phobia, which may have been caused by the initial phase of tonic pupil syndrome, in which the pupil is abnormally dilated. To our knowledge, there have not been any reports regarding secondary Meige's syndrome in patients with tonic pupil syndrome. Only one patient with Meige's syndrome has been described as having Adie's syndrome as an associated disorder [2].

The corneal reflex is conducted through a polysynaptic pathway in the lower brainstem from the ophthalmic division of the trigeminal nerve to the ipsilateral and contralateral facial nuclei [10]. Hyperexcitability of this reflex is electrophysiologically observed in patients with primary Meige's syndrome [1]. An abnormal basal ganglia input to the reflex arc is considered to facilitate this reflex. On the other hand, repeated blinking by photophobia resulting from paralysis of the pupillary sphincter may also produce hyperexcitability of this reflex, which would subsequently trigger blepharospasm.

Thus, our findings suggest that there may be two causes of secondary Meige's syndrome, one being lesions of the basal ganglia and the other primary ophthalmological symptoms such as photophobia in the present two cases.

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# Spatial and nonspatial memory involvement in myasthenia gravis


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Sirs: Myasthenia gravis (MG) is a disorder of neuromuscular transmission caused by an autoimmune reaction to peripheral cholinergic receptors. However, central nervous system involvement has occasionally been reported in MG [3, 8, 10]. Based on memory deficits found in tests of verbal, logical and visual memory, Tucker suggested that there is central cholinergic dysfunction in MG [24]. This was supported by finding cholinergic receptor autoantibodies (anti-AChR ab) in the cerebrospinal fluid of MG patients [10], although others argued that central and peripheric cholinergic receptors do not cross-react [26].

Spatial memory has been shown to depend upon normal cholinergic activity in the hippocampus of animals [11, 15]. Patients with Alzheimer's disease also suffer cholinergic deficits related to their memory disturbances [2]. These patients have losses of nicotinic receptors in the frontal cortex, the hippocampus and the caudate nucleus [17, 23, 25] as well as loss of spatial orientation [9, 13]. In order to investigate further whether patients with MG suffer from any central deficiencies, we administered several spatial memory tasks which were adaptations of tasks typically used with rats, sensitive to lesions of the hippocampus (e.g. eight-arm radial maze, Morris water maze) [16, 18, 19]. Two other memory tasks were used, a nonspatial working memory task, and a

memory task in which patients have to build a cognitive map of the space they explored while blindfolded.

We examined 19 patients with MG (5 males, 14 females; average age 49.2 years, SD 13.3; duration of the disease 6.7 years, SD 6.3). The diagnosis of MG was based on clinical and laboratory investigation including an EMG amplitude decrement on repetitive stimulation and/or the presence of anti-AChR ab in the blood. Eight patients were in MG stage IIa, nine in stage IIb and two in stage III according to Osserman. None of the patients suffered from ocular MG and they had no oculomotor deficits. All but one patient were on regular oral anticholinesterase medication, and all of them were tested when at their best. None of the MG patients had a history of memory dysfunction, and apart from the myasthenic features their neurological status was normal. In the control group for memory testing (NC) there were 20 normal subjects (8 males, 12 females; average age 42.9 years, SD 17). The MG and NC groups were of comparable educational level. Testing for all tasks was done in a rectangular room approximately 9 $m^2$ in area. Before the start, subjects were given instructions so that they understand all of the task requirements.

*Eight-arm radial maze.* A human eight-arm radial maze was recreated by placing eight identical stands at 1.4 m from a center point at an equal distance from each other. On top of the stands were eight identical cups containing one coin each. The subjects were instructed to search for coins until all eight were retrieved but were given a limit of 16 choices, and had to select each stand only once in order to receive a money reward. The subjects were instructed to visit the stands in a random sequence. A 5-s interval was imposed between choices during which the subject had to stay in the central ring, where he/she was instructed to follow a series of left or right turns in the dark. This was done in order to prevent subjects from using a strategy where they visit eight adjacent stands in a row. Errors consisted of selecting previously visited stands. Memory was measured by the number of errors (repeats) made in the first eight choices, or the total number of errors made before retrieving all coins.

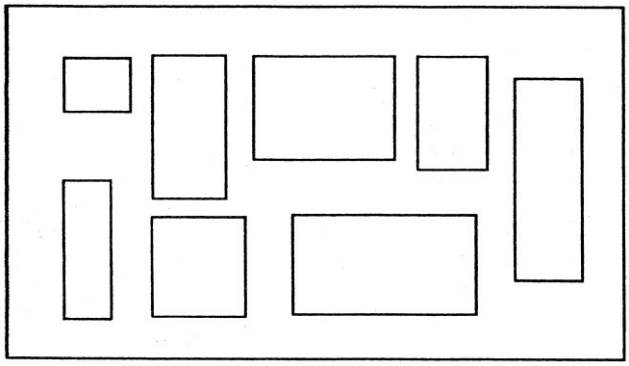

**Fig. 1** Example of the display of cards of various shapes used in the nonspatial working-memory task

*Nonspatial working-memory task.* Eight cards folded into different shapes (Fig. 1) were used. Each contained the numbers 1 to 8, and the subjects had to take a card, open it, read the number inscribed, and return it. The cards were shuffled between choices. The subject had to select each card only once, but the subject was allowed up to 16 choices. Errors consisted of selecting previously chosen cards. Memory was measured by the number of errors (repeats) made in the first eight choices, or the total number of errors made before retrieving all eight cards.

*Nonvisual spatial exploration.* In this experiment, subjects were allowed 3 min in order to explore the room with three objects (a chair, a trash can, and a stand or box) while blindfolded. They were later asked to reconstruct from memory the location of the objects in a schema of the room. Performance was measured by the difference between the real location of the objects and the location of the objects estimated by the patient (displacement).

*Invisible sensor task.* A dry version of the Morris water task was adapted for humans by hiding a sensor under the carpet of the room. This sensor emitted a pleasant sound when stepped on and the task of the subject was to locate it as quickly as possible, note its position with respect to visual landmarks in the room, then go back to the entrance. Retention was measured by allowing the subject to enter the same room by another door. Subjects had to go straight to the invisible sensor. Learning is measured by latency (seconds) to find the sensor on the second trial.

Repeated measures of expiratory peak flow and grip strength did not show fatigue before and after the memory testing in the MG patients.

The results after elimination of one outlier and application of the Bonferroni correction for multiple comparisons are shown in Fig. 2. In the first eight choices of the eight-arm radial maze, MG patients and NC performed similarly, but when allowed to continue until all stands were visited at least once, MG patients were impaired compared with NC [single-factor ANOVA: $F$ (1,36) = 8.02, $P < 0.05$]. In the first 8 choices of the nonspatial working memory task, MG patients were impaired compared with NC [single-factor ANOVA: $F$ (1,37) = 12.47, $P < 0.01$], but when allowed to continue until all envelopes were selected once, performance of the MG

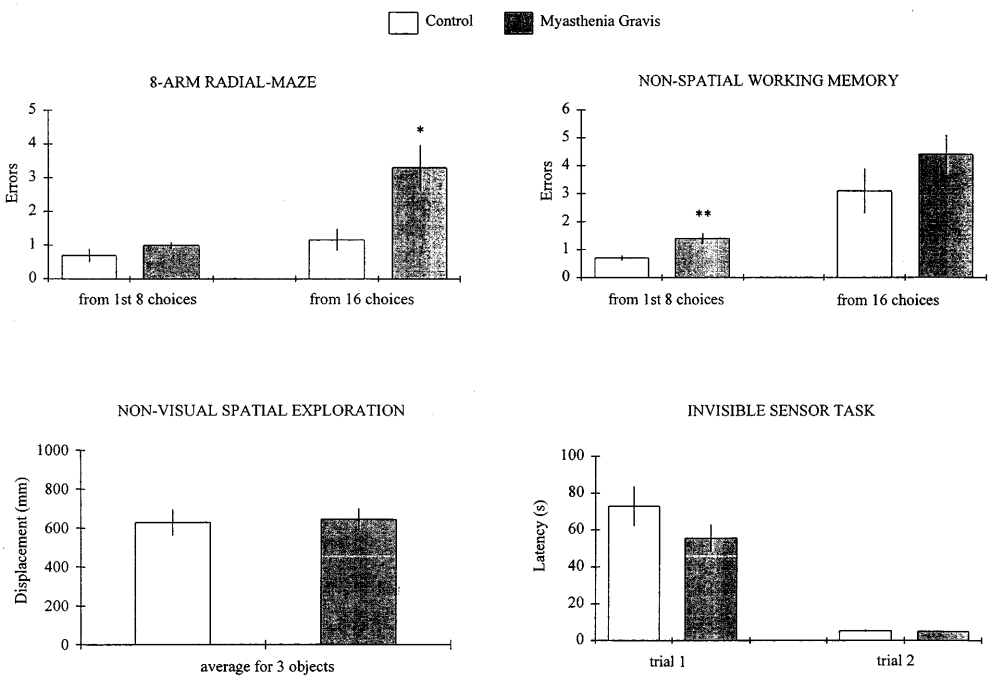


**Fig. 2** *Top*: errors made in the first eight choices (*left*) or total number of errors made (*right*) during the eight-arm radial maze and nonspatial working memory tasks. * Myasthenia gravis (MG) patients significantly impaired relative to controls ($P < 0.05$). Group averages (SEM) for normal controls (NC): 1.16 (0.33); MG patients: 3.32 (0.67). ** MG patients significantly impaired relative to controls ($P < 0.01$). Group averages (SEM) for NC: 0.65 (0.11); MG patients: 1.42 (0.18). *Bottom*: Nonvisual spatial exploration shows the difference between the real position of three objects and the position of these objects estimated by patients and controls. Invisible sensor shows the average latency to the target by patients and controls. *Vertical bars* denote SEM values

patients was similar to NC. In the nonvisual spatial exploration task, MG patients performed similarly to NC in constructing and recalling a cognitive map. The average error for placing all three objects under the blindfolded condition was similar in both MG and NC subjects. In the invisible sensor task, MG patients performed similarly to NC.

The results offer some support for previous reports of memory dysfunction in MG [7, 24]. Blockade of central nicotinic or muscarinic receptors in rats causes spatial learning impairments in the water maze and the eight-arm radial maze [5, 11]. In the present study, the MG patients were impaired in one spatial memory task (eight-arm radial maze) and not impaired in another spatial memory task (invisible sensor which is the water maze analog). This could reflect the somewhat different requirements of the two tasks. More specifically, both require memory for spatial locations, but in addition the eight-arm radial maze requires that the patient remember the selections already made in order to not repeat them. The MG patients were also impaired in our nonspatial working memory task which requires the patients to remember the selections they made. Furthermore, MG patients were not impaired in the nonvisual spatial task which requires building a cognitive map and also has a spatial and object memory component. Therefore, patients with MG may not have a problem with memory for spatial locations or objects per se, but they may have problems with remembering which selections they previously made. Monitoring of prior selections within working memory is required on the self-ordered task, which was found to be dependent on the mid-dorsolateral frontal cortex [20, 21]. The memory impairment reported here is rather specific and this may help to understand why others have not observed memory impairments in MG [1, 12]. We do not think that nonspecific factors like fatigue and inattention biased the results of the testing. Such factors would have impaired performance in all of the tasks we used by causing an increased number of errors with increased length of the testing, and this was not the case. Considering the fact that all of the patients were on regular cholinomimetic treatment, we must also ask whether this might have influenced the results of testing. In fact, cholinesterase inhibitors have been reported to facilitate maze learning in rats [6, 14]. Scopolamine, an anticholinergic agent, impairs learning in humans and rats, but this can be counteracted with an infusion of physostigmine, a cholinesterase inhibitor, at low doses [4, 14]. In the present study all patients were on oral cholinesterase inhibitors (pyridostigmine, neostigmine, distigmine, ambenonium). These quaternary amines do not cross the intact blood-brain barrier and thus seldom act centrally, as does physostigmine [22]. Consequently, the treatment could improve the motor but not the cognitive component of the patients' performance.

In conclusion, the present findings are consistent with reports indicating that a possible dysfunction of nicotinic receptors in the brain can involve memory in patients with MG and requires further investigation.

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