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Brief Report

AGE-RELATED COGNITIVE EFFECTS OF ECT AND ECT-INDUCED MOOD IMPROVEMENT IN DEPRESSIVE PATIENTS

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This explorative study investigated the interaction between electroconvulsive therapy (ECT) treatment-effect, reduced depression, and neuropsychological outcome in relation to age. Follow-up neuropsychological assessment was conducted with depressive patients treated with ECT. From a potential sample of 45 patients, the neuropsychological measures (pre-ECT, three times post-ECT, up to 12 months) and clinical data from the remaining 21 patients who completed all assessments were evaluated (mean age = 56.76; SD = 14.12; range, 33–79). ECT resulted in a decrease in the depression scores. A distinct impact of ECT and depression decrease on cognitive domains was found. Depression alleviation was mainly associated with improvement in cognitive domains such as memory, information processing, and executive function. ECT improved cognitive domains such as information processing and perception. Short-term cognitive improvement was greater in older patients but showed an increase similar to that at long-term follow-up in younger patients (<60). Current findings provide evidence that ECT may improve cognitive functioning in nondemented elderly, which has strong clinical relevance concerning the use of ECT. Depression and Anxiety 23:93–101, 2006.

Key words: *electroconvulsive therapy; mood disorders; neuropsychology; follow-up; elderly; cognition*

INTRODUCTION

Depression in the older population is a major public health problem; it has a high prevalence, is frequently comorbid with medical illnesses, has a negative impact on quality of life, and carries a high risk of suicide [Lebowitz et al., 1997; McCall et al., 1999; Serby and Yu, 2003]. According to fairly recent community-based studies, minor depression is estimated to occur in more than 10% of the older population, and major depression less frequently [Beekman et al., 1999; Forsell and Winblad, 1999]. Depression in older people is often therapy resistant, partly because of persistence and recurrence, and partly because of the interactions with medicines used to treat their systemic disorders [Fink, 2001]. An extensive literature review, including meta-analyses, of drug and electroconvulsive therapy (ECT) treatment of depression in older people between 1996 and 2001, revealed that ECT is more efficacious than antidepressants, and may therefore be the most appropriate treatment for severely depressed older people [Salzman et al., 2002]. As a consequence, in the last decade, the use of ECT has expanded for the treatment of older depressive patients.

The American Psychiatric Association Committee on Electroconvulsive Therapy [2001] considers ECT an effective treatment for severe depression. The UK

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ECT Review Group [2003] conducted a systematic review and meta-analyses of randomized controlled trials and observational studies, concluding that ECT appears to be an effective short-term treatment for depression, and that treatment with ECT is more effective than simulated ECT and pharmacotherapy. In addition, bilateral ECT is relatively more effective than unilateral ECT, and high-dose ECT is more effective than low-dose ECT. However, there is evidence that one of the adverse effects associated with ECT is cognitive dysfunction, particularly memory dysfunction [Rami-Gonzalez et al., 2001]. Contrary to this evidence, ECT has also been found to have positive effects on information processing [Hasse-Sander et al., 1998; Kalb et al., 2003], and so-called "non-memory cognition" [Calev et al., 1995]. Calev et al. argued that it is the alleviation of depression, as well as the effects of ECT itself, that led to the improvement in cognitive functioning.

With the increase of the older population, particularly the "older-old" age group, it is of growing importance to clarify and reduce the cognitive risks associated with ECT in older people. Several studies on the short-term outcome of ECT in psychiatric patients indicate that ECT is effective for treating depression in the older people [Brodaty et al., 2000; Casey and Davis, 1996; Gormley et al., 1998; Kujala et al., 2002; Mulsant et al., 1991; Rubin et al., 1993; Tew et al., 1999; Tomac et al., 1997; Williams et al., 1997]. Little is known about the effects at longer term. Wesson et al. [1997] were the first to investigate prospectively the longer term (2–4 years) outcome of ECT-treated, operationally defined depression with respect to age. Their findings suggested a significant association between increasing age and probability of improvement prognosis. A more recently published multicenter study of the Consortium of Research in ECT [CORE; O'Connor et al., 2001] also reports that age is positively associated with the response to bilateral ECT treatment of major depression; remission rates on the Hamilton Rating Scale for Depression [HRSD; Hamilton, 1967] for three age-groups—≥ 65 years, 46–64 years, and ≤ 45 years—were 90.0%, 89.8%, and 70.0%, respectively. Age, as a continuous variable, positively influenced response to treatment [O'Connor et al., 2001]. Flint and Gagnon reviewed the prior 10 years of research literature in 2002. They concluded that technical factors, such as electrical stimulation relative to convulsion threshold, electrode placement (uni- or bilateral), and frequency of treatment, may impair cognitive function and should be considered when balancing efficacy and speed of response with potential side effects. However, when administered in an optimal manner, ECT is considered a safe, well-tolerated, and effective treatment in older patients [Flint and Gagnon, 2002].

Age is also associated with an increased risk of cognitive side effects. For example, Zervas et al. [1993] reported that cognitive deficits, measured 24 to 72 h after ECT treatment, were more severe in older individuals. However, these deficits disappeared at 6-month follow-up. In contrast, some other studies found no indication for differences between older and younger patients concerning ECT response [Brodaty et al., 2000; Tew et al., 1999; Wilkinson et al., 1993]. Regarding positive effects on cognition, Wilkinson et al. found that Mini-Mental State Examination (MMSE) scores recorded 72 h to 1 week after ECT course improved in all age groups, but magnitude of improvement was largest in older patients. In their review, Flint and Gagnon [2002] commented that this unexpected finding of improved cognition following ECT points to a complicated interaction between cognitive functions, changes in depression, and ECT administration.

Based on these findings of improved cognitive performance following ECT [Hanse Sander et al., 1998; Kalb et al., 2003; Rao and Lyketsos, 2000; Wesson et al., 1997; Wilkinson et al., 1993], we studied the distinct effects on neuropsychological outcome of ECT per se and of reduced depression resulting from ECT. In addition, we investigated the ECT-induced cognitive changes in relation to the age of the patients. We expected ECT to reduce depression substantially. This alleviated depression was expected to improve some cognitive functions, that is, those affecting mainly memory and information processing. Independently, we expected that ECT would impair the quality of some cognitive functions and improve that of others.

MATERIALS AND METHODS

SUBJECTS

Patients were referred to the Psychiatric Hospital GGZ Delfland in Delft, The Netherlands, for ECT by their psychiatrists in the region of Delft. All patients in this study were recruited from this population. They met the criteria for major depressive episodes of uni- or bipolar mood disorder according to DSM-IV-R criteria and were medication resistant, which is a strict indication for ECT in the Netherlands [Nederlandse Vereniging voor Psychiatrie, 1992]. They had a pretreatment score of at least 18 points on the 17-item HRSD [Hamilton, 1967]. Exclusion criteria for this study were dementia, premorbid IQ below 70, inadequate knowledge of the Dutch language (i.e., non-native speaker), severe somatic illness, and alcohol or drug abuse. All patients provided written informed consent. Initially, a consecutive sample of 45 patients treated with index ECT between December 1, 1997, and February 1, 2000, were eligible for this study. All patients started index ECT as inpatients, and most were discharged during maintenance treatment and follow-up measures. Index ECT was defined as the first treatment course of ECT.

TABLE 1. Characteristics of the age groups

	<60 years	≥60 years	Total group
Male (*N*)	7	3	10
Female (*N*)	5	6	11
Mean age ± *SD*	46 ± 6.3	71 ± 7.5	57 ± 14
Unipolar (*N*)	7	7	14
Bipolar (*N*)	5	2	7
HRSD	22 ± 5	23 ± 7	23 ± 6
Maintenance ECT (*N*)/medication	4/8	2/7	6/15
Number of index ECT	13 ± 3.7	10 ± 3.6	12 ± 4
Number of unilateral index ECT	10 ± 4	10 ± 4	10 ± 4
Number of bilateral index ECT	3 ± 4	0 ± 0	2 ± 4

The neuropsychological assessments took place 1 week before ECT (session 1), 1 to 2 weeks after index ECT (session 2; $M = 6.9$ days, $SD = 4.75$), 6 months after index ECT (session 3), and 12 months after index ECT (session 4). From the potential sample of 45 patients, 21 patients (10 males, 11 females; mean age = 56.76, $SD = 14.12$; range, 33–79) participated in all four assessments and were evaluated. The patients who missed one or two of the following assessments due to various reasons (e.g., medical events, personal circumstances, lack of motivation, and protocol violation) were excluded from this study. Of the 21 patients, 13 met the criteria for major unipolar mood disorder, and 8 met criteria for major depressive episodes of bipolar mood disorder. The total group was divided into older (age 60 or above) or younger patients ($n = 9$ and $n = 12$, respectively). Patient characteristics, clinical outcome data, and psychometric measurements of both groups were compared (Table 1).

ECT DEVICE AND TREATMENT PROCEDURE

The ECT procedure was conducted according to the protocols of the Dutch Association of Psychiatry [Van den Broek et al., 2000], which require that all patients undergo a complete medical, psychiatric, and laboratory examination. Anesthesia was induced with intravenous thiopentone sodium (4–5 mg/kg) and succinylcholine (0.5–1.0 mg/kg). The blood oxygen level was kept above 95%. Seizures were induced with the Thymatron DGx twice weekly, which produced a customized brief-pulse, constant current, with a maximum stimulus level of 1,008 mC. Treatment was started with right unilateral d'Elia electrode placement, which was changed to bifrontotemporal bilateral placement [Kellner et al., 1997] if there was an insufficient response after six sessions. The stimulus settings were initially based on age [Abrams, 1997] and adjusted for the concurrent medication used; the stimulus setting was adjusted 5–10% upwards with the use of benzodiazepines and antiepileptics. The length of the seizures measured by electroencephalogram (EEG) was kept above 20 s. If seizure duration fell below 20 s, the stimulus setting was raised at the next session. ECT was stopped when remission was achieved, if there was a lack of further improvement, or if intolerable side effects occurred. The mean number of sessions in an ECT course was 12.17 ($SD = 3.93$, range, 5–19). After the ECT course, clinician and patient decided to continue treatment with either maintenance pharmacotherapy or maintenance ECT. Arguments for continuing ECT treatment were incomplete remission, early signs of relapse, or preference of the patient for maintenance ECT. Maintenance ECT has no fixed end point and aims to prevent recurrence of relapses, like maintenance pharmacotherapy [American Psychiatric Association, Committee on Electroconvulsive Therapy, 2001; Gagne et al., 2000].

In this naturalistic study, antidepressants and mood stabilizers were used in maintenance pharmacotherapy. Maintenance ECT was administered the same way as index ECT, and continued directly after index ECT for 6 of the 21 patients (5 unilateral, 1 bilateral). One patient, diagnosed with bipolar I mood disorder (DMS-IV code: 269.4) switched from maintenance medication to maintenance ECT after 15 months.

CLINICAL ASSESSMENT

Prior to the ECT course a physical examination was conducted to investigate contraindications to ECT. The physician who examined the patient also completed the 17-item HRSD [Hamilton, 1967]. In addition, for subjective mood evaluation, patients were asked to complete the Beck Depression Inventory [BDI; Beck et al., 1961]. These clinical assessments were not conducted blindly, because patients and clinicians were aware of treatment conditions. The mean HRSD score before index ECT for the total group was 22.52 ($SD = 5.93$; range, 13–33; median = 21); two patients had scores lower than 18. The BDI was not completed by most of the patients during the first assessment. Therefore, the results on the BDI could not be analyzed systematically in this study. During index ECT, weekly clinical assessments using the same questionnaires were made on the day before ECT administration. Index ECT was continued until the HRSD remained stable or complete remission, defined by a HRSD score below 7.0, was achieved. The mean HRSD score after ending the ECT course was 8.39 ($SD = 6.81$; range, 0–30; median = 6.5).

After completing index ECT, clinical assessments with the HRSD were made by the clinician at irregular intervals during maintenance ECT or maintenance pharmacotherapy. Unfortunately, these irregular intervals were not compatible with the neuropsychological assessments. Therefore, the HRSD could not be used

as measurement of changes in mood during all four assessments.

During each neuropsychological assessment, the patient was asked to complete the BDI and the Dutch Utrecht's Coping List [UCL; Scheurs et al., 1993] to measure the coping style of the patient, that is, the "depressive reaction pattern." The UCL, a self-rating scale measuring trait aspects of coping, consists of seven subscales, one of which is "depressive reaction pattern" (scores ranging from 7 to 28). The scale is quite reliable (Cronbach's α determined in 1,200 healthy employees, alpha = .70; in 289 patients in a general practice, $\alpha = .74$). The construct validity is good, as reflected by the observed correlations with the Zung depression scale ($r = .60$) and with trait anxiety of the State–Trait Anxiety Inventory ($r = .70$). Thus, the "depressive reaction pattern" subscale of the UCL is strongly correlated with anxiety and depression. We used this scale for measuring changes of depression because of its correlation with the Zung depression scale and its high stability [test–retest correlation: patients in health care center ($n = 360$; interval 4–5 months), $r = .69$; random sample Dutch population ($n = 229$; interval, 17 months), $r = .74$].

NEUROPSYCHOLOGICAL ASSESSMENT

Trained neuropsychologists, blind to maintenance treatment status, performed the neuropsychological assessments, separately in each patient. Neuropsychological test sessions took place during the morning and lasted up to 1.5 h. Participants were tested on attention and executive functions, memory, and intelligence. The following tests were administered: (1) the Stroop Color–Word Test [Hammes, 1978; Stroop, 1935], measuring attention and inhibition [MacCleod, 1991]; (2) Dutch 10-Word List Memory Test, measuring long-term verbal learning, parallel versions [Saan and Deelman, 1986]; (3) the subtests Information, Orientation, Mental Control, Logical Memory, Digit Span Forward and Backward, Visual Reproduction, and Associative Learning from the Wechsler Memory Scale [WMS; Wechsler, 1974, 1987]; (4) a short version of the Dutch Groninger Intelligence Test [GIT; Luteijn and Van der Ploeg, 1982], consisting of the subtests Verbal Meaning, Word Fluency (categories), Word Matrices, Visualization, and Closure Speed, resulting in an intelligence quotient; (5) the experimental Memory and Orientation Questionnaire [MOQ; Bosboom, 2002], measuring the recall of episodic and semantic memory of general and personal knowledge; (6) Benton Revised Visual Retention Test [BVRT; Benton, 1974], measuring visual episodic memory; and (7) the Subtest Digit Symbol of the Dutch Wechsler Adult Intelligence Scale [WAIS; Stinissen et al., 1970], measuring memory consolidation, sustained attention, visuomotor coordination, and motor response speed [Lezak, 1995]. Because of sensitivity to practice effects due to repeated test taking, parallel versions for the follow-up testing were used to reduce these possible practice effects [see, e.g., Lezak, 1995].

DATA ANALYSIS

Changes in neuropsychological parameters at two consecutive test sessions were analyzed both by analyses of variance (ANOVAs) and covariance (ANCOVAs) with test session as a repeated measurements factor. With regard to the ANCOVAs, δ depression (difference between two sessions) was used as covariate. The comparison of analyses with and without δ depression as covariate made it possible to separate effects of ECT and depression reduction on cognitive parameters. If analyses with the covariate δ depression, eliminating the effect of change in depression, yielded a significant result concerning a specific cognitive parameter, ECT was assumed to be responsible for the obtained effects. In case of a significant ANOVA in combination with nonsignificant ANCOVA results concerning the same parameter, effects were assumed to be caused by alleviated depression; that is, a significant ANOVA would reflect the effect of δ depression *or* ECT on neuropsychological parameters. If this effect disappears after eliminating the influence of δ depression (by using it as a covariate in the ANCOVA), the significant ANOVA effects can be attributed to δ depression and not to ECT.

In addition, age effects were analyzed by means of ANOVAs, with age category (below age 60 or age 60 and above) serving as between-subjects factor, and with sessions 1, 2, 3, and 4 serving as repeated measurements factor.

All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) version 10.0 for Windows. Tests were two-tailed, and a P value of .05 or less was considered significant.

RESULTS

The mean age of the total group of patients was 56.76 ($SD = 14.12$; range, 33–79; Table 1). There were no significant differences in patient characteristics and treatment effects on depression between the age groups.

Regarding the course of the depression scores of the UCL, a general decrease in scores was found across sessions 1, 2, 3, and 4 [$F(3, 18) = 8.45$, $P = .01$, $\eta^2 = 0.58$; mean session 1 = 19.45, mean session 2 = 14.9; mean session 3 = 15.9; mean session 4 = 16.69]. Specifically, a significant decrease in depression was found only between sessions 1 and 2 [$F(1, 20) = 14.3$, $P = .001$, $\eta^2 = 0.42$; mean session 1 = 19, mean session 2 = 15] and between sessions 1 and 4 [$F(1, 20) = 10.7$, $P = .004$, $\eta^2 = 0.35$; mean session 4 = 17]. No reduction in depression was found between sessions 2 and 3 and between sessions 3 and 4. That means that cognitive changes between sessions 2 and 3

and between sessions 3 and 4 can be specifically attributed to the effects of ECT.

As is pointed out in the Data Analysis section, cognitive changes during each interval between two consecutive time points were separately analyzed. Results of analyses with δ depression (i.e., UCL scores) as covariate reflected the effects of ECT per se on cognition because of ruling out the effect of changes in depression. If analyses with δ depression did not yield significant effects but the analyses without covariate did, the effect was attributed to changes in depression. Because there was no significant change in depression between sessions 2, 3, and 4, analyses with δ depression as covariate were only performed for differences between sessions 1 and 2 and sessions 1 and 4.

Table 2 summarizes the significant results of the AN(C)OVAs performed on the interval between sessions 1 and 2, 2 and 3 (6 months after ECT), 3 and 4 (12 months after ECT), and 1 and 4. All significant effects indicate an improvement in neuropsychological functions after ECT, except for Stroop Card 3, for which an increase in number of errors was seen.

It is evident in Table 1 that ECT improves all tapped cognitive domains, which are memory, language, attention and executive functions, and IQ. Because the smallest effect size η^2 is 0.20, all effects can be considered large. In Table 3, we relate these effects to ECT and/or δ depression (i.e., alleviation of depression). Significant effects with covariate δ depression are attributed to ECT, whereas significant effects without and nonsignificant effects with covariate are attributed to reduced depression. As reflected in Table 2, the alleviation of depression is associated with memory

TABLE 3. Summary of positive effects on neuropsychological test scores dominated by effect of elevation of depression (DEP) or ECT at short and long term

	Differences between test sessions			
Cognitive test variable[a]	1 and 2	2 and 3	3 and 4	1 and 4
WMS Paired Associates	ECT			ECT
10-Word List	DEP	ECT		
BVRT Correct Responses	ECT			
WMS Visual Reproduction				ECT
WMS Orientation	ECT	ECT		
MOQ Semantic Recent		ECT		
GIT Word Matrices			ECT	
Stroop Card II speed	DEP			ECT
Stroop Card III speed				DEP
WAIS Digit Symbol	ECT			ECT
WMS Mental Control	ECT			
GIT IQ			ECT	
GIT Incomplete Pictures				ECT
GIT Visualization			ECT	ECT

[a]See text for description of tests.

TABLE 2. Effect size (η^2) values of cognitive test variable for the significant differences between test sessions for effect of mood improvement or ECT (without covariate), and for effect of ECT (with covariate)

	Differences between test sessions											
	1 and 2[b]				2 and 3		3 and 4		1 and 4			
	Without covariate		With covariate		Without covariate		Without covariate		Without covariate		With covariate	
Cognitive test variable[a]	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*
■ WMS Paired Associates	0.23	0.029	0.23	0.037					0.47	0.019	0.48	0.027
■ 10-word List	0.23	0.029			0.31	0.021						
■ BVRT Correct Responses	0.20	0.048	0.27	0.031								
■ WMS Visual Reproduction									0.39	0.039	0.45	0.034
■ WMS Orientation	0.27	0.017	0.28	0.019	0.25	0.041						
■ MOQ Semantic Recent					0.50	0.033						
■ GIT Word Matrices							0.53	0.017				
■ Stroop Card II speed	0.38	0.007							0.48	0.026	0.48	0.039
■ Stroop Card III speed									0.40	0.048		
■ Stroop Card III faults	0.24	0.037	0.26	0.043								
■ WAIS Digit Symbol	0.28	0.017	0.28	0.024					0.43	0.028	0.47	0.029
■ WMS Mental Control			0.22	0.043								
■ GIT IQ							0.65	0.005				
■ GIT Incomplete Pictures									0.42	0.03	0.56	0.013
■ GIT Visualization							0.65	0.005			0.39	0.05

[a]See text for description of tests.
[b]Session 1, one week before ECT index; session 2, one week after ECT index; session 3, 6 months after session 3; 6 months after session 3.

improvement (verbal learning on a 10-word list), increased speed of information processing (Stroop Card II) and inhibition (Stroop Card III). ECT per se affects mainly memory improvement and speed of information processes as well, plus visual organization and mental control.

We studied age effects by evaluating possible interaction effects between the test sessions and the factor age (less than age 60, and age 60 and above). Mean age, severity of depression, and ECT parameters of each age group are shown in Table 1. A significant interaction between age and sessions 1 and 2 was found for the WMS Memory Quotient (MQ), WMS Mental Control score and WMS Visual Reproduction [$F(1, 19) = 4.6$, $P = .04$; $F(1, 19) = 5.4$, $P = .03$; and $F(1, 19) = 4.5$, $P = .05$, respectively; see Figs. 1, 2, and 3). The improvement on these tasks between sessions 1 and 2 is greater in the older group than in the younger group. However, as is clear from Figures 1–3, between sessions 2 and 3, the older group shows a decrease followed by an increase in performance between sessions 3 and 4.

DISCUSSION

We investigated the cognitive effects of ECT treatment and interpreted the results in terms of the differential effect of reduced depression and the effects of ECT in relation to age. Our hypothesis that both ECT and reduced depression specifically affect cognitive function was confirmed. The analyses we used (i.e., with and without the effect of differences in depression between pre-ECT measures and three post-ECT measures) made it possible to separate the effects of ECT treatment and reduced depression. Indeed, the results demonstrate a distinctive impact of ECT treatment per se and reduced depression on different cognitive domains. First, the ECT

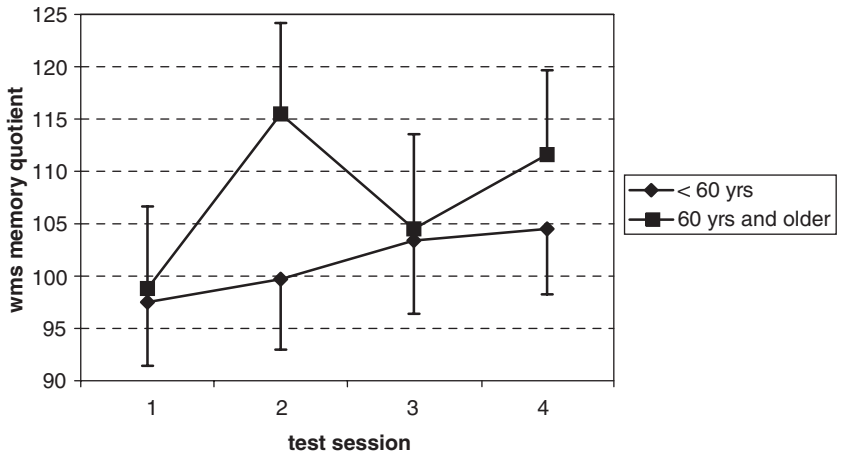

Figure 1. Mean scores [± SEM (standard error of mean)] on the Wechsler Memory Quotient (MQ) for the young and older patient groups at the four test sessions.

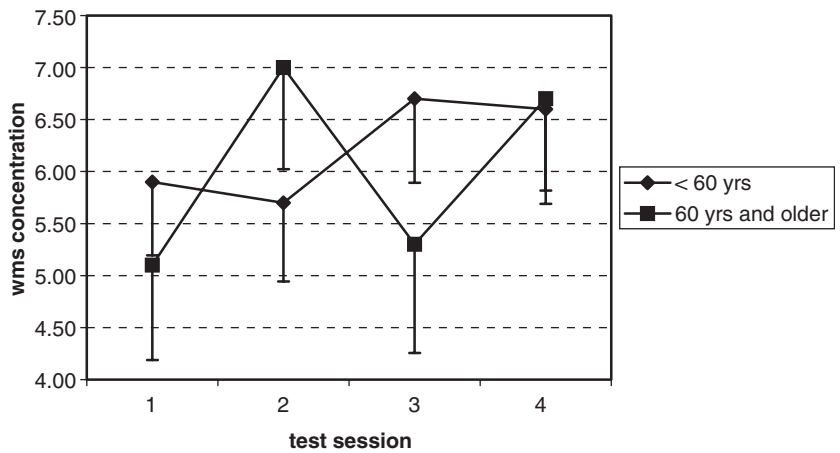

Figure 2. Mean scores (± SEM) on the subtest Wechsler Concentration for the young and older patient groups at the four test sessions.

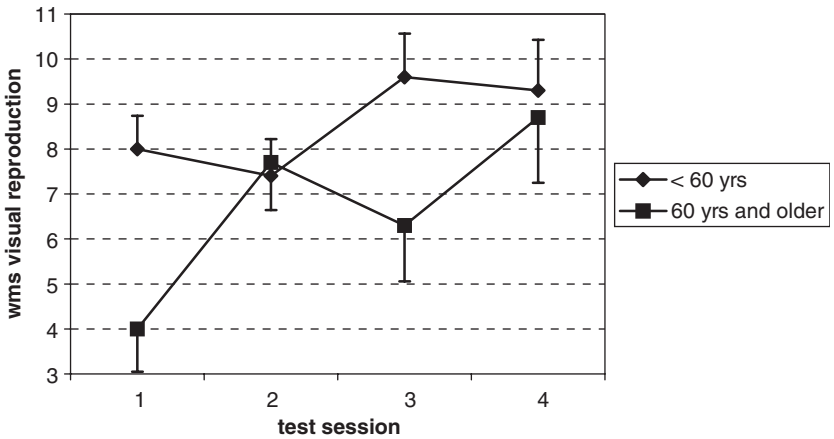

Figure 3. Mean scores (± SEM) on the subtest Wechsler Visual Reproduction for the young and older patient groups at the four test sessions.

treatment improves nearly all tapped cognitive domains [i.e., executive functions and attention, (anterograde and retrograde) verbal and nonverbal memory, and intelligence]. ECT per se affects not only memory at short term (within 2 weeks after index ECT) and at long term (up to 1 year), and speed of information processes (at long-term), but also the quality of visual organization and mental control (at long term). Reduced depression improves memory (i.e., performances on verbal learning, at short term), speed of information processing (at short term), and inhibition (at long term). Second, this study demonstrated differences between adult and older patients at short and long term regarding changes in cognitive performance after index ECT. Remarkably, cognitive improvement shortly after index ECT is more pronounced in patients over 60 years of age, but shows a similar increase in performance at long term. However, as the number of the older patients is quite small ($n = 9$) and subjects over age 80 were not included in our sample, we have to be careful in generalizing these finding to all patients.

To our knowledge, this is the first time that treatment with index ECT of a geriatric patient group with medication-resistant depression shows cognitive improvement that lasts for at least 1 year [Flint and Gagnon, 2002; Tew et al., 1999; Wesson et al., 1997; Wilkinson et al., 1993; Zervas et al., 1993]. The results, although based on a relatively small number of subjects, thus indicate that older people given ECT for severe mood disorder do not suffer cognitive decline at long-term follow-up, but even show a benefit of ECT treatment. The current findings provide evidence that for nondemented (as being one of the criteria of this study) older people, ECT may be accompanied by improved cognitive functioning that lasts for at least 1 year. This outcome provides another view on the use of ECT in older people.

The improvement in cognitive functions might be explained by γ-aminobutyric acid (GABA) involvement in ECT's mechanism [Sanacora et al., 2003], and/or by neurochemical and neuromodulation cascade effects initiated by repeated treatments [Wahlund and Von Rosen, 2003]. Indeed, increased cortical GABA concentrations have been found in depressed patients receiving ECT [Sanacora et al., 2003]. In addition, single and repeated ECT activates dopaminergic and serotonergic neurotransmission in the frontal cortex of rats [Yoshida et al., 1998]. There is also evidence that ECT may have a noradrenergic mechanism of action [Deakin et al., 1981]. The cognitive effects may be differentially related for GABA, noradrenaline (NA), serotonin (5-HT), and dopamine (DA).

In humans, higher levels of DA have been related to better working memory [Deijen, 1993], and central NA has been found to be important in maintaining attention [Smith and Nutt, 1996]. Treatment of rodents with 5-HT or GABA receptor antagonists generally produces a memory-enhancing effect, whereas GABA-ergic agonists impair retention [Deijen, 1993]. Thus, the general picture is that higher levels of DA and NA are positively associated with learning and memory, whereas higher levels of 5-HT or GABA seem to impair cognitive processes. It may well be true that the positive cognitive effects we obtained are related to increased activity of catecholaminergic neurons, which then dominate the adverse cognitive effects associated with increased levels of 5-HT and GABA. Opposed to the view of neurochemical involvement in the cognitive improvement, major or bipolar depression presents a severe illness leading to long-standing cognitive impairment from which the brain takes a substantial time to recover. Thus, even though mood is improved, the long-standing effects on cognition may take significantly more time to clear.

The differential observations of cognitive side effects of ECT may be related to the degree of cognitive

reserve (CR), which implies that innate intelligence or aspects of life experience such as educational or occupational attainments may supply a reserve against brain dysfunction in the face of acquired central nervous system (CNS) dysfunction. It has been observed that following three ECT treatments, a high-CR group forgot significantly less information after a 30-min delay compared to a low-CR group [Legendre et al., 2003]. Possibly a higher than average CR in our subjects may explain the observed ECT-induced cognitive improvement in this study.

Studies so far have been controversial regarding the association between age and the severity and persistence of ECT-related cognitive effects [Tew et al., 1999; Wilkinson et al., 1993; Zervas et al., 1993]. Our results confirm the results of Wilkinson et al. [1993], who found the largest improvement in MMSE scores in older patients. Wesson et al. [1997] showed a significant association between increasing age and better prognosis, but unfortunately they did not include cognitive measurements in their follow-up study. The more recent study of Brodaty et al. [2000] did include cognitive measures but did not provide details of ECT-techniques used. In a review, Flint and Gagnon [2002] concluded that ECT can be used safely in patients of very advanced age, with appropriate evaluation and monitoring, and administration in an optimal way. They suggest that the superior response to ECT among older compared with younger adults might not be related to aging per se but to age-related clinical factors, such as lengthier depressive episodes and more melancholic features in their mood. However, the finding that the same ECT procedure may have a more beneficial cognitive effect in the older brain may be explained by the possibility that stimulation of the neural system is instrumental in the process of restorative plasticity in especially senescent brains [Swaab, 1991]. During aging, not only degenerative processes take place but also adaptive growth responses and regenerative processes in which stimulation of neuronal systems might be beneficial. Neuronal activation might prolong optimal neural function, which may explain the superior acute effect of ECT in older people. However, our results indicate that 6 months after ECT treatment, the cognitive outcome in the older subjects declines to the level of the younger age group; that is, the superior beneficial cognitive effect in older patients seems to be temporary. It may well be true that the acute ECT treatment effect in the older age group reflects a ceiling effect whose response is normalized in the follow-up period. After the fallback at 6 months, the increase in cognition in the older age group is continued at the average, normal rate.

Limitations of this explorative study need to be acknowledged. For example, the patients in this study, who were regularly followed up over 1 year, were highly compliant and thus may represent a quite select sample of patients (i.e., selection-bias possibility). Although the data are suggestive, the sample size in this study was small; larger study group sizes will be required to confirm the present beneficial age-related effects of ECT and the distinctive impact of ECT and reduced depression on neuropsychological outcome. Still, current findings provide evidence that ECT may be accompanied by improved cognitive functioning in both adult and older depressive patients, which has strong clinical relevance concerning the use of index ECT.

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