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Review article

The impact of transsphenoidal surgery on neurocognitive function: A systematic review

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ABSTRACT

Background: Cognitive impairment following transsphenoidal surgery (TSS) among patients with pituitary tumors has been intermittently reported and is not well established. We performed a systematic review to summarize the impact of TSS on cognitive function.
Methods: We conducted a systematic search of the literature using the PubMed, Cochrane, and Embase databases through October 2014. Studies were selected if they reported cognitive status after surgery and included at least 10 adult patients with pituitary tumors undergoing either endoscopic or microscopic TSS.
Results: After removing 69 duplicates, 758 articles were identified, of which 24 were selected for full text review after screening titles and abstracts. After reviewing full texts, nine studies with a combined total of 682 patients were included in the final analysis. Eight studies were cross-sectional and one was longitudinal. These studies used a wide variety of neurocognitive tests to assess memory, attention and executive function post-operatively. Of the eight studies, six reported impairments in verbal and non-verbal memory post-operatively, while others found no association related to memory, and some reported an improvement in episodic, verbal, or logical memory. While four studies found an impaired association between TSS and attention or executive function, another four studies did not.
Conclusion: The current literature on cognitive impairments after TSS is limited and inconsistent. This review demonstrates that patients undergoing TSS may experience a variety of effects on executive function and memory post-operatively, but changes in verbal memory are most common.

1. Introduction

Pituitary tumors account for 10–15 percent of all intracranial tumors [1]. Neurocognitive impairment, specifically relating to memory and executive functioning, has previously been reported in patients harboring untreated pituitary tumors [2]. These impairments have been particularly associated with large lesions with suprasellar extension, which may obstruct the flow of cerebrospinal fluid and result in an increase in intracranial pressure [3]. Patients with pituitary tumors are at risk for a wide range of neurocognitive impairments, largely because the phenotypic behavior of these tumors can vary widely in terms of both size and hormonal status [1,4].

Transsphenoidal surgery (TSS) is widely considered surgical standard of care for pituitary tumors. Since the early 20th century, the use of endonasal TSS to access the sella for treatment of pituitary tumors has been widely practiced, primarily due to direct access and improved panoramic visualization of the ventral skull base [5]. The safety and clinical efficacy of TSS have been well established in patients with pituitary tumors [4–6].

Despite the overall efficacy of TSS, some studies have reported neurocognitive deficits post-operatively [3], while others have

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found no such association [7]. Further complicating the picture of neurocognitive function in patients harboring pituitary tumors are the relatively common abnormalities in the pituitary and hypothalamic hormones, which may affect neurocognitive function directly, and inconsistencies in measuring cognitive function itself. Cognitive function tests that have been used in patients with pituitary tumors range widely, and include tests that evaluate memory (the Rey Auditory Verbal Learning Test [3,8], the Logical Memory Test [9,10], and the Recognition Memory Test [3,11]) or executive functioning and attention (the Digit Span Test [2,12], and the Trail Making Test [3,7,8,11,12]).

As a result of this large degree of heterogeneity, the effects of TSS on cognitive function among patients with pituitary tumors have not been well established in the current literature. In this study, we undertook a systematic review of the available evidence in the literature regarding the neurocognitive impact of TSS in patients harboring pituitary tumors.

2. Methods

2.1. Literature search

The PubMed, Cochrane, and Embase libraries were searched using relevant key words and medical subject headings to identify appropriate articles for inclusion according to the PRISMA criteria. The search strategy merged different search terms for TSS (e.g., neurosurgical procedures, neuroendoscopy, microsurgery), cognitive function (e.g., mental processes, memory, attention, executive function), and pituitary tumor (e.g., pituitary neoplasm, pituitary adenoma) by using several versions of special medical terms and text words. The detailed search elements are included in Appendix A. Reference lists of selected articles were examined to ensure that all relevant English-language articles published through October 2014 were identified.

2.2. Eligibility criteria and study selection

Studies were considered if they reported cognitive status post-operatively and included at least 10 adult patients with pituitary tumors undergoing either endoscopic or microscopic TSS. All titles and abstracts were screened, and potentially relevant articles were selected for full text screening. The full text screening was conducted independently by four authors (A.A., L.W., D.J.C., E.C.) and any disagreements were resolved by consultation with the senior author (T.R.S.).

2.3. Data extraction

The following information for each study was extracted using a standardized data extraction form: characteristics of the study (authors, publication year, country of origin, sample size, study design, journal impact factor), characteristics of participants (age, gender, inclusion/exclusion criteria, pituitary tumor types, hormone status and size), characteristics of the intervention (TSS type, time elapsed between surgery and cognitive testing, other types of neurosurgeries, number of patients who had TSS), and characteristics of the outcome (the type of cognitive tests, observations of each cognitive tests).

3. Results

3.1. Study characteristics

The initial search resulted in 827 English articles (244 from Pubmed, 581 from Embase, and 2 from the Cochrane Library). These articles were selected for title and abstract screening to determine whether they were appropriate for full text evaluation. A total of 24 articles were included for full text review and nine studies were included in this final systematic review (Fig. 1). A meta-analysis was not feasible due to the high heterogeneity across studies in included patients, tumor types, controls used, and tests used to measure neurocognitive function.

Characteristics of the nine included studies in the systematic review are found in Table 1. Seven were cross-sectional and two were prospective longitudinal. The mean age of participants ranged from 33.7 to 53 years. The total number of participants per study ranged from 14 to 148. All studies included both women and men. One study did not specify gender [13]. The female percentage varied between 34% and 82%. Three studies were conducted in the United Kingdom [3,10,13], two in the United States [9,11], two in the Netherlands [8,14], and two in Germany [7,12]. All studies included at least three different types of pituitary tumors except for three studies; two of which included only patients with Cushing's disease [8,9], and one that included only patients with non-functioning adenomas [14]. Study populations were compared against a variety of controls, including patients undergoing radiosurgery [10,11,14], transfrontal surgery [3], thyroid surgery [12], and healthy controls [8]. Two studies compared outcomes in the same patients pre- and post-operatively [7,9].

3.2. Memory

All studies included in this analysis reported at least one test that tapped the memory domain after TSS. Studies included multiple different memory tests: Auditory Verbal Learning Test, Wechsler Memory Scale, Recognition Memory Test, Logical Memory Test, and Verbal Memory Test. While some studies reported impairment in verbal and non-verbal memory [3,7,8,10,12,14], other studies found no association related to memory [7,9], or an improvement in episodic, verbal, or logical memory [14,15]. Verbal recall was impaired in several studies [3,7,8,12,14]. In a study by Mussig et al., one-third of TSS patients performed below average on the Auditory Verbal Learning Test [12]. In a study by Noad et al., 19 out of 71 reported patients fell below the 10th percentile in the Visual Memory Testing, and 14 out of 71 participants fell below the 10th percentile on the Logical Memory Test [10].

Regarding specific pituitary tumors, patients treated for Cushing's disease were reported to have a decline in both immediate and delayed recall on the Auditory Verbal Learning Test [8]. In a study by Starkman et al., 14 out of 23 patients treated for Cushing's disease with TSS showed improvement in logical memory recall [9]. Patients with nonfunctioning pituitary macroadenomas showed worse associative learning in the Wechsler Memory Scale than a control group that matched for age, gender, and education [8].

Only two studies examined pre- vs post-operative differences among the same patients [7,9]. Episodic memory was improved at 3 and 12 months post-operatively in these patients [7,9]. Verbal memory was improved 12 months post-operatively [7]. Two separate studies found no association between TSS and memory [11,14]. These studies largely compared outcomes between TSS and radiotherapy.

3.3. Attention and executive function

Studies included multiple different tests in the attention and executive function domains, including the Digit Span Test, Trail Making Test, Block Design, Ruff Figural Fluency Test, d2 Test of Attention, Digit Symbol Test, Stroop, and Verbal Fluency. Reported findings for attention and executive function in patients undergoing TSS for pituitary adenoma also varied widely. While some

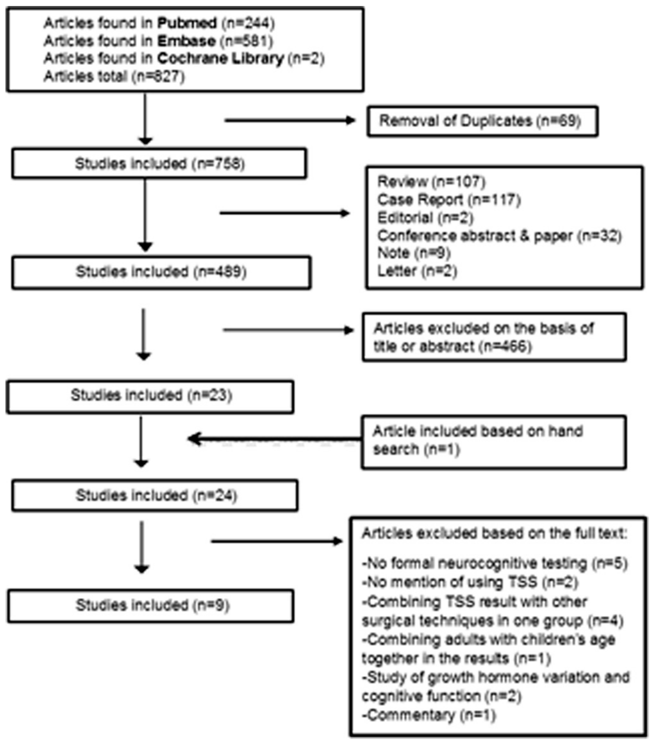

Fig. 1. Flow chart for literature search and selection of studies.

studies found an impaired association between TSS and impaired attention or executive function [7,8,10,12], others did not [9,11,13,14]. Mussig et al. observed that the performance of attention speed and executive control (measured by the Trail Making Test) was worse in the TSS group when compared to the thyroid hormone-replaced patients post-thyroid surgery [12].

In a study by Peace et al., when the Block Design subtest of the Wechsler Adult Intelligence Scale was administered to measure executive function, the researchers found that the TSS group had significantly lower scores than patients treated with medication [3]. In addition, patients who received radiotherapy scored worse in executive function than TSS alone, specifically in the Stroop Color Word Test [10].

Patients with non-functioning pituitary macroadenomas were reported to have impaired scores on the Trail Making Test, while also making more errors on the test than gender, age, and education-matched healthy control participants [8]. Other researchers observed an improvement in selective attention, as measured by the Letter Cancellation task, when comparing performance before TSS and 3 or 12 months after TSS. Similar performance improvements have been shown in attention speed and working memory 3 or 12 months following TSS [7].

4. Discussion

This systematic review demonstrates a wide range of neurocognitive findings in patients undergoing TSS for pituitary adenoma. Neurocognitive function in these patients, including both memory and attention and executive function, was measured using a wide range of neurocognitive tests. Only two studies compared neurocognitive outcomes pre-operatively and post-operatively among the same patients. The findings from study to study are not totally consistent, with some studies reporting deficits and others reporting improvement post-operatively. There are no significantly reported differences in the current literature based on tumor size or hormone status.

Although drawing a strong conclusion from the existing data is difficult, the literature reviewed here generally demonstrates that verbal memory appears to be more affected after TSS than other aspects of neurocognitive function [3,7,8,10,12,14]. Four of the studies reported in this review did not find an association between TSS and attention or executive function, while six of eight reported impairment in visual memory [9,11,13,14].

Verbal memory, the most consistently reported neurocognitive deficit in this review, depends largely on using the dominant lobe, which is the left side of the brain in 96% of right handed patients. Left side damage can lead to a decline in verbal memory and language capability [12,14,16,17]. From this review, it is impossible to determine the exact etiology of the decline in verbal memory that has been reported among patients with TSS. Isolating the effects of the surgery itself from the effects of the sellar tumor is also not possible with this review, making a true analysis of the effects of TSS difficult.

Executive function is a wide term that encompasses cognitive flexibility, inhibition, and planning. A decline in executive function may appear as errors in judgment, planning, reasoning, and/or problem solving. These varied skills are spread across the brain, but executive function as tapped by neuropsychological tasks is mainly mediated by the dorsolateral pre-frontal lobe [18]. The conflict between the results of the studies in this review on executive function may be due to the fact that each study analyzed a different aspect of executive function. For instance, Noad et al. used a test that measured inhibitory capacity [10], while Brummelman et al. measured planning capacity [14].

Many factors may explain post-surgical cognitive decline besides the direct effect of the intervention, such as age, education, post-surgical time elapsed, patient adaptive capacity, hormonal cognitive effects, or menopause-related sensitivities [13,14,19,20]. Results from a large series of transsphenoidal surgical patients suggest that post-surgical cognitive impairments do not result from tumor size as much as from the consequences of surgery itself [12]. Surgical sequelae can impact the above-lying hypothalamus, from which signals relayed through descending tracts modulate reticular formation and arousal level [21]. Such deep, midline structures regulate the arousal upon which activation of neocortical structures that mediate cognitive function depends. Post-surgical hyponatremia is also a relatively common complication of transsphenoidal surgery, possibly from the release of anti-diuretic hormone, the treatment of which may cause myelinolysis [22,23]. These relationships emphasize the importance of a pre-operative neuropsychological work-up in studying or examining the effect of TSS on cognition.

Although systematically approached, this review has limitations. First, it is limited to articles published in English only. Some relevant studies published in other languages may have been excluded. Additionally, there are many limitations related to the included studies. Few studies included in this review differentiated cognitive function deficits among different pituitary tumors types, and only two evaluated neurocognitive function in the same patients pre- and post-operatively. The phenotypic behavior and clinical presentation of patients with different types of pituitary tumors can be extremely varied; different tumor types may be more or less likely to affect neurocognitive function before and after TSS. Secretory pituitary adenomas can result in slow, progressive deterioration of brain volume. For example, patients with Cushing's disease are known to have cognitive deficits secondary to chronic glucocorticoid exposure, with several clinical studies demonstrating hippocampal damage and volume loss. This may contribute more to loss of cognition than other tumor subtypes, and future studies on the neurocognitive effects of TSS should distinguish between subtypes of pituitary tumor [19]. Furthermore, studies included in this review reported many different subtests

Table 1
Characteristics of studies included in the systematic review.

Author, year, (ref)	Country	Study type	Sample size (N)	Trans-sphenoidal group (n)	Control (n)	Control type	Sex	Age mean (SD)	Tumor type	Memory tests	Attention & executive function tests
Peace et al. [3]	UK	Cross-sectional	69	23	23	Transfrontal surgery	45F; 24M	41	Nonfunctioning adenoma; Cushing; Prolactinoma; Acromegaly; Craniopharyngioma	Auditory Verbal learning; WMS; RMT	Digit span; TMT; Block design
Starkman et al. [9]	USA	Prospective longitudinal	23	23	N/A	Same patients pre- and post-operatively	20F; 4M	33.7 (2.1)	Cushing	Logical memory; Paired Association	Vocabulary and Arithmetic tasks
Brummelman et al. [14]	Netherlands	Cross-sectional	84	39	45	Radiotherapy and TSS	29F; 55M	62 (10)	Nonfunctioning adenoma	Auditory Verbal learning	Ruff figural fluency test
Psaras et al. [7]	Germany	Prospective longitudinal	106	106	N/A	Same patients pre- and post-operatively	69F; 37M	48 (16)	Nonfunctioning adenoma; Cushing; Prolactinoma; Acromegaly;	Verbal Memory test	Digit span; TMT; d2 cancelling
Mussig et al. [12]	Germany	Cross-sectional	76	38	38	Patients undergoing thyroid surgery	50F; 26M	50 (10)	Nonfunctioning adenoma; Cushing; Prolactinoma; Acromegaly;	Verbal Learning test	TMT; Digit span; Digit symbol
Noad et al. [10]	UK	Cross-sectional	71	38	33	Radiotherapy and TSS	34F; 37M	51.1	Nonfunctioning adenoma; Cushing; Acromegaly;	Logical memory (immediate and delayed)	Stroop; Verbal fluency
Tooze et al. [11]	USA	Cross sectional	14	12	N/A	Patients receiving GKRS	9F; 5M	49.8 (17)	Nonfunctioning adenoma; Cushing	WMS	TMT; Verbal Fluency
Tiemensma et al. [8]	Netherlands	Cross-sectional	148	74	74	Age, gender, and education matched controls	122F; 26M	53 (13)	Cushing; nonfunctioning	WMS; Verbal learning	TMT; Stroop
Guinan et al. [13]	UK	Cross-sectional	90	21	19	Multiple control groups	N/A	48.8	Nonfunctioning adenoma; Cushing; Prolactinoma; Acromegaly;	WMS	WAIS

GKRS = Gamma Knife radiosurgery; RMT = Recognition Memory Test; TMT = Trail Making Test; TSS = transsphenoidal surgery; UK = United Kingdom; US = United States; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

for memory and executive function and all of the studies used different methods. Combined with the many different treatment modalities analyzed in the studies in this review (e.g., gamma knife radiosurgery with TSS, TSS only, etc.), these varied tests made heterogeneity from study to study extremely high. The initial aim of this study was to perform a meta-analysis of the effects of TSS on neurocognitive function, but the level of heterogeneity was too high for pooled analysis. More consistent pre- and post-operative neurocognitive testing for patients undergoing TSS would help produce more generalizable and useful information.

Despite these limitations, this review of neurocognitive function in patients with pituitary tumors undergoing TSS is, to our knowledge, the most current and comprehensive. The existing literature on neurocognitive effects is varied and inconsistent, and there is a dearth of high-quality, prospective data on the neurocognitive effects of TSS. Future studies of patients with pituitary tumors should attempt to standardize the measurement of neurocognitive function by using a limited number of well-validated tests for memory, attention, and executive function. Subgroup analysis of tumor types and both pre-operative and post-operative neurocognitive assessment of prospectively identified patients may result in higher quality of evidence. Based on the current literature, patients with pituitary tumors undergoing TSS may be more at risk for memory impairments than impairments in attention or executive function, but further study, especially in the form of longitudinal studies, is needed to evaluate neurocognitive outcomes more completely in these patients.

5. Conclusion

The current literature on cognitive impairments after transsphenoidal surgery is limited and inconsistent. This review demonstrates that patients undergoing transsphenoidal surgery may experience a variety of effects on executive function and memory post-operatively, but changes in verbal memory are most common.

Disclosure

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Appendix A.

Pubmed

(“Pituitary Neoplasms”[MeSH] OR Pituitary Neoplasm*[tw] OR Pituitary Tumor*[tw] OR Pituitary tumour*[tw] OR Pituitary Adenoma* [tw] OR Adenoma*, Pituitary[tw] OR Pituitary Carcinoma* [tw] OR Carcinoma*, Pituitary[tw] OR Cancer of the Pituitary[tw] OR Pituitary Cancer*[tw] OR Hypophysis tumor*[tw] OR Hypophysis tumour*[tw] OR pituitary gland adenoma*[tw] OR pituitary gland tumor*[tw] OR pituitary gland tumour*[tw] OR pituitary gland carcinoma[tw] OR pituitary gland cancer[tw] OR “Pituitary Gland”[Mesh] OR Gland, Pituitary[tw] OR Pituitary Gland* [tw]

OR Hypophysis [tw] OR Hypophyses[tw] OR Hypophysial Stalk [tw] OR Hypophysial Stalks[tw] OR Pituitary Stalk[tw] OR Pituitary Stalks[tw]).

AND

(“Neurosurgical Procedures”[Mesh] OR “Neurosurgery“[Mesh] OR ”Pituitary Neoplasms/surgery”[Mesh] OR “Neuroendoscopy”[Mesh] OR “Neuroendoscopes”[mesh] OR Neurosurg∗[tw] OR neuroendoscopy[tw] OR neuroendoscope∗[tw] OR Pituitary Neoplasms surg∗[tw] OR Pituitary Neoplasms therap∗ [tw] OR Endoscopic Transsphenoidal Surg∗[tw] OR transsphenoidal endoscopic surg∗[tw] OR endoscopic endonasal transsphenoidal surg∗ [tw] OR nasal endoscopic transsphenoidal surg∗[tw] OR Transsphenoidal[tw] OR Transsphenoidal [tw] OR Transsphenoidal microscopic surg∗ [TW] OR microscopic transsphenoidal surg∗ [TW] or ETSS [tw] or Transsphenoidal pituitary surg∗[TW] or microscopic endonasal transsphenoidal [TW] OR MTSS [TW] OR micro-surger*[TW] OR microsurger* [TW]).

AND

(“Mental Processes”[Mesh] OR Mental Process∗[tw] OR “Attention”[Mesh] OR Attention∗[tw] OR Concentration∗[tw] OR Concentrations[tw] OR “Cognition Disorders”[Mesh] OR Overinclusion[tw] OR “Memory Disorders”[Mesh] OR Memory Disorder∗[tw] OR Memory Loss∗[tw] OR Semantic Memory Disorder∗[tw] OR Spatial Memory Disorder∗[tw] OR Memory Deficit∗[tw] OR “Neuropsychological Tests”[Mesh] OR Neuropsychological Test∗[tw] OR Aphasia Test∗[tw] OR Memory for Design∗ Test[tw] OR “Memory”[Mesh] OR Memory[tw] OR “Cognition”[Mesh] OR Cognition [tw] OR “Executive Function”[Mesh] OR Executive Function∗[tw] OR Executive Control∗[tw] OR “Motor Skills”[MeSH] OR Motor Skill∗[tw] OR Motor performance[tw] OR “Psychometrics”[Mesh] OR Psychometric∗[tw] OR Psychometry[tw]).

Articles: 244.
English Articles: 244.
Date: 10/24/2014.

Embase

exp hypophysis tumor/OR (hypophyseal tumor∗ or hypophysial tumor∗ or hypophysic tumor∗ or hypophysoma or pituitary gland tumor∗ or pituitary neoplasm∗ or pituitary tumor∗ or hypophyseal tumour∗ or hypophysial tumour∗ or hypophysic tumour∗ or pituitary tumour∗).tw. OR exp hypophysis adenoma/OR (hypophys∗ or glandula pituitaria or hypophyseal lobe or hypophysis system or Infracerebral gland or pituitary or pituitary gland or pituitary lobe or hypophysis adenoma).tw. OR exp hypophysis/.

AND

exp neurosurgery/OR exp neuroendoscopy/OR exp neurological endoscope/OR exp transsphenoidal surgery/OR (Neurosurg∗ or Pituitary Neoplasms surg∗ or Endoscopic Transsphenoidal Surg∗ or transsphenoidal endoscopic surgery or endoscopic endonasal transsphenoidal surg∗ or nasal endoscopic transsphenoidal surg∗ or Neuroendoscopy or Neuroendoscopes or Endoscopic Transsphenoidal surgery).tw. OR (endoscopic neurosurgery or neuroendoscopic procedure or neuroendoscopic surgery or surgery, transsphenoidal or transsphenoid surgery or transsphenoidal treatment or Trans-sphenoidal or Transsphenoidal or Transsphenoidal microscopic surge∗ or microscopic transsphenoidal surge∗ or Microscopic endonasal transsphenoidal).tw.

AND

exp attention/OR Attentions.tw. OR exp cognitive defect/OR (cognition disorder∗ or cognitive defect∗ or cognitive deficit or cognitive disability or cognitive disorder∗OR cognitive dysfunction or cognitive impairment or overinclusion or response interference).tw. OR exp memory disorder/OR (memory blocking or memory defect or memory disorder∗ or memory impairment).tw. OR exp neuropsychological test/OR Neuropsychological Tests.tw. OR exp memory/OR (memory function∗ or remembering or reminiscence or memory).tw. OR exp executive function/OR (cognitive control or executive control or executive function).tw. OR exp motor performance/OR (motor ability or motor function or motor skill∗ or motor performance).tw. OR exp psychometry/OR psychometric test or psychometric∗ or psychometry).tw. OR exp cognition/OR (cognitive accessibility or cognitive balance or cognitive dissonance or cognitive function or cognitive structure or cognitive symptoms or cognitive task or cognitive thinking or cognition).tw. OR mental function/OR (mental process or mental processes).tw.

Articles: 584.
English articles: 581.
Date: 10/24/2014.

Cochrane Library

(“Pituitary Neoplasms” or “Pituitary Gland” or “Pituitary Tumor∗” OR “Pituitary tumour∗” OR “Pituitary Adenoma∗” or Hypophysis OR Hypophyses OR “Hypophysial Stalk∗” OR “Pituitary Stalk∗”) AND(“Neurosurgical Procedures” or Neurosurgery or “Pituitary Neoplasms surg∗” or Neuroendoscop∗ or “transsphenoidal surg∗” or “microscopic transsphenoidal surge∗” or “endoscopic transsphenoidal surg∗”) AND(attention or “cognitive defect” or “memory disorder” or “neuropsychological test” or memory or “executive function” or “motor performance” or psychometry or cognition or “mental function”)

Articles: 2.
English articles: 2.
Date: 10/24/2014.

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