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In Reply:

We thank Avidan *et al.* [1]for their interest in our study and for the opportunity to respond to their concerns, many of which had already been addressed in our article.[1] To begin with, we fully agree that recent studies have highlighted the need for control groups to separate the effects of surgery from aging or underlying disease. Unfortunately, at the time of study inception, a control group was not included, largely as a result of the budgetary limits imposed by the National Institutes of Health. The financial challenges associated with pursuing prospective randomized controlled trials are formidable and frequently mandate other designs, as is evidenced by Dr. Avidan's own *retrospective* work on cognitive dysfunction.[2] There is also controversy in longitudinal studies as to the appropriate control group and how large it would need to be to minimize crossover. In addition, our primary hypothesis examined the effect of APOE4 genotype upon cognition; therefore, the non-APOE4 subjects were, in effect, the control group. Although the overall rate of cognitive dysfunction may be higher without a "true control group," our finding of no significant effect of APOE4 genotype is still valid.

Second, Avidan *et al.* object to an arbitrary statistical threshold for the diagnosis of postoperative cognitive dysfunction (POCD). Defining POCD as deficit or no-deficit requires specifying a cutoff for amount of decline. In the absence of a criterion standard, any cutoff is arbitrary. We believe a decline of more than 1 SD represents a clinical and noticeable loss in cognitive function. First, in an assessment in which most patients improve over time, any decline is bad. Further, in other samples, we have seen a significant association between our defined POCD and cognitive difficulty reported by patients themselves in a 39-item assessment of perceived problems in memory, concentration, attention, and psychomotor coordination. The questionnaire includes items such as "I forget errands I planned to do" and "I fail to recognize people I know." A higher score is worse. Patients we classified as having POCD had a mean increase [mean (SD)] of +1.64 (22.1) in difficulties at 6 weeks after surgery, whereas no-POCD patients had a mean decrease of −2.54 (19.4), $P = 0.02$. A trend toward increased mortality at 1 yr in patients with POCD (3.16 *vs.* 1.25%, $P = 0.23$) was also reported in our article. Thus, our choice of a 1 SD decline does have some clinical relevance. Nevertheless, because any threshold is arbitrary in the absence of a criterion standard, we have also examined a continuous change score, which is calculated by subtracting the baseline from the follow-up cognitive index (mean of the four domain scores). As with the dichotomous outcome, there is no association between APOE4 and cognitive change, once again validating our finding of no significant effect of APOE4 genotype.

Third, the issue of baseline "mild dementia" was raised. As Avidan and colleagues[2] have demonstrated, baseline mild cognitive impairment or dementia may be confounders when assessing long-term POCD. However, this cognitive impairment can be in single or multiple cognitive domains and can have a variety of clinical manifestations.[3,4] The International Working Group on Mild Cognitive Impairment published their first efforts toward a consensus in this arena in 2004,[3] but only near the completion of our study. Gauthier *et al.*[4] have more recently highlighted the ongoing uncertainty and debate in this field, noting in particular that "the prognosis in terms of progression to dementia is more heterogeneous in population studies than in the setting of specialized clinics (*such as an Alzheimer's Disease Research Center*) and is driven by the nosological and exclusionary criteria being used in either setting." At the very least, further studies defining and validating the effects of baseline dementia are still needed. In our study focused on shorter-term cognitive dysfunction, we compared postoperative cognition with preoperative baseline values to make each patient his/her own "control" while acknowledging the inherent limitations to this approach.

Fourth, the etiology of POCD remains incompletely ascertained at this time, as Dr. Avidan points out. We do think, however, that it is inappropriate to conclude from our study that anesthetic factors have no effect on POCD because our study was not designed to examine that hypothesis. Thus, we made no conclusions regarding the etiology of POCD. We simply found no association between APOE4 genotype, as well as a panel of serum biomarkers, and postoperative cognitive decline, assessed either as a dichotomous or a continuous measure.

Fifth, Avidan *et al.* requested greater detail on the factor loadings used in our cognitive analyses; these are provided in table 1. We did not publish this table because we believed it would not be meaningful or interpretable to most readers. Trails-Making B scores were reversed to

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Table 1. Factor Loadings and Weights for the Neurocognitive Test Battery

Test	Factor 1	Factor 2	Factor 3	Factor 4
Loading				
Randt Short Story (Immed. Verbatim)	0.915	0.145	0.171	0.148
Randt Short Story (Immed. Gist)	0.908	0.132	0.038	0.132
Randt Short Story (Delay Verbatim)	0.88	0.167	0.274	0.108
Randt Short Story (Delay Gist)	0.878	0.184	0.228	0.060
Visual Repro. Immed.	0.197	0.896	0.227	0.144
Visual Repro. Delay	0.218	0.874	0.265	0.165
WAIS Digit Symbol	0.252	0.243	0.864	0.128
Trail-Making B	0.219	0.284	0.819	0.256
Digit Span Forward	0.048	0.096	0.149	0.881
Digit Span Backward	0.221	0.175	0.149	0.816
Weight				
Randt Short Story (Immed. Verbatim)	0.309	−0.065	−0.072	0.002
Randt Short Story (Immed. Gist)	0.332	−0.022	−0.196	0.019
Randt Short Story (Delay Verbatim)	0.278	−0.076	0.037	−0.052
Randt Short Story (Delay Gist)	0.286	−0.037	−0.006	−0.082
Visual Repro. Immed.	−0.074	0.655	−0.181	−0.066
Visual Repro. Delay	−0.071	0.616	−0.143	−0.055
WAIS Digit Symbol	−0.085	−0.168	0.705	−0.124
Trail-Making B	−0.104	−0.128	0.623	−0.017
Digit Span Forward	−0.076	−0.098	−0.076	0.652
Digit Span Backward	−0.012	−0.040	−0.123	0.578

Immed. = immediate; Repro = reproduction; WAIS = Wechsler Adult Intelligence Scale.

scale all scores, where higher is better, and log-transformed to obtain a normal distribution. After Varimax orthogonal rotation, all loadings (factor pattern matrix) are therefore positive.

Sixth, Avidan *et al.* objected to our definition of POCD and the high POCD rate that we reported. We note that 74% of our patients underwent orthopedic surgery where embolic phenomenon are reported to be more common and may account for at least a portion of the higher incidence seen in our study. Although Avidan *et al.* focus on the categorical outcome, we again emphasize that we have also presented a continuous measure of change, which expresses both the amount and the direction of change (decline and improvement) and reflects the continuous nature of cognitive functioning. We include a dichotomous definition of POCD to satisfy the need for descriptive categorization. Our categorical cognitive outcome is also intentionally inclusive. Like many medical adverse events, it is focused on identifying injury and is not ameliorated or offset by improvement in other areas. A broken arm should not be ignored or classified differently because the other arm is whole or gains compensatory strength during recovery. Thus, it is a strength of our study that we present two different means of characterizing postsurgical cognitive change; in the end, neither measure supports an effect of APOE4.

Certainly for the categorized outcome, as with any composite outcome, the number of domains influences the likelihood of observing an event. Our choice of four domains is driven directly by the tests in our battery, which are grouped very coherently in domains. The battery was chosen by clinical consideration as representative of important distinct cognitive functions. At 6 weeks, 90% (171 of 190) of patients classified as having POCD had a deficit in one factor only; none had deficits in more than two factors. Improvement of more than 1 SD on at least one factor was seen in 59% of all patients (206 of 350); 25 improved more than 1 SD on two factors. At 1 yr, 57% (166 of 291) of patients showed improvement of more than 1 SD on at least one factor. Once again, in keeping with the medical model of injury, a decline in any important domain of cognitive functioning is arguably noteworthy and should not be ignored because of improvement or compensation in other domains.

Seventh, Avidan *et al.* stated that the reported incidence rate of POCD in our study was inconsistent with the change scores on the continuous cognitive index. We appreciate the thoughtful attention to the difference between the continuous change score and the dichotomous categorization but note that they are, to some degree, "comparing apples to oranges." As discussed above, the continuous score quantifies overall response, without the necessity of an arbitrary cutoff for decline. It allows improvement in some individuals to offset others' decline in characterizing the group response. The dichotomous categorization identifies cognitive decline more specifically both in individuals and in domains. We appreciate the "glass almost full" perspective of the critique in respect to cognitive recovery but also are concerned about patients whose function may no longer be complete.

Finally, Avidan *et al.* were concerned about the time course of POCD. Of those with POCD at 6 weeks, 51% (74 of 145) also had it at 1 yr; 43% of those without POCD at 6 weeks (56 of 129) had it at 1 yr. Just two postoperative observations provide very little information for reliably estimating the time course of POCD, and this was not the intention of our study.

All of these subjects are being obeserved to 5 yr, and these data will be published when available.

Although we applaud the contributions of Avidan and colleagues to our understanding of the role of dementia in POCD, we encourage them to join us and the many other established research groups assessing POCD in conducting the rigorous prospective surgical trials necessary to provide conclusive answers. We also forcefully reject their assertion that our findings are meaningless. By focusing on our dichotomous categorization and virtually ignoring the fact that a continuous measure was also assessed, they are employing a strategy of misdirection that is unwarranted. In contrast to their mere "hope for truth," we have prospectively enrolled 394 patients to demonstrate that the APOE4 genotype is not associated with cognitive decline after noncardiac surgery.

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Permeability, Osmosis, and Edema

To the Editor:

I enjoyed the interesting article by Jungner *et al.*[1] on the effects of crystalloid *versus* albumin fluid resuscitation in rats with traumatic brain injury, and the excellent editorial by Dr. Drummond.[2] Thanks to these authors for highlighting the principles of osmosis that underlie the behavior of semipermeable membranes, a key difference between peripheral and brain vasculature.

This letter is to note two typographical errors in a key part of the editorial that render the otherwise elegant explanations incorrect. The second paragraph explains the consequences of dilutional changes in colloid osmotic pressure (COP) in the periphery and in the brain. A key sentence states, "For example, a 50% reduction in COP produces a [small] transmembrane pressure gradient- . . . but because small solvents move easily . . . fluid moves extravascularly and edema forms." This is incorrect as written; it should read, "because small *solutes* move easily." Shortly thereafter, the sentence describing the situation in the brain states, "With COP reduction, some transendothelial movement of water probably does occur, but dissolved solvent cannot follow and opposing osmolar and hydrostatic gradients develop immediately and measurable edema differences are prevented." Again, this should read, "dissolved *solute* cannot follow."

For readers less familiar with the physical chemistry, the explanation is this: A solvent (water) passes easily through a membrane, but an impermeant solute (colloid) does not. Because of an entropic effect, the solvent will diffuse into the compartment that has the higher concentration of the impermeant solute, *as if* it is acted upon by a physical driving pressure (the "osmotic pressure").* This is the phenomenon called osmosis. In our example, initially, the system is in equilibrium: the hydrostatic pressure inside the vessels exactly opposes the "osmotic pressure" due to intravascular colloid. In the next step, the colloid is diluted; now, the hydrostatic pressure overwhelms the opposing "osmotic pressure," and fluid extravasates.

Dr. Drummond's teaching point is that in the periphery, any reduction in colloid has a significant osmotic effect, because only the colloid is impermeant. The other *solutes*, small molecules such as electrolytes, pass freely through the membranes and therefore do not have an osmotic effect. In the brain, however, many solutes are impermeant (or diffuse only "with difficulty" [*i.e.*, to a small degree]). A reduction only in colloid will cause only a small reduction in the total osmotic effect. Therefore, as soon as a small amount of water has extravasated across the membrane (if any passes out at all), the balance of "osmotic pressure" and hydrostatic pressure is already restored.

There is an additional teaching point to make here: We may ask, how is it that only the colloid concentration, but not the small-solute concentration, changed with dilution in this example? The answer is two-fold: (1) The dilution was with crystalloid solution that contained small solutes of its own; and (2) the small solutes pass freely through the membranes elsewhere in the body, promptly equalizing the small-solute concentration (but not the colloid concentration) across the peripheral vasculature. The result-

* "Osmotic pressure" is *not* a real physical pressure, but an effect due to the tendency of chemical systems to seek greater entropy. In thermodynamics, the potential that drives osmosis is referred to as "chemical potential."