Measuring Retrograde Autobiographical Amnesia Following Electroconvulsive Therapy

Historical Perspective and Current Issues

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Abstract: Retrograde amnesia following electroconvulsive therapy (ECT) is a major concern for both patients and clinicians. In contemporary ECT research, retrograde autobiographical amnesia (RAA) is commonly measured with instruments assessing autobiographical memory (AM) consistency over time. However, normal AM recall loses in consistency with the passage of time, and time has a differential effect on stability of personal memories. In addition, experiencing depression is associated with a decreased ability to recall specific AMs, and this difficulty may persist in the euthymic phase of recurrent depression. Despite these scientific facts, relatively few attempts have been made to accurately measure the specific effect of ECT on AM independent of both normal and mood-associated forgetting over time. This major gap in our knowledge prevents us at present from objectively quantifying the nature and extent of RAA associated with ECT. In turn, this hinders our identifying and implementing strategies for prevention or remediation of AM deficits. The present article aims to provide an up-to-date review and historical perspective of this major methodological conundrum for ECT research, highlight current issues in retrograde amnesia assessment following ECT, and propose directions for future studies. In conclusion, we suggest methods to reliably and specifically measure the extent and progression over time of ECT-associated RAA independently from persistent depressive symptoms' contribution and normal loss in AM consistency over time.

Key Words: autobiographical memory, retrograde amnesia, depression, ECT

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Retrograde amnesia is undoubtedly the one adverse effect of electroconvulsive therapy (ECT) that raises the most prominent concerns and thus may be the main reason limiting ECT use.[1,2] Retrograde amnesia here refers to difficulties, following a course of ECT, in retrieving memories of events or facts acquired before commencing the treatment.[3] A systematic review of patients' perspective on ECT revealed that their memory loss complaints relate mostly to personal or autobiographical memory (AM).[1] Autobiographical memory is an essential component of human memory as it allows the maintenance of one's past, which represents an important basis of one's identity and continuity.[4]

Consolidation and retrieval of personal memories are dynamic processes that change over time, resulting in AM continuously being constructed and reconstructed.[5–7] Developing an accurate assessment tool for AM represents a significant methodological challenge as, by definition, the concept measured is widely dependent on individual variables (eg, affective valence of an event, age of acquisition, degree of rehearsal, etc). Depression itself is associated with AM disturbances, some of which may persist during the remitted phase of the illness (for a review, see Bergouignan et al[8]). Retrograde autobiographical amnesia (RAA) following ECT is a major concern for both patients and clinicians.[1,9] However, since Squire and colleagues'[10] seminal study in depression, relatively few attempts have been made to accurately measure the specific effect of ECT on AM independent of both normal and mood-associated changes over time. This major gap in our knowledge inhibits at present the scientific process of objectively quantifying the extent and specifying the nature of RAA associated with ECT and thus from identifying and implementing preventive or remedial strategies.

We seek here to provide an up-to-date review of this major methodological issue for ECT research and propose directions for future studies. The present article specifically aims to:

1. summarize generally shared knowledge regarding normal AM function and how it is affected by depression;
2. draw a historical perspective on the development of AM assessment in the ECT literature that has progressed independently from other advances in AM assessment, namely, neuropsychology of health, depression, and the injured brain; and
3. highlight current issues regarding common AM measures used in ECT research that represent a major challenge for current ECT practice.

AUTOBIOGRAPHICAL MEMORY IN HEALTH AND DEPRESSION

Autobiographical Memory Types and Effect of Time

The distinction between semantic and episodic components is a largely accepted view of AM organization.[7,11] The semantic component consists of general, decontextualized information about one's past (eg, occupational background, names of siblings), whereas the episodic component comprises memories of specific events situated in space and time (eg, what I did in the morning of the first day of my current job; what I saw in the airport waiting area just before taking off for New York last Wednesday).

Two major consistent findings have emerged from studies on the effects of time upon AM function. First, distribution of episodic memories across the life span reveals that AMs from late adolescence and early adulthood have the greatest survival and are the most vividly detailed; this is conceptualized as the "reminiscence bump."[12] Second, with the passage of time and repetition of similar events, or repeated retrieval of the same personal information (eg, a close relative's birthday, address of one's first workplace), there is a progressive transition from episodic to

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semantic AM.[6,13] Another postulated effect of time on AMs is the "recency effect," which proposes that free recall of specific personal memories results in preferential retrieval of events that occurred in the last few years as opposed to events from the more distant past. However, this theory is controversial because this preferential retrieval may be dependent on the assessment method used.[14] For example, if a person is required to produce an AM in relation to a cue word, such as "vacation" or "movie," he/she can spontaneously recall more events from a recent past, such as last vacation or last movie seen, resulting in a demonstration of a recency effect. However, if a person is constrained to produce a given number of AMs from each given specific period, such as childhood, young adulthood, last 5 years, the AM recall specificity might be equivalent across the time periods, resulting in absence of a demonstrable recency effect.

Consistency of Autobiographical Memory Retrieval

Despite their importance in preserving the temporal order of events in one's AM, episodic memories are not enduring in long-term accessible memory.[15] Many events from a given day can be recalled at the end of that day. However, as the retention interval increases, access to the majority, if not all, of these specific memories is rapidly lost. For example, few episodic AMs can be recalled, even of a distinctive day, at a retention interval of 1 week and of a routine day virtually none.[15] Moreover, research from the last 15 to 20 years suggests that even when successfully recalled, these AMs tend to lose consistency over time.[5,16–18]

Autobiographical memory consistency is usually measured through a test-retest procedure and quantified in terms of percentage of coherent responses over time.[17] Information regarding the same AMs is collected either at 2 time points, to calculate 1 time-interval consistency equal to (time 2 / time1) × 100 or at 3 time points, to calculate 3 time-interval consistencies, that is (time 2 / time 1) × 100; (time 3 / time 1) × 100; and (time 3 / time 2) × 100. Studies that use the one time-interval consistency typically compare 2 groups of participants or 2 types of AMs on percentage consistency. For example, Anderson et al[16] showed that, over a 2-month interval, older healthy participants (mean age, 72 years) lost significantly less in consistency than did younger (mean age, 28 years) participants: 30% versus 42%, respectively. An example of AM-type comparison is the demonstration of difference between 21% loss in consistency on recognition of personal events versus 38% loss in consistency in recognition of associated thoughts over 7 months.[19] Studies that have assessed 3 time-interval consistencies reliably find a substantial amount of loss in consistency between time 1 and time 2 (eg, 28% over 1 week,[20] 40% loss over 3 months[21]), but a relatively negligible amount of such loss between time 2 and time 3 (eg, 22% when times 2 and 3 are at 5 and 12 months' follow-up[17]; 13% when times 2 and 3 are, respectively, at 3 and 12 months[21]). These results cannot be explained only by a practice effect. In fact, Talarico and Rubin[22] observed a 27% loss in consistency in healthy volunteers retested 6 weeks after an initial recall of the same specific AM events and, in a different group, a 31% loss when this reassessment was undertaken 7 months later.

In brief, the existing literature suggests that 28% to 40% AM consistency loss is to be expected within the first 1 week to 3 months after initial AM retrieval, and then consistency appears relatively stable, at least for up to 1 year. Several researchers have proposed that the amount of loss of consistency is dependent on the type of evoked AM. For example, details regarding time and location of a specific event are more consistently recalled than information regarding participants' activity during the event.[23,24]

Overgeneral Autobiographical Memory in Depression

Autobiographical memory is crucial for maintaining personal identity across the life span and therefore is important for preserving mental health and quality of everyday functioning.[25] Thus, use of standardized instruments to measure AM function is essential in neuropsychiatry research. However, this is only a relatively recent concern when compared with traditional and more generally accepted assessments of anterograde memory.[26] Studies of AM in depression have mainly used the Autobiographical Memory Test created by Williams and Broadbent.[27] This test uses a cue-word technique where the patient is required to describe a specific AM that happened in a particular time and place, within less than 24 hours, in response to a given cue word (eg, work, sea, etc).

In depression, the most consistent finding of AM research using this instrument is overgeneral retrieval.[28–30] The AM recall of patients with depression comprises primarily personal semantic facts (general knowledge regarding oneself), extended events that occurred over a period greater than 1 day, or a frequently repeated event. This happens even when depressed patients are explicitly asked to produce a unique AM situated in a specific time and place. Recent meta-analyses have demonstrated that, under these conditions, AMs of depressed patients are still consistently less specific than AM recalls of nonclinical control subjects[31] and that reporting fewer specific AMs during a major depressive episode predicts higher depressive symptoms at follow-up independently from initial severity of depression.[29] Some studies have suggested that these AM impairments persist during the euthymic phase of depression, but this is not a consistent finding (for a review, see Bergouignan et al[8]). Recurrent depressive episodes have been associated with persistent AM difficulties during remission.[32]

Although the Autobiographical Memory Test allows tracking changes in AM specificity over time, it does not control for retention time interval (ie, the delay between acquisition of the AM and the moment of its retrieval) and encoding age that are both critical for the quality of AM retrieval.[7,33] In addition, it has not been constructed to measure stability of AMs over time, as participants are not requested to evoke the same AMs on repeated testing. Thus, the Autobiographical Memory Test does not assess consistency of AM recall. Finally, the major limitation of this test is its inability to distinguish between an individual's personal bias to report, or not, events from particular time periods and his/her capacity to do so.[11]

Summary

Normal AM recall loses in consistency with the passage of time, and time has a differential effect on stability of personal memories, depending on the AM type (eg, semantic vs episodic AM; spatiotemporal vs personal activities information). Experiencing depression is associated with a decreased ability to recall specific AMs, and this difficulty may persist in the euthymic phase of recurrent depression.

ASSESSMENT OF AUTOBIOGRAPHICAL MEMORY AND RETROGRADE AMNESIA IN THE ECT LITERATURE

Early Studies and Sine-Wave ECT

Autobiographical memory following ECT was first studied systematically by Janis[34] in 1950 in schizophrenic patients who

received bilateral sine-wave treatments. Janis[34] used open-ended questions regarding personal events both before and after final ECT and found that patients appeared to have forgotten autobiographical information relative to the initial assessment. It is interesting to observe here that, since Janis's[34] pioneering work, assessment of retrograde AM amnesia following ECT evolved independently from existing research on AM in brain injury, health, or in depression.

Squire et al[10] were the first to standardize Janis's technique and use it to assess AM function following ECT for depression. They compared 10 patients treated with thrice-weekly bitemporal sine-wave ECT with 7 control subjects with depression receiving pharmacotherapy. The method used was a semistructured questionnaire where participants were requested to generate specific details about 10 different topics related to their personal history (eg, names of classmates, details about most recent job, incidents that happened on the day John F. Kennedy was assassinated, etc). Distinction was made between remote past (events that occurred at least 3 years previously and, on average, 24 years previously) and recent past (events that occurred 3 months to 3 years before the initial assessment), but not between semantic and episodic components. Scoring consisted of the sum of the number of details provided for each theme. The AM amnesia score was defined as a significant decrease in the number of details reported after completing a course of ECT compared with the number of details generated before treatment on the same themes. Defined as such, retrograde amnesia seemed to persist for recent events but not for remote ones up to 7 months following end of treatment. This finding of a temporal gradient that appears to characterize the retrograde amnesia associated with ECT has been replicated by more recent studies using brief-pulse ECT.[35,36]

Later, in a study comparing different ECT forms, Weiner et al[37] exploited the same technique in 53 depressed patients randomly assigned to sine-wave bitemporal (S-BL), sine-wave right unilateral (S-RUL), brief-pulse bitemporal (BP-BL), or brief-pulse right unilateral (BP-RUL) ECT, but used different themes. In addition, in their Personal Memory Questionnaire, items relating to recent past events were expanded (as ECT appeared to spare remote events), and a structured format with specific, rather than open-ended, questions was used. The scoring system was also different as only questions that were answered before ECT were administered at retesting, and only consistency with baseline was measured. Amnesia was defined as percentage AM lost from baseline score. Defined as such, RAA following ECT is equivalent to contemporaneous definition of consistency loss in normal AM functioning research. Depressed patients not receiving ECT were used as a control group. The main findings of the study were as follows. Three days after finishing an ECT course, patients who received BP-RUL ECT (n = 10) were not significantly different from the control group (n = 20) on consistency loss, with about 22% versus 21%, respectively. At the same time, patients receiving S-BL (n = 13, 60% loss), BP-BL (n = 14, 44% loss), or S-RUL (n = 14, 43% loss) ECT showed significantly more consistency loss than did depressed control subjects. At 6-month follow-up, both S-RUL (n = 9, 22%) and BP-RUL (n = 8, 19%) ECT groups were comparable to depressed control subjects (n = 12, 19%) regarding consistency loss. However, the S-BL (n = 11, 38%) and BP-BL (n = 9, 30%) ECT groups showed more consistency loss compared with both the RUL ECT and control groups. Of note, neither normative data nor validation studies in healthy volunteers have been published for Squire and colleagues'[10] semistructured AM questionnaire or Weiner and colleagues'[37] Personal Memory Questionnaire.

The study of Weiner et al[37] has a major historical importance for 3 reasons. First, it modeled the method for the majority of subsequent RAA assessments following ECT for depression. Second, it demonstrated a differential pattern of AM consistency recovery following 4 types of ECT. And third, although limited by the small sample sizes of the groups, these authors' results suggested that parts of the loss in consistency in some of the experimental groups were associated to ECT independently from depression.

Contemporary Research on Retrograde Autobiographical Amnesia Following ECT

The majority of research on AM dysfunction following ECT has used variations of the Personal Memory Questionnaire of Weiner et al.[37] The 2 most frequently used variations in contemporary ECT literature are the Columbia Autobiographical Memory Interview (CAMI)[36] and the Columbia Autobiographical Memory Interview–Short Form (CAMI-SF).[38] A scoring system based on percentage consistency with baseline performance is maintained. Studies that have used this instrument have generally reported differences in consistency loss between different ECT types (eg, sine-wave BL-ECT resulting in higher consistency loss than brief-pulse BL-ECT). However, given the lack of comparison with healthy or depressed control subjects and given the natural consistency loss that characterizes normal AM function, such research neither shows nor quantifies possible retrograde amnesia. As described above, reported percentage consistency losses in the ECT literature roughly correspond to normal AM loss. Moreover, as depression itself is associated with AM disturbances, remission following ECT might be expected to be associated with some improvement in AM functioning.[8,28] By their construction, instruments based on consistency cannot capture any improvement in AM, as follow-up performance is always inferior to baseline performance. In addition, such instruments cannot reliably determine if a possible retrograde amnesia is persistent over time.

Of interest, some retrograde amnesia assessments based on the evaluation of impersonal (public) events memory before and after ECT and that allow for measuring improved performance have been demonstrated to be reliable alternatives to consistency testing.[39,40] For example, Squire and Chace[40] used a recognition test of "1-session television programs" that had aired in the 16 years previous to the study. This test allowed comparison with a non-ECT control group of depressed patients. They found that depressed patients who had just received 5 bilateral treatments recognized only about 40% of the television programs that had aired during the preceding 1 to 3 years, whereas patients who had received the same treatment but 6 months previously were comparable to patients who had never received ECT or patients who received unilateral ECT (all recognizing about 70%–75% of programs). Using a fluency-for-past-events-memory approach and a healthy control group, Lisanby et al[35] showed a more pronounced retrograde amnesia for recent impersonal events than for recent personal events, which may suggest a differential effect of ECT on these 2 types of retrospective memories. Another, more recent, example is the Daily News Memory Test-ra (DNMT-ra) from the Netherlands[39] that also has been used to quantify ECT-associated retrograde amnesia for public events. The DNMT-ra measures the free recall and ability to recognize highly publicized events that occurred in the preceding 12 months to a given assessment time point. By use of the DNMT-ra, it has been demonstrated that the retrograde amnesia for impersonal memories observed immediately following a course of bilateral ECT is reversible at 3-month follow-up.[39] All these instruments use methods that resolve the

issues associated with consistency testing, even though their results remain vulnerable to the possible test-retest effect inherent to the repeated-measures (pre-ECT, post-ECT) research designs. Unfortunately, this methodological approach has not been applied to the assessment of RAA.

Although widely used in the ECT literature and showing satisfactory face validity, the AM instruments described in the beginning of the present section lack validation studies as assessments of AM in terms of demonstration of their reliability, construct validity, discriminant validity, or simply reporting on normative data. Possibly incorrectly, researchers administering them have commonly concluded on the existence of retrograde amnesia on the basis of an illustration of percentage loss in consistency with personal memories reported at baseline. An additional problem in the literature has been confusing similarly titled, but quite different, AM interview instruments,[2,41] for example, the CAMI,[36] a nonvalidated instrument based on AM consistency, and Autobiographical Memory Interview of Kopelman et al[42] (Kopelman AMI), a validated assessment of retrograde amnesia that is described in detail below. This not uncommon error, which has even found its way into the recent Food and Drug Administration (FDA) report on ECT,[2] leads to inaccurate conclusions and becomes particularly unfortunate when they have implications for national policy decisions.

To our knowledge, only 3 studies have so far reported on use of a validated AM assessment in studies of ECT for depression, and a fourth one has reported on a translated adaptation of this validated instrument.

The Kopelman AMI and ECT Research

The Kopelman AMI has been designed and validated to provide normative data for the assessment of RAA in amnesic patients.[42] It is composed of 2 schedules (personal semantic memory and autobiographical incidents) assessing AMs from 3 time periods: childhood, early adult life, and recent life (AMs from the last year or the last 5 years). Patients with RAA of different etiologies (eg, herpes encephalitis, traumatic head injury, vascular dementia) performed significantly less than did control subjects on all variables, with the greatest difference between these groups occurring on the recent life memory score. The AMI has shown satisfactory reliability and validity as a test of RAA and is commonly used in clinical practice.[43] Interestingly, its use in the ECT literature is quite scarce. Kho et al[44] were the first to report on assessing ECT patients with the AMI. They administered it retrospectively to 20 depressed patients who had received mostly brief-pulse RUL-ECT (using an age method to determine stimulus dosage) in the previous 1 to 5 (mean = 2.3) years and compared them with 30 patients who received pharmacotherapy during the same period. The 2 groups did not differ significantly in their performance on any of the AMI subscores. As a part of randomized controlled trial comparing ultrabrief 1.5 times seizure threshold (ST) bifrontal and 6 times ST ultrabrief RUL-ECT, Sienaert et al[45] administered the AMI before treatment and at 1 and 6 weeks following the end of the allocated ECT course. They demonstrated continuous significant improvement in the overall AMI performance over time in the RUL-ECT group (n = 21) and slight, but nonsignificant, improvement at 6 weeks' follow-up in the bifrontal group (n = 20). Overall, there was no significant difference between the 2 groups, but subscore results were not reported. Neither of these studies distinguished between the AMI episodic and semantic components.

Stoppe et al[46] used a nonvalidated Brazilian adaptation of the AMI in a randomized trial comparing fixed high-charge BL and RUL ECT for older adults (aged >60 years). At 1-month follow-up, performance was comparable to baseline levels, and there was no significant difference between the groups on recall of AMs. These researchers also did not distinguish between recent and remote AMs, or between episodic and semantic AMI components. The only ECT study to date that has distinguished between these AM components was the recent O'Connor and colleagues'[47] natural prospective comparison between 3 times ST RUL-ECT and 1.5 times ST bitemporal ECT. The authors administered only the recent life section of the AMI after the first or second ECT treatment and, a second time, after the fifth or sixth treatment. They did not collect pretreatment data. However, their study demonstrated a small but significant decrease in both the personal semantic and autobiographical incidents AMI schedules between these 2 assessment points in the bitemporal group, when no significant difference was observed in the RUL-ECT group. The bitemporal group showed a significantly larger decrease in the autobiographical incidents AMI schedule on the second assessment point relative to the RUL-ECT group, although the 2 groups performed equally on this schedule at the first assessment point.

Summary

Commonly used instruments to assess RAA in contemporary ECT research are based on AM consistency and have emerged from Weiner and colleagues'[37] Personal Memory Test whose preliminary results indicated methods to distinguish between depression-associated and ECT-associated AM functioning. However, their methodology has not been pursued in this regard. Subsequently developed instruments based mainly on AM consistency do not inform clinical practice or assist our understanding of ECT-provoked RAA as they have not demonstrated their ability to distinguish the latter from normal or mood-associated forgetting over time. An alternative and validated instrument for the assessment of RAA, the AMI,[42] has not been adequately explored in the ECT literature. This is even more surprising given its potential to specify the nature, extent (relative to normative data), and long-term persistence of autobiographical amnesia following ECT.

RETROGRADE AUTOBIOGRAPHICAL AMNESIA AND ECT: CURRENT ISSUES

Food and Drug Administration's 2011 Assessment of ECT

The important consequences of inadequately measuring autobiographical amnesia in the ECT literature, despite some decades of research on this most common of patients' complaints, have very recently crystallized in an FDA report.[2,48] Since 2009, the FDA has been examining if ECT machines should remain high-risk medical devices (class III) or be reclassified as intermediate-risk (class II). Electroconvulsive therapy machines are one of the few class III devices for which premarket approval applications have not been necessary to date. Because they were already in regular clinical use before the medical devices ratings system came into effect in the 1970s, ECT devices were "grandfathered" through the process, which included 25 different types of medical devices, for example, heart valves, pacemakers, and intraocular lenses.[49] Not unreasonably, the FDA is now reviewing these decisions and seeking rigorous safety data for market approval for grandfathered devices.

In this context, the FDA Neurological Devices Advisory Panel met in January 2011, to discuss their assessment of the

evidence regarding effectiveness and safety of ECT.[2] Although effectiveness was supported by its review, a major concern was risk of cognitive and, more specifically, memory dysfunction following ECT. The FDA review concluded that, with the exception of AM, deficits observed in all other memory domains resolve days to weeks after completing an ECT course.[2(p48)]

The FDA's View on Retrograde Autobiographical Amnesia and ECT: Results of "Meta-Analyses"

In its executive summary report, the FDA asserts on several occasions that ECT is associated with AM impairment.[2] Based in large part on these considerations, the majority of the panel appears to have recommended that ECT devices remain class III.[48] The FDA's recommendation could have major implications for clinical practice because ECT would now require premarket approvals that should demonstrate its safety for individual indications. One possible, albeit extreme, consequence is that ECT could thus become unavailable in the United States until further randomized sham-controlled trials are performed to show safety and efficacy. Because the main ECT device manufacturers are based in the United States, such an event may have major negative repercussions on both United States and international use of this highly effective treatment for severe depression and also catatonia.

However, decisions based on the FDA report may be premature. The FDA's review of the evidence on autobiographical amnesia and ECT has major flaws, particularly with regard to its understanding of the nature and limits of neuropsychology instruments used in ECT studies and subsequent inappropriate calculation of "effect" and meta-analyses of these data. We have meta-analyzed cognitive change data from 44 randomized trials and 40 observational ECT studies.[50] Remarkably, none of these studies used a validated measure of autobiographical amnesia or demonstrated a difference in AM functioning relative to sham procedures, placebo, or control depressed subjects not treated with ECT.

In a more recent systematic review and meta-analysis, we have shown that it is not possible to demonstrate statistically significant AM decreases from baseline with the nonvalidated tasks used to date in the ECT literature.[51] More specifically, as stated above, the vast majority of studies present post-ECT AM results as percentage recalled from a baseline score that, irrespective of actual performance, is 100% for everybody, thus preventing actual effect size calculation. Interestingly, 2 studies that did administer instruments permitting quantification of RAA demonstrated improvement in AM retrieval at follow-up.[45,46] Despite their small sample sizes and, for 1 study,[46] substantial missing data at follow-up, the results of these studies do not appear to support the hypothesis of persistent RAA following ECT. We also have found publication bias in reporting post-ECT AM data, favoring publication of larger percentage losses relative to the estimated mean percentage loss.[51]

Although referred to as "meta-analyses,"[2(pp89–92)] the FDA AM data have not undergone such statistical syntheses. For example, the FDA quantitative review does not report a single *P* value along with described results, nor does it present actual effect sizes for any change in AM function following ECT compared with pretreatment function. Interestingly, however, the mean percentage losses in AM consistency following completion of a course of ECT calculated by the FDA (approximately 25%–40%)[2(pp89–92)] are actually similar to percentage loss in AM consistency observed in healthy populations over a few weeks or months (ie, 28%–40%).[16,17,21,22,24,51] From such data, it is clearly not possible to distinguish between the passage of time and the effects of depression or ECT upon AM function.

The FDA's View on Retrograde Autobiographical Amnesia Following ECT: Review of Evidence

In addition to the above important conceptual errors, the FDA review contains several other major inaccuracies in reviewing, reporting, and interpreting AM data from the ECT literature. First, as already noted earlier, the FDA review confuses 2 different AM assessments. Of note, it correctly states[2(p136)] that the CAMI[36] is the most commonly used measure for personal memory but then describes a completely different instrument, the Kopelman AMI.[42] Exclusively used in the ECT literature, the CAMI[36] measures consistency of recall over time but, as noted above, has not been validated to date. Furthermore, there are no published normative (healthy control) data for natural loss in consistency over time using this instrument. The test format, validity, and reliability studies described by the FDA review[2(pp20,136)] are actually about the Kopelman AMI[42] and not about the Columbia Interview, a full description of which can be found in the original publication.[38]

Second, despite being cited in the references,[2(p163)] the only randomized controlled trial[44] to date that has used the validated Kopelman AMI was not included in the FDA review of retrograde amnesia.[2(pp86,87)] As detailed above, this trial reports a significant improvement in AM 6 weeks following ECT and a normalization of AM, noted to be impaired before treatment, following unilateral ECT.

Third, the FDA has inaccurately pooled AM data. While reviewing outcomes at 3 months following ECT, the FDA review[2(p30)] inaccurately described a study by Weiner et al[37] that assessed memory 2 to 3 days after ECT and then 6 months later; unlike as stated and analyzed in the FDA review,[2(p30)] they did not collect data at 3 months' follow-up. Pooling such subacute data with long-term data would most probably bias related conclusions on long-term effects of ECT.

Fourth, the FDA inadvertently reports inflated study samples sizes in its review and analyses. None of the sample sizes listed in Table 7 of the report,[2(pp86,87)] in which percentage consistency of recall is presented, is accurate (eg, in their original publication, Weiner et al[37(p317)] report n = 46 and not 74 for follow-up assessments; Sobin et al[52(p997)] n = 45 and not 71). The cumulative effect of this inflation results in a misguidingly narrow confidence interval of estimated percentages.

Finally, some of the FDA AM analyses were based on duplicated samples. Reports that considered different research questions on the same sample set of AM data are presented and analyzed as independent studies in Table 7 of the report[2(pp86,87)] and in the graphical summary of data.[2(pp89–92)] For example, Sobin et al[52(pp997–999)] examined associations between loss of autobiographical consistency and time to post-ECT reorientation on the same sample that McElhiney et al[36(pp503–505)] used to explore the differences between bilateral and unilateral ECT. Nonetheless, the FDA "meta-analyses" consider them as independent studies.[2(pp89–92)] Reviewing and pooling the same sample twice biases the overall conclusions by overestimating its relative weight.

Autobiographical amnesia following ECT is of genuine concern for both patients and clinicians, and its nature and extent remain to be properly characterized. Unfortunately, the FDA review has not been able to provide a correct overview of the available objective evidence related to this possible adverse effect because of major conceptual and methodological errors. We find it especially worrying that governmental policies may be based on an inaccurate report from the FDA that

can have major health care implications in both the United States and worldwide.

IMPLICATIONS FOR FUTURE RESEARCH

Based on our review of the ECT literature on RAA and on other existing reviews,[2,41,50] we would recommend the following steps for future research. First, the administration of the recent life section of the Kopelman AMI[42] through a within-subject (pre-ECT, post-ECT) research design would be useful to adequately quantify RAA relative to normative data, to track changes over time, and eventually determine persistence of amnesia. Moreover, as uplifting of mood might be associated with some AM improvement, the Kopelman AMI would provide the opportunity to reliably measure this. Second, assessments based on consistencies might provide some insight on the effect of ECT on AM consistency. However, it appears essential that normative data from both healthy control subjects and depressed patients not treated with ECT are collected with appropriate time intervals to allow the dissociation between ECT-associated and normal or mood-associated loss of consistency over time. Considering this, we have recently performed validation studies of a new scoring system for the CAMI-SF in healthy volunteers reassessed on AM consistency after a 6-month interval and in severely depressed patients never treated with ECT and healthy control subjects reassessed on AM consistency after a 2-month interval.[53] With satisfactory reliability and validity, our results showed that, on initial assessment, depressed patients produced less episodic-specific AM than did healthy control subjects. However, the 2 groups showed equivalent amounts of consistency loss over a 2-month interval on all components. At reassessment, only patients with persisting depressive symptoms were distinguishable from healthy control subjects on episodic-specific AMs retrieved. We also provided normative data for natural loss in AM consistency over 6 months using the CAMI-SF and provided cutoffs for impairment. However, to inform clinical practice regarding the nature, extent, and persistence of ECT-associated RAA, the next step would be to directly compare data collected from patients receiving ECT to depressed or healthy volunteers on AM consistency.

REFERENCES

1. Rose D, Wykes T, Leese M, et al. Patients' perspectives on electroconvulsive therapy: systematic review. *BMJ*. 2003;326:1363.
2. Food and Drug Administration. Meeting to discuss the classification of electroconvulsive therapy devices (ECT). Executive summary. 2011. Available at: *http://\www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM240933.pdf*. Accessed on April 4, 2012.
3. Squire LR, Slater PC, Chace PM. Retrograde amnesia: temporal gradient in very long-term memory following electroconvulsive therapy. *Science*. 1975;187:77–79.
4. Conway M. Sensory-perceptual episodic memory and its context: autobiographical memory. In: Baddeley A, Conway M, Aggleton J, eds. *Episodic Memory: New Directions in Research*. Oxford: Oxford University Press; 2002:53–70.
5. Bahrik HP. Loss and distortion of autobiographical memory content. In: Thompson CP, Herrman DJ, Bruce D, et al, eds. *Autobiographical Memory: Theoretical and Applied Perspectives*. Mahwah, NJ: Lawrence Erlbaum Associates; 1998:69–78.
6. Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. *Psychol Rev*. 2000;107:261–288.
7. Piolino P, Desgranges B, Eustache F. Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia*. 2009;47:2314–2329.
8. Bergouignan L, Lemogne C, Foucher A, et al. Field perspective deficit for positive memories characterizes autobiographical memory in euthymic depressed patients. *Behav Res Ther*. 2008;46:322–333.
9. Prudic J. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. *J ECT*. 2008;24:46–51.
10. Squire LR, Slater PC, Miller PL. Retrograde amnesia and bilateral electroconvulsive therapy. Long-term follow-up. *Arch Gen Psychiatry*. 1981;38:89–95.
11. Moscovitch M, Rosenbaum RS, Gilboa A, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J Anat*. 2005;207:35–66.
12. Rubin DC, Wetzler SE, Nebes RD. Autobiographical memory across the adult lifespan. In: Rublin DC, ed. *Autobiographical Memory*. Cambridge: Cambridge University Press; 1986:202–221.
13. Neisser U. Nested structures in autobiographical memory. In: Rublin DC, ed. *Autobiographical Memory. Cambridge: Cambridge University Autobiographical Memory*. Cambridge: Cambridge University Press; 1986:71–81.
14. Piolino P, Desgranges B, Benali K, et al. Episodic and semantic remote autobiographical memory in ageing. *Memory*. 2002;10:239–257.
15. Conway MA. Episodic memories. *Neuropsychologia*. 2009;47:2305–2313.
16. Anderson SJ, Cohen G, Taylor S. Rewriting the past: some factors affecting the variability of personal memories. *Appl Cogn Psychol*. 2000;14:435–454.
17. Coluccia E, Bianco C, Brandimonte MA. Dissociating veridicality, consistency, and confidence in autobiographical and event memories for the Columbia shuttle disaster. *Memory*. 2006;14:452–470.
18. Rubin DC, Schrauf RW, Greenberg DL. Stability in autobiographical memories. *Memory*. 2004;12:715–721.
19. Conway MA, Collins AF, Gathercole SE, et al. Recollections of true and false autobiographical memories. *J Exp Psychol Gen*. 1996;125:69–95.
20. Nadel L, Campbell J, Ryan L. Autobiographical memory retrieval and hippocampal activation as a function of repetition and the passage of time. *Neural Plast*. 2007;2007:90472.
21. Weaver CA. Do you need a "flash" to form a flashbulb memory? *Exp Psychol Gen*. 1993;122:39–46.
22. Talarico JM, Rubin DC. Confidence, not consistency, characterizes flashbulb memories. *Psychol Sci*. 2003;14:455–461.
23. Curci A, Luminet O, Finkenauer C, et al. Flashbulb memories in social groups: a comparative test-retest study of the memory of French President Mitterrand's death in a French and a Belgian group. *Memory*. 2001;9:81–101.
24. Tekcan AI, Ece B, Gulgoz S, et al. Autobiographical and event memory for 9/11: changes across one year. *Appl Cogn Psychol*. 2003;17:1057–1066.
25. Markowitsch HJ, Staniloiu A. Memory, autonoetic consciousness, and the self. *Conscious Cogn*. 2011;20:16–39.
26. Piolino P. La mémoire autobiographique: modèles et évaluation. In: Meulemans T, Desgranges B, Adam S, et al, eds. *Evaluation et prise en charge des troubles mnésiques*. Marseille: Solal; 2003:195–221.
27. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. *J Abnorm Psychol*. 1986;95:144–149.
28. King MJ, Macdougall AG, Ferris SM, et al. A review of factors that moderate autobiographical memory performance in patients with major depressive disorder. *J Clin Exp Neuropsychol*. 2010;32:1122–1144.
29. Sumner JA, Griffith JW, Mineka S. Overgeneral autobiographical memory as a predictor of the course of depression: a meta-analysis. *Behav Res Ther*. 2010;48:614–625.

30. Williams JM, Barnhofer T, Crane C, et al. Autobiographical memory specificity and emotional disorder. *Psychol Bull*. 2007;133:122–148.
31. Van Vreeswijk MF, De Wilde EJ. Autobiographical memory specificity, psychopathology, depressed mood and the use of the Autobiographical Memory Test: a meta-analysis. *Behav Res Ther*. 2004;42:731–743.
32. Spinhoven P, Bockting CL, Schene AH, et al. Autobiographical memory in the euthymic phase of recurrent depression. *J Abnorm Psychol*. 2006;115:590–600.
33. Conway MA. *Autobiographical Memory: An Introduction. in the Self-memory System*. Milton Keynes, PA: Open University Press; 1990.
34. Janis IL. Psychologic effects of electric convulsive treatments.1. Post-treatment amnesias. *J Nerv Ment Dis*. 1950;11:359–382.
35. Lisanby SH, Maddox JH, Prudic J, et al. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry*. 2000;57:581–590.
36. McElhiney MC, Moody BJ, Steif BL, et al. Autobiographical memory and mood—effects of electroconvulsive-therapy. *Neuropsychology*. 1995;9:501–517.
37. Weiner RD, Rogers HJ, Davidson JR, et al. Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci*. 1986;462:315–325.
38. McElhiney MC, Moody BJ, Sackeim HA. *The Autobiographical Memory Interview–Short Form*. New York: Department of Biological Psychiatry: New York State Psychiatric Institute; 2001.
39. Meeter M, Murre JMJ, Janssen SMJ, et al. Retrograde amnesia after electroconvulsive therapy: a temporary effect? *J Affect Disord*. 2011;132:216–222.
40. Squire LR, Chace PM. Memory functions six to nine months after electroconvulsive therapy. *Arch Gen Psychiatry*. 1975;32:1557–1564.
41. Fraser LM, O'Carroll RE, Ebmeier KP. The effect of electroconvulsive therapy on autobiographical memory: a systematic review. *J ECT*. 2008;24:10–17.
42. Kopelman MD, Wilson BA, Baddely AD. The Autobiographical Memory Interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J Clin Exp Neuropsychol*. 1989;11:724–744.
43. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. 4th ed. New York: Oxford University Press; 2004.
44. Kho KH, VanVreeswijk MF, Murre JMJ. A retrospective controlled study into memory complaints reported by depressed patients after treatment with electroconvulsive therapy and pharmacotherapy or pharmacotherapy only. *J ECT*. 2006;22:199–205.
45. Sienaert P, Vansteelandt K, Demyttenaere K, et al. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. *J Affect Disord*. 2010;122:60–67.
46. Stoppe A, Louza M, Rosa M, et al. Fixed high-dose electroconvulsive therapy in the elderly with depression: a double-blind, randomized comparison of efficacy and tolerability between unilateral and bilateral electrode placement. *J ECT*. 2006;22:92–99.
47. O'Connor DW, Gardner B, Eppingstall B, et al. Cognition in elderly patients receiving unilateral and bilateral electroconvulsive therapy: a prospective, naturalistic comparison. *J Affect Disord*. 2010;124: 235–240.
48. Goodman WK. Electroconvulsive therapy in the spotlight. *N Engl J Med*. 2011;364:1785–1787.
49. Challoner DR, Vodra WW. Medical devices and health—creating a new regulatory framework for moderate-risk devices. *N Engl J Med*. 2011;365:977–979.
50. Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry*. 2010;68:568–577.
51. Semkovska M, Keane D, Babalola O, et al. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psych Res*. 2011;45:770–780.
52. Sobin C, Sackeim HA, Prudic J, et al. Predictors of retrograde amnesia following ECT. *Am J Psychiatry*. 1995;152:995–1001.
53. Semkovska M, Noone M, Carton M, et al. Measuring consistency of autobiographical memory recall in depression. *Psychiatry Res*. 2012;197:41–48.