



Multiple memory systems: The power of interactions

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Abstract

Two relatively simple theories of brain function will be used to demonstrate the explanatory power of multiple memory systems in your brain interacting cooperatively or competitively to directly or indirectly influence cognition and behaviour. The view put forth in this mini-review is that interactions between memory systems produce normal and abnormal manifestations of behaviour, and by logical extension, an understanding of these complex interactions holds the key to understanding debilitating brain and psychiatric disorders.

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1. Introduction

Material things are there by means of their images: knowledge is there of itself; emotions are there in the form of ideas or impressions of some kind, for the memory retains them even while the mind does not experience them, although whatever is in the memory must also be in the mind. My mind has the freedom of them all. I can glide from one to the other. I can probe deep into them and never find the end of them. This is the power of memory! This is the great force of life in living man, mortal though he is!

St. Augustine

This quote, taken from St. Augustine's book called "Confessions," is from an entire chapter dedicated to the topic of memory. The book appears to be St. Augustine's attempt to understand the complexities of his own personality. What is interesting about this paragraph, from our perspective, is that St. Augustine captures many critical aspects of our memory at a time in which little or nothing was known about this complex brain process. This quote suggests that our memory is: multifaceted and not unitary; the repository for your

own past and identity; the most important biological force in the human experience. St. Augustine goes even further and suggests that our memory allows us to change our behaviour because memory contains a record of our past history and can be replayed and analysed, it is the only force through which we can grow and change as individuals. The latter point is critical for the current treatise because it is our assertion that the organization of memory in the mammalian brain and the neural systems that mediate multiple kinds of memory must play a pivotal role in our thoughts, emotions, choices, actions, and even our personalities. Furthermore, these complex neural circuits in our brain not only contain remnants of our past that are the basis of personal identity but also exert an enormous influence on individual behaviour. Quite simply put, this view makes the bold claim that these brain systems, to a large extent, determine who we are and how we behave in particular situations.

The first section of this paper will introduce a simple but powerful theory about the organization of learning and memory processes called interactive memory systems theory (IMST). This theory is similar to the multiple parallel memory systems (MPMS) theory (White &

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McDonald, 2002) except the current theory emphasizes interactions between memory systems. The second section will briefly discuss a theory suggesting that normal and abnormal manifestations of behaviour are determined, to a large extent, by some complex set of interactions between an individual's: genetic make-up; developmental events during pre and post-natal development; and accumulated experience through life. The relationship between the two theories will also be introduced and then in the third section we will introduce an example of how a prenatal developmental event can alter the balance between two memory systems. In the last section, we will show evidence that the etiology of many of the major psychiatric disorders may be linked to alterations in the integrity of various memory systems.

1.1. Interactive memory systems theory (IMST): A precis

The foundation of modern views of the organization of memory in the mammal was built on the influential work of Pavlov, Hull, Tolman, and others (Guthrie, 1935; Hull, 1943; Pavlov, 1927; Thorndike, 1932; Tolman, 1948). Briefly, each of these scientists formulated a general theory of learning and memory in which these functions were mediated by a basic, underlying mechanism. The proposed mechanisms included classical conditioning for Pavlov, reinforced stimulus–response learning in Hull's theory, and the flexible cognitive mapping view for Tolman. Despite significant acrimony between supporters of these different positions, it now appears that all of these theorists were correct in that the mammalian brain uses all of them, as well as other types of learning mechanisms that appear to be mediated by different brain circuits.

The first direct evidence for the idea that there were multiple memory systems in the mammalian brain came from Scoville and Milner's (1957) discovery that patients with damage to the medial temporal lobe showed impairments in some types of learning and memory function but were normal in other aspects. Milner concluded from this data set that structures in the medial temporal lobe, most likely the hippocampus, were involved in complex memory processes, and that brain structures anatomically and functionally independent of the medial temporal lobe mediated other learning and memory function.

Most of the influential multiple memory theories of mammalian brain function were formulated during the 1970s and were inspired by Milner's findings. Many of these theories are dual memory formulations in which the hippocampus is the central module, while some other brain area(s), independent of the hippocampus, mediates non-cognitive S–R habit learning and memory function (Gaffan, 1974; Hirsh, 1974; O'Keefe & Nadel,

1978; Olton, Becker, & Handelmann, 1979; Tulving, 1972).

Hirsh and Kraiden (1982) were the first to provide considerable detail on the different kinds of interactions that could theoretically occur between cognitive- and habit-based memory systems. A summary of this view is captured in the following quote: "When two different systems appearing to address the same substantive matters are present, it is worthwhile to ponder how they might interact. We think that on some occasions the two systems compete; on others they cooperate. Once the fundamental differences between the two systems are understood, their differing capacities become clear. Each has capabilities that the other does not. There are certain features of knowledge that cannot be attained without using the capacities of both."

Thus, in the majority of situations both systems are processing information in parallel and it is the circumstances or details of a particular situation (e.g., the performance requirements of a task) that determine whether systems interact competitively or cooperatively.

While this work was ongoing, a parallel line of research was accumulating a significant body of evidence suggesting that the dorsal striatum, cerebellum, and the amygdala were also learning and memory systems (Diviac, 1968; Kapp, Frysinger, Gallagher, & Haselton, 1979; Schwartzbaum & Donovick, 1968; Thompson & Krupa, 1994).

The combination of innovative dual memory theories and evidence of anatomically distinct learning and memory systems provided a fertile research context in which various pairs of double dissociations were demonstrated including: hippocampus and cerebellum (Thompson & Krupa, 1994); amygdala and cerebellum (Hitchcock & Davis, 1986); amygdala and hippocampus (Kim, Rison, & Fanselow, 1993; Phillips & Ledoux, 1992; Sutherland & McDonald, 1990); hippocampus and striatum (Packard, Hirsh, & White, 1989) and hippocampus and perirhinal cortex (Gaffan, 1994).

A more recent triple dissociation of learning and memory function between the hippocampus, amygdala, and dorsal striatum is considered by some to be a watershed publication for the multiple memory systems view for several reasons. First, even though various combinations of double dissociations had already been shown, this was the first demonstration of a triple dissociation of memory functions in the mammalian brain. Second, the paper provides the first explicit description and analysis of both competitive and cooperative interactions by using a task analysis method (pp. 17–18). Finally, the triple dissociation paper and our subsequent work on interactions between memory systems have provided a template for future work in this area. This template includes novel demonstrations of: (1) competitive and cooperative interactions between various learning and memory systems (McDonald & White,

1993, 1994, 1995a, 1995b; White & McDonald, 1993); (2) memory subsystems within identified learning and memory systems (Devan, McDonald, & White, 1999; Featherstone & McDonald, 2004a, 2004b; Ferbinteanu, Holsinger, & McDonald, 1998; Ferbinteanu & McDonald, 2000, 2001, 2003); (3) ascending neurotransmitter influences on memory system balance (Kanit et al., 1998); (4) multiple strategies for solving “gold standard” learning and memory tasks (Antoniadis & McDonald, 1999, 2000, 2001; Devan & McDonald, 2001; Frankland, Dockstader, & McDonald, 1998; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; McDonald & Hong, 2000); (5) the deleterious effects of developmental perturbations on the balance between multiple memory systems (Sutherland, McDonald, & Savage, 2000); (6) necessary versus incidental learning and memory processes (McDonald, Foong, & Hong, 2004; McDonald & Hong, 2004; McDonald, King, & Hong, 2001; McDonald, Ko, & Hong, 2002). The triple dissociation experiment also inspired a theory of the organization of learning and memory in the mammal (White & McDonald, 2002).

This multiple parallel memory systems theory suggests that the mammalian brain has at least three major learning and memory systems. Each system consists of a “central structure” and a set of interconnected neural structures. The “central structures” of these different circuits include the hippocampus, amygdala, and dorsal striatum.

These memory systems acquire information simultaneously and in parallel and are always on-line. All of these systems have access to the same information during events but each system is specifically designed to represent different relationships among the elements of a learning situation. These elements include stimuli, internal and external responses, and reinforcers. The processing style of each system is determined by the intrinsic organization of the system and the input/output relations to the rest of the brain. Although they process information independently the systems can interact cooperatively or competitively to produce or influence ongoing or future behaviour.

Among the three central memory system structures the hippocampus is thought to be critical for the formation of episodic memories in which a complex representation consisting of the various elements of a situation or event is constructed (Sutherland & Rudy, 1989; Tulving, 1972). The amygdala has been implicated in the formation and storage of emotional memories (Bagshaw & Benzie, 1968; Cador, Robbins, & Everitt, 1989; Schwartzbaum, 1964). These emotional memories uniquely encode the subjective valence of the experience (positive or negative). The dorsal striatum has been implicated in stimulus–response habit learning and memory processes (Packard et al., 1989). This kind of learning occurs when the subject engages in repetitive

behaviours. For example, the voluntary behaviours elicited while one is driving a car on a repeatedly travelled route by the driver are thought to become under the control of the habit system.

1.2. *Who are you?*

The second brain theory that will be explored suggests that normal and abnormal manifestations of behaviour are determined, to a large extent, by some complex set of interactions between an individual's: genetic make-up; developmental events during pre and post-natal time periods; and accumulated experience throughout the lifespan (see Fig. 1). All of these factors can have major effects on the organization of the brain. Alterations in the organization of the brain could affect overall relationships between each learning and memory system (balance in the interactive control of behaviour), as well as the relationships of these systems with the rest of the brain. These other neural systems will be addressed in turn as each is implicated in a specific disorder. For the purpose of the present discussion the combination of factors will be referred to as the GDE (genes, development, and experience).

Within the normal range of variability, alterations in the balance between these memory/behavioural systems can lead to individual personality, affective style, choices, actions and certain strengths, and weaknesses associated with different tasks or situations (e.g., mathematics, athletics, music, social interactions, etc.). Fig. 2 shows a hypothetical outcome of complex interactions between GDE factors. One important effect of these factors is on the organization of various memory/behavioural systems with each other and other neural systems. This example represents a normal individual in which there is a balance between these systems that when activated result in relatively normal patterns of behaviour in a wide range of situations.

A logical extension of this view is that there can also be changes in the balance of these systems that lead to abnormal manifestations of behaviour including major psychiatric disorders such as schizophrenia, drug abuse, and mood disorders. Also, the way memory systems interact can produce “abnormal” talents, as in the case of savants and others who display unusual abilities (see Luria, 1968; Sacks, 1970) that may lead to great accomplishments.

In the following section, we will provide an example of the influence of a single prenatal developmental event on the organization of interactive memory systems in the adult brain. This example was selected because it is the first factor shown to have an effect on the organization of interactive memory systems. In contrast, genetic work in this area, to our knowledge, has addressed learning and memory function in a general manner or has focused on only one of the identified systems

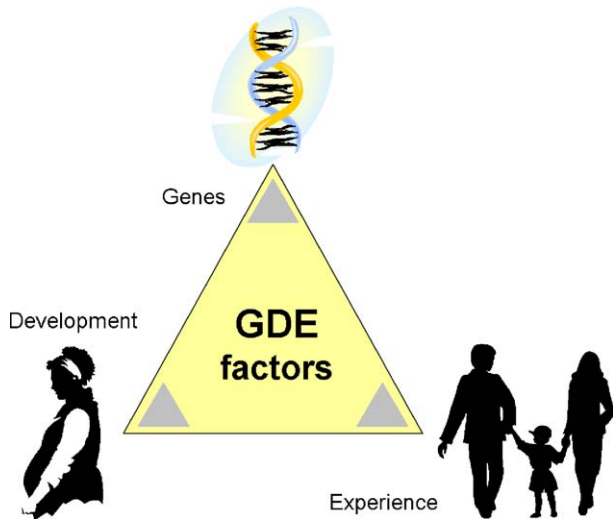


Fig. 1. According to this view, normal, and abnormal manifestations of behaviour are determined, to a large extent, by some complex set of interactions between and individual's: genetic make-up, pre- and post-natal developmental events; and accumulated experience through life.

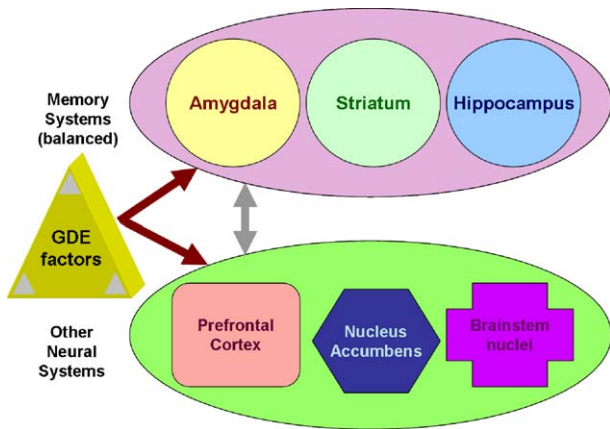


Fig. 2. A hypothetical outcome of complex interactions between genes, development, and experience (GDE) factors. A primary effect of these interactions is on the organization of various memory/behavioural systems with each other and with other neural systems. This example represents a normal individual in which there is a balance between these systems that when activated result in relatively normal patterns of behaviour in a wide range of situations.

(Kandel, 2002; Yan et al., 2002). Consequently, there have been no investigations looking at the effects of genetic manipulations on the interactions and balance between learning and memory systems. In many cases, these effects would be subtle, but could have a strong effect on thoughts and behavioural choices in adulthood. Similarly, there is a paucity of research directed at understanding the effects of different types of experience on the organization of learning and memory systems. Among the few studies done to date, the effects of experience has been considered with respect to learning and memory function in general or on one specific

learning and memory system like the hippocampus (Greenough & Chang, 1989).

1.3. Developmental perturbations: Prenatal exposure to moderate levels of ethanol on adult cognition

One of the proposals of the present theory is that developmental events are one of the main factors that influence the organization of memory systems in the mammalian brain. These events can include maternal stress, diet, and drug use, among others. If these events occur during critical brain development epochs, the organization of various brain systems could be permanently altered, affecting adult behaviour. The present discussion will focus on an animal model of prenatal exposure to moderate levels of ethanol on adult cognition.

Alcohol-related developmental disorders can be caused by low to moderate levels of consumption during pregnancy (Streissguth, Barr, & Sampson, 1990). These disorders are associated with deficits in high level cognitive abilities without the concomitant morphological and neurological defects associated with fetal alcohol syndrome induced by heavy consumption (Jones & Smith, 1973).

Consequently, we developed an animal model to try and ascertain how moderate prenatal alcohol exposure may disrupt neurobiological mechanisms of learning and memory function. The fetal alcohol exposure paradigm used in these studies consisted of rat dams receiving either a 5% ethanol diet, an isocalorically matched diet, or rat chow. In contrast to other fetal ethanol paradigms that used high levels of ethanol exposure to mimic full blown fetal alcohol syndrome, this moderate exposure regimen does not affect birth weight, litter size, neonatal mortality, offspring growth curves or whole brain weight compared to control groups (Sutherland, McDonald, & Savage, 1997).

Despite this apparent normality, neurochemical observations in the rats exposed to moderate doses of ethanol during prenatal development noted changes in various amino acid receptor subtypes and several enzymes in the hippocampus (Farr, Montano, Paxton, & Savage, 1988; Queen, Sanchez, Lopez, Paxton, & Savage, 1993; Savage, Montano, Otero, & Paxton, 1991). Interestingly, many of these changes affect mechanisms essential for normal NMDA-dependent long-term potentiation (LTP). NMDA-dependent LTP is a form of plasticity found in the hippocampus that has been linked to learning and memory functions (Davis, Butcher, & Morris, 1992; Morris, Andersen, Lynch, & Baudry, 1986), it is however, important to note that this is a controversial and complicated issue that will not be discussed here. We also found that in adulthood these rats displayed significant deficits in the induction and maintenance of LTP at input pathways from the

entorhinal cortex to the dentate gyrus of the hippocampus (Sutherland et al., 1997). These results suggest that exposure to moderate levels of ethanol during prenatal development permanently impairs NMDA-dependent plasticity mechanisms. Accordingly, we hypothesized that these neurobiological changes should also lead to learning and memory deficits on a task shown to require hippocampal function like the spatial version of the Morris water task (Morris, Garrud, Rawlins, & O'Keefe, 1982; Sutherland, Kolb, & Whishaw, 1982; Sutherland, Whishaw, & Kolb, 1983). Briefly, the Morris water task is a spatial learning and memory task that requires the subject to locate a fixed hidden escape platform from various start positions using environmental information external to the pool (Morris, 1981). A significant amount of research has accumulated to show that normal acquisition of this task is dependent on the integrity of the hippocampus in the rodent (Ferbinteanu et al., 1998; Morris et al., 1982; Sutherland et al., 1982, 1983), and human versions of this task are also sensitive to hippocampal dysfunction in the human (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002).

To test our hypothesis, rat dams consumed one of three diets throughout gestation: a liquid diet containing 5% ethanol, an isocalorically equivalent liquid diet, and laboratory rat chow. Adult offspring from each of these maternal conditions were trained on the standard, spatial version of the water task developed by Morris (1981). Surprisingly, the learning curves for the three groups were virtually identical from the beginning of training to asymptotic performance.

This pattern of behaviour on a learning and memory task that is sensitive to hippocampal dysfunction was paradoxical. One possible explanation for this lack of effect was that the neurobiological changes in the hippocampus found in the adult offspring of dams that consumed ethanol (Sutherland et al., 1997), were not sufficient to alter behaviour. Another intriguing possibility was that tasks sensitive to hippocampal dysfunction might fall along a continuum of sensitivity to this system. This is supported by evidence showing that relatively simple versions of spatial, context conditioning, and configural/relational tasks are not particularly sensitive to hippocampal dysfunction, while versions of these tasks that place a higher demand upon these cognitive systems are extremely sensitive (Frankland et al., 1998; McDonald & White, 1995a, 1995b; McDonald et al., 1997). This work suggests that the logical description of a task as spatial, contextual, or configural/relational is not sufficient to predict the necessity for hippocampal function. For the current discussion, it suggests that subtle alterations of the neurobiological integrity of the hippocampus might go undetected using tasks that place a low demand on hippocampal processing.

To test this hypothesis, we used a version of the Morris water task that was developed to demonstrate that the dorsal striatum and hippocampal learning and memory systems could acquire information in parallel and to demonstrate a competitive interaction between these memory systems. Fig. 3 shows the training procedures for this version of the water task.

During acquisition, the visible platform is located at a fixed location in the water maze on days 1–3, and on the fourth day the visible platform is replaced with a submerged hidden platform. Consequently, animals acquire both a cue response to the visible platform and also learn to use extramaze distal cues to find the hidden platform. The sequence of three visible platform days followed by a hidden platform session is repeated thrice for a total of 12 acquisition days (Sutherland & Rudy, 1988). On day 13, the visible platform is relocated in the quadrant diagonally opposite to the training goal location (McDonald & White, 1994). Fig. 4 shows the two possible response strategies animals can adopt on the competition test. Starting from the point at the edge of the pool that is equidistant to the 'old' spatial location and the visible platform currently repositioned in the opposite quadrant, subjects may choose to swim directly to the visible platform (a cue response; top panel) or visit the former spatial location of the goal, which was hidden on every 4th day of acquisition (a place response; bottom panel).

Table 1 summarizes the results of a lesion study using the combined cue-place task. Control subjects demonstrated normal performance on visible and hidden platform trials, however the group was split 50/50 on the competition test with half of the animals swimming more-or-less directly to the visible platform (a cue response) and half visiting the 'old' spatial location (a place response) before escaping to the visible platform on the competition test. Subjects with hippocampal

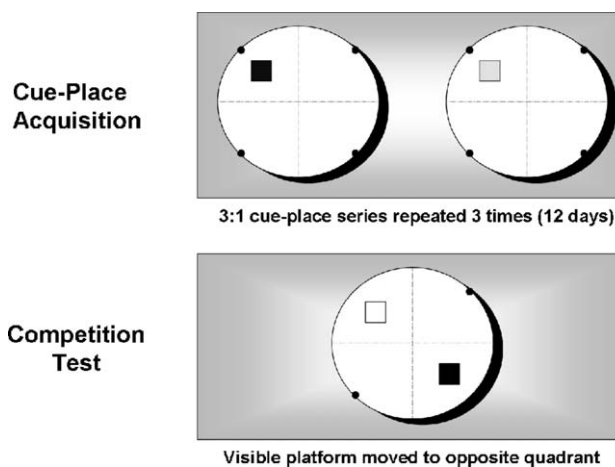


Fig. 3. The training procedures for the cue-place version of the water task.

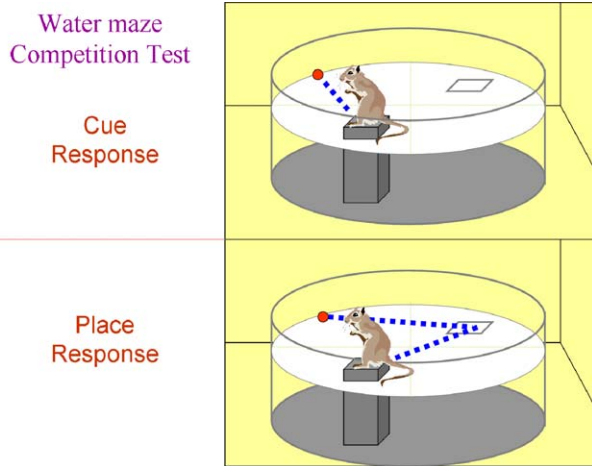


Fig. 4. Depiction of the two types of responses made by individual subjects during the competition test on the final day of cue-place training. The top panel shows a cue response in which the subject swims directly to the previously reinforced cued platform that is now located in a new spatial location. The bottom panel shows a place response in which the subject swims directly to the previously reinforced spatial location. Normal groups of rats split in the type of response they make on this competition task with approximately half using a cue response and the rest using a place response.

Table 1
Summary of the results reported by McDonald and White (1994)

Group	Acquisition phase		Competition test	
	Visible trials	Hidden trials	Cue response	Place response
Controls	Normal	Normal	<i>n</i> = 4	<i>n</i> = 4
HPC lesion	Normal	Impaired	<i>n</i> = 8	<i>n</i> = 2
DLS lesion	Normal	Normal	<i>n</i> = 2	<i>n</i> = 7

(HPC) damage demonstrated normal performance on the visible platform days, impaired performance on hidden platform days, and chose the visible platform (a cue response) on the competition test. Subjects with dorso-lateral striatum (DLS) lesions demonstrated normal performance during visible and hidden platform trials but chose the previously reinforced spatial position on the competition test. These results suggested that, among other things, perturbations of one learning and memory system can enhance the ability of another learning and memory system to control behaviour when alternative response strategies are possible (McDonald & White, 1994).

These results have important implications for the effects of moderate prenatal alcohol exposure on cognitive function because it is possible that the functional effects of this developmental perturbation on the hippocampus would be revealed in a test situation that places a higher demand on hippocampal processing than the standard version of the Morris water task. The competition test places a high demand on hippocampal processing because

Table 2
Summary of the results reported by Sutherland et al. (2000)

Group	Acquisition phase		Competition test	
	Visible trials	Hidden trials	Cue response	Place response
Controls	Normal	Normal	<i>n</i> = 7	<i>n</i> = 5
Alcohol pre-exposed	Normal	Normal	<i>n</i> = 11	<i>n</i> = 2
Pair-fed	Normal	Normal	<i>n</i> = 6	<i>n</i> = 4

an intact dorsal striatal-based memory system competes for behavioural control during the ultimate test. If the hippocampus is compromised, the habit system will gain control over behaviour. As can be seen in Table 2, the results clearly showed that adult rats that were exposed to moderate levels of alcohol during prenatal development showed a strong preference (11/13) for swimming directly to the visible platform during the competition test. In contrast, approximately half of the normal rats and half of the pair-fed rats preferred the visible platform.

This is the first demonstration, to our knowledge, of an alteration in the balance between learning and memory systems caused by a prenatal developmental event. The implications of this series of experiments should not be underestimated because they show that complex behavioural patterns in adulthood can be permanently altered by a single prenatal event. Hence, these types of events can fundamentally affect the overall organization of memory in the mammalian nervous system and can lead to abnormal behavioural patterns in adulthood.

1.4. *Psychiatric disorders: The central role of interacting memory systems*

In the scientific literature there is an emerging focus on the idea that the etiology of almost all major psy-

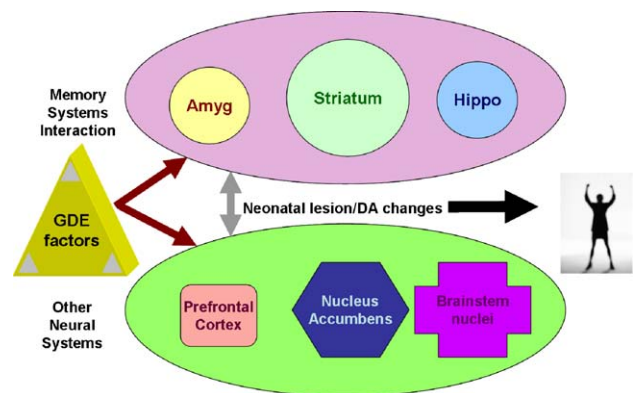


Fig. 5. A hypothetical scenario in which GDE factors alter the organization of the brain in which prenatal alterations in the hippocampus and amygdala alter their functions as well as affecting portions of the prefrontal cortex. These changes in the organization of different memory/behavioural systems and other brain regions results in the manifestation of various symptoms associated with schizophrenia.

chiatric disorders are linked to abnormalities in brain areas implicated in learning and memory processes. The evidence suggests that dramatic changes in the relationship of these systems to one another, and with other brain systems, lead to abnormal manifestations of behaviour. These cognitive and behavioural abnormalities include schizophrenia (Hanlon & Sutherland, 2000; Lipska & Weinberger, 2002); anxiety (Hariri et al., 2002); depression (McEwen, Magarinos, & Reagan, 2002; Santarelli et al., 2003; Sheline, Gado, & Kraemer, 2003); and drug abuse (Dickinson, Wood, & Smith, 2002; Everitt, Dickinson, & Robbins, 2001; White, 1996, 2002) among others.

Historically, theories about the etiology of these major psychiatric disorders have been dominated by single factor theories. The idea was that these complex brain disorders were caused by alterations in a neurotransmitter system, gene or some other single factor. There are many single factor theories of brain disorders that continue to dominate important areas of research. Examples of such theories include the idea that schizophrenia is caused by an over-activation of the neurotransmitter dopamine (Seeman, Guan, & Van Tol, 1993), or that Alzheimer's disease, in which alterations in a small number of genes leads to over-expression of beta-amyloid peptide or neurofibrillary tangles, is associated with neuronal damage and cognitive deficits (Pericak-Vance & Haines, 1995). Although single factor theories have generated a significant amount of important research, they do not accurately account for the complex etiologies of these disorders (see Hanlon & Sutherland, 2000; Lipska & Weinberger, 2002; McDonald, 2002).

In the final portion of this review we will discuss the etiology of three classes of psychiatric disorders from the interacting memory systems perspective (IMST). First, the relationship between prenatal damage to the amygdala and hippocampus, prefrontal cortex activity, and schizophrenia will be discussed. As well, the functional implications of this neural damage and disconnection syndrome are discussed. Second, the etiology of drug abuse and the role of different learning and memory systems are discussed. Finally, the role of various learning and memory systems in mood disorders is presented.

1.5. Schizophrenia

Recent work suggests that alterations in the prenatal development of the hippocampus and/or amygdala may be a critical event in the overall etiology of schizophrenia. The idea is that some possible combination of GDE factors would alter the development of the hippocampus and/or amygdala and their functional relationships to the rest of the brain. These changes would not be fully revealed until early adulthood, and possibly be triggered by experiences in adulthood (e.g., stress).

Several developmental rat models of schizophrenia have been developed with significant predictive value (Hanlon & Sutherland, 2000; Lipska & Weinberger, 2002). This work is based on the idea that the hippocampus and/or the amygdala are damaged early during brain development and that this event fundamentally alters the organization of the brain in adulthood leading to the myriad of symptoms associated with schizophrenia. For example, a neonatal lesion of the ventral hippocampus in rodents produces many of the neural and behavioural changes associated with schizophrenia in humans. These changes include alterations in areas like the nucleus accumbens and prefrontal cortex as well as changes in the relationship of the hippocampus and amygdala to these brain areas. Changes in the organization of these memory/behavioural systems and their relationships with the nucleus accumbens and the prefrontal cortex are thought to underlie the emergence of abnormalities in various dopamine-related behaviours in adulthood. These abnormalities include enlarged ventricles, increased action of postsynaptic dopamine receptors, morphological changes in prefrontal cortex and related deficits on tasks sensitive to prefrontal function (Hanlon & Sutherland, 2000; Lipska & Weinberger, 2002).

Fig. 5 shows a hypothetical scenario in which GDE factors resulted in altered relationships among various memory/behavioural systems, and their relations with other neural systems. These alterations include hippocampal and amygdala dysfunction that will result in relationship changes between these medial temporal lobes structures and prefrontal cortex. These changes would result in an increased dominance of the S–R habit system by the dorso-lateral striatum as well as other systems.

Taken together, these rodent models of schizophrenia show a strong relationship between early alterations in medial temporal lobe affecting areas with direct anatomical connections like the nucleus accumbens and the prefrontal cortex. According to this work, the alterations in dopamine related behaviour and prefrontal function are a secondary consequence of prenatal alterations in learning and memory systems like the hippocampus and amygdala.

From the IMST view, early neonatal lesions of the hippocampus and/or amygdala change the structure and integrity of brain regions like the nucleus accumbens and prefrontal cortex. The effect of this fundamental change in the organization of the brain on behaviour can best be understood by looking at the change in relationships between various memory/behavioural systems, some of which have been altered and others that have not. The idea is that certain patterns of interactions would dominate thought and behavioural control in normal subjects, and a different pattern of interactions would occur in subjects with schizophrenia.

1.6. Drug abuse

Various theories of the neural mechanisms of drug abuse have been put forward. One popular view is that addicts administer drugs for their reward or pleasure-inducing effects. This is sometimes referred to as the hedonic theory of drug addiction. Essentially the idea is that drug consumption results in the activation of dopamine cells in the ventral tegmental area which leads to dopamine release in the nucleus accumbens and prefrontal cortex (Wise, 1996). It has been suggested that increases in corticolimbic dopamine levels produce a pleasurable experience (Volkow, Fowler, & Wang, 2002) as well as affecting various cortical regions involved in attentional processes and decision-making that could affect various behaviours underlying addiction. A related theory suggests that withdrawal from addictive drugs produces reductions in dopamine release and action leading to an anhedonic state that mediates relapse to drugs. A third theory of addiction called the incentive sensitization theory (Kelley & Berridge, 2002; Robinson & Berridge, 1993) suggests that drug abuse is mediated via mechanisms linking reward to drug associated stimuli, which in turn results in compulsive behaviours linked to drug addiction. According to this view, corticolimbic dopamine release is critical for behaviours necessary for obtaining rewards (Berridge & Robinson, 1998).

Another theory focuses on various learning and memory systems in which the normal functions of these complex neural circuits become subverted leading to compulsive drug seeking behaviours (Everitt et al., 2001). In this model, drugs of abuse initiate plasticity mechanisms in different learning and memory systems that come to control behaviour of the individual over other pre-existing memories. An earlier and slightly different formulation of this view (White, 1996) suggests that experience with addictive drugs are encoded and stored like other experiences except that drugs of abuse only mimic a subset of the action of natural reinforcers in the brain. It is this differential reinforcement effect of drugs combined with these actions on distinct learning and memory systems that produce addictive behaviours. In this model, the amygdala acquires information that promotes approach and interaction with drug associated stimuli. The dorsal striatum promotes the acquisition of stimulus–response (S–R) habits and the hippocampus acquires information about the context in which drug stimuli are obtained (White, 1996).

1.7. Drug abuse and interacting memory systems theory

The interacting memory systems theory (IMST) view of the organization of memory/behavioural systems in the mammalian brain might be a powerful way of understanding the neural basis of drug addiction. The various theories mentioned above indicate the critical

role different learning and memory systems play in drug addiction in which powerful plasticity processes and associated memories are formed during drug experiences that come to dominate behavioural control. White's (1996) theory of drug addiction, in particular, is an interesting fusion of multiple learning and memory systems theory and a novel reinforcement theory.

However, future work will need to emphasize the dynamic and interactive nature of these systems and what role these interactions might play in addictive behaviours particularly when trying to develop treatment regimes. The logic behind this claim is that it appears that certain drugs of addiction modulate plasticity processes in specific learning and memory systems but not others (White, 1996), while another drug of abuse might have a different pattern of influences. This suggests that certain addictions might be heavily based on certain memory/behavioural circuits while addictions to another drug could be based on a different set of circuits, or even a different subset of circuits. For example, drug A might strongly enhance plasticity processes in dorsal striatum that is thought to mediate stimulus–response (S–R) habits (Packard et al., 1989) while drug B might elicit addictive behaviours via enhancement of plasticity processes in the hippocampus and amygdala thought to mediate contextual and stimulus–reward associations (White & McDonald, 2002). If true, the treatments necessary to deal with these subtypes of learning-based addictions would require different approaches. One approach would be to try and eliminate memories mediating the aberrant behaviour. Alternatively, enhancement of other learning and memory systems not mediating the addictive behaviours could be utilized to dislodge the suspected system from behavioural control.

Another window on the mechanisms of drug addiction that the IMST might open is an explanation for individual differences in susceptibility to drug addiction (Glantz & Pickens, 1992). We have previously argued that although these learning and memory systems affect behaviour, there are GDE factors that alter the relationships between these systems and the relationship of these systems to other brain areas. It is believed that normal and abnormal manifestations of behaviour like drug addiction are determined, to a large extent, by some complex set of interactions between these factors that can have a major effect on the organization of the brain. Thus, interactions between GDE factors can affect neurobiological integrity and impart an organizational change in the relationship of these memory/behavioural systems to one another, and with other brain systems that could make an individual more susceptible to drug addiction.

One possible neural change that could mediate addictive behaviours is via enhanced behavioural control exhibited by one memory/behavioural system. Fig. 6 shows a hypothetical scenario in which various GDE

factors interact to enhance the dominance of the S–R habit system that would lead to an increased tendency towards habitual control over behaviour. This could be influenced by the ease of access to common output sites (Ferbinteanu & McDonald, 2001; McDonald & White, 1995a, 1995b; White & McDonald, 1993) or via enhanced plasticity processes associated with cognitive processes linked to addiction.

A second possibility is that, in particular individuals, alterations in brain organization caused by GDE factors can lead to a bigger reward signal occurring when drugs of abuse are administered. This could result in an acceleration of specific types of learning and memory processes associated with compulsive drug seeking.

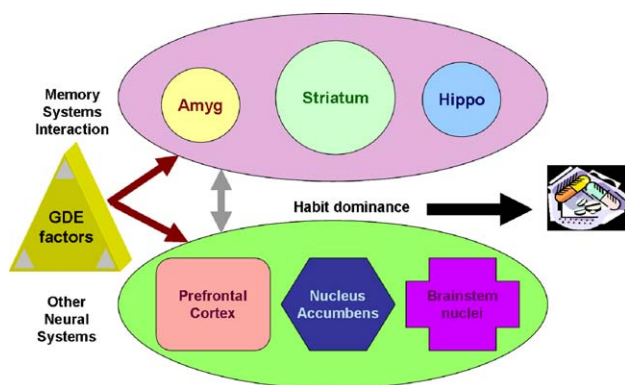


Fig. 6. A hypothetical scenario in which GDE factors alter the organization of the brain in a way that makes this individual more susceptible to drug addiction to a particular substance. The administration of this drug of abuse triggers a series of events that lead to the dominance of the S–R habit system in controlling behaviour. (The increase in size of the striatum object in this figure is designed to indicate an increased influence over behaviour and not a literal increase in size).

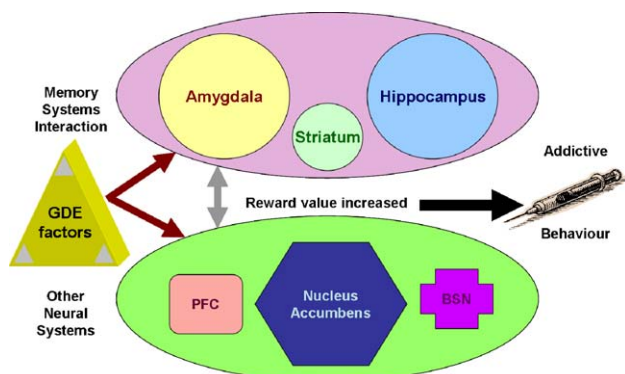


Fig. 7. GDE factors interact to alter the organization of the brain in a way that enhances reward signals when drugs of abuse are administered. The reward signal is represented by an increase in dopamine release in the ventral tegmental area/nucleus accumbens projection. This signal preferentially enhances amygdala-based pavlovian learning and memory processes that can influence addictive behaviours by an individual's tendency to approach and maintain contact with cues, individuals, and situations associated with drug administration.

Fig. 7 shows a hypothetical scenario in which the GDE factors alter the organization of the brain which results in a more powerful reward signal to a particular drug dose, possibly represented in the brain by an increase in dopamine release in the VTA/nucleus accumbens (Koob, 1992). This enhanced sensitivity of the meso- limbic dopamine system to drugs of abuse could result in an acceleration of learning and memory processes dependent on these signals (Hiroi & White, 1991) and ultimately behavioural control by these systems.

A final example is based on the idea that various GDE factors could lead to an organizational change in the brain resulting in a reduction of inhibitory control via prefrontal cortical mechanisms (Kolb, 1990). Fig. 8 shows this reduction of prefrontal inhibitory control which could result in increased behavioural control by memory/behavioural systems that require the contribution of executive systems for appropriate choice behaviours (Fuster, 1989; Moscovitch, 1994).

1.8. Mood disorders

The mood disorders include many of the most common psychiatric disorders found in the general population including depression, anxiety disorder, and obsessive–compulsive disorder (OCD). Hypotheses about the etiology of these disorders consistently suggest that disruption of major neurotransmitter systems are at the root of these brain dysfunctions. Once again, our view is that these alterations in neurotransmitter systems might be the secondary consequences of alterations to key memory/behavioural systems including the hippocampus, amygdala, dorsal striatum, and the prefrontal cortex. These mood disorders are now being linked to permanent structural and biochemical changes in these brain structures.

Depression is characterized by recurrent episodes of decreased energy, appetite, attention, and negative mood states (Cassens, Wolfe, & Zola, 1990). Alterations in the neurotransmitter serotonin are thought to be the main cause of depressive episodes and the administration of drugs that enhance serotonergic levels have had considerable success in treating depression.

A different view of the etiology and mechanisms of depression has emerged recently that links damage to the hippocampus to this disorder (Sapolsky, 2000). Furthermore, a down-regulation of neurogenesis in the adult hippocampus has also been linked to depression and serotonergic medications commonly used to treat depression up-regulate neurogenesis in hippocampus (Malberg, Eisch, Nestler, & Duman, 2000; McEwen et al., 2002). Alterations in the functions of the amygdala have also been consistently reported in depressive patients (Sheline et al., 2003) in whom the amygdala becomes overactive when responding to negative experiences.

From the IMST view these seemingly unrelated changes to the hippocampus and amygdala might not be unrelated after all. It is possible that the GDE factors might lead to elevated glucocorticoid levels. If these levels are chronically elevated they can lead to hippocampal cell death (Sapolsky, Krey, & McEwen, 1985) and neurogenesis down-regulation (Lemaire, Koehl, Le Moal, & Abrous, 2000). Any event that leads to a dampening of hippocampal function could result in increased dominance of other memory/behavioural systems (White and McDonald, 2002). Thus a secondary consequence of dampening hippocampal function would be to increase dominance of amygdala influence on thoughts and related behaviour (McDonald & White, 1995a, 1995b; Sheline et al., 2003; White & McDonald, 1993). This increased amygdala influence might lead to increases in the negative affect attached to a wider range of situations or events. Fig. 9 shows a hypothetical scenario in which, because of some complex interactions between various GDE factors, an individual suffers from depression. The depiction shows a shrinkage of the hippocampus, anatomically and functionally, and an enhancement of the right amygdala dominance of thought and behaviour. The right amygdala in humans is thought to be specialized for influencing negative emotions.

Anxiety disorders are associated with inappropriate levels of fear and related physiological and behavioural concomitants warranted by the situation or event. It is thought that disruptions of the GABAergic neurotransmitter system are central to the etiology of anxiety disorders and the widespread treatment success of the benzodiazepine drugs supports this view (Rickels & Schweizer, 1987).

Various memory/behavioural systems, particularly the hippocampus and amygdala, are thought to allow

individuals the ability to confine and constrain their fearful responses to the original event. Anxiety disorders might result from a weakening of these systems resulting in a generalization of fear to unrelated cues and situations. Thus, a subject with an anxiety disorder is thought to be unable to differentiate between cues, environments, or episodes that are associated with fear and those that are not. Many researchers have concluded that anxiety disorders must be linked with changes in the hippocampus and/or amygdala (Amaral, 2003; Hariri et al., 2002; Ledoux & Muller, 1997; Quirk & Gehlert, 2003; Walker, Toufexis, & Davis, 2003), and it is possible that these changes occur because of some interaction between the GDE factors.

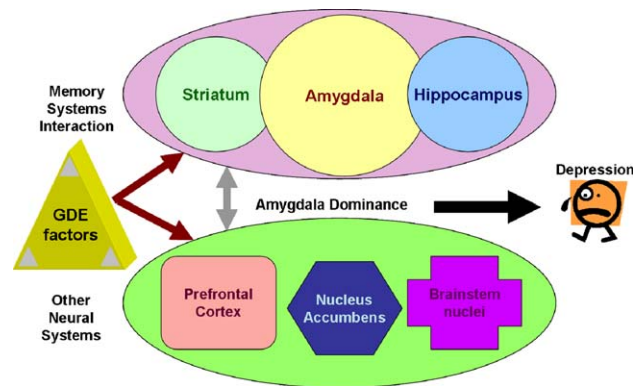


Fig. 9. GDE factors interact to alter the organization of the brain in a way that results in symptoms and behavioural patterns associated with clinical depression. Atrophy of hippocampus, anatomically and functionally, and enhancement of right amygdala dominance over thought and behaviour results in negative mood states and associated changes in behaviour.

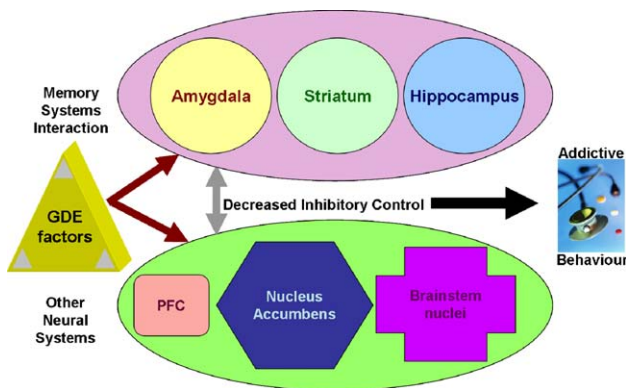


Fig. 8. GDE factors interact to alter the organization of the brain in a way that reduces prefrontal cortex inhibitory control of memory/behavioural systems like the amygdala and striatum that results in increased behavioural control by memory systems that require the contribution of executive systems for appropriate choice behaviour in highly rewarding but personally detrimental behavioural patterns.

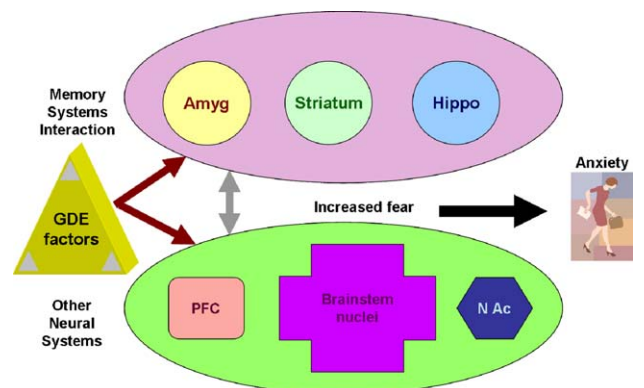


Fig. 10. GDE factors interact to alter the organization of the brain in a way that results in symptoms and behavioural patterns associated with general anxiety disorder. Changes in the hippocampus and amygdala and/or their relationship with one another resulting in general anxiety by decreasing their influence on brainstem and hypothalamic neural systems that produce the physiological responses associated with fear and anxiety. These responses would include increased heart rate, respiration, hormone release, ascending neurotransmitter release, and avoidance behaviours.

Fig. 10 shows a hypothetical scenario in which, because of some complex interactions between the GDE factors, an individual suffers from anxiety. In this individual, changes in the hippocampus and amygdala and/or their relationship with one another and other brain regions like the brainstem and hypothalamus would result in general anxiety. A loss of amygdala and hippocampal control over brainstem and hypothalamic regions that mediate the physiological responses associated with fear and anxiety would increase generalization of fear to unrelated situations.

Obsessive–compulsive disorder (OCD) is another class of mood disorder that is characterized by reoccurring obsessions and/or compulsions that disrupt normal daily functions of the individual (DSM-IV). Obsessions are defined as incessant, intrusive thoughts or impulses. Compulsions are repetitive response patterns that are thought to occur in response to various obsessions. Any attempt by the individual suffering from OCD to resist these compulsive behaviours results in high anxiety.

From the IMST view, OCD might be caused by an alteration in the relationships between the dorso-lateral striatum, prefrontal cortex, and the amygdala/hippocampus axis. These changes in the organization of these different memory/behavioural systems would be caused by interactions with the GDE factors. Dysfunction of the amygdala/hippocampus would result in heightened anxiety levels. A dampening of prefrontal cortex function would lead to a reduction in inhibitory control over thoughts and behaviour. A secondary consequence of dysfunction in these areas would be an increased dominance of the dorso-lateral striatum S–R habit system that would elicit inappropriate repetitive response patterns (compulsions).

Recent evidence supports this complex view of OCD and implicates changes in the dorsal striatum, prefrontal cortex and the amygdala/hippocampus axis (Harris & Dinn, 2003; Hoehn-Saric & Greenberg, 1997; Kim et al., 2003; Konig et al., 1998; Kuelz, Hohagen, & Voderholzer, 2004; Kwon et al., 2003; Szeszko et al., 2004).

2. Conclusions

This current review and analysis puts forth the idea that the organization of memory in the mammalian brain and the neural systems that mediate them must play a pivotal role in our thoughts, emotions, choices, actions, and even our personalities. According to this view, complex interactions between neural circuits that contain remnants of an individual's past experience not only provide the basis of your identity but also exert an enormous influence over ongoing behaviour. Interactions between these systems and related brain areas are thought to determine who we are and how we behave in

particular situations. An extension of this idea is that abnormal manifestations of behaviour are caused, to a large extent, by alterations in the relationships among different memory/behavioural systems and other brain areas.

Symptoms associated with various psychiatric disorders are hypothesized to be caused by complex interactions between a patient's genetic background, their pre- and post-natal development, and their life experiences. All of these factors can have major effects on the organization of the brain and even subtle alterations could affect the overall relationship between memory/behavioural systems (balance) as well as the relationships among memory/behavioural systems and the rest of the brain. In many instances, it is this relationship between GDE factors and interactive memory systems which ultimately determines manifestations of normal and abnormal behaviour.

In summary, evidence was provided showing a competitive interaction between two memory/behavioural systems and how a simple pre-natal developmental event affected the nature of this interaction (McDonald & White, 1994; Sutherland et al., 2000). It is important to note that although the above example shows an effect of a developmental factor on a competitive interaction between the dorsal striatum and hippocampus, it is hypothesized that synergistic interactions can be affected in this way as well that could lead to changes in thought processes and behavioural patterns. A review and analysis of research showing a central role of memory/behavioural system dysfunction and various psychiatric disorders was also presented. One idea that emerged from this analysis is that it is important to understand the primary and secondary consequences of memory/behavioural system dysfunction. That is, the symptoms of a particular psychiatric disorder are most likely mediated by changes among memory/behavioural systems during development and secondary changes that affect neurobiological processes later in life. As a result, some adult processes are altered while others are left intact, and may come to dominate thought and behaviour in the presence of down-regulated or compromised neurobiological processes.

One interesting point that emerges from the current analysis is that many of these seemingly disparate disorders affect similar neural circuits (e.g., OCD and schizophrenia). A corollary that may follow from these demonstrations is that the temporal aspects of brain damage could influence different disorders. For example, schizophrenia appears to be caused by early developmental alterations whereas OCD damage may occur later, possibly post-natal. Another possibility is the overall extent of damage or the pattern of damage within each system is different. For example the dorsal striatum can be anatomically and functionally subdivided into at least two systems (McGeorge & Faull,

1989). In a complex disorder like OCD, a unique pattern of damage to portions of each of these areas might be responsible for the psychological and behavioural effects of the brain dysfunction. Future work will be required to assess these ideas.

In closing, emerging evidence from a wide range of empirical studies suggest that learning and memory systems are at the core of many neurodegenerative and psychiatric disorders. Detailed information about the functions of these various brain systems and the interactions between them, using both basic and applied research approaches, is critical for future treatment and prevention of these debilitating disorders.

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