Neurorehabilitation of executive function

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The clinical neuropsychological literature includes under the rubric of “executive function” a wide range of cognitive processes such as focused and sustained attention, fluency and flexibility of thought in the generation of solutions to novel problems, and planning and regulating adaptive and goal directed behavior (Luria, 1966; Hecaen and Albert, 1978; Lezak, 1995). As evident by the wide scope of these processes, executive function has been used to capture the highest order of cognitive abilities. Such abilities are sometimes not only difficult to operationally define but difficult to measure, which has led to a large number of clinical and experimental neuropsychologic tests that have been developed as an attempt to tap this range of abilities (Spinn and Strauss, 1991; Lezak, 1995). Evidence from neuropsychologic, electrophysiologic, and functional neuroimaging research supports a critical role of the frontal lobes (specifically the prefrontal cortex) in executive control of goal-directed behavior (Fuster, 1997). The extensive reciprocal frontal lobe connections to virtually all cortical and subcortical structures places the frontal lobes in a unique neuroanatomic position to monitor and manipulate diverse cognitive processes.

Several neurologic disorders can cause predominantly frontal lobe damage, and in patients with these disorders, executive dysfunction is the predominant finding on examination. These disorders include traumatic brain injury, vascular compromise, neoplasms, herpes encephalitis, epilepsy, and neurodegenerative disease. Thus, very different etiologies of frontal lobe damage can produce a common set of behavioral and cognitive findings. Moreover, several of these disorders are quite prevalent (e.g., traumatic brain injury and stroke) highlighting the need to develop therapeutic strategies for compensating or alleviating executive function deficits. Although much progress has been made in remediation of sensorimotor deficits after injury, cognitive therapy remains a challenge, and excluding language function, little progress has been made with effective therapies for improving high-level cognitive abilities such as executive function.

This chapter will begin by describing the cognitive deficits observed in patients with frontal lobe damage, which has resulted in the concept of the “dysexecutive” syndrome. Next, we will review cognitive models of executive dysfunction, which can serve as a foundation for developing potential therapeutic approaches. Finally, we will review current cognitive and pharmacologic approaches towards treating executive function impairments.

30.1 The dysexecutive syndrome

Extensive frontal lobe damage may have little impact on the abilities measured by standardized intelligence tests, or other standard neuropsychologic tests, but this common observation is in marked contrast to the way that these patients perform in unintelligent ways in real life (Shallice and Burgess, 1991). The following is a brief review of the types of...
cognitive deficits that are observed in patients with frontal lobe damage, which has been called the “dysexecutive syndrome” (Table 30.1).

**Inability to initiate, stop, and modify behavior in response to changing stimuli.** The inability of patients with frontal lobe damage to alter their behavior in response to changing rules is reflected by poor performance on a commonly administered neuropsychologic measure called the Wisconsin Card Sorting Test (Berg, 1948). During this test, four stimulus cards (one with a red triangle, one with two green stars, one with three yellow crosses, and one with four blue circles) are placed in front of the patient (see Fig. 30.1). The patient is then given a deck of response cards, each card containing from one to four identical figures (stars, triangles, crosses, or circles) in one of four colors. The patient is instructed to place each response card next to one of the four stimulus cards according to one of the stimulus dimensions (i.e., color, form, or number). However, the patient is not told the correct sorting principle, but rather must infer this from the examiner’s feedback after each response. After 10 correct sorts by the patient, the examiner changes the sorting principle without warning by saying “incorrect” to previously “correct” trials. Almost invariably, patients with frontal lobe lesions understand what they are supposed to do, and can repeat the rules of the test (“I am supposed to arrange these by color, shape, or number”). Moreover, since four stimulus cards are always visible, patients do not have to remember the sorting principles. However, frontal lobe patients are unable to follow them or use knowledge of incorrect performance based on feedback to alter their behavior (Milner, 1963; Damasio, 1985).

**Inability to handle sequential behavior necessary for organization, planning, and problem-solving.** Simple daily tasks require many steps. Notably, patients with frontal lobe lesions often do not have difficulty with the individual steps that are necessary to complete a sequential task. For example, these patients can easily perform the basic operations (e.g., adding and subtracting) required to complete complex arithmetic tasks. However, when given more complex problems requiring multiple steps, the patient responds impulsively to an early stimulus.

**Table 30.1. Clinical features of the dysexecutive syndrome.**

- Inability to initiate, stop, and modify behavior in response to changing stimuli.
- Inability to handle sequential behavior necessary for organization, planning, and problem-solving.
- Inability to inhibit responses.
- Perseveration.
- Impaired working memory and strategic aspects of episodic memory.

**Figure 30.1.** During the Wisconsin Card Sorting Task, four stimulus cards (e.g., one with a red circle, one with two yellow squares, one with three green triangles, and one with four blue crosses) are placed in front of the patient (top row, depicted here in shades of grey). The patient is then given a deck of response cards (bottom row), each card containing from one to four identical figures (stars, triangles, crosses, or circles) in one of four colors. The patient is instructed to place each response card next to one of the four stimulus cards according to one of the stimulus dimensions (i.e., color, form, or number).
and fails to analyze or execute the component steps required for problem solution (Stuss and Benson, 1984). The following task: "The price of canned peas is two cans for $1.00. What is the price of one dozen cans?" is almost impossible for patients with frontal lobe damage even though they can perform the direct arithmetic task of multiplying $6$ times $31$ with ease. Similar errors occur in everyday tasks that require a series of simple steps such as wrapping a present or making a sandwich (Schwartz et al., 1998).

*Inability to inhibit responses.* The inability to inhibit prepotent responses and filter out distracting information can be revealed with a neuropsychologic test called the Stroop paradigm (Stroop, 1935). This test is based on the observation that it takes less time to read color names (e.g., blue, green, red, and yellow) printed in black type than to read color names printed in a colored ink of a different color (e.g., the word "green" printed in red). This effect is exaggerated in patients with frontal lobe lesions, especially with damage to superior medial regions (Stuss and Benson, 1986), presumably owing to an impaired ability to inhibit the interference created by reading color names printed in an incongruent ink color. A related phenomenon is that frontal patients may display a remarkable tendency to imitate the examiner's gestures and behaviors even when no instruction has been given to do so, and even when this imitation entails considerable personal embarrassment. The mere sight of an object may also elicit the compulsion to use it, although the patient has not been asked to do so and the context is inappropriate, as in a patient who sees a pair of glasses and puts them on, even though he is already wearing his own pair. These symptoms have been called the "environmental dependency syndrome." It has been postulated that the frontal lobes may promote distance from the environment and the parietal lobes foster approach toward one's environment. Therefore, loss of frontal inhibition may result in overactivity of the parietal lobes. Without the frontal lobes our autonomy from our environment would not be possible. A given stimulus would automatically call up a predetermined response regardless of context (Lhermitte, 1986a; Lhermitte et al., 1986b).

**Perseveration.** This is defined as an abnormal repetition of a specific behavior. It can be observed in patients after frontal lobe damage in a wide range of tasks including motor acts, verbalizations, sorting tests, drawing, or writing. Several different types of perseverative behavior have been described in patients with brain damage such as (1) recurrent perseveration which is the recurrence of a previous response to a subsequent stimulus within the context of an established set, (2) stuck-in-set perseveration which is the inappropriate maintenance of a category or framework of activity, and (3) continuous perseveration which is the abnormal prolongation or continuation without cessation of a current behavior (Sandson and Albert, 1987).

**Impaired memory function.** Working memory is the short-term storage of information that is not accessible in the environment and the set of processes that keep this information active for later use in behavior (Baddeley, 1986). This system is critically important in cognition, providing a critical physiologic infrastructure for such functions as reasoning, language, comprehension, planning, and spatial processing. Animal and human studies have linked this ability to the prefrontal cortex by demonstrating that frontal lesions impair working memory and normal individuals performing working memory tasks activate prefrontal cortex (Goldman-Rakic, 1987; Fuster, 1997; D'Esposito, 2001). In contrast with this severe working memory impairment, patients with frontal lobe lesions have little impairment on tasks of information storage over longer periods of time. However, frontal patients often appear "forgetful" to family members. This impairment may result from inefficiencies caused by poor attention or poor "executive" function (Shimamura et al., 1991). This type of memory deficit is due to defective retrieval, a function that requires strategy and effort, as opposed to normal storage, a more passive function. There are several other interesting features of these "real-life memory" difficulties. They are defective in recall of temporal order, that is, recalling the context of learned items, even when they can remember these items. For example, a patient instructed to remember words spoken by either a male or a female speaker may later...
recall or recognize most of the words but cannot correctly identify the speaker. Patients with frontal lobe lesions also do poorly at tasks requiring them to judge the probability that they would recognize the correct answer to a multiple-choice question (e.g., a feeling of knowing), reflecting deficient self-monitoring abilities (Janowsky et al., 1989). In addition, there is a frequent failure at carrying out an intended action, a process know as prospective memory: “remembering to remember” (Fortin et al., 2003). In summary, patients with prefrontal cortical lesions are impaired in the processes involved in planning, organizing, and other strategic aspects of learning and memory that facilitate encoding and retrieval of information.

Together, the range of deficits described above that are observed in patients with frontal lobe damage captures the essence of the dysexecutive syndrome. However, the dysexecutive syndrome cannot be considered unitary given the diverse nature of these deficits. Moreover, any single patient with a frontal lobe lesion may exhibit some of these behavioral deficits and not others. Based on clinical observations, there are two major behavioral/cognitive syndromes (Cumming, 1993) that occur after damage to different regions of the prefrontal cortex (e.g., dorsolateral versus orbitofrontal). These syndromes reflect separable circuits of connections of the prefrontal cortex with subcortical structures. Only damage to the dorsolateral prefrontal cortex causes the most severe impairments in executive dysfunction, as described in this chapter. In contrast, damage to the orbitofrontal cortex, which is intimately connected to the limbic system, spares many cognitive skills but dramatically affects all spheres of social and emotional behavior (Bechara et al., 1998; Stone et al., 1998). The orbitofrontal patient is frequently impulsive, hyperactive, labile, and lacking in proper social skills despite showing reasonable performance on cognitive tasks typically impaired in patients with damage to dorsolateral prefrontal cortex. Careful characterization of the type of deficits observed in patients with frontal lesions has allowed for the development of cognitive models of executive function that will be discussed next.

### 30.2 Cognitive models of executive function

Two broad cognitive models of executive function exist: those that propose that there is a distinct and dedicated executive control system that directs and monitors the activities of lower level systems in order to guide behavior and those that posit that there is not a dedicated “executive controller” in the brain but rather executive control emerges from the maintenance of task rules and goals. Regardless of the exact nature of the psychologic constructs of models of executive control, proponents of both types of models have reached consensus that these types of processes are likely implemented by the frontal lobes. Each of these cognitive models will be discussed briefly since such models can serve as a foundation for developing therapeutic strategies for treating patients with executive function deficits.

Based on behavioral studies of normal subjects, Baddeley first proposed the existence of a “central executive system” which actively regulates the distribution of limited attentional resources and coordinates information within limited capacity verbal and spatial memory buffers (Baddeley, 1992, 1986). The concept of the central executive system was based on the analogous “supervisory attentional system” introduced by Norman and Shallice (Shallice, 1988) that was proposed to take control over cognitive processing when novel tasks are involved and when existing habits have to be overridden. Thus, in this conceptualization of executive function, there is a dedicated portion of the brain (likely within the frontal lobes) for this set of cognitive operations. However, these models also allow for the possibility that there are many different types of control processes (i.e., updating, shifting, and inhibition) that may have separable neural substrates.

Since these control processes are proposed to have a limited capacity, each additional cognitive operation that a subject performs at one time places increasing demands on this executive control system. For example, two tasks that are performed sequentially will make minimal demands on executive control processes since these tasks can be performed
successfully by using separate processing systems. However, two tasks performed concurrently will lead to a decrement in performance, as compared to performance on either task alone, since dual-tasking requires similar processing systems and will make greater demands on executive control processes. This finding from the experimental psychology literature parallels our experience in everyday life — there is clearly a limit to how many tasks one can perform at any one time before performance suffers. Just imagine your ability to fully comprehend and remember what is being told to you while talking on your mobile telephone while driving your car. Importantly, performance on dual-tasks has been shown to be impaired in patients with frontal lobe lesions (Baddeley et al., 1997; McDowell et al., 1997), and activation of the frontal lobes has been demonstrated with functional neuroimaging in healthy young subjects when performing dual tasks (D’Esposito et al., 1995; Szameitat et al., 2002).

Other models of executive function derive from research attempting to understand frontal lobe function and rely on a more unified approach. For example, Fuster (Fuster, 1985, 1997) has proposed that the prefrontal cortex is critically important in tasks that require the temporal integration of information. In proposing his model, Fuster argues explicitly against the interpretation of a homuncular view of executive control writing that “the prefrontal cortex would not superimpose a steering or directing function on the remainder of the nervous system, but rather, by expanding the temporal perspectives of the system, it would allow it to integrate longer, newer, and more complex structures of behavior.” Likewise, Cohen and Servan-Schreiber (Cohen and Servan-Schreiber, 1992) propose that frontal lobe damage results in “a degradation in the ability to construct and maintain an internal representation of context, [by which] we mean information held in mind in such a form that it can be used to mediate an appropriate behavioral response.” In their model, disordered performance in executive function is seen as a consequence of a change to a single low-level parameter. In this way, two behaviors which appear outwardly different as indexed by poor performance on seemingly different tasks (such as the Stroop paradigm and Wisconsin Card Sorting Test) may have their roots in similar fundamental processes. Other have similar ideas (Kimberg and Farah, 1993), proposing that executive dysfunction is due to a weakening of associations among working memory representations, including mental representations of internal goals, stimuli in the environment, and stored declarative knowledge.

Consideration of these cognitive models may have implications for developing strategies for rehabilitation of executive function. If there are separable executive control processes with independent neural substrates, it may be necessary to develop therapies that target each of these individual component processes independently. Alternatively, executive function emerges from the maintenance of task rules and goals, it is possible that approaches that aim to improve one underlying function may lead to the improvement of other more specific abilities.

30.3 Rehabilitation of executive dysfunction

Intact executive function is essential for most practical skills and impaired executive function is extremely debilitating for both patients and their families. Despite considerable effort by clinicians and researchers to develop rehabilitation strategies for impaired individuals, the path toward effective treatment has been fraught with difficulty and has often yielded disappointing results. Two main approaches, cognitive therapy and pharmacologic intervention, are possible for improving executive function.

Cognitive therapies

It is challenging to develop a standard cognitive therapeutic approach for executive function impairments for several reasons. First, as we have discussed, there are a wide variety of deficits that can result from frontal lobe injury that fit into the rubric of executive disorders (e.g., planning, inhibition, initiation, and self-awareness). Second, there are multiple neurologic conditions that can result in frontal
lobe damage (e.g., traumatic brain injury, stroke, and encephalitis). Third, many patients with frontal lobe injury exhibit behavioral deficits such as a lack in self-awareness, poor motivation, or mood disorders that cause a serious impediment to the rehabilitation process. Thus, it is difficult to generalize rehabilitation interventions for such diverse cognitive and behavioral deficits, and such unique patient populations. As a result, many different techniques have been developed, and research studies testing the validity of such techniques are usually presented as case studies describing interventions on individual patients or small series of cases. This leads to uncertainty that these techniques are generalizable.

These limitations as well as different cognitive models of executive function have led to a divergence in the general approach taken by rehabilitation specialists. There are two primary approaches in executive function rehabilitation; a focus on improvement of a real-life function in a particular setting, such as driving skills, or on a specific type of executive deficit as measured in the laboratory, such as selective attention (Mateer, 1999b). The goal of both of these approaches is that the interventions will eventually generalize across settings and skills. The specific rehabilitation strategy then employed, regardless of the general approach, falls within three distinct but overlapping categories: environmental manipulation, training of compensatory techniques, and direct interventions aimed at improving the underlying deficit (Mateer, 1999b). Environmental manipulation focuses on factors external to the patient, such as decreasing distracters, simplifying task demands or allowing more time and eliminating the need to do certain tasks. Compensatory techniques are devised to allow the patient to accomplish a task in a new manner that minimizes the impaired skills, such as encouraged use of organizers/planners or increasing self-awareness. Direct interventions attempt to restore the same skills that are affected by the damage. This is primarily accomplished via repetitive training exercises providing structured practice. The selection of a strategy is usually made on the basis of the type and severity of the deficit, level of self-awareness, and the degree of environmental dependency.

Despite the variety of approaches and strategies, the overall goal is the same—to improve the functioning of individuals in the setting that they live and work by transitioning them from a dependent, externally monitored state to one that is independent and internally monitored. Likewise, the overall organization of a rehabilitation plan is fairly uniform: (1) evaluate the individual's cognitive and behavioral profile, (2) assess the impact on real-life functioning, (3) establish specific, individualized goals, (4) select an intervention strategy, (5) formulate and deliver the plan, and (6) monitor and evaluate the effectiveness of treatment, making adjustments as necessary (Mateer, 1999a, b).

The approach of addressing impairments in specific executive symptoms has been the focus of considerable effort and has utilized many of the strategies described above. A review of the literature reveals that many of the interventions directed at impaired initiation, behavior sequencing, and inhibitory control have employed environmental manipulations and compensatory strategies while those addressing impairments in focused, sustained, selective, alternating, and divided attention, in working memory and prospective memory have often utilized direct interventions (see Table 30.2 for representative examples of published interventions). A comprehensive review of all published reports studying the rehabilitation of executive function is beyond the scope of this chapter. However, it may be helpful to explore several examples of the different rehabilitation options offered by these different strategies.

Environmental manipulations while employing factors external to the patient have no expectations of changing the patient's capacities or abilities. Although it may be an effective strategy for improving function, it places great demands on other individuals and is inflexible. Unlike compensatory strategies and direct interventions, environmental manipulations have not often been investigated in a formal manner; however a recent review outlines available external cueing devices for patients with initiation problems and prospective memory deficits, and offers recommendations for their use, identifies factors important for
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Table 30.2. Representative examples of published rehabilitation interventions directed at improving deficits in different executive functions. Interventions directed at impaired initiation, behavior sequencing, and inhibitory control have employed environmental manipulations and compensatory strategies while those addressing impairments in focused, sustained, selective, alternating, and divided attention, in working memory and prospective memory have often utilized direct interventions.

<table>
<thead>
<tr>
<th>Impaired executive function</th>
<th>Published study</th>
<th>Rehabilitation techniques</th>
</tr>
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<tbody>
<tr>
<td>Initiation and sequencing of behaviors</td>
<td>Craine, 1982</td>
<td>Training specific behavioral sequences for highly repetitious activities (e.g., grooming dressing). Cues and checklists extensively used.</td>
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<tr>
<td></td>
<td>Sohlberg, 1988</td>
<td>Self-analysis cues encouraged awareness of lack of initiation and led to more initiation.</td>
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<td></td>
<td>Gervin, 1991</td>
<td>Paired external cues (song lyrics) with a recorded tempo and melody used to help pacing.</td>
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<td></td>
<td>Burke et al., 1991</td>
<td>Job training by organization of daily tasks to be completed in the same order each day.</td>
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<tr>
<td></td>
<td>Schwartz et al., 1995</td>
<td>A system of coding errors of action.</td>
</tr>
<tr>
<td>Inhibitory control</td>
<td>Alderman and Ward, 1991</td>
<td>Response-cost paradigm: tokens exchanged for rewards and tokens lost for negative behaviors.</td>
</tr>
<tr>
<td>Attention and working memory</td>
<td>Sohlberg and Mateer, 1987</td>
<td>AFT: auditory and visual tasks to exercise and challenge focused, sustained, selective, alternating, and divided attention.</td>
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<tr>
<td></td>
<td>Gray et al., 1992</td>
<td>Computerized-attention retraining: reaction time (RT) training, rapid number comparison, digit symbol transfer, alternating Stroop program, and divided attention tasks.</td>
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<tr>
<td></td>
<td>Sturm et al., 1997</td>
<td>Computerized-adaptive training programs for alertness and selective and divided attention.</td>
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<tr>
<td></td>
<td>Schmitter-Edgcombe and Beglinger, 2001</td>
<td>Consistent mapping (responding to same class of stimuli) training results in improved automatic attention response.</td>
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<td></td>
<td>Cicerone, 2002</td>
<td>Task treatments derived from working memory experimental procedures: &quot;n-back&quot;, random generation, dual-task procedures, and emphasized deliberate use of attention strategies – improved attention, and working memory.</td>
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<td></td>
<td>Brooks et al., 2003</td>
<td>Virtual reality training promotes procedural learning in people with memory impairments.</td>
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<td></td>
<td>Mazer et al., 2003</td>
<td>Visual attention training and visuoperceptual training improve driving performance (no difference).</td>
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<tr>
<td>Prospective memory</td>
<td>Sohlberg et al., 1992a, b</td>
<td>Prospective memory training; repetitive sessions designed to increase time after instruction patient remembers to carry out planned action.</td>
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<tr>
<td></td>
<td>Van den Broek et al., 2000</td>
<td>Electronic memory aid to manage prospective memory errors.</td>
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<tr>
<td></td>
<td>Tam et al., 2003</td>
<td>Computer software and on-line tele-communication to improve skills.</td>
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selecting a particular device, and suggests ways to monitor their efficacy (O'Connell et al., 2003).

An example of the compensatory techniques is the response–cost procedure developed by Alderman and colleagues (Alderman and Ward, 1991). It is used to treat problems with disinhibition, such as repetitive speech and aggressive behavior. In this paradigm, the patient is given tokens that can be exchanged for a
reward, however each time the patient violates a rule set forth by the therapist they lose a token and eventually may drop below a set point to receive the reward. This technique has shown to be successful where as other paradigms such as “time-outs” and positive reinforcement were not (Alderman et al., 1995). Compensatory approaches for impairments in sequencing of actions, as outlined by Schwartz and colleagues (Schwartz, 1995), include a system of coding errors of action, which assists individuals in recognizing errors in omission or order and is transferred to improvements in daily functioning. Compensatory strategies such as these often rely on factors external to the patient, similar to environmental manipulation, but attempt to change the underlying behavior, frequently by attempting to improve self-awareness.

Another type of compensatory approach is substituting an entirely new behavior or skill, such as the use of a memory device. A memory journal training protocol was developed to instruct patients on how to compensate for prospective memory impairments (Donaghy and Williams, 1998). Additionally, technologic advancements are making an impact in this area as a recent survey revealed that 36% of physicians treating traumatic brain injury advocate portable electronic memory devices for their patients (O’Neil-Pirozzi et al., 2004), although cost has been identified as a significant barrier (Hart et al., 2003). New electronic aids are being developed explicitly to aid in the rehabilitation of prospective memory impairment (van den Broek et al., 2000).

Strategies employing direct interventions probably occupy the largest extent of the executive rehabilitation literature. An example of a frequently used intervention is Attention Process Training (APT) (Sohlberg et al., 1992a, b), although other commercially available programs exist. The rationale is that practice on graded tasks of attention will promote recovery of damaged neural pathways in patients and result in a restoration of attention abilities that can be applied in multiple settings. The goal is to re-train attentional abilities by the completion of a repetitive series of auditory and visual exercises over 1 to 2 months. The tasks proceed in a hierarchic fashion of escalating difficulty, feedback is provided and different types of attention are addressed: focused, sustained, selective, alternating, and divided. A controlled study of 23 traumatically brain-injured (TBI) patients was designed to evaluate the effectiveness of the APT program (Park et al., 1999). It was found that although there was significant improvement in the TBI group before and after training, there was no difference when compared to the control group.

A recent meta-analysis further evaluated all studies that used such direct intervention techniques, not just the APT. Specifically, it compared the results of studies that only evaluated pre- and post-training performance in patients to those that also incorporated control subjects (Park and Ingles, 2001). Thirty studies with a total of 359 participants met the authors’ selection criteria. The analysis revealed that studies that did not use control comparisons revealed large effect sizes while those studies with control comparisons tended to be non-significant, thus suggesting the positive effects of training were the result of practice effects on the tests. This serves to highlight the methodologic significance of establishing controls to assess practice effects when designing studies to evaluate the effectiveness of any intervention. It is important to note, however, that further analysis of individual studies revealed that patients with significant frontal lobe injury were able to learn a variety of specific skills through practice despite the minimal evidence for direct retraining of general attentional processes. This finding was also supported by encouraging results in several studies that have directly focused on the less common approach of specific-skill training, such as the training of activities of daily living (ADLs) (Carter et al., 1983) and driving (Kewman, 1985), suggesting that rehabilitation focused on specific, important skills to the patient might be a powerful rehabilitation approach. Although large-scale studies are beginning to appear, it is clear that further controlled studies employing combinations of the two approaches, specific-skill training and process re-training, that also utilize combinations of the three strategies are needed to help direct the practice of executive rehabilitation in patients with frontal lobe damage.
Technologic innovations, such as virtual reality (Brooks and Rose, 2003) and tele-rehabilitation (telecommunication combined with on line software) (Tam et al., 2003) have also started to make its mark on the rehabilitation of cognitive deficits through direct interventions. Although currently applied to memory deficits, these approaches are fertile areas for rehabilitation directed at executive impairments.

Pharmacologic therapies

The function of the cerebral cortex is clearly influenced by the diffuse inputs from brainstem neuro-modulatory systems mediated by neurotransmitters such as dopamine, acetylcholine, and serotonin. Based on the anatomic distribution of brainstem dopaminergic projections (see Fig. 30.2), there is a logical basis for proposing a role for dopamine in prefrontal cortical function (for a review, see Arnsten, 1997). The mesocortical and mesolimbic dopaminergic systems originate in the ventral tegmental area of the midbrain and project to prefrontal cortex, anterior cingulate cortex, anterior temporal structures such as the amygdala, hippocampus, and entorhinal cortex and the basal forebrain (Bannon and Roth, 1983). Also, there is an anterior/posterior gradient in the brain for the concentration of dopamine where it is highest in the prefrontal cortex (Brown et al., 1979).

The functional importance of dopamine to prefrontal function has been demonstrated in several ways. First, in monkeys depletion of dopamine in the prefrontal cortex or pharmacologic blockade of dopamine receptors induces impairment in working memory tasks (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991). This working memory impairment is as severe as in monkeys with lesion of the prefrontal cortex, and is not observed in monkeys in which other neurotransmitters, such as serotonin or norepinephrine, are depleted. Furthermore, dopaminergic agonists administered to these same monkeys reverses their working memory impairments (Brozoski et al., 1979; Arnsten et al., 1994).

Studying Parkinson's disease (PD) patients "on" and "off" their dopaminergic replacement medication has also made the link between dopamine and prefrontal function. In several studies, PD patients have been found to be impaired on tasks thought to be sensitive to frontal lobe function when they were off their dopaminergic medications (Cooper et al., 1992; Lange et al., 1995; Fournet et al., 1996; Gotham et al., 1980). In one study, the tasks performed poorly by PD patients (the Tower of London, a spatial working memory task, and a test of attentional set-shifting) have also been shown to be specifically impaired in patients with frontal lobe lesions (Lange et al., 1992). This evidence for a specific role of dopamine in prefrontal function is strengthened by the concurrent findings that PD patients perform similarly on and off their medications on long-term memory tasks thought to be sensitive to medial temporal lobe function.

Administration of dopamine receptor agonists to healthy young subjects, which stimulate dopamine receptors in the same way dopamine does, also provides a viable method for examining the role of dopaminergic systems in higher cognitive functions.

![Figure 30.2. Schematic illustration of three brainstem dopaminergic projection systems. The mesocortical and mesolimbic dopaminergic systems originate in the ventral tegmental area of the midbrain and project to prefrontal cortex, anterior cingulate cortex, anterior temporal structures such as the amygdala, hippocampus, and entorhinal cortex and the basal forebrain. The nigrostriatal dopaminergic system originates in the substantia nigra and projects to the striatum.](image-url)
in humans. Healthy young human subjects when given bromocriptine (D-2 receptor agonist) (Luciana et al., 1992; Luciana and Collins, 1997), or pergolide (D-1 and D-2 receptor agonist) (Müller et al., 1998) perform better on working memory tasks when compared to when they are given a placebo. In these studies, the dopaminergic medication had a very specific effect on working memory since it had no effect on other cognitive abilities such as attention or sensorimotor function. Converging on these findings, normal subjects that were administered sulpiride, a D2 receptor antagonist, were impaired on several tasks sensitive to frontal lobe function. Importantly, the impairments could not be accounted for by generalized sedative or motoric influences of the medication (Mehta et al., 1999).

Interestingly, in another study, the effects of bromocriptine on prefrontal function were not the same for all subjects, but interacted with the subject's working memory capacity (Kimberg et al., 1997). Subjects with lower baseline working memory abilities off the drug, tended to demonstrate cognitive improvement on the drug, while those with higher baseline working memory abilities worsened. A similar relationship between dopamine and prefrontal function has been observed in monkeys administered dopaminergic agonist and antagonists. Specifically, a U-shape dose–response curve is observed demonstrating that a specific dosage produces optimal performance on working memory tasks (Arnsen, 1997). This observation suggests that “more” is not “better” but rather there is an optimal level of dopamine concentration that is necessary for optimal function of the prefrontal cortex.

Although these preliminary studies in normal humans are encouraging, there have only been a few studies that have attempted to improve prefrontal deficits in patients. For example, in one such study (McDowell et al., 1998), patients who suffered prefrontal damage from traumatic brain injury were assessed on and off bromocriptine while performing several clinical experimental measures of executive function (e.g., Stroop task, the Wisconsin Card Sorting Task, the trail-making task, dual-task). Significant improvement in performance of traumatic brain injury patients was observed on bromocriptine, as compared to placebo, on all tasks requiring executive control processes. In contrast, bromocriptine did not improve performance on measures with minimal executive control demands, even if they were cognitively demanding, or other simpler tasks requiring basic attentional, mnemonic, or sensorimotor processes. This pattern of findings provides evidence that the dopaminergic system may specifically modulate executive control processes, and may not be critical for basic mnemonic processes. In another study (Powell et al., 1996), 11 patients with traumatic brain injury or subarachnoid hemorrhage (2 months to 5 years previously) were treated with bromocriptine for a long duration. Bromocriptine treatment was followed by improvement in motivation, which was maintained after withdrawal of the medication in eight of the patients. Finally, in a study of eight patients with vascular or degenerative dementia (Imamura et al., 1998), a 25-day treatment of 10 mg of bromocriptine resulted in reduced perseveration, whereas general attention and overall cognitive function was not affected by the medication.

An important priority for future research should be to further study the effect of dopaminergic drugs on prefrontal function both in healthy young subjects and those with frontal lobe disorders. Based on the studies thus far, dopaminergic pharmacologic intervention may be viable complement to the cognitive therapy in helping to alleviate executive dysfunction.

### 30.4 Conclusions

Executive function is a concept meant to capture the highest of cognitive abilities. The type of cognitive operations thought to be “executive” in nature allow us to control the enormous number of internal and external representations available to us necessary to guide our behavior in real time, either moment-by-moment or year-by-year. The neural basis of these executive control processes are beginning to mapped out, both on a neuroanatomic and neurochemical level, using sophisticated cognitive neuroscience methodology such as functional magnetic resonance
imaging (MRI). Improved understanding of the physiological basis of executive function will lead to a narrower and more useful view of prefrontal cortical function that will hopefully allow the development of new therapies, both cognitive and pharmacological, in patients with specific cognitive difficulties from damage to this critical region of the brain.

REFERENCES


