Longitudinal Cognitive and Neurobehavioral Functional Outcomes Before and After Repairing Otic Capsule Dehiscence

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Objective: Patients with peripheral vestibular dysfunction because of gravitational receptor asymmetries display signs of cognitive dysfunction and are assumed to have neurobehavioral sequelae. This was tested with pre- and postoperatively quantitative measurements in three cohort groups with superior semicircular canal dehiscence syndrome (SSCDS) symptoms: 1) superior canal dehiscence (SCD) repaired via a middle cranial fossa craniotomy and canal plugging only; 2) otic capsule defects not visualized with imaging (no-iOCD) repaired with round window reinforcement (RWR) only; or 3) both SCD plugging and subsequent development of no-iOCD followed by RWR.

Study Design: Prospective patient series.

Setting: Tertiary referral center.

Patients: There were 13 adult and 4 pediatric patients with SSCDS who had completion of neuropsychology test batteries pre- and every 3 months postoperatively. Eight patients had no-iOCD and RWR exclusively, 5 had SCD and plugging exclusively, and 4 had both SCD plugging and then development of no-iOCD with RWR. These cohorts included SSCDS with 2 different dehiscence locations.

Interventions: Completion of a neuropsychology test battery preoperatively and at 3, 6, 9, and 12 months postoperatively that included: Beck Depression Inventory-II (BDI); Wide Range Intelligence Test (WRIT FSIQ) including average verbal (crystallized intelligence) and visual (fluid intelligence); Wide Range Assessment of Memory and Learning (WRAML), including the four domains of verbal memory, visual memory, attention/concentration, and working memory; and Delis–Kaplan Executive Function System (D-KEFS). The Dizziness Handicap Inventory (DHI) and the Headache Impact Test (HIT-6) were also completed to assess the impact of their disease on activities pre- and postoperatively.

Main Outcome Measures: Quantitative and statistical analysis of their cognitive and neurobehavioral function.

Results: The pattern of differences between the SCD group and the no-iOCD group from WRAML verbal, visual, and attention test performance indicate different postoperative clinical trajectories. For the WRAML, there was a statistically significant improvement for visual memory and verbal memory for the no-iOCD only and both (SCD and subsequent no-iOCD) groups, but no mean improvement for the SCD only group. By contrast, the no-iOCD group had significantly lower scores on the WRAML attention test preoperatively, but they recovered postoperatively to match the other groups. The preoperative findings and postoperative outcomes did not differ significantly among patient groups on the WRAML working memory test, D-KEFS motor scores, D-KEFS number and letter scores, or Wide Range Intelligence Test scores. There was a significant decrease in the BDI for all groups. The IQ scores were unchanged. There was a statistically significant improvement in the DHI and HIT-6 scores postoperatively in all groups.

Conclusions: There was a marked overall improvement in cognitive and neurobehavioral function postoperatively. Variability may result from duration of underlying disease before intervention. The initial decrement or delay in performance improvement measured in several patients may represent brain reorganization. Greater longitudinal data and greater subject numbers are necessary to better understand and optimize cognitive recovery. Key Words: Cognitive dysfunction—Depression—Memory—Migraine—Otic capsule dehiscence syndrome—Perilymph fistula—Superior canal dehiscence syndrome—Traumatic brain injury.

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Clinicians managing patients with peripheral vestibular disorders are challenged with signs and symptoms of altered cognitive function, which often introduce challenges when trying to elicit a cogent history. Cognitive alterations seem to be associated with many vestibular asymmetries (1) and with otic capsule defects. Nearly a quarter century ago, Black et al. (2) reported that the majority of patients with perilymph fistula (PLF) experience altered cognitive status. Similar cognitive changes...
have recently been described in patients with superior semicircular canal dehiscence syndrome (SSCDS) symptoms (3). Video recordings of consenting patients before and after intervention help to further document these obvious alterations in ways that complement standardized neuropsychological testing (4–12).

Recently, a prospective cohort of 12 patients with long-term follow-up and with SSCDS, 6 with radiographic evidence of superior canal dehiscence (SCD) treated with a middle fossa approach and plugging; and 6 with no visible imaging otic capsule dehiscence (no-iOCD) treated with round window reinforcement (RWR) was reported (3). It has been suggested that the term SSCDS be replaced with otic capsule dehiscence syndrome (OCDS) because the same SSCDS symptoms and diagnostic findings can occur with lateral and posterior semicircular canal dehiscence, internal carotid artery-cochlea dehiscence, posterior semicircular canal-jugular bulb dehiscence, posttraumatic hypermobile stapes footplate (Dr. Arun Gadre, personal communication, August 1, 2015) and in patients with no-iOCD (3,6,13–17).

This study used a battery of neuropsychological tests to provide the first quantitative characterization of the preoperative and postoperative cognitive function changes in patients undergoing surgical management of their OCDS. A comprehensive neuropsychology test battery was administered preoperatively and at 3, 6, 9, and when possible 12 months postoperatively. This battery included: the Beck Depression Inventory-II; the Wide Range Intelligence Test including average verbal (crystallized intelligence) and visual (fluid intelligence); the Wide Range Assessment of Memory and Learning, including the four domains of verbal memory, visual memory, attention/concentration, and working memory; and the Delis–Kaplan Executive Function System (for an in-depth description of these neuropsychology tests, see Supplemental Digital Content, http://links.lww.com/MAO/A351) (18–28). These neuropsychological tests showed distinctive patterns that provide greater insight into the nature of the cognitive dysfunction these patients experience and suggest that additional interventions may maximize and/or accelerate their cognitive recovery. These OCDS patients, with two different dehiscence locations and resolved surgically, may provide a novel opportunity to gain deeper insight into cognitive neuroscience.

METHODS

Subjects

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration. Our Institutional Review Board approved these studies.

Seventeen healthy subjects with SSCS/OCDS who had SCD, no-iOCD, or both agreed to participate in and completed the study. There were 13 adults and 4 children. The entire cohort had a mean age of 39.5 years (range, 12.99–60.29 yr) at first surgery, with 5 males and 12 females. Group 1 (no-iOCD only) (n = 8) had a mean age at first surgery of 39.4 years (range, 12.99–60.29 yr), with two males and six females. Group 2 (both SCD and subsequent no-iOCD) (n = 4) had a mean age at first surgery of 43.42 years (range, 33.46–53.79 yr), with one male and three females. It should be noted that in Group 2 (SCD and no-iOCD) all RWR operations occurred subsequent to SCD plugging of a radiographically identified SCD. Group 3 (SCD only) (n = 5) had a mean age at first surgery of 36.36 years (range, 14.48–56.30 yr), with two males and three females. At the time of manuscript submission, the entire cohort had a mean age of 41.58 years (range, 14.82–62.67 yr). Group 1 (no-iOCD only) had a mean age at the time of manuscript submission of 41.65 years (range, 14.82–62.67 yr, n = 8). Group 2 (SCD and subsequent no-iOCD) had a mean age at the time of manuscript submission of 46.11 years (range, 36.93–57.10 yr, n = 4). Group 3 (SCD only) had a mean age at the time of manuscript submission of 37.86 years (range, 15.63–58.72 yr, n = 5). The patient demographies and clinical features for each subject are summarized in Tables 1 and 2. The methods for the diagnostic studies performed can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (2,29–31).

Dizziness Handicap Inventory

The methods for the Dizziness Handicap Inventory (DHI) studies performed can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (32).

Headache Impact Test

The methods for the Headache Impact Test (HIT-6) studies performed can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (33,34).

Computerized Dynamic Posturography

The methods for the computerized dynamic posturography studies performed can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (35–37).

Neuropsychology Test Battery

Completion of a neuropsychology test battery preoperatively and at 3, 6, 9, and 12 months postoperatively that included: Beck Depression Inventory-II (BDI); Wide Range Intelligence Test (WRIT FSIQ) including average verbal (crystallized intelligence) and visual (fluid intelligence); Wide Range Assessment of Memory and Learning (WRAML-2), including the four domains of verbal memory, visual memory, attention/concentration, and working memory; and Delis–Kaplan Executive Function System. Detailed information regarding each of these neuropsychology tests can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351).

Statistical Analysis

The scores from each test were analyzed by mixed design analysis of variance (ANOVA), with patient group (SCD, RWR, or both surgeries) as a between subjects factor and the test time (preoperative, early postoperative, and late postoperative times) as the repeated measures factor (SYSTAT 11 software). Least significant differences post-hoc tests were used for paired comparisons in cases where significant main or interaction effects were shown by ANOVA. A criterion of p < 0.05 was regarded as significant.

RESULTS

Although not the focus of the present study, once each patient completed their final surgical procedure and
| Patient | Sex | Age at First Surgery | Current Age* | Diagnosis at Initial Referral | Surgery 1 | Surgery 2 | Surgery 3 | Postoperative Complicating Factors | Last Surgery to First Assessment | Last Surgery to Most Recent Assessment | First Surgery to Most Recent Assessment |
|---------|-----|---------------------|--------------|-----------------------------|-----------|----------|----------|-----------------------------------|-------------------------------|-----------------------------------|----------------------------------------|
| 1       | M   | 12.99               | 14.82        | TBI, migraine               | R         | RWR      | L        | ELH, resolved                     | 1 month                       | 6 months                          | 8 months                              |
| 2       | F   | 17.19               | 18.86        | Conversion disorder, migraine| R         |          |          | None                              | 6 months                       | 8 months                          | 8 months                              |
| 3       | F   | 35.32               | 37.31        | Migraine                    | R         | RWR      | L        | None                              | 2 months                       | 12 months                         | 12 months                             |
| 4       | F   | 43.03               | 45.43        | Migraine, ELH               | L         | RWR      |          | None                              | 4 months                       | 12 months                         | 12 months                             |
| 5       | F   | 46.82               | 48.96        | Migraine, hemiplegic migraine| L         | RWR      | L        | Appendicitis, severe vomiting     | 3 months                       | 10 months                         | 11 months                             |
| 6       | F   | 49.29               | 52.60        | Migraine, ELH               | R         | RWR      |          | ELH                               | 3 months                       | 6 months                          | 6 months                              |
| 7       | F   | 50.32               | 52.51        | Migraine, Menière disease   | R         | RWR      |          | ELH                               | 2 months                       | 9 months                          | 9 months                              |
| 8       | M   | 60.29               | 62.67        | Autophony                   | L         | RWR      |          | ELH                               | 2 months                       | 12 months                         | 12 months                             |
| 9       | F   | 33.46               | 36.93        | Migraine                    | R         | R SC D   | R         | Migraine, intermitent             | 3 months                       | 17 months                         | 29 months                             |
| 10      | F   | 35.47               | 37.45        | Migraine, fall while rock climbing| R         | R SC D   | L         | Chronic EtOH abuse                | 2 months                       | 2 months                          | 13 months                             |
| 11      | M   | 50.94               | 52.95        | SCD, migraine               | R         | R SC D   | R         | ELH, Irlen syndrome               | 2 months                       | 4 months                          | 11 months                             |
| 12      | F   | 53.79               | 57.10        | MVA, concussion, migraine   | R         | R SC D   | R         | ELH                               | 3 months                       | 13 months                         | 22 months                             |
| 13      | M   | 14.48               | 15.63        | Migraine, concussion        | R         | R SC D   |          | Withdrew from study               | 3 months                       | 9 months                          | 9 months                              |
| 14      | F   | 16.38               | 17.28        | Migraine                    | R         | R SC D   |          | None                              | 4 months                       | 9 months                          | 6 months                              |
| 15      | F   | 39.98               | 41.38        | Migraine                    | R         | R SC D   |          | None                              | 3 months                       | 9 months                          | 6 months                              |
| 16      | M   | 54.66               | 56.30        | Otolithic crisis of Tumarkin, ELH | L         | R SC D   |          | ELH                               | 3 months                       | 6 months                          | 6 months                              |
| 17      | F   | 56.30               | 58.72        | SCD, migraine               | L         | R SC D   |          | ELH, slowly resolved              | 9 months                       | 18 months                         | 21 months                             |

*As of 4/1/2015 (age in years); ELH indicates endolymphatic hydrops; EtOH, ethanol; RWR, round window reinforcement; SCD, superior canal dehiscence.
### TABLE 2. Patient history, symptoms, physical findings and results of diagnostic studies before surgical intervention

| Group 1 Patients with otic capsule dehiscence syndrome and no imaging visible otic capsule dehiscence only | Hearing Internal Sounds | Cognitive Dysfunction | Spatial Disorientation | Migraine Character | Trauma | Endolymphatic Hydrops | vCEMP | Moving Platform | High-Resolution CT |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Increased HA | Eyes blinking, autophony | Positive | Yes | Yes | No | Yes | 247, light sensitivity | Snowboarding accident, LOC | Bilateral | Left | Positive, bilateral |
| 2 | Increased HA | Eyes blinking, autophony | Positive | Yes | Yes | No | Mild | 247, severe | Concussion after falling down stairs, later flu and vomiting | Right | No | Positive, right |
| 3 | Dizziness, nausea | Autophony, eye movement, chewing | Positive | Yes | Yes | No | Yes | 247, light sensitivity, vestibular migraine with episodic rotational vertigo | No | Right | Right | Normal |
| 4 | Dizziness, nausea, vibration, left head | No | Negative | Yes | Yes | No | Mild | Frequent, light sensitivity | No | Bilateral | Left | Positive, left |
| 5 | Dizziness, nausea, agitation | Eyes blinking, heartbeat, swallowing, autophony | Positive | Yes | Yes | Yes | Yes | 247, light sensitivity, left hemiplegic migraine, ocular migraine, rare vestibular migraine | No | Right | Left | Positive |
| 6 | Dizziness, nausea, HA | Heartbeat | Positive | Yes | Yes | No | Mild | Frequent, light sensitivity | Airplane flight descent | Bilateral | Right | Absent |
| 7 | Dizziness, nausea, HA | Eyes blinking, heartbeat | Not performed | Yes | No | Yes | No | Positive | No | Bilateral | Bilateral | Positive |
| 8 | Ear pressure, increased tinnitus | Autophony | Positive | Yes | Yes | No | No | None | No | Bilateral | No | Positive, left |

| Group 2 Patients with otic capsule dehiscence syndrome and having superior canal dehiscence and subsequently another otic capsule dehiscence not visualized with imaging | Hearing Internal Sounds | Cognitive Dysfunction | Spatial Disorientation | Migraine Character | Trauma | Endolymphatic Hydrops | vCEMP | Moving Platform | High-Resolution CT |
|---|---|---|---|---|---|---|---|---|---|
| 9 | Tilting, nausea | Breathing, chewing, head strike | Positive | Yes | Yes | No | Yes | Migraine | No | Right | Right | Absent |
| 10 | Dizziness, nausea, HA | TMJ movement | Positive | Yes | Yes | Yes | Yes | Migraine, ocular migraine | No | Right | Bilateral | Positive, bilateral |
| 11 | Legs buckle, nausea | Eyes moving, autophony | Positive | Yes | Yes | No | Mild | No | No | No | Bilateral | Right |
| 12 | HA | None | Positive | Yes | Yes | No | No | Daily nystagmus | Right | Not performed | SCD, bilateral |

| Group 3 Patients with otic capsule dehiscence syndrome and having superior canal dehiscence only | Hearing Internal Sounds | Cognitive Dysfunction | Spatial Disorientation | Migraine Character | Trauma | Endolymphatic Hydrops | vCEMP | Moving Platform | High-Resolution CT |
|---|---|---|---|---|---|---|---|---|---|
| 13 | Dizziness, HA | Autophony, joint movement | Positive | Yes | Yes | Yes | Yes | Daily nystagmus | No | Right | Right | Absent |
| 14 | Dizziness, HA | Joint movement, chewing, heartbeat | Positive | Yes | Yes | Yes | Yes | Daily nystagmus, light sensitivity | Right | No | Positive, right |
| 15 | Dizziness, nausea, pain | Eyes moving, head strike, breathing, autophony | Positive | Yes | Yes | No | Mild | Daily nystagmus, light sensitivity | No | Right | Bilateral |
| 16 | Sound distortion | Thumping | Positive | Yes | Yes | Yes | No | Occasional | None | Sudden hearing loss with rotational vertigo, left |
| 17 | Tilting, nausea | Eyes moving, head strike, joint movement, food flowing, autophony | Positive | Yes | Yes | Yes | Mild | Daily nystagmus, light sensitivity | Bilateral | Bilateral | Absent |

*See video links in (4–6). 247 indicates migraine headache present constantly, 24h per day and 7 days per week; 256 Hz, ability to hear or feel the vibration of the head of the tuning fork when applied to knees and elbows; cVEMP positive, increased amplitude response and decreased threshold; Dizziness, gravitational receptor asymmetry type of vertigo in g, as if on a boat, rocking, wavy, tilting, being pushed, tilting, or sense of floor falling out from under them; Endolymphatic hydrops, abnormal summating potential/action potential ratio with electrocochleography; HA, headache; MVA, motor vehicle accident; SCD, superior canal dehiscence; TMJ, temporomandibular joint.
medical management resolved any of the factors complicating their postoperative recovery, their presenting symptoms and signs were returned near their baseline before developing SSCDS/OCDS. Additional information regarding the limitations of reporting the hearing and cVEMP outcomes can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (30). We completed quantitative comparisons of postural control using computerized dynamic posturography to better understand the changes in vestibular function as a consequence of surgical intervention using this more system-based approach.

The MRI with CISS sequences that demonstrated plugging of the superior semicircular canal in the 4 patients (patients 9–12) who subsequently developed no-iOCD and treated with RWR can be observed in Figure 1.

The neurobehavioral features of the patients attributed to neurological and psychiatric disorders (Tables 1 and 2) resolved over time (for example, see patients 1 and 2 (4,6)).

Dizziness Handicap Inventory

The DHI data revealed that there was a highly significant improvement pre- versus postoperatively (repeated measures ANOVA, \( F(1,11) = 254.6, p < 0.001 \)) overall and for each group (Fig. 2), but no significant difference between patient groups (repeated measures ANOVA, \( F(2,11) = 1.8, p > 0.2 \)). For the no-iOCD patients, the mean DHI score was 74 (range, 48–98, SD ± 17.48) preoperatively and 1.33 (range, 0–4, SD ± 1.63) postoperatively. This improvement was statistically significant (\( p < 0.001 \)). For the both SCD and no-iOCD patients, the mean DHI score was 78.5 (range, 64–88, SD ± 11.0) preoperatively and 19.5 (range, 0–42, SD ± 19.1) postoperatively. This improvement was statistically significant (\( p < 0.001 \)). For the SCD only patients, the mean DHI score was 72.5 (range, 68–76, SD ± 4.12) preoperatively and 8.5 (range, 4–18, SD ± 6.4) postoperatively. This improvement was statistically significant (\( p < 0.001 \)).

The DHI physical subscores differed significantly across patient groups (repeated measures ANOVA, \( F(2,11) = 7.5, p < 0.01 \)), despite the fact that all groups showed a significant reduction after surgery (repeated measures ANOVA, \( F(1,11) = 168.1, p < 0.001 \)). This difference was because of a significantly higher postoperative subscore (least significant differences test) in the group given operations for both SCD plugging and subsequent no-iOCD RWR (7.00 ± 5.29 (SD)) than for either the SCD plugging alone (2.00 ± 1.63 (SD), \( p < 0.05 \)) or no-iOCD with RWR alone (0.33 ± 0.82 (SD), \( p < 0.01 \)) groups.

Headache Impact Test

Migraine headache was present in 88% (7/8) of subjects with no-iOCD only, 100% (4/4) of subjects with SCD and subsequent no-iOCD, and 80% (4/5) of subjects with SCD only. Interestingly for these patients the migraine headaches by clinical report resolved in all patients (4–6), including those with vestibular migraine, ocular migraine, and hemiplegic migraine (Table 2); however, the HIT-6 data revealed that there was a highly statistically significant improvement pre- versus postoperatively (\( p < 0.001 \)) overall and between groups (Fig. 3), yet there are two patients who quantitatively became Class II and one patient remained a Class IV. The remaining 11 patients became Class I. For the no-iOCD
patients, the mean HIT-6 score was 74 (range, 68–78 [all Class IV], SD = 4) preoperatively and 45.7 (range, 42–49 [all Class I], SD = 3.14) postoperatively. This improvement was statistically significant ($p < 0.001$). For the both SCD and subsequent no-iOCD patients, the mean HIT-6 score was 69.3 (range, 57–78 [one Class III, three Class IV], SD = 9.7) preoperatively and 46.8 (range, 36–53 [two Class II and two Class I], SD = 8.10) postoperatively. This improvement was statistically significant ($p < 0.001$). For the SCD only patients, the mean HIT-6 score was 69.8 (range, 61–76 [all Class IV], SD = 6.34) preoperatively and 44.5 (range, 36–61 [one Class IV and three Class I], SD = 11.27) postoperatively. This improvement was statistically significant ($p < 0.001$). Both indicates SCD plugging, subsequent development of no-iOCD managed with RWR; no-iOCD, no imaging visible otic capsule dehiscence only managed with RWR; SCD, superior semicircular canal dehiscence only managed with middle cranial fossa approach and plugging. Copyright © Ear and Skull Base Center, used with permission.

As shown in Table 1, 15 of 17 patients (88.2%) were diagnosed with migraine and/or migraine variants and managed medically using drugs to prevent migraine from occurring (e.g., topamax, zonegran, verapamil, or tricyclic antidepressants) before undertaking surgical intervention. For the no-iOCD patients ($n = 7$), the mean duration of treatment was 11.3 months preoperatively (range, 2–19 mo, SD = 6.8 mo). For the both SCD and subsequent no-iOCD patients ($n = 4$), the mean duration of treatment was 19.8 months (range, 4–62 mo, SD = 28.2 mo). For the SCD only patients ($n = 4$), the mean duration of treatment was 36.5 months (range, 14–60 mo, SD = 21.2 mo).

**Computerized Dynamic Posturography**

Figure 4 shows the pre- versus postoperative posture performance for each group using the weighted composite score. Based on the independent samples Kruskal–Wallis test, there was no difference across groups for the preoperative or postoperative continuous EQ (CEQ) scores, either from the overall composite score or from the subscores for conditions 1 to 6. Although there were no significant differences in postoperative performance in each group analyzed separately, there was a significant
improvement in postoperative composite score when combining all three groups \( (p = 0.044, \text{Wilcoxon signed-rank test}) \).

**Beck Depression Inventory-II**

The preoperative scores from the Beck Depression Index-II (BDI) indicated mild depression in all three groups. There was significant and parallel improvement to the minimal depression range after surgery in all three groups \( (F(1,18) = 9.8, p < 0.01) \), which appeared on the first postoperative test session (Fig. 5).

**Wide Range Intelligence Test**

No significant differences were found in Wide Range Intelligence Test (WRIT FSIQ) scores; including average verbal (crystallized intelligence) and visual (fluid intelligence) when comparing pre- and postoperative performance and also between the three groups.

**Wide Range Assessment of Memory and Learning**

The Wide Range Assessment of Memory and Learning-2 (WRAML), including the four subtests of verbal memory, visual memory, attention/concentration, and working memory, revealed differences in both the preoperative status and postoperative recovery among the patients with the no-iOCD only group treated with RWR, the SCD only group treated with plugging, and those with SCD treated with plugging who subsequently developed no-iOCD treated with RWR (Fig. 5).

For the verbal subtest, the SCD only group (plugging) showed a delayed improvement on the WRAML verbal subtest; it was significantly lower than the no-iOCD only group treated with RWR and the both SCD (plugging) and subsequently developed no-iOCD (RWR) group for the first postoperative test (ANOVA and then least significant differences tests). All three groups showed statistically significant improvement in the verbal subtest by the most recent neuropsychology test battery assessment (Fig. 5).

For the visual subtest, unlike patients with no-iOCD only (RWR) or both SCD (plugging) and subsequently developed no-iOCD (RWR) (Fig. 5), the SCD only (plugging) group did not show statistically significant improvement at either the initial or most recent postoperative testing session. They remained significantly lower than either of the other groups (analysis of variance with repeated measures on test times and a between groups factor of operative history, and then least significant difference tests). By contrast, there was a statistically significant improvement in the visual subtest scores for the no-iOCD only (RWR) group and the both SCD (plugging) and subsequently developed no-iOCD (RWR) group at both the initial postoperative assessment and the most recent assessment.

Preoperatively, the no-iOCD only (RWR) group showed abnormally low scores on the WRAML attention/concentration subtest (Fig. 5, 95% confidence interval of 55.271 to 91.229 re: normal of 100); however, the performance normalized after surgery. There were significant test time effects overall (improvement in all groups), initially (preoperative) worse in the SCD only (plugging) and subsequently developed no-iOCD (RWR) group for the no-iOCD only (RWR) or both SCD (plugging) and subsequently developed no-iOCD (RWR) group treated with RWR and the both SCD (plugging) and subsequently developed no-iOCD (RWR) groups factor of operative history, and then least significant differences tests). All three groups showed statistically significant improvement in the verbal subtest scores preoperatively compared with the first and the most recent neuropsychology test battery assessments across all three groups.

**Delis–Kaplan Executive Function System**

Analysis of variance showed that there was significant postoperative improvement in both the Delis–Kaplan Executive Function System (D-KEFS) motor score \( (F(2,28) = 10.31, p < 0.01) \) and the number and letter score \( (F(2,28) = 6.04, p < 0.05) \). There were no significant differences between the treatment group responses (Fig. 6).

**DISCUSSION**

Discussion of the current limitations in reporting outcomes of surgical intervention in these patient cohorts can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (30,38,39).

Since the focus of this work was on understanding the degree of cognitive impairment and recovery after...
intervention, we elected to focus on two more global measures of vestibular function, the DHI and also the continuous equilibrium scores obtained via computerized dynamic posturography before and after intervention. As shown in Figure 2, the DHI data revealed that all patient groups reported a highly statistically significant perceived improvement for pre- versus postoperative status. On the other hand, dynamic posturography showed no significant differences in postoperative performance when each group was analyzed separately, despite a significant improvement in postoperative composite score when all three groups were combined. Hence, the groups did not differ clinically on these standard response metrics either pre- or postoperatively.

Most of the symptoms that disrupt the lives of patients with SCD, no-iOCD, and/or PLF are related to the severe, cognitive and neurobehavioral functional outcomes.

FIG. 5. Top left, the preoperative scores from the Beck Depression Index-II (BDI) indicated mild depression in all three groups. There was significant and parallel improvement to the minimal depression range after surgery in all three groups (F(1,18) = 9.8, p < 0.01), which appeared on the first postoperative test session. Note that this recovery is rapid and significantly better, even a few months after surgical intervention. Top right, for the Wide Range Assessment of Memory and Learning-2 (WRAML) verbal subtest, the SCD only group treated with SCD plugging showed a delayed improvement on the WRAML verbal subtest; it was significantly lower than the no-iOCD only group treated with RWR and the both SCD and no-iOCD group treated with RWR and SCD plugging for the first postoperative test (ANOVA and then least significant differences tests). All three groups showed statistically significant improvement in the verbal subtest by the most recent neuropsychology test battery assessment. (\(p < 0.05\) by least significant differences tests. Only the between groups differences are indicated). Bottom left, for the WRAML visual subtest, unlike patients with no-iOCD only treated with RWR or both SCD and no-iOCD treated with SCD plugging and RWR surgeries, the SCD only group treated with SCD plugging did not show statistically significant improvement at either the initial or most recent postoperative testing session, and remained significantly lower than either of the other groups (analysis of variance with repeated measures on test times and a between groups factor of operative history, and then least significant difference tests). There was a statistically significant improvement in the visual subtest for the no-iOCD only group treated with RWR and the both no-iOCD and SCD group treated with RWR and SCD plugging, respectively at both the initial postoperative assessment as well as at the most recent assessment. (\(p < 0.05\) and \(p < 0.01\) by least significant differences tests. Only the between groups differences are indicated). Bottom right, for the WRAML attention/concentration subtest, preoperatively, the no-iOCD group treated with RWR only showed abnormally low scores on the WRAML attention/concentration subtest (Fig. 1, 95% confidence interval of 55.271 to 91.229 re: normal of 100); however, the performance normalized after surgery. There were significant test time effects overall (improvement in all groups), initially (preoperative) worse in the no-iOCD only than the SCD only and the both SCD and no-iOCD patients (\(p < 0.02\), Fisher’s Least Significant Difference [LSD] test), but the same afterward. (\(p < 0.05\) by least significant differences tests. Only the between groups differences are indicated).
Chronic, uncompensated asymmetric sensory deficits (3–7, 9–12). The acute and chronic sequelae include direct and indirect sensorimotor processing, interoceptive, and cognitive neuronal networks that contribute to fear, anxiety, and altered cognitive performance. The relationship of these networks to vestibular information processing is described in detail in reviews (40,41).

These symptoms are, in part, a consequence of the fact that visual and vestibular sense-organs are anchored in the head. Sensations of visual motion and inertial motion are interpreted within the assumed context of stable head control. This assumption of head stability provides the basis for interpreting balance-related information from the head-fixed sensors in terms of the outside world. The perceptual assumption of stable motor control has two important implications. First, abnormal dynamic postural control can produce unexpected visual (e.g., optic flow or oscillopsia), head motion, or proprioceptive information. The autonomic and cognitive symptoms associated with these apparent sensory mismatches (including “visual-vestibular mismatch”) all fall within the rubric described by the sensory conflict hypothesis for motion sickness, simulator sickness, and cybersickness (42–47). Degradation of cognitive test performance would be expected. Second, individuals with vestibular abnormalities may adapt functionally by relying on sensory signals that restore a relatively stable level of control. If balance control becomes more responsive to spatial information in the visual channel, a balance phenomenon referred to as visual balance dependence develops. This can be defined operationally as increased sway in response to full-field motion of the visual surround (“optic flow”), a phenomenon that has been observed in patients with primary vestibular disorders (48). If balance control becomes more responsive to somatosensory (tactile and proprioceptive) information, somatosensory dependence develops. These changes in relative central weighting of multisensory signals may have cognitive consequences. Treatment that resolves the sensorimotor control performance would be expected to normalize the cognitive consequences.

However, balance-related information also affects limbic and cortical networks related to anxiety and threat assessment (41,49). It is an open question whether resolution of the peripheral asymmetry alone is sufficient to reverse chronic, adaptive changes in cognition via these mechanisms.

**Cognitive Functional Differences Between SCD and No-iOCD Patients**

Further discussion of the cognitive differences between SCD and no-iOCD patients can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (50–59).

Clinically, cognitive alterations are nearly universal in patients with superior canal dehiscence syndrome, whether because of an actual SCD or a no-iOCD. In contrast to these disorders that result in gravitational receptor dysfunction type of vertigo, it is uncommon in patients with rotational receptor dysfunction type of vertigo such as with benign positional vertigo, vestibular neuronitis, or other disorders producing true rotational vertigo. Patients with a no-iOCD and/or SCD often use the following descriptors when describing their cognitive function: “fuzzy, foggy, spacey, out-of-it; memory and concentration are poor; difficulty reading – as if the words are floating on the page; trouble finding the right words; and forgetting what I wanted to say.”

Gurvich et al. (60) published an excellent review of the role of the vestibular system on cognition and psychiatry. The two key anatomical regions that provide links between the vestibular system and neural networks involved in cognitive and emotional processing are the parabrachial nucleus and the hippocampus (49,61–63);
however, many of the neuroanatomical regions that are linked to the vestibular system are also implicated in several psychiatric illnesses. The past decade has observed an increased interest in the relationship between the vestibular system and mood, cognition and psychiatric symptoms with studies demonstrating vestibular stimulation can produce changes in mood, cognition, and psychiatric symptoms (64–66). It is also the case that many individuals with SCDS have been assigned a neurological or psychiatric diagnosis before their vestibular disorder was diagnosed and have experienced resolution of their “psychiatric disorder” after surgical intervention (4,5,9–11) (Table 1). This unfortunately is common with children (4,5). The hippocampus is consistently implicated in cognition and models of psychiatric disorders and there is a large body of evidence supporting vestibular–hippocampal interactions (67–71).

Smith et al. and Zheng et al. reported that modulation of memory, but not spatial memory, occurs with vestibular lesions and can be influenced by galvanic vestibular stimulation (72,73). These findings may lead to additional treatment strategies that may accelerate or maximize recovery after repairing a no-iOCD or SCD.

Further discussion of these issues from the historical perspective can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (74,75).

**Altered Spatial Orientation**

A discussion of the relationship between diseases producing otic capsule dehiscence syndrome and altered spatial orientation can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (76–79).

**Migraine Headache**

A discussion of the relationship between diseases producing otic capsule dehiscence syndrome and migraine headache can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (3–7,9–12,80–82) (also see Fig. 3 and Table 2).

**Current Cohort**

**Beck Depression Inventory-II**

The preoperative scores from the BDI indicated mild depression in all three groups. There was significant and parallel improvement to the minimal depression range after surgery in all three groups ($F(1,18) = 9.8, p < 0.01$), which appeared on the first postoperative test session (Fig. 5). There were no significant differences between any of the three groups. These findings are not unexpected, as most of these patients have experienced a delay in diagnosis despite having observed several physicians and completed numerous diagnostic studies. Many have been told “it is all in your head” and their interpersonal relationships and work performance have also been threatened or adversely impacted. Many patients develop severe depression because of their inability to perform their normal tasks. As shown in Figure 5, this recovery is rapid and significantly better, even a few months after surgical intervention.

**Wide Range Intelligence Test**

The finding that the WRIT showed no change in IQ is not surprising and serves as an internal control for these subjects. It would not be expected that these chronic, uncompensated gravitational receptor asymmetries would alter inherent intelligence.

**Wide Range Assessment of Memory and Learning**

The WRAML, including the four subtests of verbal memory, visual memory, attention/concentration, and working memory, revealed differences in both the preoperative status and postoperative recovery among the patients with no-iOCD treated with RWR, SCD treated with SCD plugging only, and those with SCD and subsequent development of no-iOCD who required both SCD plugging and subsequent RWR (Fig. 5).

For the verbal and visual subtests, the SCD only (plugging) group recovered function differently than the no-iOCD only (RWR) group and the both the SCD (plugging) and subsequently developed no-iOCD (RWR) group (Fig. 5). This is likely multifactorial. It is not unexpected that the both SCD treated with SCD plugging and subsequent development of no-iOCD treated with RWR group recovered in a similar manner as each patient had time to undergo vestibular compensation after closing the superior semicircular canal dehiscence before determining that they also developed a new no-iOCD and treating that dehiscence with a RWR surgery. Table 1 shows that these SCD (plugging) patients who subsequently developed a no-iOCD and had RWR had a mean time from first SCD plugging surgery to most recent neuropsychology assessment of 18.75 months, whereas the SCD only group treated with SCD plugging was 9.6 months. It is possible that there is a finite amount of brain recovery or reorganization that occurs as a function of time and that the process of vestibular compensation delayed the recovery of memory and learning as reflected by WRAML visual and verbal subtests. It should be noted that the WRAML visual subtest scores worsened at the first postoperative assessment in the SCD only patients. It may be that improvement of vestibulomotor function was necessary via vestibular compensation to eliminate these “cognitive jamming” mechanisms before visual recovery could occur. There were also two children included in the SCD only cohort who had factors potentially impacting their test performance. There was a statistically significant improvement in the verbal and visual subtests for the no-iOCD only group treated with RWR and the both SCD and subsequent development of no-iOCD group treated with SCD plugging and RWR, respectively at both the initial postoperative assessment and the most recent assessment.

Although speculative, there are five additional mechanisms that could explain the differences in recovery that
we observed in the SCD only group treated with plugging in both the visual and verbal domains: 1) direct vestibular processing effects; 2) erroneous or ambiguous motion information that creates an increased cognitive load for normal balance and navigation functions; 3) acute prodromal (e.g., Sopite syndrome [relates symptoms of fatigue, drowsiness, and mood changes to prolonged periods of motion]) and autonomic effects; 4) fear, anxiety, and phobic responses; and 5) parabrachial nucleus cells have both superior semicircular canal and linear acceleration sensitivity.

Preoperatively, the no-iOCD only (RWR) group showed abnormally low scores on the WRAML attention/concentration subtest (Fig. 5); however, the performance normalized after surgery. If a no-iOCD is at the modiolus, it would be expected that CSF pulsations would repeatedly stimulate the otolithic end-organs on the affected side whereas with a SCD there is no direct communication with the CSF, so perhaps it is the case that the no-iOCD patients have more ongoing impairment of attention/concentration. Ultimately, there were significant test time effects overall (improvement in all groups) by the most recent neuropsychology assessment.

**Delis–Kaplan Executive Function System**

Analysis of variance showed that there was significant postoperative improvement in both the D-KEFS motor score and the number and letter score. There were no significant differences between the treatment group responses (Fig. 6). This recovery of executive function was rapid and robust and not impacted by vestibular compensation as the no-iOCD patients experienced nearly immediate improvement anecdotally and our short-term follow-up intervals in the SCD only group treated with SCD plugging (4–7.9–11). These functions measured by the D-KEFS largely depend on prefrontal cortex.

**Learning Effects**

A discussion of learning effects can be found in the Supplemental Digital Content (http://links.lww.com/MAO/A351) (83–85).

**CONCLUSION**

These data represent the first demonstration that cognitive dysfunction in patients with otic capsule defects resulting in OCDS, regardless of etiology, exist, can be measured and that improvements in depression and cognitive function can be accomplished with appropriate, targeted, vestibular surgery.

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**REFERENCES**

1. Bilgrei R. The psychology of vestibular disorders part I: Cognitive aspects of vestibular disorders. https://vestibular.org/sites/default/files/page_files/Documents/Cognitive Aspects of Vestibular Disorders.pdf. (Accessed October 8, 2015).
2. Black FO, Peszecker S, Norton T, et al. Surgical management of perilymphatic fistulas: A Portland experience. *Am J Otol* 1992;13:254–62.
3. Wackym PA, Wood SJ, Siker DA, et al. Otic capsule dehiscence syndrome: Superior canal dehiscence syndrome with no radiographically visible dehiscence. *Ear Nose Throat J* 2015;94:E8–24.
4. Wackym PA. Traumatic otic capsule dehiscence syndrome after snowboarding accident. Patient 1 describing his symptoms before and after round window reinforcement surgery. https://www.youtube.com/watch?v=7azu9szaZSk Published June 8, 2015. (Accessed October 8, 2015).
5. Wackym PA. Right perilymph fistula: Dizziness, migraine headaches and cognitive dysfunction. Patient 2 describing her symptoms before and after round window reinforcement surgery. https://www.youtube.com/watch?v=9xVNXeNGySw Published August 6, 2015. (Accessed October 8, 2015).
6. Wackym PA. Left otic capsule dehiscence syndrome with hemiplegic migraine. Patient 5 describing her symptoms before and after round window reinforcement surgery. https://www.youtube.com/watch?v=9-xVNXeNGySw Published August 6, 2015. (Accessed October 8, 2015).
7. Wackym PA. Cognitive dysfunction due to otic capsule dehiscence syndrome. The second patient describing her cognitive dysfunction and recovery is patient 15. https://www.youtube.com/watch?v=IpNzUXlAf6g Published May 18, 2015. (Accessed October 8, 2015).
8. Wackym PA. Tuning fork testing in otic capsule dehiscence syndrome. https://www.youtube.com/watch?v=8zg_k0SVOes. Published April 21, 2015. (Accessed October 8, 2015).
9. Wackym PA. Otic capsule dehiscence syndrome in one ear after a bicycle accident. https://www.youtube.com/watch?v=IkFozqOBEc. Published April 5, 2015. (Accessed October 8, 2015).
10. Wackym PA. Traumatic otic capsule dehiscence syndrome after skiing accident. https://www.youtube.com/watch?v=2-kD5ygKreE. Published April 5, 2015. (Accessed October 8, 2015).
11. Wackym PA. Otic capsule dehiscence syndrome in one ear after a car accident. https://www.youtube.com/watch?v=1N9T6uqM. Published April 5, 2015. (Accessed October 8, 2015).
12. Wackym PA. Vestibular migraine. Patient video describing symptoms before and after treatment with Topamax. https://www.youtube.com/watch?v=Zy7YjCDnLYM Published April 12, 2012. (Accessed October 8, 2015).
13. Young L, Isaacson B. Cochlear and petrous carotid canal erosion secondary to cholesteatoma. *Otol Neurotol* 2010;31:697–8.
14. Meklejohn DA, Corrales CE, Boldt BM, et al. Pediatric semicircular canal dehiscence: Radiographic and histologic prevalence, with clinical correlations. *Otol Neurotol* 2015;36:1383–9.
15. Park JJ, Shen A, Loberg C, et al. The relationship between jugular bulb position and jugular bulb related inner ear dehiscence: A retrospective analysis. *Am J Otolaryngol* 2015;36:347–51.
16. Bear ZW, McEvoy TP, Mikulec AA. Quantification of hearing loss in patients with posterior semicircular canal dehiscence. *Acta Otolaryngol* 2015;135:974–7.
17. Elmali M, Pollat AV, Kucuk H, et al. Semicircular canal dehiscence: Frequency and distribution on temporal bone CT and its relationship with the clinical outcomes. *Ear J Radiol* 2013;82: e606–9.
18. Diagnostic and Statistical Manual of Mental Disorders, 4th ed
19. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
20. Beck AT, Rial WY, Rickets K. Short form of depression inventory: Cross-validation. *Psychol Rep* 1974;34:1184–6.
21. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol* 1984;40: 1365–7.
22. Sharp LH, Lipsky MS. Screening for depression across the lifespan: A review of measures for use in primary care settings. *Am Fam Physician* 2002;66:1001–8.
23. Glutting J, Adams W, Sheslow D. Wide Range Intelligence Test. Wilmington, DE: Wide Range; 2000.
24. Coalson D, Raiford S. WAIS IV Technical and Interpretive Manual. San Antonio, TX: Pearson; 2008.
25. Sheslow D, Adams W. Wide Range Assessment of Memory and Learning. 2nd ed Lutz, FL: Psychological Assessment Resources; 2004
26. Delis DC, Kramer JH, Kaplan E, et al. Reliability and validity of the Delis-Kaplan executive function system: An update. J Int Neuropsychol Soc 2004;10:301–3.
27. Schmidt M. Hit or miss? Insight into executive functions. J Int Neuropsychol Soc 2003;9:962–4.
28. Delo D, Kaplan E, Kramer J. Examiner’s Manual. San Antonio, TX: Pearson; 2001.
29. Margolis RH, Rieks D, Fournier EM, et al. Tympanic electrocochleography for diagnosis of Ménière’s disease. Arch Otolaryngol Head Neck Surg 1995;121:44–55.
30. Wackym PA, Ratigan JA, Birk JD, et al. Rapid cVEMP and oVEMP responses elicited by a novel head striker and recording device. Otol Neurotol 2012;33:1392–400.
31. Black FO, Lilly DJ, Nashier LM, et al. Quantitative diagnostic test for perilymph fistulas. Otolaryngol Head Neck Surg 1987;96:125–134.
32. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424–7.
33. Yang M, Rendas-Baum R, Varon SF, et al. Validation of the Postural Sway of Patients with Vestibular Disorders. Arch Otolaryngol Head Neck Surg 2012;138:1358–65.
34. Bayliss M, Batenhorst A. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424–7.
35. Winter DA. Biomechanics and Motor Control of Human Movement. New York: Wiley; 2004.
36. CDP Protocols. Natus Balance and Mobility Web site. http://resourcesonbalance.com/for-clinicians/computerized-dynamic-posturography/cdp-protocols/. Accessed October 8, 2015.
37. Wood SJ, Reschke MF, Black FO. Continuous equilibrium scores: Factoring in the time before a fall. Gait Posture 2012;36:487–9.
38. Vlaskaros PV, Prokas K, Tavoulari E, et al. Efficacy assessment and complications of surgical management for superior semicircular canal dehiscence: A meta-analysis of published interventional studies. Eur Arch Otorhinolaryngol 2009;266:177–86.
39. Ward BK, Agrayaw Y, Nguyen E, et al. Hearing outcomes after surgical plugging of the superior semicircular canal by a middle cranial fossa approach. Otol Neurotol 2012;33:1386–91.
40. Balaban CD, Jacob RG, Furman JM. Neurologic bases for comorbidities of balance disorders, anxiety disorders and migraine: Neurotherapeutic implications. Expert Rev Neurother 2011;11:739–94.
41. Staab JP, Balaban CD, Furman JM. Threat assessment and loco-motion: Clinical applications of an integrated model of anxiety and postural control. Semin Neurol 2013;33:297–306.
42. Guedry FE Jr. Psychophysics of vestibular sensation. In: Vestibular System Part 2: Psychophysics. Applied Aspects and General Interpretations. Berlin: Springer; 1974.3–154.
43. Kennedy RS, Berbaum KS, Collyer SC, et al. Spatial requirements for visual simulation of aircraft at real-world distances. Hum Factors 1988;30:153–61.
44. Kennedy RS, Berbaum KS, Lilenthal MG. Disorientation and postural ataxia following flight simulation. Aviat Space Environ Med 1997;68:13–7.
45. Kohl RL. Sensory conflict theory of space motion sickness: An anatomical location for the neuroconflict. Aviat Space Environ Med 1983;54:464–5.
46. Oman CM. Motion sickness: A synthesis and evaluation of the sensory conflict theory. Can J Physiol Pharmacol 1990;68:294–303.
47. Reason J, Brand J. Motion Sickness. London: Academic Press; 1975
48. Redfern MS, Furman JM. Postural sway of patients with vestibular disorders during optic flow. J Vestib Res 1994;4:221–30.
49. Balaban CD, Thayer JR. Neurological bases for balance-anxiety links. J Anxiety Disord 2001;15:53–79.
50. Bechterew W. Ergebnisse der Durchscheidung des N. acusticus, nebst Erörterung der Bedeutung der semicirculären Canäle für das Körpergleichgewicht. Pfliigers Arch f d ges Physiol 1883;30:312–47.
51. Bergquist F, Ludwig M, Dutia MB. Role of the commissural inhibitory system in vestibular compensation in the rat. J Physiol 2008;586 (Pt 18):4441–52.
52. Smith PF, Curthoys IS. Mechanisms of recovery following unilateral labyrinthectomy: A review. Brain Res Rev 1989;14:155–80.
53. Balaban CD, Hoffer ME, Gottshall KR. Top-down approach to vestibular compensation: Translational lessons from vestibular rehabilitation. Brain Res 2012;1482:101–11.
54. Pashler H. Dual task interference in simple tasks: Data and theory. Psych Bull 1994;116:220–44.
55. Andersson G, Yardley L, Luxon L. A dual-task study of interference between mental activity and control of balance. Am J Otol 1998;19:632–7.
56. Yardley L, Gardner M, Bronstein AM, et al. Interference between postural control and mental task performance in patients with vestibular disorder and healthy controls. J Neurol Neurosurg Psychiatry 2001;71:48–55.
57. Tańkowski ME, Redfern MS, Jennings JR, et al. Cognitive requirements for vestibular and ocular motor processing in healthy adults and patients with unilateral vestibular lesions. J Cognitive Neurosci 2005;17:1432–41.
58. Al-Yahya E, Dawes H, Smith L, et al. Cognitive motor interference while walking: A systematic review and meta-analysis. Neurosci Biobehav Rev 2011;35:715–28.
59. Watanabe K, Funahashi S. Neural mechanisms of dual-task interference and cognitive capacity limitation in the prefrontal cortex. Nat Neurosci 2014;17:601–12.
60. Garvich C, Maller JL, Lithgow B, et al. Vestibular insights into cognition and psychiatric disorders. Brain Res 2013;1537:244–59.
61. Wackym PA, Balaban CD. Molecules, motion, and man. Otolaryngol Head Neck Surg 1998;118:S13–23.
62. Balaban CD, McGuire DC, Zhou J, et al. Responses of primate caudal parabrachial nucleus and Kölliker-fuse nucleur neurons to whole body rotation. J Neurophysiol 2002;88:3175–93.
63. Balaban CD. Projections from the parabrachial nucleus to the vestibular nuclei: Potential substrates for autonomic and limbic influences on vestibular responses. Brain Res 2004;996:126–37.
64. Dodson MJ. Vestibular stimulation in mania: A case report. J Neurol Neurosurg Psychiatry 2004;75:168–9.
65. Levine J, Toder D, Geller V, et al. Beneficial effects of caloric vestibular stimulation on denial of illness and manic delusions in schizoaffective disorder: A case report. Brain Stimul 2012;5:267–73.
66. Winter L, Kruger TH, Laurens J, et al. Vestibular stimulation on a motion-simulator impacts on mood states. Front Psychol 2012;3:499.
67. Besnard S, Machado ML, Vignaux G, et al. Influence of vestibular input on spatial and nonspatial memory and on hippocampal NMDA receptors. Hippocampus 2012;22:814–26.
68. Brandt T, Schautz F, Hamilton DA, et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. Brain 2005;128:2732–41.
69. Hufner K, Hamilton DA, Kalla R, et al. Spatial memory and hippocampal volume in humans with unilateral vestibular deafferentation. Hippocampus 2007;17:471–85.
70. Sharp PE, Blair HT, Etkin D, et al. Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. J Neurosci 1995;15:173–89.
71. Smith PF, Horii A, Russel N, et al. The effects of vestibular lesions on hippocampal function in rats. Prog Neurobiol 2005;75:391–405.
72. Smith PF, Geddes LH, Baek JH, et al. Modulation of memory by vestibular lesions and galvanic vestibular stimulation. Front Neurol 2012;3:499.
76. Baek JH, Zheng Y, Darlington CL, et al. Evidence that spatial memory deficits following bilateral vestibular deafferentation in rats are probably permanent. *Neurobiol Learn Mem* 2010;94:402–13.

77. Smith PF, Darlington CL, Zheng Y. Move it or lose it: Is stimulation of the vestibular system necessary for normal spatial memory? *Hippocampus* 2010;20:36–43.

78. Deroualle D, Lopez C. Toward a vestibular contribution to social cognition. *Front Integr Neurosci* 2014;8:16.

79. Smith PF, Darlington CL. Personality changes in patients with vestibular dysfunction. *Front Hum Neurosci* 2013;7:678.

80. Furman JM, Marcus DA, Balaban CD. Vestibular migraine: Clinical aspects and pathophysiology. *Lancet Neurol* 2013;12:706–15.

81. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol* 2010;6:573–82.

82. Wackym PA. Ultrastructural organization of calcitonin gene-related peptide immunoreactive efferent axons and terminals in the rat vestibular periphery. *Am J Otol* 1993;14:41–50.

83. Heilbronner RL, Sweet JJ, Attix DK, et al. Official position of the American Academy of Clinical Neuropsychology on serial neuropsychological assessments: The utility and challenges of repeat test administrations in clinical and forensic contexts. *Clin Neuropsychol* 2010;24:1267–78.

84. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. *Clin Neuropsychol* 2012;26:543–70.

85. Jessup AB, Grimley MB, Meyer E, et al. Effects of diabetic ketoacidosis on visual and verbal neurocognitive function in pediatric patients presenting with new onset type 1 diabetes. *J Diabetes Metab* 2014;5:383.