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Rehabilitation of frontal lobe functions

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Introduction

- Frontal lobe brain damage, which is highly prevalent, can have devastating effects on life quality. Yet the functions of the frontal lobes are difficult to define, variable and pose unique challenges to rehabilitation workers.

The cognitive and behavioral changes subsumed under the labels "the frontal lobe syndrome" or "executive dysfunction" are among the most challenging to rehabilitation workers. These heterogenous capacities are subject to multiple and varying definitions. Their expression varies widely across and within patient groups as well as within a single individual tested on multiple occasions. Rehabilitation of these capacities is hampered by the lack of insight among patients. Many such patients are impaired in real-life situations, but not in the laboratory, further challenging the implementation of interventions specific to patients' true handicaps.

Nonetheless, frontal lobe functions are critical to adaptive functioning, including complex information processing, decision making and social interaction. Indeed, they are considered important in the differentiation of higher from lower species. Deficits in these functions can cause marked handicap, to the point of devastating functional independence. The complexity of these capacities renders them highly sensitive to brain changes. The prevalence of frontal or executive dysfunction is therefore very high, affecting patients' engagement with all forms of rehabilitation.

In this chapter, we begin by clarifying a framework of frontal lobe functions meant to organize existing studies and to pose questions for future research. We also describe the most common causes of frontal dysfunction. We follow with a review of the literature on rehabilitation of these functions, updated from a previous review (Turner & Levine, 2004). We then close with implications for future research and clinical recommendations.

Frontal lobe functions: four functional domains

- The capacities associated with the frontal lobes (more precisely, the prefrontal cortex) are involved in higher-level cognition, behavioral control, attention and social functioning.
- The association of these functions with the frontal lobes is incomplete; posterior, diffuse and nonstructural damage can mimic the effects of frontal damage.
- In focal lesion patients, there is no evidence for a generic frontal lobe, or dysexecutive, syndrome. The term "executive," often used synonymously with "frontal," is reserved for a specific category of frontal lobe functions.
- There are at least four categories of frontal function: energization, executive, self-regulation and metacognition. These are defined by anatomical localization and connectivity as well as function.

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- Behavior following diffuse brain damage cannot be easily attributed to a specific lesion location; one or more of the categories of frontal lobe function may be implicated.
- Frontal functions are flexibly assembled over time into different networks within the frontal regions and between frontal and posterior regions, as required by task context and complexity.

"Frontal" functions are diverse capacities involved in higher-level cognition, behavioral control, attention and social functioning. While it may seem a truism that these functions are affected by damage to the frontal lobes (or to be more precise, to the prefrontal cortex anterior to the motor strip), this association is by no means complete. Diffuse damage, posterior damage, or damage to deep structures interconnected with the frontal cortex can mimic the effects of frontal damage. Because frontal functions lie at the apex of cognition, they are also sensitive to changes associated with psychiatric conditions, fatigue, pain, and toxic or metabolic conditions, to name a few. Conversely, frontal damage does not necessarily imply "frontal" dysfunction; it depends on the location of the damage and the specific function in question. While we acknowledge the limitations of defining psychological processes according to anatomy, we nonetheless use the term "frontal" in keeping with historical usage. Furthermore, this nomenclature avoids ambiguity as executive functions can be regarded as a subset of frontal functions (see below).

There are numerous theories of frontal lobe function (Damasio, 1996; Duncan *et al.*, 1996; Goldman-Rakic, 1987; Luria, 1966; Miller, 1999; Shallice & Burgess, 1991; Stuss *et al.*, 1995; for a brief review, see Turner & Levine, 2004), each emphasizing different elements of the frontal lobe syndrome or perspectives on frontal processes. We have adopted a classification delineating four categories of frontal functions (Stuss & Alexander, in press). This system is derived from research on patients with focal prefrontal lesions, incorporating the distinctions previously proposed by major theories of frontal function. Another advantage of this classification is that each function describes a clinical syndrome that is a potential rehabilitation target, allowing for increased precision of interventions. However, as discussed in more detail at the end of this section, we do not regard these functions as discrete or modular. They rather interact in a dynamic manner. Effects of brain damage depend on which system or systems are affected, as well as effects on the systems' interaction through altered connectivity.

The proposal of different functional domains within the frontal lobes is based on principles of anatomical differentiation and connectivity (Pandya & Yeterian, 1996; Sanides, 1970), and secondarily on more recent evidence for functional fractionation within the frontal lobes. The first major division (Stuss & Levine, 2002) is based on the evolution of architectonic development. There are two major functional/anatomical dissociations within the frontal lobes. The first (*executive*), evolving from a hippocampal, archicortical trend, is localized in lateral prefrontal cortical cortex (LPFC), and related to spatial and conceptual reasoning processes. The second (*behavioral/emotional self-regulatory*), evolving from the paleocortical trend and situated in ventral (medial) prefrontal cortex (VPFC), is related to emotional processing. These two major functional divisions within the frontal lobes follow two of the three proposed frontal-subcortical circuits involved in cognitive and/or emotional processing (Alexander *et al.*, 1986; Cummings, 1993). The third frontal-subcortical circuit (the two related to motor functioning are not considered) maps onto another functional division within the frontal cortex, associated with *energization regulating*, related to superior medial regions. The fourth category of frontal functions (*meta-cognitive*) is suggested by recent research on higher order integrative functions of the frontal polar area 10.

Executive cognitive functions

Executive functions are the high-level *cognitive* functions mediated primarily by one region of the frontal lobes, the LPFC, and concerned with the control and direction (e.g., planning, monitoring, activating, switching, inhibiting) of lower level,

more automatic functions (Stuss & Alexander, in press; Stuss *et al.*, 2002; Stuss & Levine, 2002). Tests commonly used by many clinicians as measures of frontal lobe "executive" functioning (such as the Wisconsin Card Sorting Test (WCST); Trail Making Test Part B; the Stroop Interference subtest; and specific measures within verbal fluency tasks) are indeed more sensitive in general to focal LPFC (and also not generally to orbitofrontal/ventral medial) pathology (Goldman-Rakic, 1987; Milner, 1963; Petrides & Milner, 1982; for review see Stuss & Levine, 2002). However, the tests are complex and multifactorial, and individuals can fail for many reasons (e.g., Anderson *et al.*, 1991).

A series of simple reaction time tasks have led to dissociations of executive functions within the frontal lobes that appear to be consistent across tasks, with the left ventrolateral prefrontal region involved in task-setting (e.g., bias and false positive errors; Alexander *et al.*, 2003, 2005; Stuss *et al.*, 1995, 2002) and the right lateral prefrontal area important in output monitoring and checking (Stuss *et al.*, 2002, 2005a; Vallesi *et al.*, 2007; Picton *et al.*, 2006; see also Deutsch *et al.*, 1987; Glosser & Goodglass, 1990; Pardo *et al.*, 1991; Rueckert & Grafman, 1996; Wilkins *et al.*, 1987; Woods & Knight, 1986). These same control mechanisms appear to be responsible for the domain general individual variability that is observed in several neurological disorders (Stuss *et al.*, 2003; see also Chapter 3 by Stuss and Binns in this volume).

Behavioral/emotional self-regulatory functions

An important function for the VPFC, because of its involvement in emotional responsiveness (Nauta, 1971; Pandya & Barnes, 1987) and reward processing (Fuster, 1997; Mishkin, 1964; Rolls, 1996, 2000), is behavioral self-regulation. This self-regulation is necessary in situations where cognitive analysis, habit or environmental cues are not sufficient to determine the most adaptive response (Eslinger & Damasio, 1985; Harlow, 1868; Penfield & Evans, 1935).

Affective reversal learning, measuring the acquisition and reversal of stimulus-reward associations, is sensitive to VPFC pathology (Elliott *et al.*, 2000; Rolls, 2000) and is dissociable from attentional (extra-dimensional) set-shifting found after LPFC lesions (Dias *et al.*, 1996, 1997; see also Fellows & Farah, 2005). This dissociation reinforces the distinction between "executive" attentional and affective/emotional behavioral measures. Higher-level decision-making tasks involving reward processing in unstructured situations, such as the gambling task developed by Bechara and colleagues (Bechara *et al.*, 1994), may also be sensitive to damage in this region for obvious reasons; however, these tests may also be multifactorial in nature, requiring other processes such as those we called executive (e.g., planning and monitoring; Levine *et al.*, 2005; for review, see Dunn *et al.*, 2006). The inability to regulate behavior according to internal goals and constraints is also being assessed by naturalistic multiple subgoal tasks (Schwartz *et al.*, 1998, 1999), as well as more structured paper-and-pencil laboratory versions (Burgess *et al.*, 1998, 2000; Levine *et al.*, 1998, 2000a), these tasks also being multifactorial.

Energization regulating functions

The energization function is defined as the capacity to generate and maintain actions important for adequate performance of the other functions. It has been replicably related to the superior medial region of the frontal lobes (Alexander *et al.*, 2005; Stuss *et al.*, 2001a, 2003, 2005a). In its most extreme form, extensive damage to more superior medial (anterior cingulate and superior medial) frontal pathology results in abulia, or severe apathy. However, this diminished energization can be demonstrated even in less clinically obvious cases. Patients with damage in this region are slow in generating lists of words in the absence of a language deficit, particularly in the first 15 seconds (Stuss *et al.*, 1998); have notably slower reaction time (RT) particularly if tasks are more demanding (Alexander *et al.*, 2005; Stuss *et al.*, 2002, 2005a); are deficient in maintaining over time the benefit of a warning stimulus

(Stuss *et al.*, 2005a); and have problems maintaining a selected target such as in the Stroop interference test (Stuss *et al.*, 2001a). The clinical tests, such as verbal fluency and Stroop, lack specificity and tap other cognitive (often executive – see below) abilities. Perhaps the best measures to evaluate impaired activation are demanding reaction time measures.

Metacognitive functions

The fourth frontal lobe functional category is postulated on the basis of recent research (see Burgess *et al.* 2005; Christoff & Gabrieli, 2000; Stuss & Alexander, 1999, 2000; Stuss *et al.*, 2001c for reviews). The frontal polar region Brodmann area 10, possibly more particularly on the right, appears to be maximally involved in the metacognitive aspects of human nature: integrative aspects of personality, social cognition, autonoetic consciousness, theory of mind and humor (Shammi & Stuss, 1999; Stuss *et al.*, 2001b, 2001c; Tulving, 1985; Wheeler *et al.*, 1997). Although this division is not based on the circuitry proposed by Alexander *et al.*, 1986, there is some evidence suggesting that the connectivity within the frontal regions provides it with unique integrative capability (Burgess *et al.*, 2005, 2007; Pandya, personal communication). Because area 10 is among the most recently evolved of human brain regions, it may be uniquely positioned to integrate the higher-level executive cognitive functions, and emotional or drive-related inputs (although seemingly not reducible to these functions; Siegal & Varley, 2002; Shammi & Stuss, 1999; Stuss *et al.*, 2005b) positioning this region for more self-reflective, metacognitive functions (Stuss & Alexander, 1999, 2000). There is also debate as to how much this functional category is associated with damage to a more general area including the anterior medial regions. The neuropsychological assessments in this category of frontal lobe functions are generally experimental.

Functional systems

The evidence for specific functional categories within the frontal lobes does not imply that frontal lobes are simply a series of independent processes. Depending on task demands, there is the fluid recruitment of different processes anywhere in the brain into different networks (Stuss, 2006). For some tasks, only one functional region may be necessary; in others, one or more anatomically distinct frontal processes within the frontal lobes may be recruited (a "within-frontal lobe" network). In some simple repetitive tasks, the more automatic nonfrontal processes may function independently (Shallice & Burgess, 1993); as task demands increase or alter, there may be increased involvement of different frontal (more "strategic") regions, even to the point where it appears all frontal regions are involved (Stuss *et al.*, 1999). Under other conditions the network may function "top-down." In disorders with more diffuse pathology, then, there may well be "executive" dysfunction. However, these should not be made synonymous with frontal lobe dysfunction. Regardless, some of the rehabilitation techniques described in this chapter may be effective in these populations, but perhaps in conjunction with other approaches.

Summary

Frontal lobe functions are heterogenous and centrally involved in higher level cognition, behavioral control, attention and social functioning. Although "frontal" dysfunction can arise from nonfrontal damage, we retain use of this term for simplicity and historical consistency. The use of the term "executive functions" as synonymous with "frontal functions" can be misleading as executive functions are but one class of frontal function. We adopt the following classification system for organizing frontal functions as potential targets for rehabilitation: executive/cognitive functions associated with the lateral prefrontal cortex, behavioral/emotional self-regulatory functions associated with the ventral (medial) frontal cortex, energizing regulating functions associated with the medial prefrontal cortex, behavior and metacognitive functions associated with the frontopolar cortex. Although these functions can be differentially affected by localized

brain damage, they interact through extensive interconnections and can be multiply affected by clinical disorders.

Disorders affecting frontal lobes

- Stroke, tumors and traumatic brain injury (TBI) are the most prevalent forms of acquired brain injury affecting frontal function, although frontal function may be affected by many other conditions.
- Middle cerebral artery strokes affect the lateral prefrontal cortex and thus are maximally expressed via executive/cognitive deficits. Anterior cerebral artery strokes affect the medial prefrontal cortex and thus affect energizing functions. Hemorrhagic infarcts arising from anterior communicating artery (ACoA) aneurysms affect ventromedial prefrontal cortex and basal forebrain, causing self-regulatory and mnemonic dysfunction.
- Tumors affect frontal function through both localised and distal effects. Meningioma effects are fewer relative to faster-growing tumors.
- In terms of prevalence and overall economic impact, TBI is the most important cause of frontal dysfunction, affecting behavior through both diffuse and localized frontal damage, with consequences for all frontal functions, especially self-regulatory.
- Although localization effects are often consistent across etiologies, considering effects of specific etiologies on different frontal functions may increase the specificity of interventions.

As noted above, frontal functions are vulnerable to disruption in any cerebral system, anterior or posterior, cortical or subcortical, as well as to changes in psychological status (e.g., anxiety) and daily fluctuations (e.g., fatigue). Although nearly every neurological or psychiatric disorder can affect frontal function, the most prevalent forms of acquired brain injury that have specific effects on prefrontal systems are strokes tumors, and traumatic brain injury (TBI).

Stroke

Strokes or cerebrovascular accidents (CVAs) occur due to occlusion and hemorrhage, with the former accounting for more than 80% of strokes (Robinson & Starkstein, 1997). Although less prevalent, hemorrhagic events are relevant to the study of frontal lobe dysfunction as 85–95% of aneurysms develop at the anterior portion of the cerebral arterial supply (DeLuca & Diamond, 1995). Strokes involving the distribution of the main trunk or anterior branches of the middle cerebral artery result in unilateral damage to lateral prefrontal brain regions, producing what has been described as a dorsolateral stroke syndrome (Anderson & Damasio, 1995), involving cortical regions across the entirety of the lateral surface of the prefrontal cortex with associated impairments in executive/cognitive functions, often accompanied by unawareness.

Infarcts arising from anterior cerebral artery aneurysms in the superior medial frontal regions produce a dorsomedial frontal-lobe syndrome in which energization is affected. The anterior communicating artery (ACoA) bridges the right and left anterior cerebral arteries (feeding the medial surface of the frontal lobes) as well as sending branches more inferiorly into white matter and basal forebrain regions. It is the source of almost 85% of all ruptured aneurysms within the cerebrum (Anderson & Damasio, 1995). Hemorrhagic damage following ACoA rupture can affect ventral, medial and polar frontal regions as well as basal forebrain regions involved in memory. Thus patients with ruptured ACoA aneurysms can have problems with behavioral self-regulation (Bottger *et al.*, 1998; Mavaddat *et al.*, 2000), self-awareness (Diamond *et al.*, 1997), and memory, including confabulation (DeLuca & Diamond, 1995; Gilboa *et al.*, 2006).

Tumors

Frontal lobe tumors account for one-fifth of all supratentorial tumors (Price *et al.*, 1997). Non-frontal tumors can also cause deficits through diaschisis (i.e., the impairment of neuronal activity in a

functionally related but distant region of the brain; von Monakow, 1914) and disconnection of frontal structures from other cerebral regions (Lezak, 1995; Lilja *et al.*, 1992). Neurosurgical approaches through the frontal lobes should also be taken into consideration.

Gliomas and meningiomas are the most common histological classifications of supratentorial tumors (Nakawatase, 1999), with fast-growing glioblastomas resulting in a poorer cognitive profile than a slower growing meningioma (Price *et al.*, 1997). Tumors may produce additional cognitive dysfunction by inducing seizures, increased intracranial pressure, edema and paraneoplastic syndrome. As described earlier, the reliance of frontal function upon extensive neural networks increases the susceptibility of higher cognitive processes to these secondary neuropathological processes (Tucha *et al.*, 2000).

Traumatic brain injury

Owing to its high incidence (80000 to 90000 disabled per year in the USA) and prevalence (5.3 million in the USA disabled by TBI; National Center for Injury Prevention and Control, 1999), and its specific effects on the frontal lobes and their interconnections, TBI is arguably the most important single cause of frontal lobe dysfunction. Although interpretation of TBI effects is complicated by the co-occurrence of physical disability, it is the cognitive and behavioral consequences of TBI that are truly enduring, with a greater impact on outcome than physical symptoms (Brooks *et al.*, 1986; Dikmen *et al.*, 1995; Jennett *et al.*, 1981). The chronic disability of TBI is accentuated by its tendency to take place during early adulthood, affecting behavior for decades.

Traumatic brain injury induces a dizzying array of neuropathologies, the interpretation of which is complicated by time course effects and interaction with noninjury factors (e.g., the psychosocial milieu). For our purposes, a distinction between diffuse and focal injury provides a useful heuristic (Levine *et al.*, 2002). Diffuse axonal injury (DAI) is a crucial neuropathology and cause of coma in TBI (Adams *et al.*, 1982; Gennarelli *et al.*, 1982; Povlishock, 1992; Povlishock *et al.*, 1992; Strich, 1956). It is characterized by disconnection and eventual demise of axons, the result of a complex process studied at the molecular level (Maxwell *et al.*, 1997; Povlishock & Christman, 1995). The behavioral consequences of this widespread disconnection syndrome include impaired arousal, inattention and slowed information processing, particularly on complex tasks (Stuss & Gow, 1992). The otherwise intact environment in which DAI occurs (15 per 1000 axons damaged in a typical motor vehicular accident injury; Povlishock, 1993), is ripe for subsequent neuroplastic changes such as axonal sprouting and synaptogenesis (Christman *et al.*, 1997; Povlishock *et al.*, 1992), as revealed through functional neuroimaging studies of patients with TBI (for review, see Levine *et al.*, 2006).

Focal parenchymal injury in TBI is typically due to contusion resulting from inertial forces causing localized damage in ventral and polar frontal and anterior temporal areas where the brain is confined by bony ridges of the inner skull, regardless of the site of impact (Clifton *et al.*, 1980; Courville, 1937; Gentry *et al.*, 1988; Ommaya & Gennarelli, 1974). There is evidence that focal atrophic damage may exist in these regions even when lesions are not visible on conventional MRI (i.e., localized diffuse injury; Berryhill *et al.*, 1995). The location of focal cortical contusions along the ventral trend corresponds to the self-regulatory and metacognitive deficits known to occur in TBI patients (Levine, 1999; Levine *et al.*, 1998, 2000a).

Summary

Nearly all neurological and psychiatric illnesses can affect frontal function. The most prevalent forms of acquired brain injury affecting frontal function, however, are strokes, tumors and traumatic brain injury. Each etiology can cause specific effects depending on the location and nature of the disease. For example, MCA strokes affect dorsolateral (executive/cognitive) functions, ACA strokes affect

energization regulation functions, ACoA strokes affect self-regulatory and mnemonic functions. Tumor effects depend on location and other factors such as distal (diaschisis) effects, neurosurgical approaches and paraneoplastic syndrome. Traumatic brain injury, the most common and costly of these disorders, affects frontal function (especially self-regulation) through diffuse axonal injury and focal ventral frontal contusions.

Rehabilitation of frontal dysfunction

- Fifty-five studies involving rehabilitation of frontal dysfunction were identified.
- Most of the published work involves case studies, regarded as a lesser class of evidence. Only nine studies were identified as randomized control trials, the highest class of evidence.
- Nearly all studies involved patients with acquired brain injury, although details regarding etiology, epoch and lesion location were often not described.
- Most reported interventions for energization regulating functions involved dopamanergic agonists. A small number of case studies used nonpharmacologic interventions.
- Interventions for executive/cognitive functions were divided into those addressing broadly defined problem solving and planning versus those addressing a specific executive cognitive function, usually working memory.
- Interventions for behavioral/emotional self-regulatory functions were designed to train patients to bridge the gap between intention and action. Studies demonstrated efficacy of programmatic goal management training, verbal self-regulation and external cueing techniques.
- Interventions for metacognitive functions attempted to increase awareness of deficits or to more directly increase error monitoring and self-correction, the latter showing case study evidence for improving difficult, impulsive behavior.

We previously reviewed literature on rehabilitation of frontal dysfunction to 2003 (Turner & Levine, 2004). Interventions specifically addressing attention or memory disorders or behavioral dyscontrol were not included, nor were holistic interventions. Forty interventions drawn from 34 papers were identified and tabulated. The papers were organized according to four categories: cognitive control, planning/problem solving/goal direction, initiation/motivation and self-awareness/self-monitoring – corresponding closely to the executive cognitive, self-regulatory, energizing and metacognitive categories described above, which will be used henceforth.

Few of the studies we reviewed contained the design ingredients necessary to draw firm conclusions about treatment effectiveness: control groups, randomization, evidence of real-life generalization and long-term follow-up (Levine & Downey-Lamb, 2002). Furthermore, patient characteristics such as etiology, epoch and lesion location were often not described. Most of the published work involved case studies, which are relevant for forming hypotheses but do not provide sufficient empirical evidence for widespread clinical application.

Of the 15 additional studies identified here, there were five randomized control trials (including a brief rehabilitation probe), four group interventions (two without control groups; two with nonrandomized controls) and six case reports – a distribution similar to that observed in our previous review. Ten of the 15 studies report on TBI samples, with the remaining studies reporting on mixed TBI/CVA, "brain injured" or aging samples.

This updated review incorporates our previous findings with these new reports and builds upon recent reviews of cognitive (Cicerone *et al.*, 2005), executive function (Cicerone *et al.*, 2006) and self-awareness (Lucas & Fleming, 2005) rehabilitation interventions in a number of ways. By framing our review within the four domains of frontal lobe functioning, we were able to broaden our inclusion parameters relative to these earlier reviews (Cicerone, 2000; Cicerone *et al.*, 2005). This was most evident within the domain of "Energization" where we included "apathy" and "abulia" to our search criteria and reviewed reference lists from

two recent review papers on the topic (Stuss *et al.*, 2000; van Reekum *et al.*, 2005). In addition to the expanded breadth of the review we were also able to stratify the intervention studies by class of evidence using methods adapted from Cicerone (2000), thereby providing both a comprehensive survey of the rehabilitation interventions specifically targeting frontal dysfunction as well as a qualitative assessment of the state of the literature with respect to empirically validated treatment options.

Executive/cognitive functions

Interventions in this category may be loosely grouped into interventions designed to remediate broadly defined problem-solving and planning skills and those targeted towards improving capacity within a single domain of executive functioning (typically working memory).

Problem solving and planning

The evaluation of problem-solving training (PST; von Cramon *et al.*, 1991) remains the only RCT of problem-solving interventions in the literature. The intervention targeted specific problem-solving goals (e.g., orientation, definition, alternative generation). A control group received memory training. Over an average of 25 sessions, gains for the problem-solving training group were observed on tasks of reasoning, problem solving and experimental planning. However, there was only qualitative evidence of training generalization and no follow-up data were reported. Importantly, length of training was nonstandard across participants with additional training provided for patients demonstrating apathetic or abulic symptomatology. A supplemental single case study (von Cramon & Matthes von Cramon, 1994) also reported success in remediating specific vocational tasks using a variant of this program, but there was no effect on awareness ratings or evidence of generalizability. More recently, interactive strategy modeling training was used to improve problem-solving efficacy in a noncontrolled group study of 20 TBI subjects (Marshall *et al.*, 2004). Participants were trained in deductive problem-solving techniques to facilitate target picture identification from within a large picture array. Following training to pre-established criteria on 12 training arrays, participants were assessed on novel arrays. Relative to pre-training performance, participants demonstrated a decrease in the number of questions needed to solve the problem, an increase in percentage of constraint questions and an overall increase in question-asking efficiency. Gains were maintained at 1-month follow-up. Soong *et al.* (2005) used an analogy-based approach to problem-solving training in a pilot study with 15 brain-injured persons. Participants were trained to solve everyday life problems over 20 sessions using analogies drawn from successfully solved problems in their own personal histories. Training was delivered across several modalities (i.e., web-based, computer or therapist led) and while results did not vary across mode of intervention, all three groups demonstrated significant change in knowledge of concepts surrounding instrumental activities of daily living, performance on the category test of the Halstead–Reitan Battery and an experimental measure of self-efficacy in problem-solving. There was no comparison group to control for nonspecific effects of the intervention nor were any follow-up assessments reported. Fox *et al.* (1989) reported on the efficacy of specific criterion questions as cues to solve real-life problems in a small controlled study of patients with ABI ($N = 3$) using scenarios and staged interactions. Finally, Park *et al.* (2003) describe a single case of improved functional outcome following a problem-solving intervention involving explicit consideration and strategic evaluation of problem-solving alternatives in real-life situations.

In a brief "rehabilitation probe" experiment (see also Levine *et al.*, 2000b described below), Hewitt *et al.* (2006) theorized that training in explicit retrieval of autobiographical information regarding event planning would aid in overall planning efficacy following TBI. Following 30 min of training on the use of autobiographical memory recollections to aid planning in everyday life situations, patients

with TBI ($N = 15$) showed moderate improvements in planning efficacy, number of steps in their plans, and number of autobiographical memories retrieved on an event description task relative to a matched control group of 15 TBI patients who received no training. There was no report of generalization to other measures.

Executive function and working memory

In the only published RCT explicitly targeting the enhancement of remediating deficits within a specific domain of higher cognition, McDowell *et al.* (1998), administered bromocriptine to a group of 24 TBI subjects to aid working memory and executive control performance in a double-blind, crossover, placebo-controlled study. The authors report improvement related to drug administration on an experimental measure of dual-task performance and several neuropsychological measures of executive functioning. More recently, Kraus and colleagues (2005) utilized amantadine to improve executive functioning in a sample of 22 TBI subjects in an open-label, noncontrolled study design. Significant improvement on an index of executive functioning, comprised of performance on a letter fluency task and Trail Making Test, Part B, was reported following a 12-week course of treatment (400 mg daily). Interestingly, there was no evidence of improvement in either attention or memory domains suggesting a domain-specific effect of the intervention. No follow-up or generalization data were reported.

Specific remediation of executive functioning (i.e., working memory) was also addressed in a recent brief report by Serino *et al.* (2006). Nine TBI patients with working memory deficits and six TBI patients without working memory deficits were trained on multiple forms of the Paced Auditory Serial Attention Task (PASAT). Following training, performance improved on tests of working memory, divided attention, executive functioning (letter fluency) and long-term memory. No improvements were observed on tests of speeded processing or vigilance, again supporting the specificity of the intervention. There were no observed differences between the pre- and post-intervention scores for those participants who did not demonstrate working memory deficits, illustrating the importance of defining target groups for rehabilitation. No follow-up or generalization data were reported.

Stablum *et al.* (2000) conducted a controlled group study to assess the feasibility of improving dual-task performance in TBI patients through direct training. Both treatment and control patients improved on the dual-task paradigm, but the rate of improvement was greater for the treatment group. There was evidence of generalization to another working memory task (PASAT) and gains were evident at 3 months on neuropsychological and functional measures. These findings were replicated with a group of ACoA aneurysm rupture patients. Cicerone (2002) utilized a staged training program involving increasingly demanding dual-task paradigms to successfully improve "working attention" (again measured by PASAT) in four mild TBI participants relative to controls. Reduced attentional dysfunction in daily activities was also noted. Deacon & Campbell (1991) successfully used external cuing in a group study of decision-making speed wherein external cueing preferentially improved choice reaction times in TBI patients relative to controls; accuracy was not affected. The effect was carried over into noncued situations, providing some evidence of a generalized enhancement in decision-making speed.

Behavioral/emotional self-regulatory functions

Interventions within this category include those explicitly directed towards bridging the gap between intention and action, a deficit described as "goal neglect" (Duncan, 1986; Luria, 1966) with interventions targeted towards re-establishing endogenous control of behavior. Rath and colleagues (2003) used an RCT design in a cohort of 46 TBI subjects. Treatment consisted of two distinct phases, with the first 12-week phase consisting of emotional self-regulation training. In the second

phase, subjects were trained in problem-solving skills in a manner similar to the problem-solving training procedure described above (von Cramon *et al.*, 1991). Controls received a program of conventional cognitive rehabilitation. Improvements specific to treatment included reduced perseverative responding on the WCST and improved problem solving on self-report and role play measures. Treatment gains were stable at 6 months with anecdotal report of generalization to real-life behaviors. The addition of an emotional self-regulation represents a novel approach to self-regulation interventions and was considered essential to facilitating successful problem orientation before progressing to the problem solution phase of the intervention.

Webb & Glueckauf (1994) randomly assigned 16 patients with TBI to a high-involvement goal-setting group (including active strategies for prioritization and goal monitoring) or a low involvement group (including pre-assigned goal lists but no formal monitoring training). Both groups made equivalent gains on ratings of goal attainment and goal change from pre- to post-testing, but maintenance of gains at 2-month follow-up was restricted to the high-involvement group.

Levine and colleagues (2000b) drew upon Duncan's (1986) theory of goal neglect to institute a program of goal management training (GMT) in a brief "rehabilitation probe" in which 30 TBI subjects received GMT or motor skills training (MST). Goal management training consisted of five training stages: stopping (periodic suspension of ongoing behavior), stating the main task, partitioning the task into subgoals, encoding and retention of the goals, and monitoring. The results suggested a beneficial effect of GMT training, measured by experimental planning tests, over and above gains demonstrated in the MST group (due to repeated test administration or contact with the trainer). A more extensive application of GMT was successfully applied in a single case study of a post-encephalitic patient, with training adapted to improve meal preparation (Levine *et al.*, 2000b, experiment 2).

Levine and colleagues (2007) applied GMT within a large-scale cognitive neurorehabilitation program for aging that also included psychosocial and memory-skills training (Stuss *et al.*, 2007). The training, although expanded in time from the original rehabilitation probe to 4 three-hour sessions, was reduced in complexity by emphasizing the first three stages: (stopping ongoing behavior, stating the main task and splitting the task into subgoals). Outcome measures included desktop simulated real life tasks (SRLTs; e.g., organizing a carpool) videotaped and scored according to the trained concepts. Forty-nine participants were randomized to two groups, one of which received the intervention immediately and the other of which was waitlisted prior to rehabilitation. Results indicated improvements in SRLT performance as well as self-rated executive deficits coinciding with the training in both groups. These gains were maintained at long-term follow-up. However, it was not possible to empirically demonstrate the specificity of these improvements to GMT as the assessment was done before and after the entire cognitive neurorehabilitation program.

In a RCT of 67 healthy older adults with executive complaints randomized to an 11-session version of GMT plus psychosocial training or a waiting-list group, van Hooren and colleagues (2006) found fewer executive complaints, reduced annoyance and reduced anxiety in the intervention group. There was no effect on objective assessment of outcome using the Stroop test, which is not a sensitive measure for this intervention.

The latest version of GMT has an enhanced emphasis on periodic suspension of ongoing activity as a critical prerequisite to on-line evaluation of goal hierarchies, task-splitting and monitoring of performance. Active practice with simulated and real-life complex tasks is incorporated both within and outside of training sessions. Mindfulness practice is also incorporated to bring awareness to the present moment and reduce distractibility. This program has been administered in a 15-hour RCT in groups of patients with mixed-etiology acquired brain injury, with standard outpatient group rehabilitation techniques (e.g., diet, energy conservation, brain health education) as the control treatment. Results indicate positive effects on measures of sustained attention

and planning that are sustained at long-term follow-up (O'Connor *et al.*, 2006). Luria & Homskaya (1964) suggested that self-regulation is mediated by covert, "inner speech" that provides a critical bridging mechanism between the general intention to solve a problem and its concrete solution. Arco *et al.* (2004), described a verbal self-regulation procedure to reduce impulsivity in four males who had sustained severe head injury. Impulsivity was reduced and stabilized for two of the four with impulsive behavior rates reduced but unstable after treatment for the other two subjects. A case study by Cicerone & Wood (1987) documented the remediation of a planning deficit in a patient with TBI through the re-establishment of inner-speech to guide behavior. Performance improved on a standardized planning task and gains were maintained at 4-month follow-up. However, generalization required 12 weeks of further training. A follow-up study replicated these findings in a larger sample of six mixed-etiology subjects, with 5/6 showing gains. Two patients who received explicit generalization training spontaneously applied the techniques in novel situations (Cicerone & Giacino, 1992; see also Stuss *et al.*, 1987).

Goal-directed behavior may also be facilitated with external cueing, as suggested by case studies involving verbal instruction and task checklists (Burke *et al.*, 1991; Delazer *et al.*, 1998; Giles & Morgan, 1990; Hux *et al.*, 1994; O'Callaghan & Couvadelli, 1998) and an electronic paging system combined with task-specific checklists (Evans *et al.*, 1998). In this latter study, it was reported that the auditory cueing itself was sufficient to re-establish the connection between intention and action. A similar result is reported in a recent TBI group study in which simulated real-life tasks were administered with and without the provision of random auditory "alerting" cues (Manly *et al.*, 2002). Random auditory cues were used as a prosthetic "marker" to remind patients to monitor ongoing behavior in completing a complex, lifelike planning task. Patients' performance on the cued version of the task was comparable to that of normal controls, suggesting that the auditory alerts higher-order goals into consciousness, facilitating more adaptive goal-directed behavior. This tone prosthetic has been incorporated into the current version of GMT.

Energization regulating functions

Pharmacologic interventions

Most of the interventions in this category of frontal dysfunction involve pharmacologic treatments with catecholaminergic agents, a literature that has been reviewed more extensively elsewhere (Muller & von Cramon, 1994; van Reekum *et al.*, 2005). In their recent report, Newburn & Newburn (2005) utilized a standardized apathy evaluation scale (AES) to measure the impact of selegeline, a dopaminergic agonist, in four TBI patients presenting with apathetic characteristics but without evidence of depression. All four subjects demonstrated reduced apathy following the start of treatment and improvements were reported both on standardized measures as well as in clinical presentation. There was no report of follow-up after drug cessation. Previously we reviewed a report by Powell (1996), wherein treatment with bromocriptine was related to improvements on measures of active rehabilitation participation, reward responsivity and measures of executive functioning in 11 subjects, with treatment gains stable in eight of the 11 patients 2 weeks after withdrawal of treatment. This finding is similar to that of the first case-controlled report of bromocriptine administration for the treatment of frontal lobe syndrome (Parks *et al.*, 1992) wherein bromocriptine administration ameliorated abulic symptoms. However, their interpretation of improvements in problem-solving and memory domains was complicated by practice effects on neuropsychological measures. A review of bromocriptine administration following acquired brain injury by Muller & von Cramon (1994) concluded that while bromocriptine has been successful in the domain of energizing functions, its utility in treating executive or problem-solving deficits remains unproven (but see 'Executive/Cognitive' section above). Another dopamine agonist, amantadine, was administered in a double-blind placebo-controlled case

study in a patient with a severe abulic and apathetic syndrome with positive results (van Reekum *et al.*, 1995). In a recent report, administration of a serotonergic agonist, sertraline, was unsuccessful in raising alertness levels in a group of 11 traumatically brain-injured subjects (Meythaler *et al.*, 2001).

Behavioral interventions

Very few reports of nonpharmacologic treatment of energization deficits were identified, although positive case study evidence has been reported with checklists (Burke *et al.*, 1991) and external cueing systems (Sohlberg *et al.*, 1988).

Metacognitive functions

Within the realm of metacognitive deficits following frontal dysfunction, deficient awareness of one's impairments and their consequences (i.e., the capacity to retain an "objective" view of oneself while maintaining a sense of subjectivity; Prigatano, 1991) is one of the most commonly addressed in the rehabilitation literature. Interventions typically fall within two categories, those addressing awareness of deficits and those more directly targeted at error monitoring and self-correction.

Deficit awareness

Cheng & Man (2006) adopted an RCT design to evaluate the efficacy of their Awareness Intervention Program (AIP). Awareness levels of 11 TBI participants in the treatment group were compared with a control group of 10 matched TBI subjects enrolled in a conventional rehabilitation program. Upon completion of the 32-session AIP, the treatment group scores on the Self-Awareness of Deficits Scale was significantly lower (i.e., greater awareness) than the control group. No between-group differences were observed on the IADL scale or Functional Independence Measure at the end of training, signifying that the increased awareness may not have effected functional change as assessed by these measures. No follow-up data were reported. Medd & Tate (2000) employed a matched-randomized control design to investigate the efficacy of an anger management and awareness intervention. Traumatic brain injury participants (N = 16) were randomly assigned to a 6-hour self-instructional training program or to a waitlist condition. There was some gain in anger management measures post-intervention and at 2-month follow-up. There was no change in awareness measures. Two small group (N = 3) studies successfully used awareness board games to improve deficit awareness (Chittum *et al.*, 1996; Zhou *et al.*, 1996). There was only partial evidence, however, that knowledge of these deficits translated into increased awareness.

Several reports describe the use of a more experiential approach, wherein predicted task performance is contrasted with actual performance as a means of increasing deficit awareness in the realm of planning (Cicerone & Giacino, 1992), memory (Rebman & Hannon, 1995; Schlund, 1999), and calculation and verbal recall abilities (Youngjohn & Altman, 1989). Ownsworth & McFarland (2000) used a similar approach to improve deficit awareness and anticipatory awareness of future consequences in a group of 21 ABI subjects. In their sample, improvements in self-regulation and reduction in sickness impact were observed following the intervention and remained stable at 6-month follow-up. DeLuca (1992) has described a "tailored" approach to the remediation of a severe confabulatory disorder following ACoA aneurysm rupture in which the treatment team and family members were provided with explicit direction as to when and how to confront patients with respect to their confabulatory behavior. Improved awareness and reduced confabulation following treatment was reported in two patients.

Error awareness and self-monitoring

Deficient self-monitoring of inappropriate or maladaptive behavior is a common sequelae of brain injury. Such behavioral disorders (e.g., impulsivity, aggression, sexual disinhibition) are highly

refractory to treatment and significantly interfere with successful community reintegration (Alderman *et al.*, 1995). Rehabilitation or management of severe behavioral disorders is beyond the scope of this review, but has been reviewed extensively elsewhere (Alderman, 2004). We have limited our review to those interventions where self-monitoring and error correction (as a subcategory of self-awareness) was the primary rehabilitation target.

Targeted remediation programs involving structured feedback, cueing and formal efforts to recognize inappropriate behaviors are often part of interventions to enhance self-monitoring. A recent report by Fleming *et al.* (2006) describes a 10-week intervention program focused on client-centered goals, real-world task performance, error monitoring and multiple feedback mechanisms. Gains in deficit awareness were observed across all participants from pre- to post-intervention; however, these gains were only maintained in 2/4 participants at 4-week follow-up. Moreover, the authors report a link between improved self-awareness and increased emotional distress in all participants, suggesting that emotional stability must be closely monitored throughout any such intervention aimed at increasing deficit awareness. Ownsworth and colleagues (2006) reported a single case report of an error-awareness intervention for a person who had sustained a severe TBI. Using a client-selected target behavior, a system of error monitoring, role reversal and feedback was implemented. Error rates declined and self-corrective behaviors increased over the treatment period. Of note, measures of self-awareness did not improve, suggesting that error monitoring and correction can be improved even though general deficit awareness may remain. Additional case study evidence has been reported for the use of monitoring, feedback, error correction and verbal self-regulation to reduce inappropriate behavior, with some evidence for generalization and maintenance of gains at long-term follow-up (Burke *et al.*, 1991; Cicerone & Tanenbaum, 1997; Lira *et al.*, 1983).

Alderman *et al.* (1995) described the case of a herpes encephalitis patient whose disruptive verbal intrusions were successfully reduced through a formal self-monitoring training (SMT) designed to improve one's ability to attend to one's own behavior and then, through operant conditioning, reduce problem behaviors (Alderman & Burgess, 2003). Self-monitoring training was also successfully employed in a study by Knight and colleagues to reduce problem behaviors in three brain-injured patients (Knight *et al.*, 2002). While operant conditioning methods produced more rapid results (Alderman, 2004), those obtained through SMT were more lasting. More recently, Dayus & van den Broek (2000) used SMT techniques to reduce delusional confabulations in a single patient recovering from subarachnoid hemorrhages. Gains in this patient remained stable at 3-month follow-up. Cicerone & Giacino (1992) described two cases where a verbal reinstatement strategy was used to improve self-monitoring. Improved error monitoring was reported during standardized task performance with evidence of generalization across tasks. However, error rates returned to baseline upon cessation of treatment. In the second case anecdotal evidence indicated that treatment was associated with a reduction in socially inappropriate behavior, even when external prompting was ceased.

Summary and evaluation

- Of 55 published studies on rehabilitation of frontal lobe functions, only 16% meet criteria for Class I evidence sufficient to guide treatment.
- The lack of high-quality evidence reflects the heterogeneity in frontal lobe functions. Researchers tend to focus on clinical observations rather than working from theory.
- Experimental work using rehabilitation probes and carefully described, homogenous patient groups may provide a solid basis for later applications in clinical samples.
- Further work is needed to clarify the importance of metacognitive awareness to rehabilitation outcomes.
- There is a need for validated tasks of real-life function suitable for pre-/post-intervention assessments.

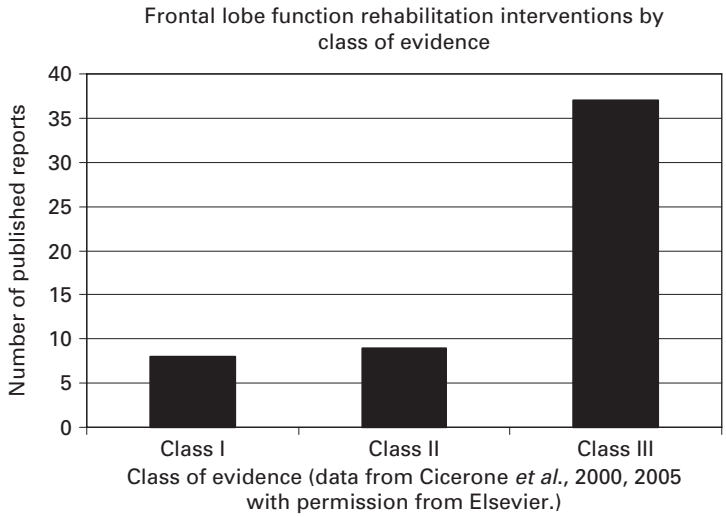

Figure 27.1. Frontal lobe function interventions by class of evidence. Interventions were selected based on criteria described in Turner & Levine (2004) and the revised criteria

- Increasing numbers, and relative successes, of drug trials for remediating frontal dysfunction point to pharmacology, possibly combined with behavioral interventions, as a promising area of future research.

We identified a total of 55 published studies on rehabilitation of frontal lobe functions (an increment of 15 from our earlier review; Turner & Levine, 2004). As seen in Figure 27.1, only 16% of these meet criteria for Class I evidence sufficient to guide treatment. Significant design limitations, including the lack of control groups, limitations in the selection of outcome measures, lack of follow-up assessment, and lack of generalisation significantly limit the conclusions derived from this literature. In short, there are no standardized, widely accepted methods for rehabilitation of frontal lobe functions.

This deficiency in evidence-based treatments is accentuated when the ubiquity and handicap of frontal lobe dysfunction is taken into consideration. The heterogeneity in definitions of frontal lobe functions is a major source of confusion in the design and reporting of treatments. Although we report interventions in four categories, this classification was a posteriori. It is more common for interventions to use a clinical observation or syndrome as a starting point (e.g., sexual disinhibition, abulia) rather than work top-down from an established theory of frontal lobe function. Notable exceptions include studies specifically addressing working memory (e.g., McDowell *et al.*, 1998; Stablum *et al.*, 2000) and behavioral/emotional self-regulation (e.g., Rath *et al.*, 2003). In this respect, "rehabilitation probes" (Hewitt *et al.*, 2006; Levine *et al.*, 2000b; Manly *et al.*, 2002) – experiments designed as proof-of-principle, provide a good starting point, even if the clinical implications are limited at first.

Even theory-driven interventions, however, are insufficient unless they are applied to the right patient population (see Chapter 3 by Stuss and Binns in this volume, on the importance of minimizing group variability). As defined above, different frontal syndromes arise from different etiologies and lesion locations. As one example, energising regulation functions are closely associated with the medial prefrontal cortex. Although in its early stages, work in patients with energizing regulation deficits suggests that dopaminergic agonists may be effective (e.g., Newburn & Newburn, 2005; Powell, 1996).

The vast majority of patients with frontal dysfunction have complex or diffuse etiologies. While such patients are the ultimate recipients of interventions being developed today, early establishment of the validity of these interventions is well-served by research in well-defined patient populations. Practical considerations, however, limit the number of such patients available for trials. Groups of patients with circumscribed deficits in frontal functions without complicating comorbidity are hard to assemble.

In syndromes with a recovering course, time since injury appears to be a critical factor in treatment planning. Interventions may be most effective at a stage where spontaneous recovery processes can be maximally engaged (Robertson & Murre, 1999). In other words, intervention before basic arousal and attentional mechanisms have recovered, or following the full course of naturalistic recovery, is often less effective than intervention in between these stages.

Recently, functional brain-imaging techniques have been employed to more precisely define brain-based rehabilitation targets and to identify the neural correlates and mechanisms of altered behavioral performance post-intervention (see Chen *et al.*, 2006 for review). Using this approach, neural markers are used to differentiate alterations owing to natural recovery processes from intervention-specific changes and to characterize the relationship between brain function and behavior and/or functional outcome following rehabilitation. These imaging techniques may be of particular importance in the rehabilitation of frontal lobe functions where clear operational definitions and reliable behavioral measures are lacking.

Metacognitive interventions provide an interesting point of reflection on the nature of frontal lobe functions and rehabilitation. Many regard deficit awareness as a necessary prerequisite to behavior change. Yet there is some evidence for dissociations between awareness and behavioral/functional improvement (i.e., in some studies awareness improved without functional change, in others functional change occurred without changes in awareness levels).

A similarly interesting theoretical point relates to generalization: how does one attain generalization in frontal patients, for many of whom the core deficit is a failure to extrapolate rules and principles from one situation (e.g., the clinic) to another (e.g., real-life)? The assessment of real-life behavior, ultimately essential to establish the validity of interventions for frontal dysfunction, is of particular concern. There are few psychometrically validated, performance-based measures of real life functions from which to choose, and none of these have alternate forms for use in pre-/post-intervention assessments.

Finally, although we have segregated pharmacologic and behavioral rehabilitation interventions in our review, a growing literature is beginning to demonstrate the efficacy of a combined drug/behavioral approach to remediate both cognitive and motor disorders (e.g., hemiplegia and aphasia) following brain damage (Walker-Batson *et al.*, 1995; for review, see Phillips *et al.*, 2003). While the mechanisms underlying the efficacy of such a combined approach remain unclear, it is believed that catecholaminergic and cholinergic neuromodulation facilitates neuroplastic change, primarily by altering synaptic strength through long-term potentiation/depression mechanisms, thereby potentiating learning capacity during concurrent behavioral interventions (Floel *et al.*, 2005; Meintzschel & Ziemann, 2006). We did not uncover published reports of combined therapies specifically targeting frontal lobe dysfunction. However, the importance of these neuromodulators in frontal lobe functioning, and the relative success of pharmacologic interventions in the energizing and executive domains we report here, suggest that such combined therapeutic approaches may be a promising area of future research.

Conclusions and recommendations

Frontal lobe functions are critical to adaptive functioning and quality of life. These functions are sensitive to numerous brain diseases, especially

strokes, tumors, traumatic brain injury and psychiatric disorders. As these functions are at the apex of cognition, they are sensitive to damage throughout the neuraxis. The true prevalence of handicap owing to frontal lobe dysfunction is inestimable, with societal costs surely in the billions.

Considering the foregoing, it is remarkable that there are no standardized, accepted rehabilitation methods for people with deficits due to frontal lobe damage. In the fields of speech and language or physical therapy, numerous efficacious interventions have been derived from established, validated models. Patients may be classified according to the specific system affected. Outcome measures are available to objectively assess functional changes. These features provide a framework for conducting RCTs, including long-term follow-up. In the case of frontal lobe functions, broadly accepted theoretical frameworks are hard to come by, there is no classification system for patients with heterogenous deficits, and few outcome measures exist by which generalization may be assessed. The framework for conducting high-quality research in rehabilitation of frontal lobe functions has yet to be built.

We have attempted to describe frontal lobe functions and classify interventions according to one model by which four fundamental functions are identified: energization, executive, self-regulation and metacognition. While this model may require modification according to future research, it provides an example of objective classification of deficits required for the appropriate targeting of interventions, just as an analysis of linguistic capacity would influence selection of language rehabilitation.

Rehabilitation of frontal functions is in its infancy. Evidence from a few high-quality studies and carefully conducted clinical group studies shows promise for both behavioral and, increasingly, pharmacologic interventions. Moreover, the application of neuroimaging techniques will help to better define targets, evaluate and ultimately enhance rehabilitation strategies by integrating neural and behavioral measures both pre- and post-intervention. The questions posed by rehabilitation of frontal functions (e.g., is metacognitive awareness necessary for functional improvement? Can generalization be trained in patients who lack mental flexibility?) concern the highest forms of consciousness in humans. Research on these questions can therefore feed back into theory, ultimately contributing to a foundation necessary for the building of interventions.

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