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Editorial

Memory and ECT: From Polarization to Reconciliation

Discussions of the cognitive effects of electroconvulsive therapy (ECT) have been polarized for decades. Critics of the treatment often claim that patients only seem improved after ECT because they are "punch drunk"—too confused to maintain a depressed state (Sterling, 2000). Others contend that profound and permanent amnesia is common and a clear sign that the treatment causes brain damage (Frank, 1990). Still others have charged that the adverse effects are more pervasive than retrograde amnesia, with ECT impairing the most complex of human cognitive functions, i.e., intelligence, creativity, judgment, foresight, etc. (Breeding, 2000).

In contrast, practitioners and researchers often state that the adverse cognitive effects of ECT are transient. Within a few weeks of the acute treatment course, cognitive function is restored. If any residual deficit is acknowledged, it is restricted to gaps in memory for events that occurred close in time to the treatment. Some state that the memory loss is limited to the period of the treatment, while others extend this to a period of a few weeks or months surrounding the ECT course. Complaints of pervasive and persistent memory loss have often been attributed to causes other than ECT, typically persistent psychiatric disability.

Both views are out of keeping with clinical experience and research. Scores of studies have failed to find an association between clinical outcome and the depth of any cognitive deficit during or following ECT (Sackeim, 1992). People do not get better because they are confused or amnestic. To the contrary, many cognitive domains, including "intelligence," improve shortly following ECT (Sackeim et al., 1992). On the other hand, virtually all patients experience some degree of persistent and, likely, permanent retrograde amnesia. A series of recent studies demonstrates that retrograde amnesia is persistent, and that this long-term memory loss is substantially greater with bilateral than right unilateral ECT (Weiner et al., 1986b; McElhiney et al., 1995; Lisanby et al. [in press]; Sackeim et al. [in press]. It has also become clear that for rare patients the retrograde amnesia due to ECT can be profound, with the memory loss extending back years prior to receipt of the treatment.

As a field, we have more readily acknowledged the possibility of death due to ECT than the possibility of profound memory loss, despite the fact that adverse effects on cognition are by far ECT's most common side effects. Individual differences and hypersensitivity to side effects characterize virtually all medical procedures and pharmacological treatments. That ECT would have an especially narrow range of amnestic effects would be a remarkable exception.

Undoubtedly, reaching consensus on this fundamental issue has been impeded by the fact that memory complaints are subjective and can have multiple determinants. Some of the neuropsychological deterioration seen after ECT is due to natural progression of an

underlying illness. In young patients, seemingly irreversible cognitive decline may accompany the first manifestation of a psychotic disorder (Wyatt, 1991). When ECT is used early in the treatment of such patients, the precipitous cognitive decline is at times wrongly attributed to this therapeutic intervention. Similarly, ECT may unmask an underlying dementia in older patients.

It is also the case that in all populations studied (normal, neurological, psychiatric), current mood state is the most important correlate of subjective evaluation of memory function (Coleman et al., 1996). We believe that our memory (and other cognitive functions) are less intact when we are depressed. On the other hand, regardless of the population studied, subjective evaluations and objective measures typically show poor association (Sackeim and Stern, 1997).

Another complication is that some patients with persistent memory complaints following ECT have no treatment-related deficits. Rather, the subjective experience of cognitive deficit is related to ongoing psychopathology. While there is compelling evidence that this occurs with some frequency (Freeman et al., 1980), for understandable reasons the profession has not emphasized this phenomenon. In the consent form recommended by the 1990 APA Task Force Report on ECT (American Psychiatric Association, 1990), it was acknowledged that a minority of patients report severe memory problems, with the comment that, "The reasons for these rare reports of long-lasting impairment are not fully understood" [p. 158]. Some of the reasons were understood, but it is uncomfortable for the field to be perceived as "blaming the victim," and attributing memory complaints to unresolved psychiatric disturbance, even if true.

However, aside from each of these possibilities, some patients experience profound memory loss due to ECT. Most ECT practitioners have encountered fully credible patients who are distressed by the magnitude of their persistent post-ECT amnesia. Skeptics will argue that complaints of memory loss do not necessitate true disability, and that we have no objective "dipstick" to verify that memory is truly impaired. On the other hand, there is no dearth of patients who have received ECT who believe that the treatment was valuable, often life saving, who are not litigious, who return to productive activities, and yet report that a large segment of their life is lost. These patients often report a classic temporal gradient in their retrograde amnesia, with the memory loss most accentuated for the time period (months to years) closest in time to the treatment, with sparing of more remote memories. It is hard to imagine that such reports of a classic retrograde amnestic syndrome, with sparing of other cognitive functions, are simply fabricated. Attributing these subjective deficits to ongoing psychopathology or natural disease progression would seem disingenuous and defensive.

There have been few personal accounts of the amnesia following ECT (Wolfe, 1969). In this issue of *The Journal of ECT*, Anne B. Donahue provides a compelling description of the nature and impact of the persistent memory loss she experiences. In many ways this is a courageous statement, acknowledging the clinical benefit of the treatment, and alerting the field about the mismatch between our efforts to assess objectively cognitive alterations and the phenomenology of the memory loss. Donahue's paper also underscores the public relations fallout and, more critically, the turmoil to individuals that result when former patients experience chronic and pervasive memory loss and yet the field denies the possibility of its occurrence.

Fortunately, the tide has turned. The field has greater awareness of the common am-

nestic effects of the treatment, and reconciliation is occurring with the experience of exceptional patients with substantial and sustained memory loss. The newly revised APA Task Force Report (APA, in press) on ECT states:

In many patients the recovery from retrograde amnesia will be incomplete, and there is evidence that ECT can result in persistent or permanent memory loss. Owing to a combination of anterograde and retrograde effects, many patients may manifest persistent loss of memory for some events that transpired in the interval starting several months before and extending to several weeks following the ECT course. There are individual differences, however, and, uncommonly, some patients may experience persistent amnesia extending several years prior to ECT. Profound and persistent retrograde amnesia may be more likely in patients with preexisting neurological impairment and patients who receive large numbers of treatments, using methods that accentuate acute cognitive side effects (e.g., sine wave stimulation, bilateral electrode placement, high electrical stimulus intensity).

This change in attitude and understanding compel closer clinical and research attention to the cognitive effects of treatment. The papers in this special issue highlight some of the key unanswered questions.

TREATMENT TECHNIQUE AND AMNESIA

It has become increasingly clear that the sophistication with which ECT is conducted impacts not only on short-term cognitive effects, but also on the likelihood of long-term persistent changes. Lerer and colleagues review the effects of treatment schedule (using bilateral ECT) on adverse cognitive effects. This work (Lerer et al., 1995; Shapira et al., 1998) has demonstrated a principle regularly used by clinicians. Increasing the interval between treatments reduces the magnitude of cognitive impairment. In terms of long-term consequences, the choice of electrode placement (right unilateral versus bilateral ECT) may be more consequential than the electrical dosage administered and perhaps the treatment schedule (Weiner et al., 1986b; Sackeim et al., 1993; McElhiney et al., 1995; Lisanby et al., in press; Sackeim et al., in press). It appears that high dosage right unilateral ECT is as effective as robust forms of bilateral ECT, but has significantly less probability of resulting in marked and persistent retrograde amnesia (Abrams et al., 1991; Sackeim et al., in press; McCall et al., in press). Further refinements of ECT technique may additionally limit cognitive side effects. Perhaps the most attractive possibility is shortening the width of the brief-pulse stimulus. The pulse widths most commonly used are an order of magnitude longer than that needed for neuronal depolarization, and thus necessarily involve stimulation after neurons have fired (Sackeim et al., 1994).

Some practitioners have held the view that the focus of ECT research in the last two decades on optimizing stimulus dosing and waveform, electrode placement, and spacing of treatments was largely academic. High intensity treatment (e.g., high fixed dosage bilateral ECT) is the least complicated to administer and has the highest probability of efficacy. Given the view that all adverse cognitive effects are transient, with rapid resolution, for some there was little incentive to adopt new treatment methods. As recent research has consistently demonstrated that treatment technique impacts on the magnitude of persistent memory loss, this position becomes difficult to defend.

INDIVIDUAL DIFFERENCES AND ADVERSE COGNITIVE EFFECTS

It would be comforting to attribute all the negative cognitive outcomes with ECT to poor technique. However, regardless of how ECT is performed there are individual differences. Using the same technique, clinicians regularly encounter patients who respond to ECT without any cognitive alterations (or, indeed, may show resolution of preexisting cognitive deficits during and following the ECT course) as opposed to patients who develop delirium. Why?

Over the 65 years of use of convulsive therapy, there have been scores of studies examining the patient characteristics (phenomenology, clinical history, treatment history, biology) that predict therapeutic outcome (Scott, 1989; Nobler and Sackeim, 1996). Essentially, there has been one systematic report on the patient characteristics that predict short- and long-term cognitive outcome after ECT (Sobin et al., 1995). That study suggested that patients with pre-ECT global cognitive impairment and those with prolonged disorientation in the postictal state have more profound short- and long-term retrograde amnesia. This would suggest that treatment techniques be "softened" especially for patients with these characteristics. However, practitioners routinely face issues of this type that are unexplored. Does preexisting neurological illness (stroke, Parkinson's disease, dementia, etc.) predispose to long-term cognitive deficits? What is the contribution, if any, of comorbid substance abuse, concurrent antidepressant or antipsychotic pharmacotherapy, cardiac illness (low cardiac output), benzodiazepine use, etc., to post-ECT cognitive deficits? We have no answers to these questions.

PREVENTION AND TREATMENT OF COGNITIVE DEFICITS

The side effects of many pharmacological treatments are actively treated (e.g., anticholinergics for neuroleptic-induced extrapyramidal symptoms). Electroconvulsive shock (ECS) is the most common procedure used to induce amnesia in animals to screen pharmacological compounds for protective effects on memory. Our estimate is that between 50–100 compounds have shown benefit in ECS models (Krueger et al., 1992). For example, in this issue Andrade and colleagues review research on herbal preparations that ameliorate the cognitive effects of ECS in animal models (Joseph et al., 1994; Faruqi et al., 1995; Andrade et al., 1995; Vinekar et al., 1998), and discuss the strengths and weaknesses of animal models in generalizing to human ECT.

The interest of the pharmaceutical industry in using ECS as a screening method for identifying compounds with promemory effects is not to develop adjunctive medications for ECT. The ECT market is too small, and the predominant aim has been to develop medications for the treatment of dementing disorders (Krueger et al., 1992). Consequently, only a handful of studies have tested pharmacological adjuncts for protective effects in ECT (Stern et al., 1991; Prudic et al., 1999).

Concerted research in this area has the potential for making an important clinical contribution, as well as advancing our understanding of the neurobiology of ECT's amnestic effects. One example illustrates these possibilities. There is considerable interest in the notion that ECT results in altered glutamatergic transmission, particularly in prefrontal and medial temporal lobe structures (Morinobu et al., 1997; Pilc et al., 1998; Hiroi et al., 1998), and that this increased excitatory transmission contributes to amnestic effects

(Chamberlin and Tsai, 1998). Long-term potentiation (LTP) has been commonly viewed as a model of memory formation, and ECS results in long-term disruption of LTP in the dentate gyrus (Stewart et al., 1994; Stewart and Davies, 1996). The NMDA antagonist, ketamine, protects against this disruptive effect (Stewart and Reid, 1994), raising the possibility that use of ketamine as an anesthetic, as opposed to the standard short-acting barbiturates, or use of other glutamatergic antagonists may have a protective effect on cognition (Reid and Stewart, 1997).

THE NATURE AND NEUROBIOLOGY OF ADVERSE COGNITIVE EFFECTS

There are additional goals for future research on the cognitive consequences of ECT. We need to 1) better characterize the nature of memory deficits (i.e., what is forgotten), 2) better characterize the neural systems implicated in these amnestic effects, particularly the role of prefrontal versus medial temporal lobe memory systems, and 3) determine the impact of ECT on neurocognitive functions other than memory (Calev et al., 1995).

It has been commonly thought that the memory deficits following ECT reflect medial temporal lobe dysfunction (Squire, 1981; 1986a;1986b; Sackeim, 1992). The most prominent deficits are anterograde amnesia (rapid forgetting of newly learned information) and a temporally graded retrograde amnesia. ECT patients do not show deficits in priming, skill acquisition, or other types of procedural (nondeclarative) memory (Cohen and Squire, 1980; Squire et al., 1984; Graf et al., 1984; Squire et al., 1985). The rapid forgetting rate (Squire, 1981), preserved metamemory ("feeling of knowing") (Shimamura and Squire, 1986), and other features (Squire, 1982) distinguish the amnesia following ECT from that due to diencephalic lesions or Korsakoff's syndrome. This pattern, largely restricted to episodic, declarative memory, suggests that the underlying disturbance is one of consolidation and/or retrieval (Squire and Alvarez, 1995). The reversibility of amnesia, with the recovery of memories over time, particularly implicates an impaired retrieval process. The established role of medial temporal lobe structures in memory processes (Shimamura and Squire, 1987; Nadel and Moscovitch, 1997), the low threshold for afterdischarge and seizure elicitation in the hippocampus (Ajmone Marsan, 1972; Bragin et al., 1997), and the disruption by ECS of hippocampal processes implicated in memory (e.g., LTP) (Reid and Stewart, 1997) support the view that medial temporal lobe dysfunction is key.

However, there is hardly any physiological evidence linking medial temporal lobe dysfunction to the memory deficits following ECT. In this issue, we report that the development of EEG (electroencephalographic) theta activity in left frontal and temporal sites is associated with greater retrograde amnesia for autobiographical information, partially supporting the medial temporal lobe hypothesis. In contrast, there is consistent evidence that ECT exerts its most profound physiological effects in prefrontal cortex, as assessed by reductions in cerebral blood flow (Rosenberg et al., 1988; Silfverskiöld and Risberg, 1989; Nobler et al., 1994) and metabolic rate (Volkow et al., 1988; Guze et al., 1991), and the induction of EEG slow-wave activity (Fink and Kahn, 1956; Weiner et al., 1986a; Sackeim et al., 1996). Thus, there is the paradox that the most prominent cognitive effects are linked to a different brain region than the most pronounced physiological effects. There is a compelling need to examine associations between the magnitude of

cognitive effects and regional alterations in functional brain activity (e.g., metabolic rate) and biochemical parameters.

It is noteworthy that the classic deficits associated with hippocampal damage are a profound anterograde amnesia and a less marked retrograde amnesia (Russell and Nathan, 1946; Milner, 1970; Damasio et al., 1985). In contrast, ECT results in a rapidly resolving anterograde amnesia and persistent retrograde amnesia (Squire, 1986a; Weiner et al., 1986b; Sackeim et al., in press). In addition, the retrograde amnesia following hippocampal damage is believed to be greater for autobiographical than public (impersonal) events (Nadel and Moscovitch, 1997). We have recently shown that the opposite is the case following ECT (Lisanby et al., in press). Both in the short and long term, patients who received ECT had denser amnesia for events in the world (public knowledge) than for events in their own lives. Frontal lobe damage can result in profound retrograde amnesia (Stuss and Benson, 1986; Kopelman, 1992; Moscovitch, 1994; Shimamura, 1994), in some comparisons as great as temporal lobe pathology (Kopelman et al., 1999), and presumably due to the disruption of retrieval processes. In amnesic patients (with brain damage), anterograde and retrograde memory loss are often weakly associated, and there is evidence that tests of frontal lobe function can covary with the magnitude of retrograde amnesia (Kopelman, 1991). Thus, a reasonable argument can be made that our traditional view that the (retrograde) amnestic effects of ECT result from functional disruption of medial temporal lobe structures is wrong, and the retrograde amnesia may, in fact, have an important frontal lobe involvement.

Resolving this issue, while of obvious importance to our understanding of the neurobiology of retrograde amnesia, is also of clinical significance. The development of alternative electrode placements, such as the bifrontal (Lawson et al., 1990; Letemendia et al., 1993; Bailine et al., 2000) and the asymmetric (Swartz, 1994) techniques, are predicated on the notion that avoidance of temporal lobe stimulation minimizes adverse cognitive effects, while frontal lobe stimulation preserves efficacy. If prefrontal changes subserve the retrograde amnesia these efforts may be largely in vain.

The prefrontal cortex is linked to a variety of "executive functions," including working memory (holding information online), logical reasoning and abstraction, set shifting, temporal organization of behavior, planning, memory for the context of events, and inhibition of competing, prepotent responses (Baddeley, 1986; Stuss and Benson, 1986; Goldman-Rakic, 1987; Diamond, 1990; Fuster, 1990). Tasks assessing prefrontal functions may load on different dimensions than tasks presumed sensitive to medial temporal lobe function (episodic, declarative memory), and there is some evidence that performance on prefrontal tasks predicts the adequacy of memory for the source or context of information (Glisky et al., 1995) and retrograde amnesia (Kopelman, 1991). Executive functions are fundamental to organizing one's life and controlling behavior, yet there has been little investigation of the impact of ECT on this domain (Jones et al., 1988).

SUBJECTIVE EXPERIENCE OF COGNITIVE EFFECTS

In this issue, Prudic and colleagues summarize what is known about patients' own assessments of the effects of ECT on cognition. It appears that over time there has been a detectable shift. In older studies, largely using sine wave stimulation, a long-term detrimental impact was observed, especially with bilateral ECT (Squire et al., 1979;

Squire and Slater, 1983). Modern studies report that within a few days of ECT the vast majority of patients evaluate their memory as improved (Sackeim et al., 1993; Sackeim et al. (in press). This shift may be attributable to the advances in ECT technique (use of titration, brief pulse stimulation, etc.).

However, we should not be sanguine. ECT research has mainly relied on a single instrument to obtain self assessments of memory function, the Squire Subjective Memory Questionnaire (SSMQ) (Squire et al., 1979). The SSMQ is limited in the dimensions of metamemory that it examines, and is extraordinarily complex in its instructions. Patients are asked to rate their current functioning for discrete cognitive activities relative to their functioning before the onset of the index episode of depression. Perhaps not surprisingly, it has been shown that a substantial number of responses to the SSMQ are of doubtful validity. It is not infrequent for patients to state that their current cognitive function a few days after ECT is superior to that before the onset of the depressive episode, an unlikely phenomenon (Coleman et al., 1996). Broader-based assessment techniques are needed. It is especially surprising that direct and simple inquiries about whether ECT has had a positive or detrimental effect on memory have not been used in recent research. An older literature illustrated that such direct inquiries were effective in distinguishing ECT waveforms (Medlicott, 1948) and electrode placements (Cannicott, 1962; Fleminger et al., 1970).

Prospective patients, family members, and the public often want to know the frequency with which patients report substantial memory impairment following ECT. While we believe that such reports are infrequent, there is little objective evidence to support this judgment or to even broadly estimate base rates. Indeed, our estimates of the probability of death with ECT are based on a more secure empirical foundation (Abrams, 1997) than our estimates of marked subjective memory loss. This should be a readily resolvable issue, and calls for a large sample study in community settings.

In short, as the quality and sensitivity of neurocognitive research in ECT have improved, increasing evidence has accumulated that some degree of persistent memory loss is common. As the dialectical political battles of the 1960s and 1970s recede, there is greater acceptance and acknowledgment by the profession that ECT may infrequently result in extensive retrograde amnesia. At the clinical level, this shift in perspective highlights the need for practitioners to update what is communicated in the consent process and to monitor cognitive outcomes. This shift also presents many challenges for research, the most important of which is to further reduce or eliminate these adverse effects of ECT.

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