AMINERGIC TRANSMITTER SYSTEMS IN COGNITIVE DISORDERS

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INTRODUCTION

The major categories of cognitive disorders defined in the DSMIV include various types of dementias, deliriums, and amnestic disorders (American Psychological Association, DSMIV, 2000). The goal of this chapter is to present a thorough, but certainly not exhaustive, summary of the evidence for dysregulations in aminergic neurotransmitter systems in several representative cognitive disorders. Aminergic transmitter systems include the biogenic amine acetylcholine (ACh), the catecholamines dopamine (DA), norepinephrine (NE), epinephrine (Epi), and the indoleamine serotonin (5-HT). For a more detailed discussion of the neuropharmacology and chemoanatomy of aminergic transmitter systems the reader is referred to the earlier chapter by Mathé and Svensson in this book.

Not surprisingly, there is considerable variation in the extent of the literatures on the neurochemical dysregulations accompanying delirium, dementia, and amnestic disorders. The scope of our review will be limited to several syndromes for which there is considerable evidence implicating specific aminergic transmitter systems to these cognitive disorders. Thus, the discussion of the dementias will be limited to dementia of the Alzheimer s type (DAT) and AIDS-associated dementia (AAD). The discussion of amnestic disorders will be limited to those that accompany chronic alcohol consumption (Korsakoff s syndrome) or administration of the psychostimulants MDMA (Ecstasy). Finally, the discussion of delirium will focus on the ability of several drugs or toxins to impair aminergic function. This chapter will focus exclusively on clinical populations. However, valuable corroborating evidence for links between certain cognitive dysfunctions and specific aminergic populations can be found in various animal models of these cognitive disorders. Several of these models are discussed in other chapters

within this book.

An important issue that permeates any summary and interpretation of the neurochemical dysfunctions accompanying neuropsychiatric disorders is the considerable variation in the methods used to collect such data, and the relative strength of inferences supported by these various methods. A review of the literature reveals neurochemical data collected from post-mortem tissue, biopsy tissue, analysis of cerebral spinal fluid (CSF), neuroimaging techniques with transmitter-selective markers, and finally a reverse deduction on the basis of drug effects (therapeutic or of abuse). There are obvious limitations to constructing hypotheses about the neurochemical bases of complex cognitive disorders on the basis of these types of data. Several of these methods lack the spatial resolution for highlighting regional contributions within distributed neural systems and, more importantly, rarely capture the dynamics and subtleties of chemotransmission likely to be at the heart of many cognitive disorders. As such, the over-interpretation of negative data (i.e. seemingly intact neurotransmitter systems in neuropsychiatric populations) is particularly problematic. In this regard, the use of animal models with more precise neurochemical methods can be invaluable in formulating and testing hypotheses about the neurochemical bases of cognitive disorders (see Sarter and Bruno, this volume). Throughout this chapter we will point out the source of the neurochemical evidence supporting the relationship between dysregulation in aminergic system and the cognitive disorder, along with any concerns surrounding the interpretation of such evidence.

Of course, simply documenting a specific neurochemical impairment in a patient

diagnosed with a cognitive disorder is not *sufficient* evidence to conclude a causal relationship between the neurochemical deficit and the cognitive construct. Extending these correlations into the realm of causality is a difficult task particularly when it comes to clinical populations. The primary strategy for probing the causal relationship between two variables is to manipulate levels of one of the variables and look for systematic changes in the other variable. While this can be readily done in experimental animals, and, in fact, should be a critical component of any animal model of neuropsychiatric condition, this is often difficult to achieve in clinical populations. Certainly one can examine, either between subjects or, ideally, within subjects whether the cognitive impairments worsen as markers of the neurochemical pathology become more severe (i.e. with time since onset in a neurodegenerative condition). A second strategy, and one that is often used in studies of the biological bases of disease is a type of *post hoc* logic in which the causal relationship between neurochemical pathology and symptom is inferred on the basis of the effectiveness of pharmacotherapeutics. This, however, can be a risky strategy and may lead to both false positives (i.e. the drug does not directly interact with neurochemical systems that are necessary and sufficient for the disease but rather modulates the activity of these systems) and false negatives (i.e. the drug effects the critical neurochemical systems but does not replicate , in sufficient physiological fashion, signal processing within this damaged system). We will identify, in this chapter, those few situations in which such strong relationships exist between the degree of neurochemical dysfunction and the cognitive symptoms.

DEMENTIAS

The DSM-IVdefines dementias as a syndrome of multiple cognitive deficits that include memory impairments and at least one of the following, aphasia, apraxia, agnosia, or disturbances in executive functions (American Psychiatric Association, DSMIV, 2000). The memory impairment is a necessary feature of the diagnosis, progressing from an early presentation of difficulty in learning new material to eventually an inability to remember previously learned material (memory). The impairments in executive function are related to disorders of the frontal lobe and involve the ability to think abstractly and to plan, initiate, sequence, monitor and inhibit complex behavior. These cognitive deficits must represent a marked decline from a previous level of functioning and must also be severe enough to cause significant impairment in social or occupational functioning. There are a number of dementia syndromes including, dementia of the Alzheimer s type (DAT), frontal lobe dementia (DFL), vascular dementia, dementia of the Lewy Body type (LBD), AIDS-associated dementia (AAD), dementia associated with Huntington s disease, dementia associated with Pick s disease, dementia due to other general medical conditions, and substance-induced persisting dementia. The two dementias that have received the most attention with respect to possible roles of aminergic transmitter systems are DAT and AAD. Each of these syndromes will be discussed below.

Dementia of the Alzheimer s type

The search for a neurochemical basis of Alzheimer s dementia (DAT) began in earnest almost forty years ago with the hope that such an identification would lead to the development of effective pharmacotherapies. This exploration was fueled by the identification of a dopaminergic component to Parkinson s disease and the ensuing success of L-DOPA-based

replacement pharmacotherapy . Over the ensuing decades, a great deal of evidence has revealed aminergic dysfunctions in DAT, and these are summarized below. Unfortunately, the development of efficacious pharmacotherapies for DAT has not met with the same degree of success as seen in the treatment of Parkinson s disease (PD). This probably reflects the fact that a simply replacement strategy designed to elevate *tonic* levels of deficient neurotransmitters (e.g. acetylcholine), borrowed from our experience with PD, is inconsistent with the normal functions of such systems in information processing (see Sarter and Bruno, 1997, 1999 for a discussion of this issue).

Most of the attention on the neurochemical bases of dementia has focused on DAT. This is the result of two observations. First, while certainly not homogeneous in nature, DAT reveals the most consistent profile of neurochemical dysregulations of any of the dementias. Second, the cognitive deficits in DAT correlate best with the reduction in various markers of cholinergic transmission (Francis et al., 1985; Lehericy et al., 1993), and the prominent focus on pharmacotherapeutics has occupied considerable attention. In addition to deficits in cortical cholinergic transmission, the literature reveals clear and consistent reductions in markers of adrenergic, serotonergic, and, to a lesser degree, dopaminergic transmission in DAT. An overview of these findings appears below.

Cholinergic systems in Alzheimer s dementia

The earliest and most consistent neurochemical abnormalities to appear in the brains of DAT occur in the cholinergic system. The decline in cholinergic transmission is not uniform throughout the brain. There are significant reductions in the basal forebrain cholinergic system where there is estimated to be a 30-90% loss of neurons with no loss in other cholinergic rich areas, particularly brain stem (Mesulam, 1996). This loss of neurons manifests itself in a reduction in the biosynthetic enzyme choline acetyltransferase (ChAT) in temporal lobes and more moderate reductions in frontal lobes. Biopsy studies suggest that the decline in cortical ChAT activity can occur within 1 year of the onset of clinical signs (Bowen et al., 1983). Consistent with the loss of basal forebrain neurons is an accompanying reduction in the density of, presumably presynaptic, nicotinic receptors in cortex and parahippocampal gyrus as measured post-mortem (Perry et al., 1995) and *in vivo* with PET (Nordberg, 1996).

A recent study investigated the relationship between declines in nicotinic receptor binding (nAChR) and vesicular ACh transport sites (vesamicol binding), using autoradiographic methods, in medial temporal cortex in DAT (Sihver et al., 1999). In age-matched controls, binding was particularly high in layers I, III, and V. Autopsied tissue analysis revealed that binding was reduced in all layers in DAT by 40-55%. While the loss of nAChR binding correlated well with the reduction in ChAT activity, vesamicol binding was only reduced by 25%, suggestive of some compensatory activity within residual cholinergic terminals.

The bases for the selective vulnerability of basal forebrain cholinergic neurons, as

opposed to other populations of cholinergic neurons, remains unclear. Autoradiographic studies demonstrate the presence of high affinity ^{125}I-NGF binding sites (presumably corresponding to TrkA) in nMB and striatum but not in the pedunculopontine nucleus. Immunohistochemical studies have revealed TrkA expression on nBM and the cholinergic interneurons of the striatum. This supports the hypothesis that there is a relationship between the dependence upon NGF and the neuronal vulnerability in DAT. In DAT, the number of neurons expressing TrkA was decreased in nBM, likely as a result of cholinergic neuronal loss (Boissiere et al., 1997). While neither NGF levels or mRNA are altered in DAT there may still be more subtle problems with receptor function/transduction.

As with any other neurodegenerative disease, early detection is an important goal. The ability to develop an *in vivo* imaging protocol for revealing cholinergic denervation is viewed as paramount in this quest. ChAT, the most specific marker expressed by cholinergic neurons, does not have an available tracer for imaging studies. Recently, however, a tracer, C-11-labeled N-methyl-4-piperidyl-acetate (C-11-MP4A), has been developed for the catabolic enzyme acetylcholinesterase (AChE). AChE activity in cortex is mainly due to expression within cholinergic neurons and their axons (Mesulam and Geula, 1992). The use of this tracer has revealed that AChE activity is reduced in DAT (Herholz et al., 2000; Kuhl et al., 1999) and that this reduction correlates well with reductions in regional cerebral blood flow or glucose metabolism, particularly in temporo-lateral regions of cortex (Herholz et al., 2000).

Finally, it should be stated that the functional consequences of a loss of cortical cholinergic innervation need not be limited to direct changes in inter-neuronal communication. A double immunocytochemical study for ChAT and reduced NADPH (as a marker for NO) revealed inputs to cortical microcirculation (Vaucher and Hamel, 1995), raising the possibility that cholinergic denervation will also result in inadequate cortical perfusion. In fact, cortical microvascular abnormalities appear to be intimately related to the pathophysiology of the disease. Regional cholinergic denervation and reduced NADPH has been reported on cortical microvessels in DAT. Moreover, the deficits in cortical perfusion parallel the regional differences in cortical cholinergic denervation (i.e. temporal regions are more affected than primary motor and somatosensory regions). These changes raise the interesting possibility that the cholinergic denervation may compromise the ability to adapt enhanced cortical persusion to neuronal activity associated with tasks related to arousal and attention (Tong and Hamel, 1999).

Noradrenergic/adrenergic systems in Alzheimer s dementia

There are consistent changes in noradrenergic and, to a lesser extent, adrenergic systems in DAT. The progressive loss of NE neurons in locus coeruleus (LC) has been documented using post-mortem as well as biopsy tissue samples (see Mann, 1998 for a review). In contrast to the loss of cortical cholinergic inputs discussed above, there is little relationship between the extent of loss of NE in LC and the cognitive deficits seen in DAT (Palmer et al., 1987a,b,1993). These losses in NE may, however, contribute to important non-cognitive behavioral impairments that accompany the syndrome such as depression and wandering. These non-cognitive

components represent a disturbing set of complications that contribute to patient suffering, caregiver stress and health costs, particularly as these complications may expedite the institutionalization of victims of DAT.

The loss of NE neurons in LC results in reduced noradrenergic innervation of cortex. NE levels and high affinity [^{3}H]NE uptake are consistently reduced in temporal and parietal cortex. Interestingly, these changes in NE uptake are seen in patients that have displayed clinical symptoms for less than 2 years - suggesting that such dysfunctions occur rather early in the course of the disease (Palmer et al., 1987a).

The mechanisms underlying the loss of NE neurons in LC in DAT are not well understood. Recently, it has been speculated that this loss reflects the accumulation of an endogenous neurotoxic compound in DAT. In this regard, a recent study compared levels of the neurotoxic MAO-A metabolite of NE, 3,4-Dihydroxyphenylglycolalderhyde (DOPEGAL), in post-mortem tissue samples from DAT victims and age-matched controls (Burke et al., 1999). The authors reported a 2.8-3.6-fold increase, relative to that seen in controls, in DOPEGAL levels in LC from DAT tissue.

As mentioned above for cortical ACh, there is some speculation that compensatory increases in NE transmission might accompany the loss of NE neurons in LC in DAT. There are higher levels of NE in CSF in aging and in DAT (Raskind et al., 1999). *A priori* such increases could reflect increased release of NE and/or decreased metabolism and clearace. This issue was

addressed by comparing the ability of the $_2$ antagonist yohimbine to increase NE release levels in CSF of young adult controls and DAT patients. Administration of yohimbine led to greater levels of NE in CSF in DAT patients than in young controls, consistent with the capacity for greater synthesis/release of NE following the neuronal loss accompanying the dementia (Raskind et al., 1999).

Post-mortem analyses of adrenergic receptors reveal changes in both number and affinity in DAT. Receptor binding of $_1$ (post-synaptic), using [^{3}H]prazosin, revealed a 50% reduction in Bmax and affinity in hippocampus with no change in frontal cortex or nBM. The loss of $_1$ sites probably reflects a loss of receptors on glutamatergic neurons. In contrast, receptor binding of $_2$ (pre-synaptic), using [^{3}H]yohimbine, revealed a 50% reduction in Bmax and a 66% reduction in affinity in nBM with no changes in hippocampus or frontal cortex (Shimohama et al., 1986). The loss of $_2$ sites may represent the loss of noradrenergic inputs from LC to basal forebrain. Theoretically, declines in this input could contribute to the cognitive deficits seen in DAT as $_2$ receptor activity may positively modulate ACh release in hippocampus and cortex (Tellez et al., 1999).

There is also evidence indicating changes in brain stem adrenergic systems in DAT. The biosynthetic enzyme pheylethanolamine-N-methyl transferase (PNMT) exibits a progressive loss (50-88%) in LC, frontal cortex, hippocampus and amygdala (all areas with significant neuronal degeneration) but not in cerebellum or motor cortex (areas with little neuronal degeneration). This pattern has led to the hypothesis that the loss of Epi-containing neurons is secondary to

some initial degeneration of target neurons and the consequent loss of growth factors that might be critical for the induction of synthetic enzymes within the afferent neurons (Burke et al., 1987). Interestingly, the loss of LC neurons correlated positively ($r = 0.71$) with the loss of PNMT activity. There was an accompanying loss of mitogenic activity, as measured by brain derived growth factor (BDGF), consistent with the hypothesized loss of growth factors. Moreover, while there was a significant reduction in PNMT staining in afferents adjacent to the degenerating neurons there was no change in PNMT staining in projections adjacent to intact blood vessels.

Serotonergic systems and Alzheimer s dementia

Although somewhat more variable than the effects seen in adrenergic systems, there are several reports indicating widespread serotonergic dysfunctions in DAT. There is also some suggestion that these impairments may occur relatively early in the disease (Bowen et al., 1983; Palmer et al., 1987c). As is the case with decreases in adrenergic transmission, however, there is little evidence that changes in serotonergic transmission are contributing significantly to the cognitive deficits seen in DAT. Rather, dysfunctions in serotonergic transmission are likely to contribute to affective disorders that accompany DAT (Court and Perry, 1991). Post-mortem analyses reveal significant reductions in 5-HT levels in frontal cortex (Arai et al., 1984; D Amato et al., 1987; Palmer et al., 1987), temporal cortex (Palmer et al., 1987), hippocampus (Cross et al., 1984), hypothalamus (Sparks et al., 1988), nucleus basalis Meynert (Sparks et al., 1988) and basal ganglia (Sparks et al., 1988). Reductions in the levels of 5-HIAA, the principal metabolite of 5-HT metabolism, and the number of 5-HT reuptake sites in cortex (Palmer et al., 1987a) are consistent with the interpretation that there is a loss of serotonergic innervation to

cortex. These autopsy studies have been corroborated by ante-mortem data showing reduced concentrations of 5-HT and 5-HIAA as well as diminished 5-HT uptake (Palmer et al., 1987b). This decline in presynaptic indices of serotonergic transmission is paralleled by a reduction (30-40%) in the number of 5-HT-positive neurons in the median and dorsal raphe nuclei (Chen et al., 2000).

The mechanisms underlying these reductions in markers of serotonergic transmission are unclear. In this regard, several studies have investigated the relationship between the decline in these markers and more traditional neuropathologies seen in DAT. There is a negative correlation between the number of tangles and 5-HT or 5-HIAA content in cortex from biopsy tissue samples (Palmer et al., 1987a). Neurofibrillary tangles also appear within the dorsal and medial raphe, however the magnitude of the loss of raphe neurons does not correlate with the density of tangles (Chen et al., 2000).

As is the case with the noradrenergic systems described above, strong evidence supporting a relationship between declines in serotonergic transmission and the cognitive impairments seen in DAT is not available. Although declines in cortical and basal forebrain 5-HT content could impact on cortical cholinergic function and, hence, certain cognitive functions. There are clear indications, in the animal literature, for a 5-HT_2 (Zhelyazkova-Savova et al., 1997) and 5-HT_4 (Consolo et al., 1994) receptor-mediated release of cortical ACh. On these grounds, the impact of drugs that affect serotonergic transmission on cognitive function in DAT merits additional study.

A role for the deficits in 5-HT function in the agitation syndrome seen in DAT has been substantiated. A recent study examined the relationship between level of 5-HT activity and the degree of agitation in a group of DAT patients (Mintzer et al., 1998). 5-HT activity was assessed using fenfluramine (5-HT uptake inhibitor)-induced serum prolactin. DAT patients, with and without accompanying agitation, were challenged with an oral dose of fenfluramine (60 mg). Increases in serum prolactin were larger in the agitated than in the non-agitated group. Moreover, within the agitated group, there was a positive correlation between the degree of agitation and the increase in serum prolactin.

Dopaminergic systems in Alzheimer s disease

Changes in dopaminergic systems in Alzheimer s disease differ from those seen in cholinergic and noradrenergic in two important ways. First, they are more variable than those reported for these other two classes of aminergic transmitter systems. Second, to the extent that there are dysfunctions, they appear to be more localized to changes in dopaminergic receptors rather than to dopaminergic innervation to critical target regions. Post-mortem concentrations of DA have been repeatedly found to be unaltered in the cerebral cortex of patients with DAT (Palmer and DeKosky, 1993). This result has been corroborated with ante-mortem diagnostic craniotomies for DA, DOPAC, and HVA levels (Palmer et al., 1987B), although there is a report of reduced levels of HVA and HVA/DA ratios from CSF in DAT (Reinikainen et al., 1990).

Much of the focus on the role of mesolimbic and mesocortical dopaminergic systems and DAT has been fueled by the observation that up to 80% of patients with Parkinson s disease manifest some signs of dementia (Brown and Marsden, 1984). Likewise, extrapyramidal motor dysfunctions have been reported in 20-80% of DAT patients (Merello et al., 1994). Caution must be exercised not to over-interpret these data to suggest that the involvement of the striatal DA system is similar in the two diseases. While one PET study, using ^{18}F-fluorodopa, revealed no evidence for dysfunction of DA terminals in DAT patients with parkinsonian features, others have reported markers of degeneration of nigrostriatal systems (see Leverenz and Sumi, 1986). A recent single photon PET (SPET) study compared the specific striatal uptake of the D2-receptor ligand [^{123}I]-IBZM in DAT patients without extrapyramidal symptoms with age-matched controls to test the hypothesis that alterations in striatal DA may actually be part of a profile in DAT independent of any parkinsonian symptomatology (Pizzolato et al., 1996). The DAT patients exhibited a decrease in D2-receptor ligand binding relative to controls. The source of this reduced binding can not be determined from this particular study. Reductions could be at the level of cholinergic interneurons, corticostriatal terminals, and/or striatopallidal projections.

Joyce and colleagues have conducted a series of autoradiographic studies on the density and pattern of D2 receptors in post-mortem tissue from subjects with DAT using the highly selective ligand [^{125}I]epidepride. These studies have focused on two structures within the medial temporal lobe - the hippocampus (molecular layer of the dentate gyrus) and the amygdala (basolateral area). The binding studies reveal a modular organization of D2 receptors in rostral and mid-levels of temporal cortex (i.e. higher order association cortex) with high densities in

dentate gyrus, CA3 and subiculum (Joyce et al., 1993). There is a loss of these modules in tissue from DAT subjects (Joyce et al., 1998). Interestingly, those areas that are most affected by the formation of more traditional neuropathologies (i.e. plaques and tangles) are the regions that appear to be losing the D2 receptor binding. Those regions exhibiting diminished D2 receptor binding also show a reduction in the number of pyramidal neurons staining for D2 mRNA. There was no evidence for a reduced dopaminergic innervation to hippocampus as measured by changes in the expression of tyrosine hydroxylase.

Dysfunctions in D2 receptor activity in DAT have prompted investigations of a possible relationship between the D2 receptor gene (DRD2), the A1 allele and Alzheimer s disease (Pizzolate et al., 1996; Small et al., 1997). These studies have addressed the hypothesis that the A1 allele, like the APOE4 allele, is a major risk factor in late-onset DAT. The A1 allele is associated with reduced DRD2 binding sites as well as reduced visuospatial function and prolonged P300 latencies - characteristics of DAT. While still an intriguing hypothesis, the initial study found that the A1 allele does not contribute to risk for DAT - either alone or in combination with the APOE4 allele. The study also demonstrated that the A1 allele, that contains the gene that codes for the DRD2, does decrease significantly with aging in both DAT patients and in controls (Small et al., 1997). Thus, one must be careful to include age-matched controls in future studies exploring relationships between the A1 allele and risk for DAT.

AIDS-associated dementia

The pandemic of HIV-1 infection has evolved into a worldwide problem with a preferential affliction of younger adults and children. It has been conservatively estimated that roughly 7-14% of adult HIV-infected people will eventually experience a syndrome of moderate to severe cognitive deficits known as AIDS-associated dementia (AAD). This dementia presents with attentional impairments, memory deficits and reduced alertness (Sarter and Podell, 2000). In addition, AAD has all of the hallmarks of a subcortical dementia in that there is little evidence for a cortical disconnection syndromes (and the attendant apraxias, agnosias, aphasias) It is accompanied, on the otherhand, by psychomotor slowing, bradykinesia and altered posture and gait mimicking advanced Parkinson s disease (Berger and Arendt, 2000).

The pathophysiology of AAD has remained somewhat elusive. The specification of the underlying neuropathologies, which are undoubtedly complex and multifactorial, is made difficult by the fact that neurons are not directly infected by HIV; rather it is thought that infected non-neuronal cells secrete diffusable toxic substances (Sarter and Podell, 2000). Two brain regions that appear to be preferentially affected in AAD are the frontal lobes and the basal ganglia (Hall et al., 1996). Radiologic data support correlations between tissue loss in basal ganglia and whether HIV-positive patients are presenting with or without dementia. Children that present with AAD show extensive calcification within the basal ganglia (Berger and Nath, 1997). There is also diminished rCBF in the basal ganglia in patients presenting with AAD (Berger and Arendt, 2000).

The involvement of the dopaminergic system in AAD was suggested, early on, by the observation that patients were extremely sensitive to the extrapyramidal side effects of DA receptor blockers (Berger and Arendt, 2000; Nath et al., 2000). This heightened sensitivity is suggestive of decreased DA receptor activity a scenario similar to that seen in Parkinson s disease. In this regard, stereological studies reveal decreased (25%) neuronal density in SN_{pc}, but without the presence of Lewy Bodies as is typically seen in Parkinson s disease. This reduction in neuronal density may be driven by the viral nuclear regulatory protein *Tat*. Preclinical studies in rats demonstrate that intraventricular injections of *Tat* result in oxidative stress in striatum (Aksenov et al., 2001) and ultimately produce apoptotic cells predominantly in basal ganglia (see Berger and Nath, 1997). Moreover, DA-related drugs of abuse (i.e. amphetamine, cocaine) may synergize with viral proteins such as *Tat* to produce enhanced neurotoxicity (Nath et al., 2000). While there was a trend toward lowered concentrations of DA and HVA from the caudate at autopsy in AIDS patients, relative to controls, these differences become more pronounced and statistically significant if one focuses exclusively on those AIDS patients who manifested dementia (Sardar et al., 1996). These data are also supported by less direct measures of diminished CSF HVA levels in seropositive subjects and preliminary observations suggesting a trend toward a correlation between the decrease in HVA levels and cognitive deficits (Sardar et al., 1996).

MEMORY DISORDERS

The disorders contained with the Amnestic Disorders category of the DSM IV (American Psychological Association, 2000) are characterized by a disturbance in memory that

is either due to the direct physiological effects of a general medical condition or due to the persisting effects of a substance (i.e. a medication, a drug of abuse, or exposure to a toxin). Individuals with amnestic disorders are impaired in their ability to learn new information or are unable to recall previously learned information or past events. These deficits are most readily seen on tasks that require spontaneous recall and may also become apparent when the person is required to recall stimuli presented at some earlier time. Amnestic disorders may be preceded by an evolving clinical picture that includes disorientation and confusion, and thus the differential diagnosis between delirium and an emerging amnestic disorder merits caution (American Psychological Association, 2000).

In this section, we will examine two substance-induced memory disorders. First, we will discuss alcohol-induced persisting amnestic disorder (Korsakoff s syndrome) that is apparently due to the vitamin deficiency associated with prolonged, heavy ingestion of alcohol (Fadda and Rossetti, 1998). While the neuropathology accompanying this syndrome is complex, there is significant evidence for impaired noradrenergic transmission in the amnestic disorder. Second, we will review evidence for a significant and long-lasting memory deficit associated with repeated administration of the illicit recreational drug 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy). The preclinical and, to a lesser extent, clinical literatures indicate that this drug is neurotoxic for serotonergic nerve terminals and collectively raises the possibility that this amnestic syndrome is related to decreases in this aminergic system.

Korsakoff s syndrome

Korsakoff s syndrome (or disease or psychosis) represents the chronic amnesic phase of the Werkicke-Korsakoff syndrome. The outstanding clinical feature of this amnesia is a selective and permanent anterograde memory loss (McEntee and Mair, 1980; Squire et al., 1993) with accompanying impairments in learning. Neuropsychometric data reveal that, as a group, Korsakoff patients have average intellectual capabilities (as measured by WAIS IQ), but severe memory impairments as revealed by the WAIS and WMS. Korsakoff s syndrome is associated with a thiamine deficiency that is secondary to the nutritional deficiencies of alcoholics. Long-lasting alcohol abuse is not a necessary condition as Korsakoff s syndrome has been reported in nutritionally-depleted non-alcoholics as well (McEntee and Mair, 1980; Victor et al., 1989).

The syndrome presents with a very characteristic midline diencephalic and brain stem neuropathology. Post-mortem studies reveal small punctate lesions in the periventricular region (along the walls and floor of the third and fourth ventricles) and the periaqueductual regions of the brain stem and diencephalon. There is often, but not always, damage to the mediodorsal nucleus (MDN) of the thalamus and to the mammillary bodies (see McEntee and Mair, 1980 for a review). There is a significant amount of controversy surrounding the necessary and sufficient neuropathologies for the amnesic syndrome. Mammillary body lesions are present in most cases and the frequency of this pathology has led to the speculation that it is a critical condition for the amnesic syndrome. However, there are several cases of such lesions without an accompanying amnesia, suggesting that damage to mammillary bodies may not be sufficient for the syndrome (see McEntee and Mair, 1980 for a discussion of this issue). Others (i.e. Victor et al., 1989)

have suggested that lesions of the MDN are crucial for the memory impairments (Markowitsch, 1988). However, there are reported cases of Korsakoff patients with amnesia yet no MDN lesions (although these patients had significant lesions of the mammillary bodies). Thus, it may be that damage to *either* the MDN or mammillary bodies is necessary for the memory deficits.

Three observations have prompted a great deal of speculation, during the past two decades, about the neurochemical bases of Korsakoff s syndrome. First, a number of aminergic systems course through or near the sites of these brain lesions (Fadda and Rossetti, 1998) . Second, there is a long history of animal research demonstrating memory impairments following lesions or pharmacological manipulations that disrupt aminergic systems (see Mair and McEntee, 1983 for a discussion of this literature). Finally, there are preclinical neurochemical data demonstrating that conditions of thiamine deficiency can result in altered precursor transport, synthesis and turnover in several aminergic systems (see Witt, 1985, for a review).

Adrenergic Transmission and Korsakoff s Syndrome

The greatest focus on the aminergic components of Korsakoff s amnesia has been directed toward the brainstem locus coeruleus (LC) system and noradrenergic projections to telencephalon. While several reports indicate diminished noradrenergic transmission in Korsakoff s syndrome, the data are by no means consistent. CSF levels of the NE metabolite MHPG were reported to be reduced (by 41%) in a large group of Korsakoff s patients, even when corrected for plasma MHPG concentrations. Importantly, the reductions in MHPG from CSF correlated with the degree of memory impairments (McEntee et al., 1984). Nucleolar

volume of LC (a measure of activity within LC neurons) was found to be reduced in LC and post-mortem levels of NE were diminished in LC and target regions such as supraoptic and paraventricular nuclei (Mayes et al., 1988). As was the case with CSF levels of MHPG, the reductions in nucleolar volume in LC were greatest in those patients who were most amnestic.

There are, however, several studies that are not consistent with the above findings. Martin and colleagues (Martin et al., 1984) did not observe any change in CSF MHPG levels, nor did they find a correlation between MHPG levels and memory function when a larger sample size was studied. More recently, Halliday s group (Halliday et al., 1992) conducted a quantitative study of LC integrity comparing 4 uncomplicated alcoholics with 9 Korsakoff s patients. These authors report no group differences in the number, morphology, or distribution of pigmented LC neurons. Moreover, the analysis of LC neuronal number reveals a rather marked variability within the control group (s.d. = 20%) and a significant aging-related decline in neuronal counts. Thus, it may be premature to attribute the source of reductions of presynaptic markers of noradrenergic transmission to a loss of neuronal number within the LC. While it would appear that cell loss within the LC does not account for the amnesia seen in Korsakoff s syndrome, it still remains possible that other, more subtle, changes in adrenergic transmission are critical to the symptoms of this disease. The sources of variation among these collective studies are considerable and may contribute to the inconsistency of findings. First, the various neuroanatomical and neurochemical measures utilized in these studies (nucleolar volume of LC, number of LC neurons, morphology of LC neurons, CSF metabolite levels, and post-mortem NE tissue levels) differ in their capacity to reveal physiologically meaningful alterations

in noradrenergic transmission. Second, there is significant variation in the sample sizes in these studies. Given the inherent variability of neuropathology in human disease, studies with considerable differences in sample size will be expected to have very different statistical powers for revealing effects. Finally, the discussion above regarding the profile and distribution of lesions in the Korsakoff s syndrome does not support a uniform neuropathology - thus, there may be multiple variants of this syndrome that are reflected in differential contributions of particular aminergic systems.

Cholinergic Transmission and Korsakoff s Syndrome

The potential role of dysfunctions in cholinergic transmission in Korsakoff s amnesia has received significant attention and is justified by several observations. First, cholinergic blockade in healthy subjects produces memory impairments (Kopelman and Corn, 1988). Second, as described earlier in this chapter, there is a significant correlation between the well-established memory deficits and various markers of impaired cholinergic transmission in Alzheimer s dementia (Francis et al., 1985). This raises the possibility that other syndromes characterized by memory deficits are mediated by dysregulations in cholinergic transmission. Third, basal forebrain lesions accompanying certain vascular insults are accompanied by memory impairments (Damasio et al., 1985). Finally, biochemical data suggest that thiamine deficiency can eventually result in diminished levels of acetyl-CoA and reduced turnover of ACh (Barclay et al., 1981; Witt, 1985).

A more direct link between the basal forebrain cholinergic system and Korskoff s syndrome has been suggested by the observation of a significant reduction (47%) of the number of magnocellular neurons (presumably cholinergic) within the nucleus basalis of Meynert in autopsied brains from three patients (Arendt et al., 1983). However, reductions in basal forebrain neurons in Korsakoff s disease are not consistently reported. Mayes and colleagues (Mayes et al., 1988) conducted a series of post-mortem morphometric measurements on basal forebrain cholinergic nuclei from patients diagnosed with Korsakoff s prior to death. They report no reduction in number or nucleolar volume of basalis neurons, although the authors comment on the fact that many of these neurons were shrunken and exhibited a loss of Nissl substance. A more recent and complete analysis compared basal forebrain magnocellular neurons among controls, alcoholics, Wernicke s encephalopathy patients who did not present with amnesia, and Wernicke s patients who later developed a classical Korsakoff s amnesia (Cullen et al., 1997). Cell number (Ch4 cholinergic neurons) did not differ significantly between nonalcoholic controls and alcoholics. Ch4 cell number in the Wernicke s encephalopathy group was modestly, but significantly reduced (24%) below control levels. However, cell number was comparably reduced (21%) in the Wernicke s group that developed Korsakoff s syndrome. The authors conclude that nucleus basalis neurons are lost in thiamine deficient alcoholic patients, but that cell loss is relatively minor and does not account for the profound memory disorder seen in Korsakoff s syndrome. Furthermore, they raise the interesting possibility that this loss in Ch4 cell number might contribute to attentional dysfunctions seen in both Wernicke and Korsakoff patients.

Serotonergic Transmission and Korsakoff s Syndrome

An early study on serotonergic transmission in Korsakoff s syndrome reported abnormally low levels of the 5-HT metabolite 5-HIAA (21% decrease) in some, but not all patients (McEntee et al., 1984). Halliday and colleagues (Halliday et al., 1992) utilized more direct immunohistochemical techniques to compare the number of 5-HT-positive raphe neurons in alcoholics that manifested Korsakoff s syndrome with those that did not. While they report a significant (50%) reduction in the number of 5-HT-positive neurons, this value was similar in both groups of alcoholics. The relative contribution of alcohol toxicity vs thiamine deficiency on serotonergic neurons in the median raphe nucleus was addressed in a more recent report from this laboratory (Baker et al., 1996). The authors report no difference between the number of 5-HT neurons in alcoholics without Korsakoff s syndrome and age-matched controls. However there was a substantial loss (nearly 70%) of serotonergic neurons in brains from previously diagnosed Korsakoff s patients. These data suggest that the cell loss in the raphe reflects the thiamine deficiency rather than the effects of alcohol *per se.*

Dopaminergic Transmission and Korsakoff s Syndrome

The role of mesocortical and mesolimbic DA systems in the memory disorders associated with Korsakoff s syndrome has received little attention. This is somewhat surprising given the observation that chronic alcohol consumption is associated with reductions in rCBF and glucose metabolism in medial frontal lobe (Adams et al., 1993), and that dopaminergic systems exert important modulatory influences on cognitive activity mediated by frontocortical neurons (Dolan

et al., 1995). One study reported significant reductions (23%) in CSF levels of the DA metabolite HVA in Korsakoff s patients (McEntee et al., 1984). However, these results were not consistently seen in all patients and, unlike several of the reports with the NE metabolite MHPG, did not correlate strongly with memory impairments.

As discussed earlier, the therapeutic efficacy of drugs with relatively selective actions on specific transmitter systems can provide insights into the contributions, in this case, of aminergic systems to the memory disorders associated with Korsakoff s syndrome. The most extensively studied therapeutic agents for the treatment of Korsakoff s amnesia have been drugs that affect the monoamines, norepinephrine, dopamine and serotonin. McEntee and Mair (1980) compared the effects of twice daily oral administrations of clonidine (an $_2$ NE agonist), amphetamine (an indirect monoaminergic agonist), L-DOPA (an indirect monoaminergic agonist), and ephedrine (a NE agonist, with weak amphetamine-like actions) on memory performance in a small population of Korsakoff s patients. Clonidine treatment produced significant improvement, compared with placebo, on several items on the Wechsler memory scale (i.e. memory passages, visual reproduction). A SPECT imaging study tested the hypothesis that frontal lobe function would be increased by clonidine-induced adrenoreceptor stimulation and that the ability of clonidine to increase metabolic activity would correlate with the drug s ability to enhance memory function (Moffot et al., 1994). The acute administration of clonidine increased performance on a verbal fluency task, although this effect was variable and not always distinguishable from the effect of placebo. Nevertheless, the increase in neuropsychological performance was correlated with the increased metabolic activity in left dorsolateral frontal

cortex and, to a lesser extent, in posterior cingulate cortex and thalamus. However, a clinical trial with a larger group of subjects was unable to demonstrate a therapeutic effect of clonidine (O Carroll et al., 1993). McEntee and colleagues report smaller, and less consistent, effects with amphetamine (McEntee and Mair, 1980) and ephedrine (Mair and McEntee, 1986). Similar therapeutic effects on a verbal recall test were seen in six Korsakoff s patients following a week-long administration of the indirect adrenergic agonist methylphenidate (O Donnell et al., 1986). The effects of these adrenergic agonists must be viewed cautiously, however, as it is possible that drug-induced changes in attentional processing might account for some of the anti-amnesic effects of the drugs (McEntee and Mair, 1990). Finally, a possible role for dysfunctions in serotonergic transmission in Korsakoff s amnesia is supported by a study demonstrating that the 5-HT uptake inhibitor fluvoxamine enhanced memory in a small group of patients. Interestingly, the reported improvements of fluvoxamine correlated with the reductions in the CSF levels of the 5-HT metabolite 5-HIAA (Martin, 1989).

MDMA-induced memory deficits

Recreational usage of the illicit drug 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) first became highly visible in the mid-1980s. Its consumption has evolved worldwide so dramatically over the past two decades that it poses serious health risks. Demonstrations of MDMA-induced selective impairments in memory coupled with suggestions of neurotoxicological damage (particularly to brain serotonin systems) suggest that repeated consumption of MDMA promises to be increasingly seen as a diagnostic group in the future.

Consumption of MDMA is associated with profound effects on mood. Users generally report feelings of elation, energy, confidence, and enhanced sociability while on the drug. The period of withdrawal is associated with feelings of depression, lethargy, and irritability (Curran and Travill, 1997). A number of studies indicate that the psychological effects of MDMA extend beyond changes in mood to selective impairments in memory. Tests designed to evaluate general information processing speed (i.e. simple reaction time, choice reaction time, Sternberg task response time) and sustained attention reveal no significant differences between MDMA users and various control groups (Krystal et al., 1992; Parrott et al., 1998). However, a number of studies indicate significant impairments in a variety of tasks that assess memory function. MDMA users exhibit mild to moderate decrements, when compared to alcohol users (Curran and Travill, 1997), in working memory the initial and delayed paragraph test of the Wechsler Memory Scale (Krystal et al., 1992), and deficits in delayed and non-delayed word recall (Morgan, 1998; Parrott and Lasky, 1998).

One difficulty associated with ascribing performance deficits in these laboratory tasks to deficits in memory is that MDMA-users rarely report memory impairments. There have been several surveys of recreational MDMA-users and they have not revealed subjective evidence for memory deficits (see Krystal et al., 1992). In this regard, Parrott and colleagues (Parrott et al., 1998) raise the interesting possibility that perhaps these apparent memory deficits really reflect a change in cognitive strategy rather than memory deficits *per se*. Afterall, MDMA users do report a change to a more phenomenological, less verbal style not only when on the drug but for some time thereafter. Thus, future studies on neuropyschological function should be expanded

to include a range of non-verbal as well as verbal memory tasks and other measures of cognitive strategy.

The preclinical and clinical neurotoxicological literature suggests serious grounds for concern over repeated use of MDMA (ecstasy). Animal studies reveal damage to several markers of serotonin (5-HT)-containing neurons (decreased 5-HT and 5-HIAA) levels, diminished 5-HT uptake), particularly in hippocampus (Frederick and Paule, 1997; Steele et al., 1994). The reported impact on hippocampus is particlarly important given the vast literature implicating its role in memory processes (see Nadel and Bobbot, 2001 for a review). The human neurotoxicology literature, although less extensive, is entirely consistent with the animal studies. Levels of 5-HIAA in CSF are reduced in subjects who have a history of repeated MDMA use (McCann et al., 1994; Ricaurte et al., 1990). These decreases in CSF 5-HIAA correlate with the extent of memory impairments in abstinent MDMA users (Bolla et al., 1998). A PET imaging study found ecstasy users to have reduced 5-HT transporter binding in a number of brain regions, including frontal and temporal cortices (Szabo et al., 1997). Little is known about the effects of MDMA usage on post-synaptic 5-HT receptor function. A recent study (Reneman et al., 2000) has used SPECT imaging and the 5-HT_{2A} receptor ligand [^{123}I]-5-I-R91150 to assess the density of 5-HT_{2A} receptors and, importantly, to correlate changes in the density of this receptor with performance on a memory recall test. Although the sample sizes are small, there was a significant increase in the density of 5-HT_{2A} binding in occipital cortex in repeated MDMA users (cumulative consumption of at least 50 tabs) relative to controls. There was a strong negative correlation ($r = -0.98$) between performance on the word recall test and binding

in the MDMA group and no significant correlation in the control group. It is important to point out that the MDMA users in this study had been drug abstinent for 2-11 months (mean 4.6 months) prior to this study.

The demonstration of memory deficits in drug abstinent MDMA users raises the important issue of the permanency of these neuropsychological deficits. In addition to the SPECT study cited above (Reneman et al., 2000) the study by Parrott and Lasky (1998) was conducted 2 and 7 days after drug consumption, whereas the study by Krystal et al., (1992) tested MDMA users who had not taken the drug for an average of 66 days. Collectively, these investigations suggest that the memory deficits induced by repeated MDMA usage may be long-lasting or even permanent. If so, this leads to the chilling conclusion that the mild to moderate deficits reported in these studies represent only the tip of the iceberg, and that many of these users may remain at high risk for more severe aging-related memory deficits as they experience an age-related loss of 5-HT-containing neurons.

Future research in the area of MDMA-induced amnestic disorders will have to confront several methodological and interpretational challenges. First, as is the case with any study on an illicit drug, the illegal status of MDMA, and its potential neurotoxic effects, highly constrains experiments and precludes the use of more traditional double-blind, placebo-controlled designs. Second, it is often difficult to get pre-drug baseline performance data on cognitive tasks in the MDMA group (although see Parrott and Lasky, 1998 for an example of baseline performance in the drug group). Third, future studies should more carefully identify appropriate control groups

against which to compare the performance of the MDMA group. MDMA users tend to be poly-drug users and, thus, it is important to include control groups that have a history of use of several drugs (e.g. alcohol, cigarettes, cannabis, LSD, cocaine, inhalants) but not of MDMA. The comparison of MDMA-users to a poly-drug user control group was accomplished in Morgan (1998). Fourth, it will become important to determine how much MDMA needs to be consumed prior to the emergence of these memory deficits. This is a difficult issue to address. Parrott and Lasky (1998) state that their ...regular users were comparatively more impaired than the novice users... , however, it is not clear how these two groups were defined. In a different study, Parrott and colleagues (Parrott et al., 1998) found no differences in memory deficits between users who had consumed >10 tabs of MDMA vs those that had consumed <10 tabs. Finally, an issue confounding the specification of both the dose sufficient to produce memory deficits and the attribution of MDMA to such syndromes is the fact than MDMA tablets often contain impurities (e.g. ketamine) that affect both dose and also impair neuropsychological function in their own right (Parrott et al., 1998).

DELIRIUM

The DSMIV defines deliriums as a general disturbance in consciousness that gives rise to changes in cognition that are not related to an existing dementia or evolving dementia (American Psychological Association, 2000). Cognitive changes include disorientation (to time/space), reductions in awareness of the environment and impairments in the ability to focus, sustain, or shift attention. Memory (particularly of recent events) may also be temporarily impaired. The delirious state can also be associated with a number of other disorders, including, disturbances in

sleep-wake cycles, psychomotor activity, and emotion (anxiety, fear, depression, irritability).

Delirium typically develops over a short period of time (i.e. hours/days) with a fluctuating presence and severity. The two primary etiological conditions associated with delirium are a) general medical conditions (i.e. head trauma, vascular diseases, metabolic disturbances) and b) sustance-induced (i.e. medications, drugs, toxins). The discussion below will focus on the contributions of aminergic transmitter systems to delirium in elderly patient populations (50% of elderly patients may become delirious upon admission to hospitals) and following various medications (several substances that affect aminergic systems can induce delirium).

Cholinergic transmission and delirium

The link between cholinergic transmission and delirium has been fostered by three observations. First, it is generally believed that ACh plays an important role in the global cognitive disruption characteristic of delirium (Perry and Perry, 1995), including, decreases in wakefulness (Baghdoyan, 1997), and impairments in attentional processes (Sarter and Bruno, 1997). Second, medications with anticholinergic properties often precipitate episodes of delirium (see below). Finally, physostigmine (an indirect cholinergic agonist) has been shown to be effective in the treatment of delirium (Granacher et al., 1976).

A recent empirical study by Han and colleagues (Han et al., 2001) evaluated the

longitudinal association between the use of cholinergic medications and the severity of delirium in a large cohort of elderly medical inpatients with diagnosed delirium. They also determined whether this association is modified by the presence of dementia in delirious patients. The results indicated an increase in the severity of delirium associated with several measures of cholinergic medication but a pre-existing condition of dementia did not increase this association. However, this latter point requires additional study as most of these patients were only mildly demented and thus, cholinergic deficits may be less evident in these patients.

Another linkage between cholinergic deficiency and delirium has been revealed using a functional competitive binding assay for serum anticholinergic activity developed by Tune and Coyle (1981). The assay measures the ability of the patient s serum to block central muscarinic receptors. An association between delirium and elevated serum anticholinergic activity has been demonstrated in two studies of elderly medical patients (Flacker et al., 1998). The basis of the serum anticholinergic activity is not known, however, it is generally thought to reflect residual levels of medications or their metabolites. It should be pointed out, however, that there is a significant amount of overlap in the serum anticholinergic activity in delirious and non-delirious patients, suggesting the importance of other contributing factors.

In spite of these supporting observations, there are certainly some exceptions to the suggested relationship between cholinergic transmission and delirium (see Han et al., 2001 for a discussion of this issue). There are at least three factors that could account for such discrepant findings. First, different studies utilize different measures of ACh medication exposure (i.e.

serum ACh level, number and dose of cholinergic medications, aggregate risk score of ACh potency) and the relationship between these measures has not been clearly specified. Second, the effects of cholinergic medications on delirium may be confounded by other risk factors such as age, dementia, and a variety of comorbid conditions. Collectively, the evidence suggests that delirium is adequately viewed as a disorder based on multiple transmitter abnormalities. Additionally, various risk factors interact with neuropathological processes to produce heterogeneous symptoms of delirium (Flacker and Lipsitz, 1999).

Serotonergic transmission and delirium

A postulated role for 5-HT in delirium is not surprising, given the evidence, from both animal and human literatures, linking serotonergic transmission with several of the functions affected by delirium, such as, wakefulness, mood and cognition (Meneses, 1999). Interestingly, there are suggestions that delirium can be associated with either excessive activation or reduction in serotonergic transmission. Elevated levels of the 5-HT metabolite 5-HIAA have been reported in ill, delirious, nondemented patients when compared to control populations of healthy subjects as well as when compared to groups of non-delirious alcoholics and patients on antipsychotics (Banki et al., 1978). Consistent with these CSF findings, the literature contains reports of a serotonin syndrome characterized by confusion, restlessness and tremor. This syndrome can be precipitated by medications that act as 5-HT agonists such as, L-tryptophan, MAO inhibitors, and fluoxetine (Steiner and Fontaine, 1986).

Several reports have linked the occurrence of delirium with *reduced* serotonergic

transmission - or at least with reduced levels of tryptophan. Plasma tryptophan and tryptophan to large neutral amino acid ratios were significantly lower, post-surgery, in a group of delirious patients (van der Mast et al., 1996). Moreover, a retrospective study demonstrated that patients with early symptoms of delirium tremens exhibited improved Mini-Mental Status Exam scores, sleep/wake cycle, and reduced tranquilizer use following daily treatments with L-tryptophan (Hebenstreit et al., 1989).

Dopaminergic transmission and delirium

Finally, abnormalities in dopaminergic transmission have also been linked to delirium and acute confusion. Dopamine agonists such as L-DOPA (Birkmayer, 1978), pergolide (Cummings, 1991), and buproprion (Golden et al., 1985) have been reported to lead to delirium. In some cases, dopaminergic antagonists such as haldol are effective in relieving the symptoms of delirium.

CONCLUSIONS

A review of the available clinical literature clearly reveals multiple dysregulations in aminergic transmission accompanying a wide range of cognitive disorders. However, there is considerable variation in the consistency and magnitude of some of these linkages. These discrepancies no doubt reflect at least two interacting variables. First, the individual cognitive disorders are indeed syndromes with multiple neuropathologies and etiologies. Thus, it is not

surprising that transmitter profiles vary within heterogeneous, and often small groups of patients. Second, there is a wide range of methodologies used to characterize the integrity of aminergic systems accompanying these cognitive disorders. One obviously is constrained when assessing neurochemistry in clinical populations and care should be taken in comparing data obtained by such discrepant and often indirect measures. Nonetheless, there is little doubt that deficits in adrenergic transmission correlate well with neuropsychological performance in a number of cognitive disorders. The challenge facing us now is to better understand the relationships between damage to a particular transmitter system within a brain region and deficits in the various psychological functions that characterize these cognitive disorders.

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