009).

Pathological studies of the hippocampus in schizophrenia indicate lower neuronal size, possibly fewer neurons of specific types, and lower levels of a range of pre-synaptic proteins, particularly in the terminal fields of projections from the entorhinal cortex (Sawada et al., 2005). Additionally, recently evidence suggests adult neurogenesis may be reduced in schizophrenia, which may contribute to impaired cortical-to-hippocampal connectivity (Reif et al., 2006).

Although much work remains in identifying the genetic architecture of the mnemonic impairment in schizophrenia, there are some promising leads associated with the disorder's distinctly developmental course. An example involves the neuregulin (NRG1) gene, which has been linked independently to schizophrenia vulnerability (Stefansson et al., 2002) and to the regulation of LTP in the hippocampus (Kwon et al., 2005). One mechanism by which this regulation may occur involves decreased NRG1 signaling, which may perturb the activity-dependent maturation of AMPA receptors, in turn degrading the development of hippocampal NMDA receptors in a manner that would mimic the developmental course of schizophrenia (Li et al., 2007). Imaging studies have linked NRG1 genotype to modulation of neural activity during episodic memory encoding and retrieval in healthy individuals (Krug et al., 2010). However, examination of more than single SNPs within particular candidate genes is needed to advance our understanding of the mechanisms by which neuregulin may impact memory function.

Neurofibromatosis type I

A complementary approach to the search for susceptibility genes for complex traits such as memory involves the study of specific chromosomal mutations associated with memory dysfunction. An important benefit of this approach is that it facilitates the use of translational models, as the genetic cause of the disorder is well characterized. Mouse models for individual candidate genes provide an opportunity to investigate the function of these genes, and how they may impact on cognitive and neural phenotypic features associated with a given syndrome. As such, single gene disorders have dramatically enhanced our understanding of the molecular mechanisms of memory, and how they are perturbed in the context of particular genetic mutations (Bearden et al., 2008).

Neurofibromatosis type I (NF1), or von Recklinghausen disease, affects 1/4000 people world-wide, making it one of the most common single-gene disorders impacting learning and memory in humans. This disease is caused by mutations in the NF1 gene on chromosome 17q11.2 which encodes neurofibromin, a rat sarcoma viral oncogene homolog (Ras) GTP-ase activating protein (GAP) that is highly expressed in the brain and has a key role in modulating hippocampal inhibition during learning (Brannan et al., 1994). There is substantial evidence implicating the Ras signaling pathway in synaptic plasticity and long-term memory formation. Studies of mice with a heterozygous-null germ-line Nf1 mutation (Nf1+/− mice) have shown that these animals have enhanced inhibitory transmission, which is likely mediated by enhanced release of the main inhibitory neurotransmitter in the central nervous system [GABA (gamma-aminobutyric acid)]. This increased inhibitory transmission seems to directly cause deficits in spatial learning in the Morris water maze (Costa et al., 2002; Silva et al., 1997), a hippocampal-dependent task, and deficits in LTP. Other hippocampal physiologies are unaffected by the Nf1+/− mutation, suggesting a relatively selective effect on LTP. The spatial learning deficits of Nf1+/− mice closely resemble those observed in human NF1 patients (Shilyansky et al., 2010; Silva et al., 1998), suggesting that the mouse model is highly relevant to the human condition.

Costa and colleagues also found that the LTP deficits in these Nf1+/− mutant mice can be rescued by genetic and pharmacological manipulations that decrease Ras gene function (Costa et al., 2002) indicating that the learning deficits associated with NF1 are likely caused by excessive Ras gene activity. These models have important implications for the development of targeted treatments for memory dysfunction. For example, memory deficits associated with Nf1 mutations can be reversed in adult mutants with a brief treatment of farnesyl transferase inhibitors (Li et al., 2005). Insights into the mechanisms responsible for NF1 may result in the development of sustainable treatments for this disorder and other disorders involving learning and memory deficits caused by dysfunction in this signaling pathway (Krab et al., 2008).

Common vs. rare genetic mechanisms

While neurofibromin and APOE genes work through different mechanisms, they do show convergence on a final common pathway of hippocampal disruption. In NF1 this takes the form of increased GABA-ergic inhibition and resulting decreases in hippocampal LTP. The effects of APOE-4 genotype in mice involve decreased dendritic spine density in primary hippocampal neurons (Dumanis et al., 2009). The overlap of these neuronal changes may provide a mechanistic explanation for shared memory phenotypes across neuropsychiatric disorders. At the same time, subtle phenotypic differences may be useful for dissecting the underpinnings of these complex disorders.

Methodologic considerations: polygenicity, genetic pleiotropy, and phenotype definitions

How does variation in a gene affect the expression of that gene and the functioning of the gene product? The genetic basis of LTM is clearly complex, likely involving similar phenotypes based on the combined actions of several (perhaps hundreds) of different genes together with environmental exposures (Risch and Merikangas, 1996). Acting individually, such genes may have little effect on the disease phenotype (Bearden et al., 2009). The methods used to map genes for disorders with simple inheritance patterns (i.e., Mendelian disorders) depend on the fact that within a family, individuals displaying the affected phenotype could be assumed to possess the same genetic mutation. Clearly, different genetic analysis techniques are required for complex, multiply determined traits. The main approaches for genetic investigation—linkage and association studies—can be differentiated in terms of their focus on either variants of large effect or variants of small effect, and the feasibility of these different approaches has largely been based on the opportunities for assaying common or rare genetic variants in well-powered studies. Additionally, while most genetic research has focused on alterations at the single-nucleotide level, it is now clear that structural copy number variation occurs more frequently than had previously been realized, and that such variation may be important in generating disease phenotypes (Sudmant et al., 2010).

Given the complexity of the neurobiological substrates of memory, there are likely many genes in which functional variation can affect aspects of memory (polygenicity) (see Figure 8). Conversely, genes likely affect neural networks and multiple brain functions, not isolated brain regions (Green et al., 2008). As such, a single gene can be involved in multiple cognitive (and perhaps non-cognitive) processes (pleiotropy). Thus, a systems approach is necessary to understand pleiotropic effects on cognitive functions, including memory. For example, examining genetic correlations between multiple brain structures and multiple cognitive processes can provide a window into the shared genetic variance across neural circuits and cognitive domains, as well as unique genetic influences on particular, sometimes highly correlated, neurocognitive processes (e.g., (Kremen et al., 2009; Panizzon et al., 2011)).

While molecular-genetic data are essential for understanding how a genotype connects to a disease phenotype, or associated intermediate phenotype, attempts at gene identification will fail without well-defined phenotypes. Interpretation of measures and/or specific cognitive abilities showing low heritability is confounded by variation in the psychometric properties of cognitive tasks. Thus, rigorously defined psychological constructs are critical for moving the field forward. The same principles apply to traits derived from brain structure, where even seemingly objective choices of phenotypes can influence the results (Winkler et al., 2010).

Future directions

Genetic information has the potential to inform key questions related to the cognitive neuroscience of human memory. However, despite reasonably high heritability, thus far few replicable genetic associations have been identified for normal variation in memory function. Is the genetic structure of memory too complex to be tractable? Or, do we need to further refine the phenotypes we are using in order to interrogate more specific memory sub-processes? Further advancement in our understanding of the genetics of human memory will depend on further developing the theory and methods for defining memory phenotypes, at both the behavioral and neural level, and characterizing the function of relevant genes and

gene networks at the molecular level. Below are suggestions for specific innovations needed to move the field forward.

Translational studies in animal models provide a valuable means of interrogating the underlying biology of specific memory phenotypes. Memory deficits represent a scientifically tractable and physiologically plausible target for psychopharmacologic treatment. Rare structural mutations provide useful models, as the underlying genetic etiology is already known, and effects tend to be large. The cellular mechanisms modulated by particular genes of interest can be readily studied in rodent transgenic or mutant models. As evidenced by the development of a viable treatment for cognitive deficits in NF1, based on findings in a mouse model (Li et al., 2005), such models allow us to test pharmacologic agents that can reduce or attenuate memory deficits.

Improving methods for high-throughput cognitive phenotyping (for example, web-based assays of multiple memory functions) will allow studies to amass substantially larger samples than can be collected in the laboratory. One prominent example of such a study is the “Test My Brain” web-based testing environment, in which study participants consent and participate in cognitive testing entirely online (Wilmer et al., 2010). This is a key innovation needed to accrue adequately powered samples to identify genes of small effect on memory function.

Finally, in the post-genomic era, one of the biggest challenges faced by interdisciplinary scientists is the lack of tools to manage the complexity of knowledge rapidly being amassed across disparate methods, models and data types (Sabb et al., 2008). Informatics resources can advance the collation of empirical knowledge that will help to bridge the currently wide gap between genome, cognitive constructs and disease syndromes (Parker et al., 2009). Computational methods have been developed to identify large sets of relationships within online databases such as MEDLINE and statistically rank these for potential relevance (Wren et al., 2004). Such tools can advance our understanding of the genetic architecture of memory by helping researchers to identify previously unsuspected relationships across disciplinary boundaries, select specific phenotypic measures, and develop multilevel models that specify both within- and between-level associations (Figure 9).

Conclusions

Given the central importance of learning and memory to adaptive behavior, there are likely multiple-possibly even hundreds - of genes of small to moderate effect that influence memory phenotypes in the general population. Many of these genes may contribute to disease susceptibility via their impact on brain systems mediating memory function; as such, these genes may not have been identified by previous studies using syndromic status (e.g. “schizophrenia”) as the phenotypic target. From a neural systems standpoint it is plausible that cognition has both domain-general and domain-specific heritable contributions. Examining associations between genes and intermediate phenotypes will help to strengthen evidence for biological connections between genetic mechanisms and memory disorders; this mechanistic approach will also help to reduce spurious associations (Green et al., 2008). As discussed here, investigation of memory phenotypes expressed across multiple syndromes and species, using an interdisciplinary, systems-level approach, will accelerate the discovery of new treatments for memory dysfunction.

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List of terms

AD	Alzheimer's disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APOE	apolipoprotein E
CA1 to CA4	Cornu Ammonis areas 1 through 4 of the hippocampus
CaMKII	calcium/calmodulin-dependent protein kinase II
DZ	dizygotic
fMRI	Functional magnetic resonance imaging
g	General intelligence
GAP	GTP-ase activating protein
h^2	heritability
ICC	Intraclass correlation
IQ	Intelligence quotient
KIBRA	Kidney and brain protein
LTM	Long term memory
LTP	Long term potentiation
MRI	Magnetic resonance imaging
MZ	Monozygotic
NF1	Neurofibromatosis I
NMDA receptor	N-methyl-d-aspartate receptor
RAS	Rat sarcoma protein family

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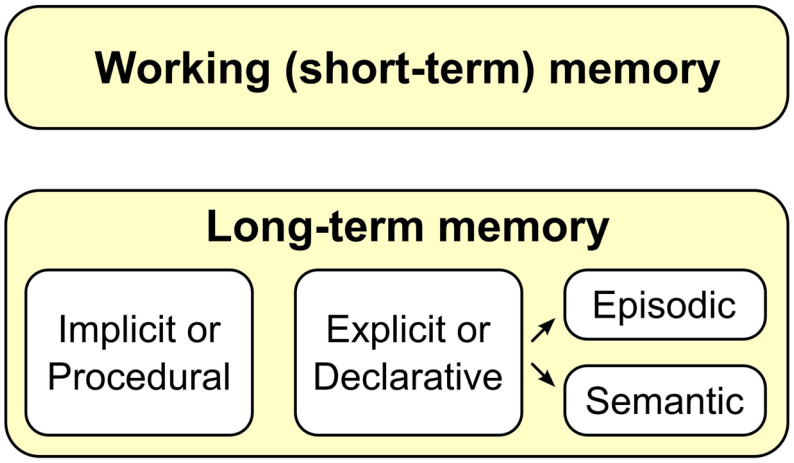

Figure 1.
Long-term memory may be subdivided into categories and it differs structurally and functionally from working and short-term memory.

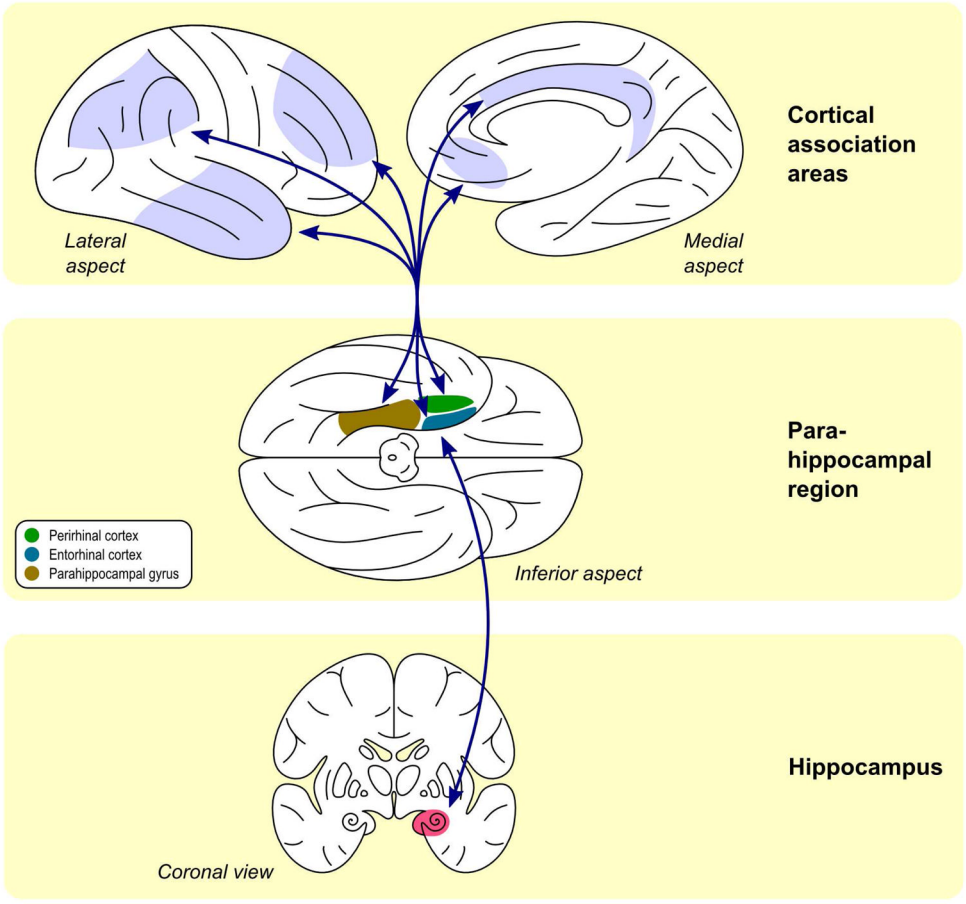

Figure 2.
Information from multiple cortical association areas converge on areas that surround the hippocampus, namely, entorhinal, perirhinal and parahippocampal regions. These regions are interconnected and project to the hippocampus itself. Efferents from the hippocampus reach the surrounding areas and then project back to the same cortical regions from where the inputs were originated [adapted from (Eichenbaum, 2000)].

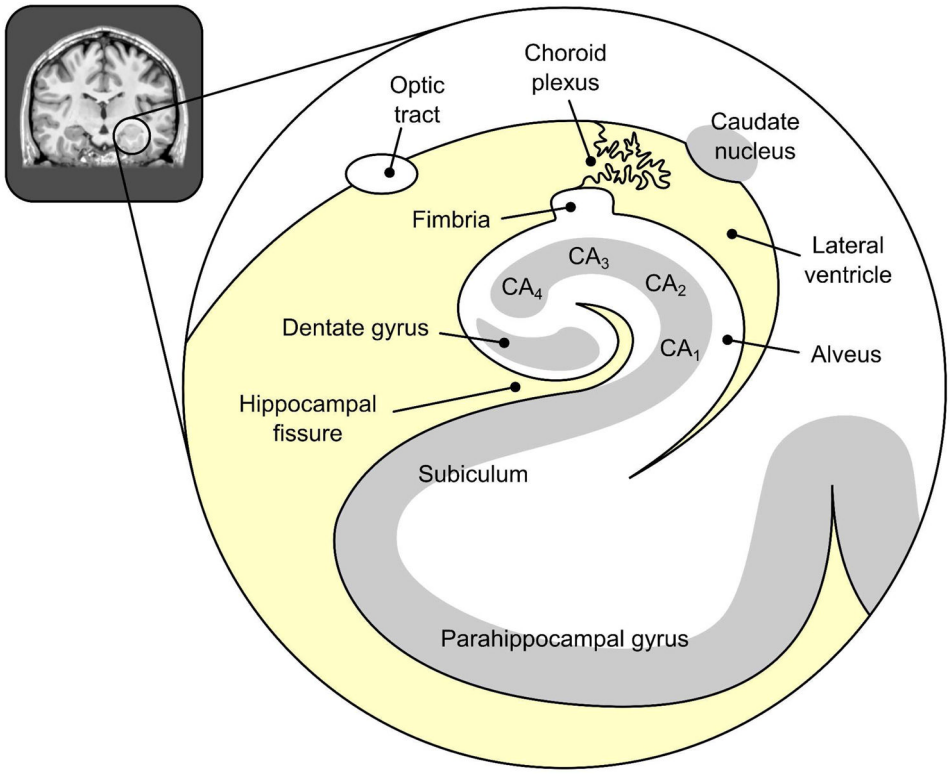

Figure 3.
Schematic illustration of the main structures within and surrounding the hippocampus, as seen from a coronal slice through its anterior part.

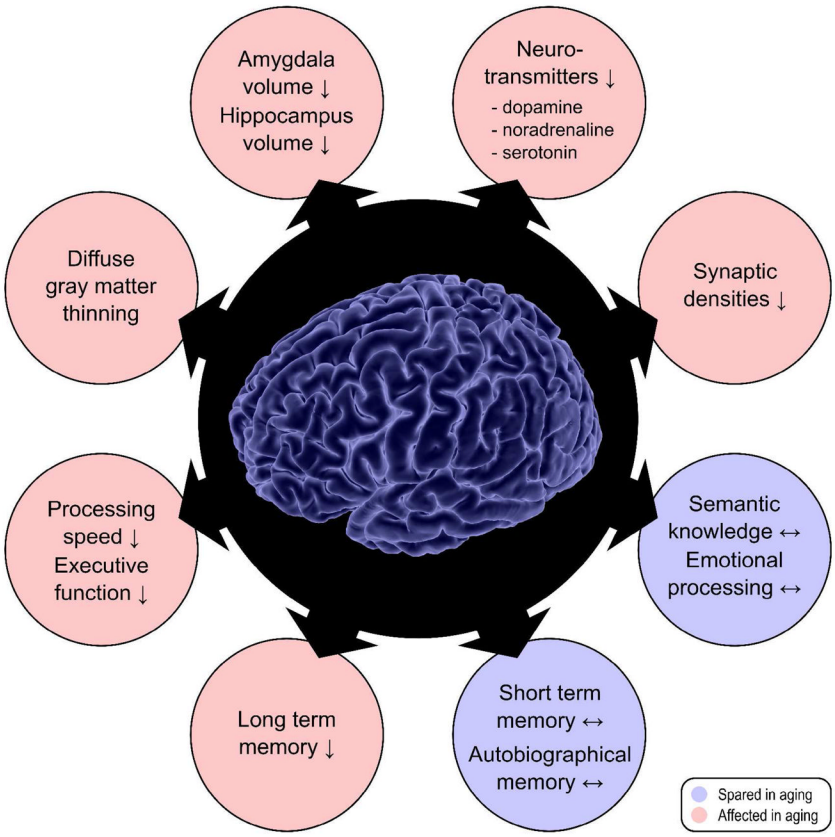

Figure 4.
Structural, functional and cognitive changes observed as a function of normal aging. Some cognitive functions are selectively preserved.

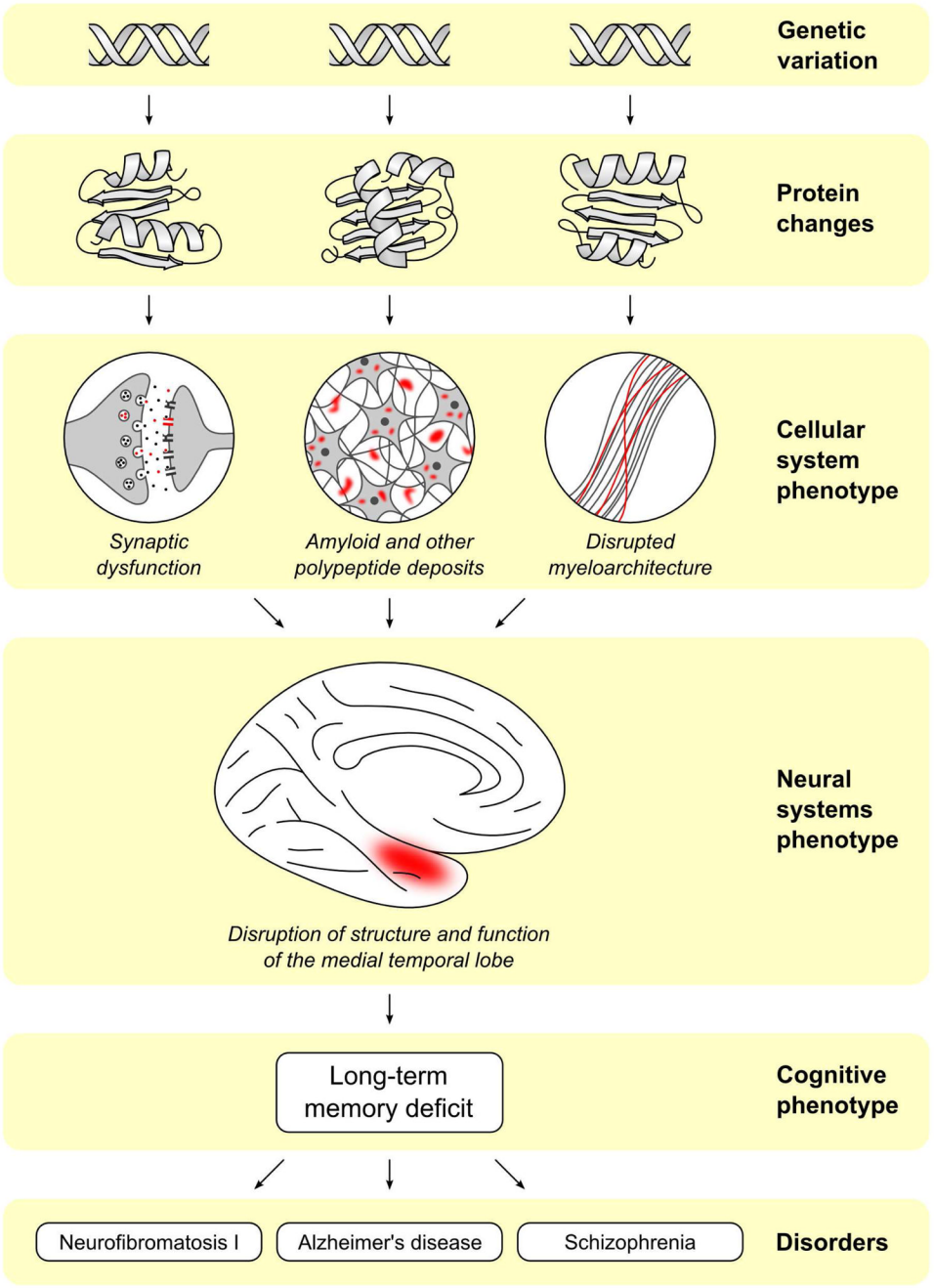

Figure 5.
Long-term memory (LTM) deficits are a central feature of multiple disorders (both complex and Mendelian). LTM may serve as an endophenotype for these disorders, as the downstream expression of multiple underlying genetic, cellular, and neural systems abnormalities.

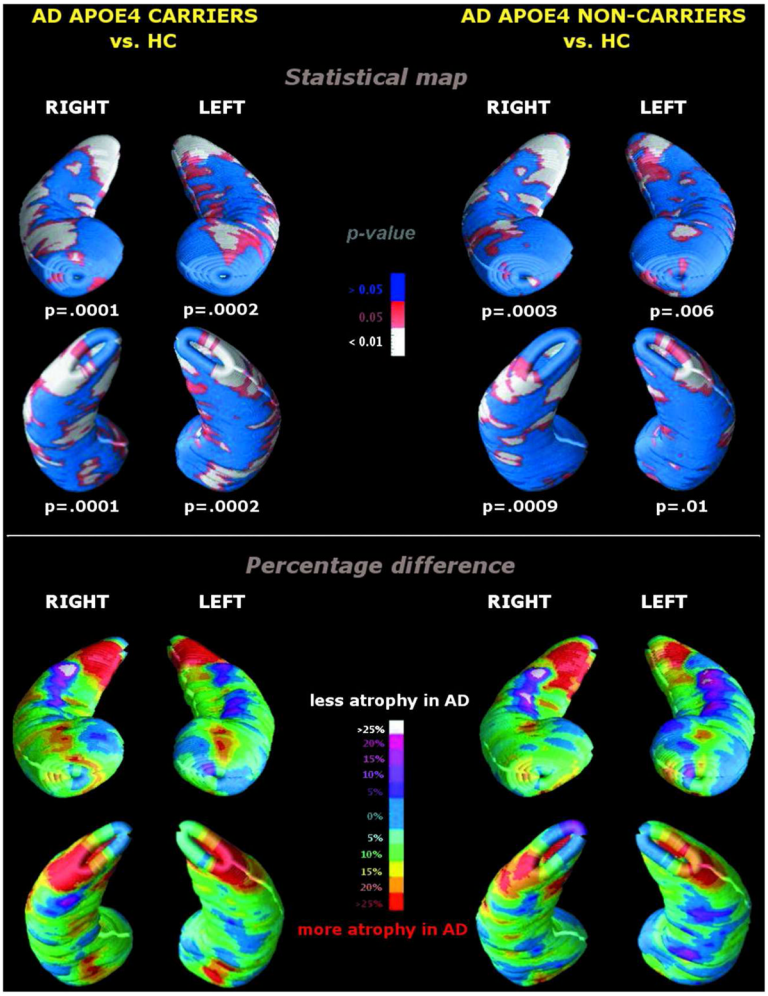

Figure 6.

Patterns of hippocampal atrophy in AD patients with (left panel) and without the APOE ε4 allele (right panel) compared with demographically matched healthy controls. Top: statistical maps. White regions correspond to an uncorrected threshold of $p<0.05$. Comparisons were significant after correction for multiple testing by permutation testing, both in the ventral and dorsal hippocampal portions, bilaterally. Bottom: percentage hippocampal differences. Values are color-coded to express the percentage difference in radial size between AD patients and healthy controls. Values greater than 15% (yellow to red regions) denote statistically significant atrophic areas and red regions correspond to areas of severe hippocampal atrophy (differences greater than 25%) [from (Pievani et al., 2010)]

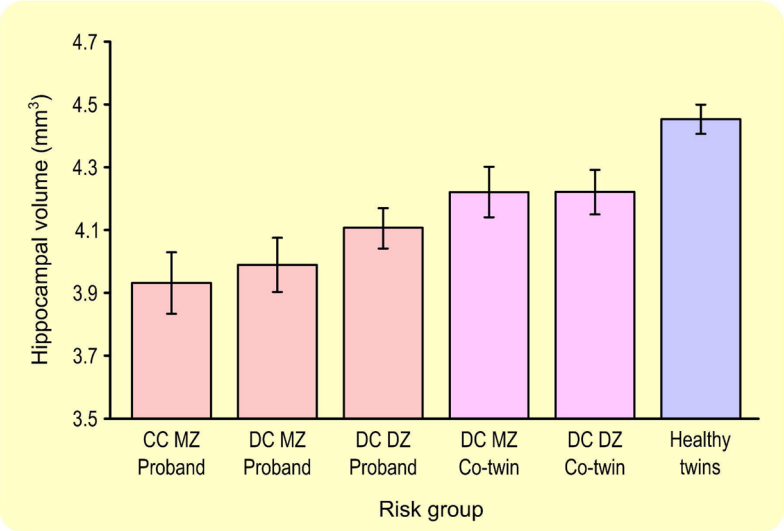

Figure 7.
Mean hippocampal volumes and standard errors in subjects with diagnosis of schizophrenia (probands), compared to their monozygotic (MZ) or dizygotic (DZ) twins, concordant (CC) or not (DC) with the diagnosis, and compared with a group of healthy control twin pairs (MZ and DZ). Hippocampal volumes are reduced according to the putative genetic loading for the disorder [adapted from van Erp et al. (2004)].

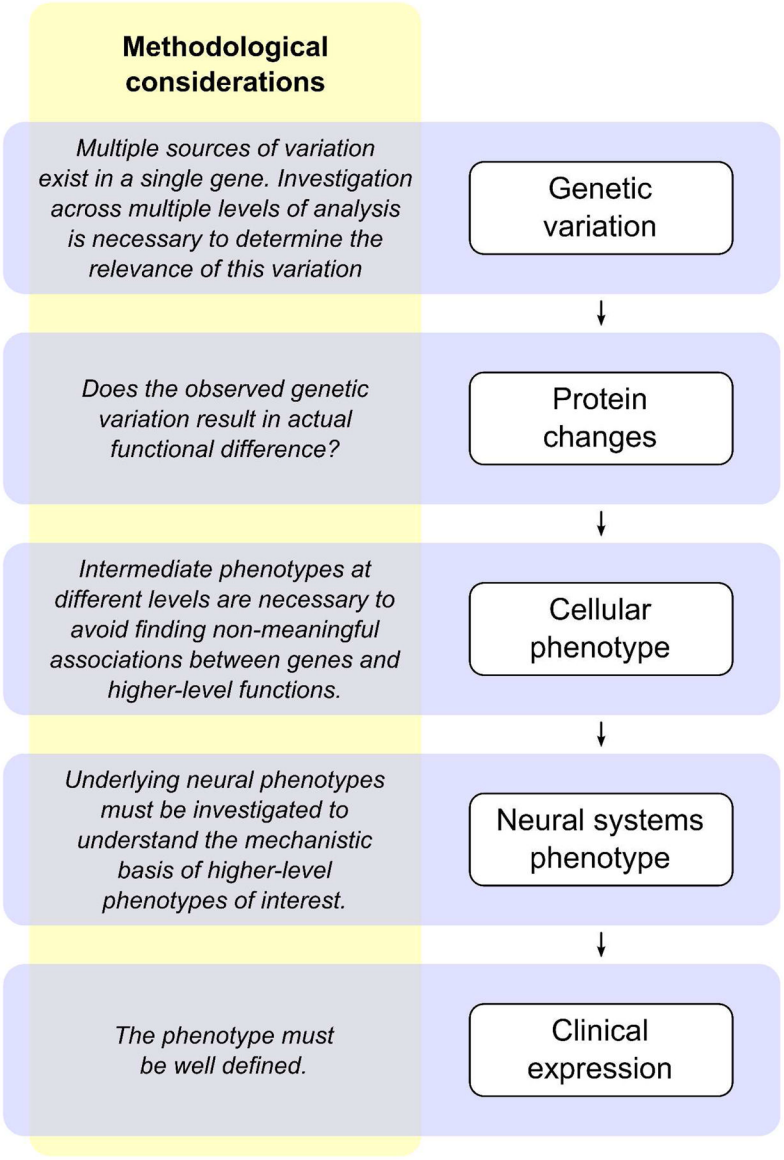

Figure 8.
Complex traits or disorders, such as memory or AD, which influence and are influenced in multiple ways, can only comprehensively be understood by disentangling their mechanisms at each expression level. Successful research at any level of analysis must build on discoveries on all other levels.

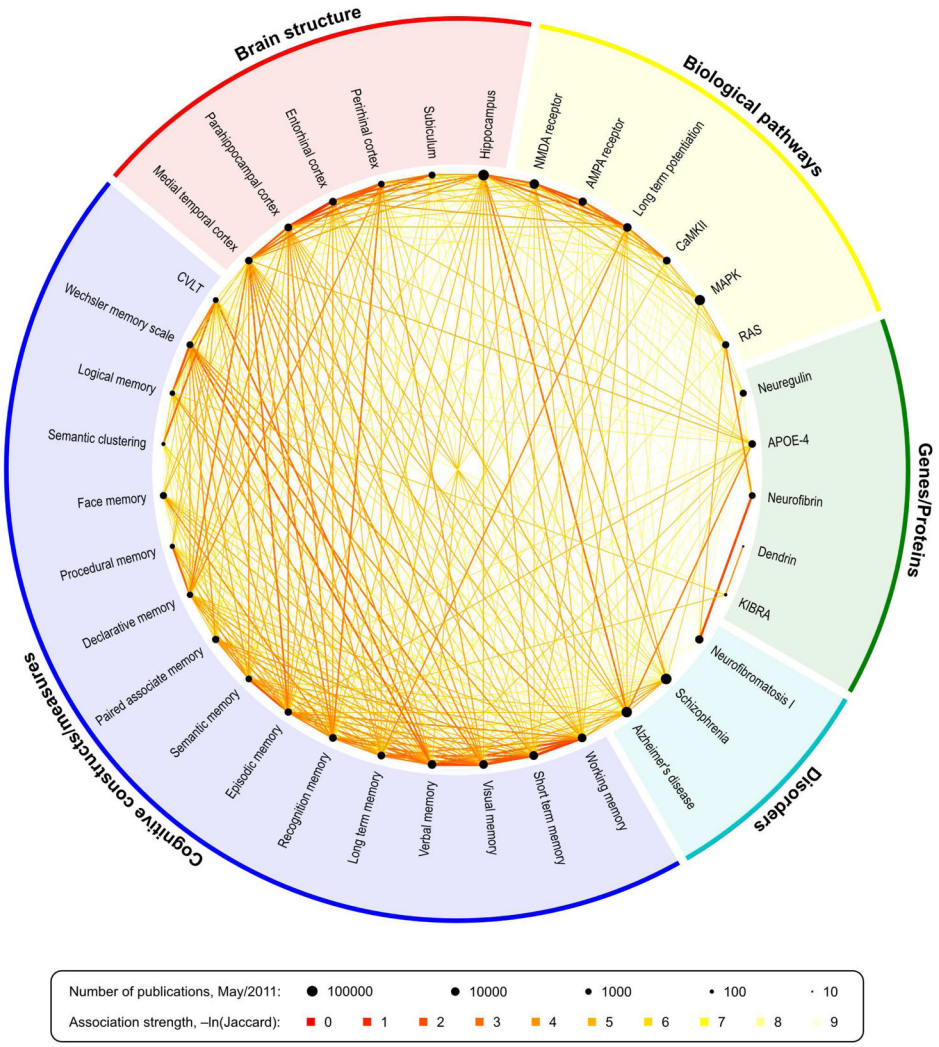

Figure 9.

Relationships between keywords in published literature can expose interesting links between fields and highlight areas where important pieces may be missing, as well as evidence emergent patterns of research. In this figure, each point around the circle represents the relative quantity of publications of a given keyword in relation to the others, in logarithmic scale, as retrieved from PubMed in May/2011. The links represent the strength of the association, scaled by the natural logarithm of the Jaccard coefficient. The smaller numbers indicate stronger associations. See also the Supplemental Material for an interactive depiction of these relationships, and http://www.pubatlas.org/ for more literature mining and visualization tools.

Table 1

Heritabilities of memory and non-memory cognitive tasks

Task	Cognitive domain	Heritability (h^2)
IQ (Vocabulary/Matrix Reasoning)	General intellectual function	0.80 (Finkel et al., 1998)
Penn Conditional Exclusion Test	Executive function	0.12 (Glahn et al., 2010)
Stop Signal	Response inhibition	0.53 (Friedman et al., 2006)
SCAP (Spatial Working Memory Capacity)	Spatial working memory	0.46 (Glahn et al., 2006)
Digit Span	Verbal working memory	0.29–0.65 (Finkel et al., 1995b)
Stroop Color-Word Interference Task	Executive/inhibitory control	0.50 (Stins et al., 2004)
Digit Symbol	Processing speed	0.76 (Posthuma et al., 2001)
Continuous Performance Test	Sustained attention	0.49–0.89 (Fan et al., 2001)
Verbal Fluency	Language	0.34 (Swan and Carmelli, 2002)
Penn Face Memory Test (immediate/delayed)	Visual (face) memory	0.42 (Glahn et al., 2010)
California Verbal Learning Test	Verbal declarative memory (list-learning)	0.56 (Swan et al., 1999)
Logical Memory (WMS-III) *	Verbal declarative memory (story)	0.55 (Finkel and McGue, 1993)
Visual Reproduction (WMS-III) *	Visual (design) memory	0.55 (Finkel and McGue, 1993)
Hand Motor Skill	Procedural learning/memory (motor skill learning)	0.41 (Francks et al., 2003)
Rotary pursuit task	Motor skill learning	0.50–0.70 (Fox et al., 1996)

* statistic based on a similar but not identical test

Table 2

Heritabilities for structures implicated in memory

Structure	Heritability (h^2)
Whole brain volume	0.66 (Wright et al., 2002)
Gray matter density	0.82–0.95 (Baare et al., 2001; Thompson et al., 2001)
White matter volume	0.82–0.87 (Baare et al., 2001)
Frontal lobe volume	0.59–0.90 (Thompson et al., 2001; Wright et al., 2002)
Frontal gray matter	0.77 * (Wallace et al., 2006)
Temporal lobe volume	0.55 (DeStefano et al., 2009)
Temporal lobe gray matter volume	0.80 * (Wallace et al., 2006)
Hippocampal volume	0.40–0.54 (DeStefano et al., 2009; Sullivan et al., 2001)

* pediatric sample