EFFECT OF THE ALLERGIC INFLAMMATORY DISEASE IN THE UPPER RESPIRATORY TRACT TO THE COGNITIVE FUNCTIONS AND THE PHYSICAL PERFORMANCE

PHD THESIS

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II. **Tokodi Margaréta**, Csábi Eszter, Kiricsi Ágnes, Molnár H. Andor, Rovó László. Bella Zsolt. Az egyszeri allergéndózis hatása az explicit - implicit emlékezetre sportoló és nem sportoló parlagfű allergiás betegeken. Ideggyógyászati Szemle 2018;71(1–2):25–33. DOI: 18.071/71.0025 (IF: 0.376)

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I. Melitta Pajk, Alexandra Cselko, Csaba Varga, Aniko Posa, **Margareta Tokodi**, Istvan Boldogh, Sataro Goto, Zsolt Radak. Exogenous nicotinamide supplementation and moderate physical exercise can attenuate the aging process in skeletal muscle of rats. Biogerontology 2017. 05.05. DOI: 10.1007/s10522-017-9705-9 (IF: 2.27)

ABSTRACTS ON THE TOPIC OF THE DISSERTATION

I. **Tokodi Margaréta**, Bella Zsolt, Csábi Eszter, Kiricsi Ágnes, Kollár Edit, Rovó László (2014). Az egyszeri allergéndózis (nazális provokáció) hatása a fizikai teljesítőképességre és a kognitív funkcióra parlagfű allergiás betegeken. Otorhinolaryngologia Hungarica 2014;60(2):104. 43th MFOE Congress, Tapolca

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V. Edit Kollár, Zsolt Bella, Ádám Bach, Vera Matievics, **Margaréta Tokodi**, Ágnes Kiricsi, Balázs Sztanó, László Rovó (2015). Sleep disordered breathing problems due to vocal cord paralysis. Konferencia neve, ideje, helye: 3rd Congress of European ORL-HNS (otolaryngology-head and neck surgery), Prague

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ABBREVIATIONS

AR vol. 0–7	Acustic Rhinometry, nasal cavity volume from 0 to 7 cm^3
AR vol. 2.2–5.4	nasal cavity volume from 2.2 to 5.4 cm^3
AR vol. 2–5	nasal cavity volume from 2 to 5 cm^3
AR	acoustic rhinometry
FEV1	forced expiratory volume in 1st second
HST	Harvard step test
LM	Late measurement, 8 hours after nasal provocation
M0	basic measurements on both occasions,
mUV / VIS	UV-B / UV-A and visible light
NIPF	nasal inspiratory peak flow
NP	nasal provocation
NP-M10	measurement 10 minutes after nasal provocation
NP-M30	measurement 30 minutes after nasal provocation
PIF	peak inspiratory flow
RL	Rhinolight
STAI	Spielberger's State-Trait Anxiety Inventory
TNS	total nasal symptom score
TSS	total symptom score
V1	first visit
V2	second visit

LIST OF CONTENTS

1. INTRODUCTION

1.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY WITH NASAL PROVOCATION TEST

1.1.1. About allergic inflammatory disease in the upper respiratory tract

The allergic rhinitis is an IgE-mediated allergic inflammation of the nasal mucosa which is one of the most common chronic diseases with a prevalence of 20% in developed countries[1,2]. Its frequency is increasing according to data of WHO (2-3% per year), by 2050 it could affect up to 50% of the population in developed countries[3]. In Hungary here are 3 million patients with allergies, their number has doubled in the past 20 years[4]. The development of allergic rhinitis is determined by a combination of genetic and environmental factors, and significant familial reccurence. Symptoms are triggered by seasonal or perennial allergens that cause persistent or intermittent complaints. Classic symptoms are sneezing,itching, rhinorrhea and nasal congestion[5,1], which interfere with sleep, concentration in learning and working, and leisure activities[6-8]. Several well-known and frequently used methods of treating allergic rhinitis are used. Avoiding allergens is effective, but often not fully feasible (eg ragweed, weed). The basic drug therapy is antihistamines and local nasal steroids, additionally cromolyns, anticholinergics and leukotriene antagonists can be considered[9-12]. As a sole cause of treatment, we have good experiences with sublingual immunotherapy[13-15].

In allergic rhinitis, initial allergen exposure causes sensitization, resulting that antigen presenting cells form T and B lymphocytes, allergen-specific T cells, and allergen-specific IgE antibodies. In case of repeated pollen exposure, relevant allergens create crosslinking of mast cells' IgE receptors and release "pre-fabricated" stored hypersensitivity mediators, primarily histamine, that is responsible for immediate symptoms within 5 to 15 minutes (early phase). After 6-12 hours, infiltration of inflammatory cells in the nasal tissue, especially Th2 T lymphocytes, eosinophils and basophils, occur in the area of exposure, resulting in late-phase allergic reactions. Newly formed mediators are the result of leukotrienes, prostaglandins, platelet activating factor and bradykinin-induced changes (vasodilation, increased vascular permeability, glandular secretion, stimulation of afferent nerve fibers)[16]. In the background of chronic allergic inflammatory processes (nasal congestion, loss of odor, nasal hyperreactivity) are Th2 lymphocytes, their cytokines; IL-3, IL-5 are responsible for eosinophil cell infiltration, the IL-4 stimulate B cells for specific IgE production. IL-4 additionally enhances the expression of adhesion molecules (VCAM-1) on the vascular endothelium, thus facilitating inflammatory cell infiltration E. Nasal allergen provocation models the early phase of allergic reactions.

1.1.2. Diagnosis of allergic rhinitis

An allergy questionnaire (Appendix) for distinguishing between rhinitis and allergic rhinitis can also be used in family practice.[17] In the diagnosis of allergic rhinitis, the first step is to complete a simple allergy questionnaire. Based on the 5 yes and 5 no responses, allergic rhinitis can be suspected and allergy tests are recommended. Skin test with inhaled allergen is inexpensive, reproducible and provides immediate response. It is not possible to administer antihistamines in the treatment of systemic steroid therapy and localized skin lesions. As a second line test, from serum anti-allergic antibody (IgE specific) can be detected (ELISA, RAST). If the skin test and/or spec. IgE results and clinical symptoms are not consistent, allergen-specific nasal provocation (NP) can be performed, which in the case of a positive response causes typical allergic symptoms (rhinorrhea, nasal congestion, itching, lacrimation). The effect of NP on a variety of allergen-sensitive patient groups[18,19] has been studied already (dust mite, cat dander)[20-24]. In seasonal allergic rhinitis, the temporal association of the development of upper respiratory symptoms with the seasonal increase in circulating IgE specific antibodies against the allergen (ex. Ragweed), provides further evidence that systemic manifestations are pathophysiological factors of the disease[24]. The same phenomenon can be reproduced in experimental environments. Three consecutive days using NP with ragweed pollen extraction, Naclerio et al.[21] found that serum specific anti-ragweed IgE antibodies increased even two weeks after the provocations, and for two more weeks this level was maintained. In addition to the IgE response, other evidence also supports the idea that allergic rhinitis in the blood exhibits systemic changes even in the presence of NP. For example, in patients with allergic rhinitis, peripheral eosinophilia and basophilia develop during a given pollen season[22,23]. Peripheral eosinophilia is also induced by NP in allergic rhinitis patients[20]. This phenomenon can be detected 6 hours after provocation and is still present for at least 24 hours.

1.1.3. Rhinolight photo therapy

UV radiation was used to treat immuneproliferative disorders at the beginning of the 19th century when Finsen cured lupus vulgaris (skin tuberculosis) with phototherapy[25]. Since then, photo therapy has been successfully used in many ways in dermatology, such as atopic dermatitis and numerous skin diseases[26]. The mechanism of UV therapy is based on eosinophilic and T-cell apoptosis and histamine degranulation replacement. Our team demonstrated first that the use of (mUV / VIS) Rhinolight therapy in the treatment of allergic rhinitis resulted in a significant improvement in total nasal symptoms (TNS)[27]. In the study, individual scores were significantly lower than the baseline in sneezing, rhinorrhea and pruritis, but nasal congestion was not affected by the therapy. 90% of the clinical symptoms were improved by endonasal phototherapy, both in intermittent and persistent rhinitis[28,27]. Garaczi et al.[29] compared the symptoms of moderate/severe ragweed allergic patients treated with endonasal phototherapy to patients treated with monotherapy (antihistamine) as base therapy. The TNS of the first group significantly decreased, while the symptoms of those receiving conventional treatment remained unchanged. Bella et al.[30] investigated the effect of endonasal phototherapy of 24-weed pollen on allergic rhinitis patients. One group only received phototherapy and the other received antihistamines and nasal steroids next to the light therapy. Nasal symptoms were significantly improved in both groups. Significant symptomatic improvement happened in the treatment of monotherapy group at the 75% of patients, while this improvement reached 87% of patients receiving combination therapy.

1.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

1.2.1. Allergy affects on cognitive functions

There are also a limited number of studies on the effect of allergic symptoms on cognitive functions often providing conflicting results. Some of these studies have found no changes in certain cognitive functions, such as verbal and visual memory, the speed of information processing[2], and attention processes between healthy people and people with allergy[31,1]. Kremer et al.[2] explained these results by suggesting that people with allergy put more mental effort into execute the tasks, which compensates for the decreased performance in certain cognitive areas. In contrast, there are studies that report decreased attention capacity and information processing ability[32-34], a functional decline in short-term and verbal memory[35,36], slower decision-making, and locomotor functions in people with allergy compared with non-allergic control groups[33]. Wilken et al.[37] compared groups with symptomatic versus non-symptomatic allergy and found that symptoms decreased vigilance, which results in attention capacity and working memory disorders, as well as increased reaction time. According to Blank and Remschmidt[38], allergy affects cognitive functions by the allergy-induced inflammation reaction, which interferes with neural activity and this, in turn, influences the function of the central nervous system and the peripheral nervous system. Marshall et al.[33] concur and extend the results that allergy symptoms decrease concentration and motivation, increase anxiety and emotional distress, and also lead to mental exhaustion and mood disorders. Allergy symptoms together initiate biochemical changes that have a direct effect on the function of the central nervous system. In addition, some authors suggest that it is the antihistamine used for the treatment of allergy that causes cognitive function deficits[39,40], whereas other studies suggest that antihistamine treatments decrease vigilance[31,41].

1.2.2. Physical performance

The relevant literature according to the correlation between sports and allergy shows that physical exercise improves the symptoms of allergic rhinitis, including the decrease in nasal blockage as a characteristic improvement[42-44]. In addition, sports, such as longdistance running or swimming, may not only decrease airway resistance but also improve endurance and lung capacity[42,43]. A large number of studies on the effect of sports on cognitive functions have found that regular physical exercise has a beneficial effect on nervous system functions, thus on a range of cognitive functions including attention, executive functions, short-term memory, decision-making, and locomotor functions[45-51].

1.2.3. The effect of physical activity on allergic symptoms

Physical exercise is a well-known cause of allergic diseases such as asthma[52,53], urticaria[54] and anaphylaxis[55] in susceptible patients. However, the effect of sport on allergic and non-allergic rhinitis not many has been studied so far. In the field of outdoor exercise, Blackley[56] investigated and demonstrated first that the sneezing symptoms of allergic rhinitis patients deteriorated as a result of exercise. This was presumably triggered by increased pollen exposure. In these patients, Blackley explicitly opposed physical exercise. Conversely, later in the study of Richerson and Seebohm[44], sport lowered the respiratory tract resistance of the nose in individuals with allergic rhinitis. Nasal congestion was actually improved by exercise, and sport was then recommended as a therapy for patients with allergic rhinitis. Since then, several studies have confirmed that the swelling of the nasal mucosa significantly decreases as a result of workout in allergic and non-allergic patients[57-59]. Helenius et al.[43] measured lung capacity, concluded that active sports not only improve the function of the nose, but also increase lung capacity up to 200 l/min, especially for endurance athletes such as long distance running and swimming. Recently, it has also been shown that in endurance sports, allergic rhinitis diagnosed by a physician in athletes is more common than in other athletes or in the control group. However, only half of those with allergic rhinitis take antiallergic drugs[42]. Silvers et al.[60] examined nasal symptoms in the allergic rhinitis and control group during exercises in the room. Based on previous studies, that nasal resistance improves, as an effect of exercise, the symptoms were followed during and after exercise by a questionnaire method. Indoor exercise was chosen because there are several influencing factors at the outdoor excercise, such as pollution, pollen, cold air, which can greatly contribute to the symptoms of rhinitis[61,60].

1.2.4. The effect of physical activity on cognitive functions

Controversial studies on the effect of sport on cognitive functions have been written. According to Etnier et al.[62], exercise can only slightly improve cognitive functions. On the other hand, Katona and his team's[63] results show that good fitness and regular exercise have a beneficial effect on the functioning of the vegetative nervous system, one observed form of it is the atypical low resting heart rate[47]. Medium intensity exercise improves cognitive performance[45,64,65,48,49]. There are some studies that have shown that aerobic athletes performed better than the nonaerobic control group in performing various cognitive tasks[66,46,50]. In aerobic capacity sports, predominantly the higher level of cognitive executive functions prevail over anaerobic capacity sports. Mann et al.[67]studied players in their own sport field and other athletes, who did not operate in that specific sport by sport-specific cognitive tests. Individuals with their own sports performed significantly better in declarative memory, attention, perception, decision-making skills, and on the field of work memory[67]. Davids et al.[68], who have examined the benefits of interceptive sports such as tennis and squash, received interesting results. These sports require strong co-ordination between the athlete's body, part of his body, the hand-held sports equipment, and the moving object such as the ball. The response time of interceptive athletes was significantly faster than athletes who play “closed”, self-paced sports like golf or swimming. Kramer et al.[69] demonstrated that one-hour walking, three times a week for six months has increased significantly increased the amount of gray matter in the frontal and temporal cortex as well as in the front white matter compared to the control group. This was measured with magnetic resonance imaging (MRI) objectively.

1.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

1.3.1. Explicit and implicit memory

Explicit and implicit memory function was examined in several patient groups already [70-76]. For instance, in amnesic patients the severe damage of explicit memory was demonstrated by „multiple-choice" questionnaire[75], however, in the research of implicit memory task; „the weather prediction", they performed just as well as the healthy control group. Gobel et al.[73] compared the performance of mild cognitive impairment amnesic and Parkinson's disease patients to healthy persons. Based on their results, in measuring the implicit learning „sequence learning-task", the lower activity of medial temporal lobe did not affect implicit learning. Lower performance in explicit memory was demonstrated in women with post-traumatic stress disorder. This result correspond with the results of that study that war veteran men with post-traumatic stress disorder were examined [76]. Csábi et al.[72] examined the explicit and implicit systems involvement in children with sleep-related breathing disorders. The involved children provided lower explicit memory performance compared to the control group, although the implicit learing process remained intact. Thus dissociation was found between the involvement of the two types of memory system in the case of children with and without sleep disorders. The examination of insomnia patients[70] found lower results as well when compared to the healthy group, in testing the explicit memory performance with doublet learning test. Huntington's disease patients[74] were studied with two types of implicit tasks. The patient group performed worse in the "probabilistic classification learning task" than the control group, but in the artificial grammar learning there were no differences between the results of the two groups. Studies have also been made on the impact of stress on explicit memory. Based on their results, Hidalgo et al.[77] assume that stress is not influencing the explicit memory function. In contrast in another study[78] reported deteriorating explicit memory performance.

2. AIMS OF THE THESIS

2.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY AFTER NASAL PROVOCATION TEST

High prevalence, increasing steroid phobia and the need of avoiding long-term medication also stimulated the development of new therapeutic options. The blended mixed UV-B / UV-A and visible light (mUV / VIS) light therapy (Rhinolight®), was developed by researchers from the University of Szeged. Our team has previously reported in several communiqués[30,28,29,79,27] about its beneficial effects in perennial and seasonal allergic rhinitis. A recurring therapeutic question is whether treatment prior to seasonal pollen release is suitable for preventing the onset of the symptoms. Allergen-specific NP is a well known clinical method to detect allergic sensitization that can not be clearly determined by the prick test and spec-IgE methods[21]. The changes of nasal air flow (NIPF, rhinomanometry and/or acustic rhinometry) and symptoms triggered by nasal application of a standard amount of the examined allergen, are recorded[17].

Since patients had difficulty tolerating drug withdrawal during the symptom period, our present studies were performed during a symptom-free period following specific allergen NP. We tested the effects of targeted high dose nasal ragweed provocation with a diagnostic test (human, randomized, double blind, placebo controlled, prospective study) for intranasal phototherapy in pretreated and untreated (placebo) allergic patients.

Rhinolight (RL) phototherapy may significantly reduce the number of eosinophilic cells and T lymphocytes through apoptosis, which also results in a decrease in local IL-5[80]. In light of all these effects, phototherapy is expected to reduce the nasal symptoms of early allergic reactions by [30,28,29,79,27].

2.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

Despite the high prevalence of hay fever, no study has so far assessed the effect of symptoms on cognitive functions and physical performance together. This study aims to investigate the acute allergic effects of allergic rhinitis on respiratory parameters, fitness, and cognitive functions. Does regular sport activity modify the influencing effect of allergic symptoms induced by single acute allergen exposure on respiratory, cognitive, and physical outcomes? This open prospective clinical study compares the performance of athletes with allergic rhinitis to non-athletes with allergic rhinitis. This study was motivated by the low number and conflicting results of studies published so far and our aim was to assess the effects of allergic rhinitis on breathing parameters, fitness, and cognitive functions in athletes.

2.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

The purpose of this study is to explore the effects of allergic rhinitis on the function of different memory systems. Whether regular sport influence the functioning of cognitive abilities and the effect of allergic symptoms on the quality of life? In the open, prospective clinical study, we compared allergic athletes to people who are allergic but do not sport. The controversarial results of the so-far published studies justified our research, which aims to examine to whether extent allergic rhinitis affects the explicit and implicit memory, in ragweed-allergic active athletes.

3. MATERIALS AND METHODS

3.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY AFTER NASAL PROVOCATION TEST

3.1.1. Participants

In the study, 24 patients participated with allergy rhinitis caused by ragweed, of which 12 received intranasal phototherapy (Rhinolight phototherapy: mUV/VIS RL group), to the 12 patient in the conrol group was administered placebo. The people we examined were selected by access-based sampling, they volunteered. Each participant was informed in detail about the course of the investigation, the inconvenience caused by the provocation and signed a declaration of consent before starting the trial. They could ask for a break at any time during the test, or to interrupt it without reason. In the course of the test, we have complied with the relevant ethical rules (license number 1983/2005).

3.1.2. Procedure

The tests were measured at the Department of Oto-Rhino-Laryngology and Head-Neck Surgery of the University of Szeged. The participants participated in the study had moderate/severe symptoms of ragweed allergy in season, which was confirmed by detectable specific IgE in blood or prick skin tests. In each case, two examinations (visit 1 (V1) and visit 2 (V2)) were carried out in ragweed pollen-free period, with nine days between the two measurements. Initially, basic measurements (M0) were made on both occasions, then nasal respiratory function was measured 10 minutes (NP-M10), 30 minutes (NP-M30) and 8 hours (late) after NP, and we registered symptoms based on total nasal symptoms score (TNS) and total symptom score (TSS). During the NP, nasal mucosa of test subjects was stimulated with 0.2 ml of 30 IR/ml ragweed allergen per each side.

3.1.3. Intranasal phototherapy

In the RL group, both nose mucous membranes were treated 4 times with the mixture of ultraviolet and visible light (mUV/VIS) between the two measurement times. The starting dose was 1.6 J/cm^2, the dose was increased by 0.25 J/cm^2 each time, giving a fourth dose of 2.6 J/cm^2. The duration of a treatment is 3 minutes. Radiation is wide, high spectrum (Rhinolight Ltd, Szeged, Hungary, 180 mW, composition of 5% UVB, 25% UVA and 70% visible light)[27]. The placebo group received low intensity visible light therapy.

3.1.4. Nasal respiratory function tests

These studies are suitable for the objective assessment of nasal breathing, NP-specific objective evaluation[17]. During acoustic rhinometry (AR) testing, with the aid of a tube and a nasal adapter, audible sound made by a sound generator is introduced into the nasal cavity, whose reflection from different distances is measured with the help of a computer program. Thus, the nasal cavity cross-section and the nasal cavity volume can be determined at any distance from the nose inlet[81]. We measured nasal volume between 0-7 cm^3 and 2.2-5.4 cm^3 from the nasal inlet (GM Instruments, UK).

During the examination of the Nasal Inspiratory Peak Flow (NIPF), the maximum inhaled air flow was measured [L/min][82], providing information on both nasal nodes at the same time (Clement Clarke, UK).

3.1.5. Measurement of nasal and total symptom score

After each measurement, patients immediately filled out a symptomatic diary. The symptom points are subjectively assessed to evaluate the strength of the individual symptoms, which is rated by the patient on a scale of 0 to 3, where 0 means asymptomatic. The total nasal symptom score (TNS)[83] refers to sneezing, rhinorrhea, nasal congestion and itchy nose, with a maximum score of 12 points. The total symptom score (TSS)[84] includes, besides the above mentioned, itching throat, itching eyes and coughing, with a possible maximum score of 21 points.

3.1.6. Statistical analysis

During the study, we worked with SPSS 22.0 statistical software package. Comparison of the mean values of the two groups was performed with a two-sample t-test, the comparison of the two measurement times was done by paired t-test. Data are reported as means ±S.E.M.

3.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

3.2.1. Partcipants and procedure

We enrolled 35 participants in the study but due to unpleasant symptoms, several of them did not able to complete the tests after NP. Finally, a total of 14 subjects with ragweed allergy including five women and nine men completed the whole examination and their results were analyzed. The group of athletes (average age: 42.14±5.98 years; average time spent in education:18.57±4.92 years) consisted of seven subjects who did regular training at least five times (7.5 h) a week. The control group also consisted of seven untrained subjects (average age: 42.29±5.76 years; average time spent in education: 18.14±1.67 years). The two groups were matched in age and level of education (paired-sample t-test analysis). The subjects involved in the study had allergic rhinitis confirmed by specific immunoglobulin IgE or prick test and showed moderate to medium symptoms to ragweed in the allergy season. Each subject was informed about the purpose of the study, and signed an informed consent. Ethical regulations were adhered through out the study. The ethics approval of this study is granted by the Regional and Institutional Human Medical Biological Research Ethics Committee, Clinical Research Coordination Center, University of Szeged (ethical license no. 3368, File no. 43/2014). The study was carried out in a pollen-free period of the year at the Department of Oto-Rhino-Laryngology and Head-Neck Surgery of the University of Szeged. Each participant was tested on two sessions; first at baseline with no symptoms and then, on a second session, immediately after allergen-specific NP which was performed using ragweed allergen (Stallergenes, France) at a dose of 0.2 ml of 30 IR/ml for each nostril. Both sessions took around 90 min for each subject, and respiratory functions were measured first, followed by neuropsychological functions, and finally fitness indicators.

3.2.2. Assessment of respiratory functions

Acoustic rhinometry (AR) (GM Instruments, UK) is an objective measurement based on the sound reflection of the nasal cavity. It is a static type of respiratory function test to assess nasal cavity volumes in the range of 0–7 (AR vol. 0–7) and 2–5 cm 3 (AR vol. 2–5) from the nostrils[81]. Dynamic respiratory function tests included NIPF (L/min) measurement (Clement Clarke, UK)[82]. Lung volume and its changes compared with time [forced expiratory volume in 1 s – FEV1 (L)] and airflow [peak inspiratory flow – PIF (L/s)] were monitored by spirometry (Thor Laboratories, Hungary). From the test values, we could infer the width or stenosis of the airways[85].

3.2.3. Assessment of fitness index

The Harvard step test (HST), a relatively well-known test in this area, was used for the objective assessment of physical fitness. The test involved the subject stepping up and down a platform at a rate of 120 steps/minute for 5 min. After this exercise had been completed, the subject's pulse rate was measured at 1–1.5, 2–2.5, and 3–3.5 min. The fitness index was calculated using the following equation: time of exercise in seconds×100/sum of pulses×2. Guiding values are summarized in a standard table[86].

3.2.4. Assessment of cognitive functions

To map the neuropsychological functions of the brain, we used tests that covered all of its function areas and were able to indicate minor alterations. Executive functions were assessed using letter and semantic fluency tests, where the participant had to list as many words as possible either beginning with a specified letter (letter fluency) or from a specified category (semantic fluency) in 60 s[87]. In our experiment, in the case of letter fluency, we used letter "t" before the provocation and letter "k" after the provocation. In case of semantic fluency, we used "animal" category before the provocation and "food products" category after the treatment. We measured the number of correct words, the perseverations, and errors both in letter and semantic fluency tasks. The verbal component of short-term memory was tested using a digit span test, in which the subjects had to repeat a growing list of numbers in a predefined order[88]. Complex working memory capacity was measured by a backward digit span, in which subjects again had to repeat an increasing list of numbers, but this time in reverse order. Each digit span test consisted of four series and the subjects had to repeat at least two of them correctly to proceed to the next span. The shortest span consisted of three items, the longest contained nine items, and only the correctly repeated ones were accepted.

The short-term verbal and complex memory capacity of the subject was defined as the longest span that the subject could repeat correctly[88]. The visual component of the short-term memory was tested using a Corsi block-tapping test, which involves tapping 2-cm-diameter cubes randomly fixed on a black board in the sequence shown by the researcher. Each span consisted of four series and the subject had to repeat at least two of them correctly to proceed to the next span. The shortest span consisted of three items, the longest contained nine items, and only the correctly repeated ones were accepted. The short-term visual span of the subject was defined as the longest span that the subject could repeat correctly[88]. The level of anxiety was assessed using Spielberger's State-Trait Anxiety Inventory (STAI) that measures the level of both state anxiety and trait anxiety. The subjects had to assess on a scale of 1–4 how each statement characterizes them[89].

3.2.5. Statistical analysis

The SPSS 22.0 Statistics software was used throughout the study. The average values of the two groups were compared using the two-sample t-test and the two testing sessions were separately compared in each group using the paired t-test. Data are reported as means±SD.

3.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

3.3.1. Participants

The study started with 35 participants, but due to the unpleasant symptoms many of them did not complete the nasal post-provocation measurement. Eventually 14, ragweed-allergic patient has completed all the tests, of whom five were women and nine men. In the study seven athlete (mean age 42.14±5.984 year; avarage of school education: 18.57±4.93) and as a control group seven non-sportmen (mean age 42.29±5.765 year; avarage of school education: 18.14±1.68) participated, all of them are allergic to ragweed. The two groups were matched by age [$t(12)=-0.045$, $p=0.964$] and educational attainment [$t(12)=0.218$, $p=0.831$]. Among the participant athletes there were swimmers and water polo players, who train for five or more times a week. The members of the control group live a life without physical activity. We selected the individuals to the study by access-based sampling, they volunteered. All participants were informed about the process of the study, the inconvenience caused by provocation and they also signed a declaration of consent. During the examination they could ask for break, or they could interrupt without explanation. During the research we followed the ethical rules that apply here (ethics registration number: 43/2014, license number 3368).

3.3.2. Procedure

The tests were carried out at the University of Szeged's Oto-Rhino- Laryngology and Head- Neck Surgery Department. The persons involved in the study were allergic to ragweed by seasonal moderate/severe symptoms, which were demonstrated by bloodtest specific IgE or skin prick tests. Each participant was tested twice, a week passed between the two measurements. The first measurement was the baseline measurement in a ragweed-free period. During the NP both nostril's nasal mucosa of the test subjects were stimulated with 0.2 ml 30 IR/ml dose of ragweed allergen (Stallergenes, France). Specific NP with an allergen is suitable to detect the given allergen's role in allergic rhinitis. Besides that it is capable of exploring sudden intense nasal reaction and its consequences as well[1,90,21].

The provocation was performed under medical supervision. We started test recording 10-15 minutes after the provocation. In both measurement we changed the order of tests, in order to avoid learning and sequence effects. The testing took approximately one and a half hours.

3.3.3. Tasks

3.3.3.1. Measurement of the explicit memory

We used subtests of the Rivermead Behavioural Memory Test[91], as immediate and delayed story recall, in order to measure explicit memory. During the assignment, the investigator reads a story that the test person must recall immediately, then after a predetermined time of delay must recall again. The story contains 21 thoughts, and the verbatim recall of each unit is worth a point, while the recall of the content is half a point. During the two surveys, we used different stories to avoid learning effects.

3.3.3.2. Measurement of the implicit memory

In order to measure implicit memory, we used the Alternating Serial Reaction Time Task (ASRT), which is suitable for simultaneous measurement of general skill and sequence-specific learning[92,93]. During the task the test subjects had to react as fast and accurate as possible, to visual stimuli appearing in one of the four empty circles on the computer screen, with the help of a special keyboard designed for this purpose. After pressing the corresponding key, the next stimulus appeared 120 ms later. In both session the test subjects completed 20 blocks. Each block contained 85 keypress, of which the first five stimuli were trials, followed by a nine-fold sequence ten times, of which each second element was random (ie: 2r1r4r3, where numbers indicate the elements of a sequence, while the "r" stands for random element). Each block lasted approximately one and a half minutes, thus the entire task took a total of 20-30 minutes. Between blocks the test subjects could take a break, and they also received feedback about their results on the computer screen from the previous block, regarding accuracy and response time[94,93]. In order to check that the test subjects did not recognize the hidden sequence, we asked them after completing the task, if they had noticed any principles during the task. We evaluated the recognition of sequence inn their answers with a help of a 1 to 5 scale (1 – did not notice any difference, 5 – recognized the sequence). None of the participants recognized the hidden sequence.

3.3.3.3. Criteria for evaluating the Alternating Serial Reaction Time task

During the ASRT-task the elements of the specified sequence alternate with random elements (ie: 2r1r4r3r), however some of the triple stimuli (so called: TRIPLET) occured more frequently, than others. For example the 2_1, 1_4, 4_3, or the 3_2 are more frequent triplets, because the third element could be part of the sequence but could be random element as well. In contrast, the 1_2 or 4_1 triplets are less frequent, because the third element can only be random. Based on previous literature[95,92,93] the more frequently occuring triplets are called high frequency triplets, the less common triple stimuli are called low frequency triplets. Of the 64 possibility, 16 is high frequency triplet which occurred in 62.5% during the task, thus can be more predictable, than the 48 low frequency triplet, which occurred in 37.5%. Based on previous literature the test subjects became faster with high, than with low frequency triplets, which we call as sequence-specific learning. The type of acceleration on solving the task, which is independent of the type of triplet is called general skill learning[92,93,96]. Thus, this task is enable us to measure both in separately these two aspects of implicit learning at the same time.

During the statistic analysis of the ASRT-task, we classified the 20 blocks was grouped five times which are called EPOCH, so we received a total of four epochs. In the course of the analysis in case of accuracy was avaraged, while the reaction time was calculated by median, and only the proportion of correct answers were taken into account. These were analyzed separately for both high and low frequency epochs. Based on previous studies[92,93], we have select two types of stimuli triplets in the analysis: the repetitions (ie: 222, 333) and the trills (ie: 212, 313).

3.3.4. The statistic analysis of The Rivermead Behavioural Memory Test and the Alternating Serial Reaction Time task

We used paired-sample t-test to compare the explicit memory performance between the groups. To analyze the reaction times obtained during the ASRT task, a mixed design ANOVA analysis was used for each condition. The TRIPLET (low and high frequency) and EPOCH (1-4) were the coherent pattern factor, while the independent pattern factor was the GROUP (athlete and control group).

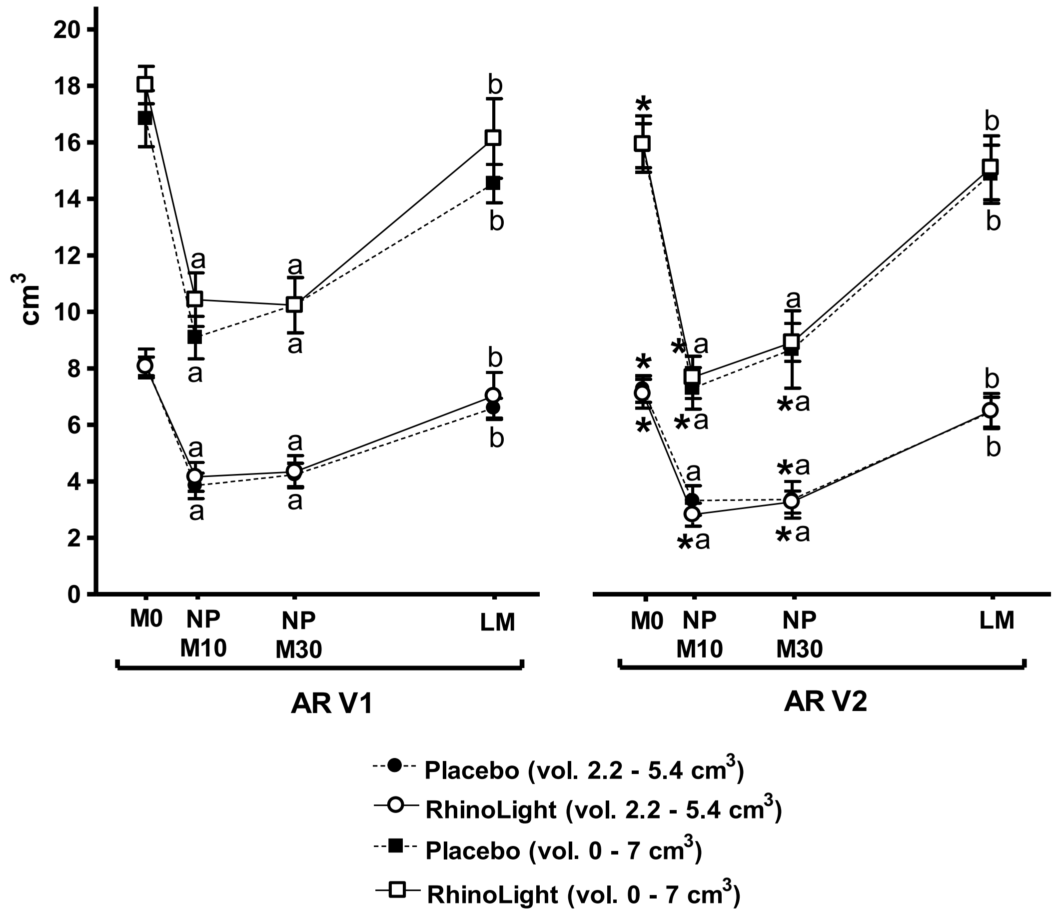
4. RESULTS

4.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY AFTER NASAL PROVOCATION TEST

At V1, there were no significant differences between the two groups' measurement of M0, NP-M10 and NP-M30 and late response parameters either. There were no significant differences between the groups in the 4 measurements at the V2 case either.

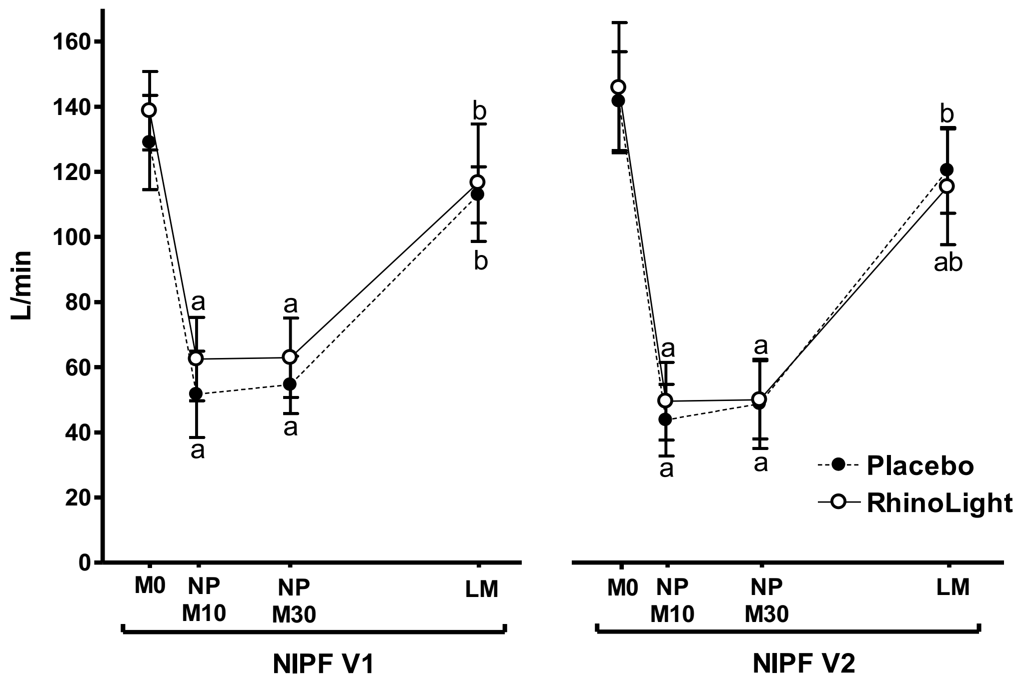
We found significant deterioration at the same parameters of V1 and V2, in V2 the vol. indicator 2.2-5.4cm^3, in M0 and NP-M30 measurements at the placebo group, in NP-M10 and NP-M30 measurements at the vol. 0-7cm^3 parameters, we found better results at the first measurement **(Fig. 1)**. In the comparison of the two measurements of the RL group to the V1 occasion, there were significantly better results at V1 vol. 2.2-5.4cm^3 parameters, M0, NP-MP10 and NP-M30 measurements, at the vol. 0-7cm^3 indicator there was significant difference in M0 an NP-N10 measurement in favor of the first test **(Fig. 1)**.

Comparing the M0 measurement at the same time with NP-M10 and then NP-M30, vol. 2.2-5.4 cm^3, we found significant differences in the parameters of vol. 2.2-5.4 cm^3, and vol. 0-7 cm^3 and NIPF, the values decreased as a result of the provocation at both V1 and V2 occasions in both groups **(Fig. 1)**.



1. figure. *:V1 vs. V2 at the same parameters where $p < 0.05$; **a**: a significant difference vs. M0 at the same measurement time where $p < 0.05$; **b**: NP-M30 vs. late measurement at the same time where $p < 0.05$; The error bars in the figure indicate the standard error.

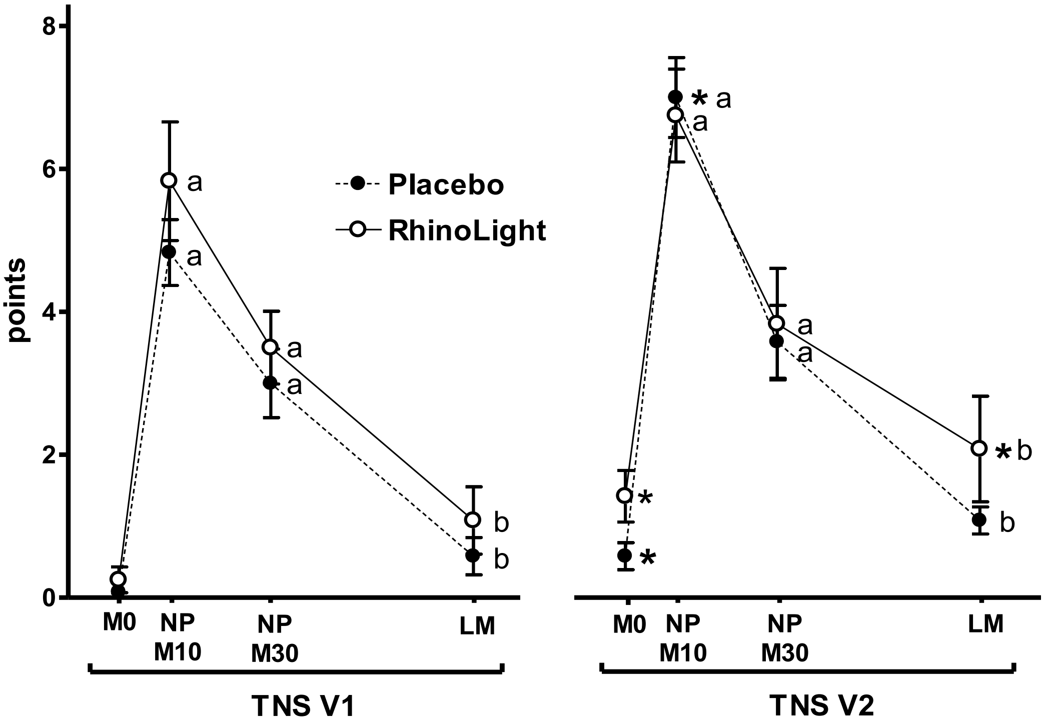
At V1 and V2, the results measured in NP-M30 compared to the late measuring times in volumes of 2.2-5.4cm^3, vol. 0-7cm^3 and NIPF showed significant change in both groups. Symptomatic worsening significantly improved during late measurement. There was only one significant difference between the M0 and the late measurement in the NIPF parameter, in V2 the RL group had significantly better results than the M0 **(Fig. 2)**.



2. Figure. *:V1 vs. V2 at the same parameters where $p < 0.05$; **a**: a significant difference vs. M0 at the same measurement time where $p < 0.05$; **b**: NP-M30 vs. late measurement at the same time where $p < 0.05$; The error bars in the figure indicate the standard error.

Neither V1 nor V2 in the M0, NP-M10 and NP-M30 measurements, nor the TNS and TSS parameters of the late response, there was no significant difference found between the two groups.

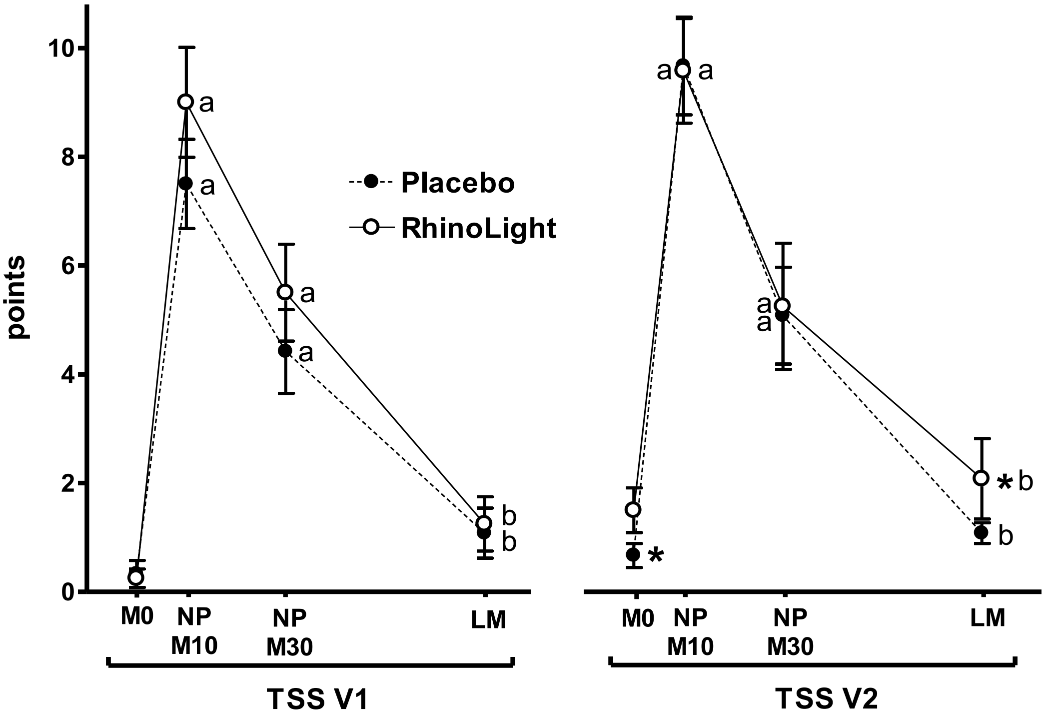
The V1 vs. V2 had a significant deterioration at the same parameters, in V2 at the placebo group during the M0 measurement in the TNS **(Fig. 3)** and TSS **(Fig. 4)** indicators, and in the NP-M10 measurement in the TNS parameter.



3. Figure. *:V1 vs. V2 at the same parameters where p <0.05; **a**: a significant difference vs. M0 at the same measurement time where p <0.05; **b**: NP-M30 vs. late measurement at the same time where p <0.05; The error bars in the figure indicate the standard error.

In the RL group during M0 the TNS, while in late measurement at the TNS **(Fig. 3)** and TSS **(Fig. 4)** indicators showed significant deterioration in the occasion of V2, compared to the V1. Comparing the M0 measurements at the same time with the NP-M10, then NP-M30, we found significant difference in the parameters of TNS **(Fig. 3)** and TSS **(Fig. 4)**, the values decreased as a result of the provocation at both V1 and V2 occasions in both groups.

Compared to the results measured at V1 and V2 in NP-M30 and the late occasions TNS **(Fig. 3)** and TSS **(Fig. 4)** showed significant changes in both groups. Symptomatic worsening significantly improved during late measurement.



4. Figure. *:V1 vs. V2 at the same parameters where p <0.05; **a**: a significant difference vs. M0 at the same measurement time where p <0.05; **b**: NP-M30 vs. late measurement at the same time where p <0.05; The error bars in the figure indicate the standard error.

4.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

4.2.1. Baseline measurements

At baseline, there is a significant difference between the athletes and the non-athletes in the HST **(Fig. 5)** and PIF values **(Fig. 6)**. No significant differences were found between the two groups for the other respiratory parameters or neuropsychological functions.

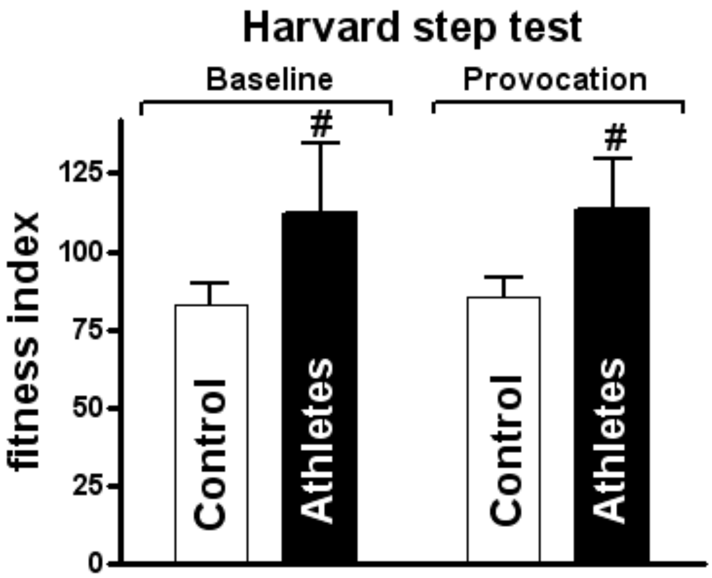


Figure 5. Fitness index of allergic athletes vs. non-athletes based on Harvard step test (HST). The results of athletes were significantly higher both before and after provocation. The performance did not decline in either group after provocation. The error bars in the figure indicate the standard error.
#: significant difference vs. the control ($p<0.05$).

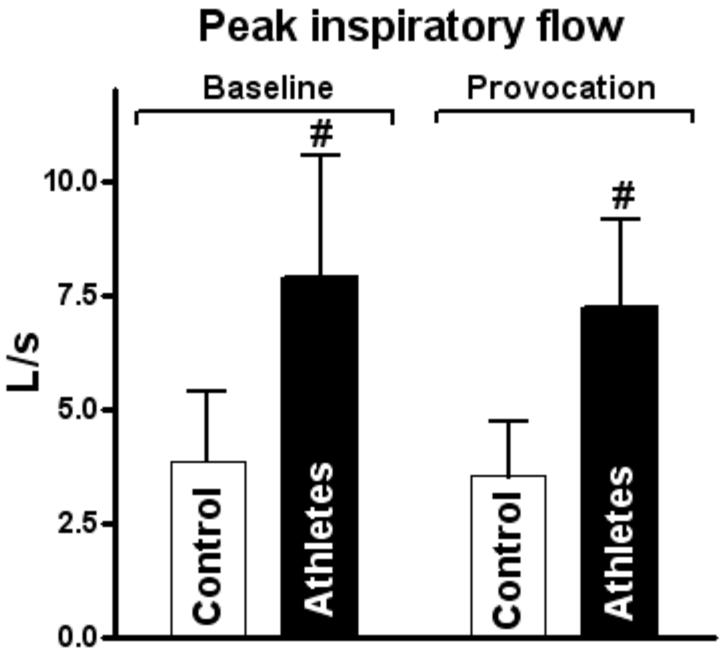


Figure 6. Peak inspiratory flow (PIF) of allergic athletes vs. non-athletes. PIF of athletes was significantly higher before and after provocation. PIF did not decrease significantly in either group after provocation. The error bars in the figure indicate the standard error. #: significant difference vs. the control (p<0.05).

Table I Results of respiratory, and cognitive tests (mean±SD)

	Baseline Control	**Baseline Athletes**	**Provocation Control**	**Provocation Athletes**
FEV_1 [L]	3.43±1.08	4.13±0.78	3.21±0.78	4.13±0.66
Letter fluency/ all words [points]	16.43±4.27	21.43±8.12	14.00±6.32	19±5.19
Letter fluency / repetition [points]	0.14±0.37	0.57±0.97	0.29±0.48	0.14±0.37
Letter fluency / error [points]	0.29±0.48	0.29±0.48	0.00±0.00	0.43±0.53
STAI/ state [points]	34.14±4.52	39.43±14.09	38.86±9.31	37.71±6.37
STAI/ trait [points]	40.57±8.79	42.33±5.24	41.71±5.05	39.33±7.63

FEV1, forced expiratory volume in one second; STAI, Spielberger’s state-trait anxiety inventory;

4.2.2. Measurements after provocation

Following NP, the two groups showed no differences in the parameters of nasal cavity volume in both ranges **(Fig 7)**. However, there is a significant difference in PIF values in favor of the athlete group. The lung capacity results of the athlete group were unsurprisingly significantly higher **(Fig 6)**.

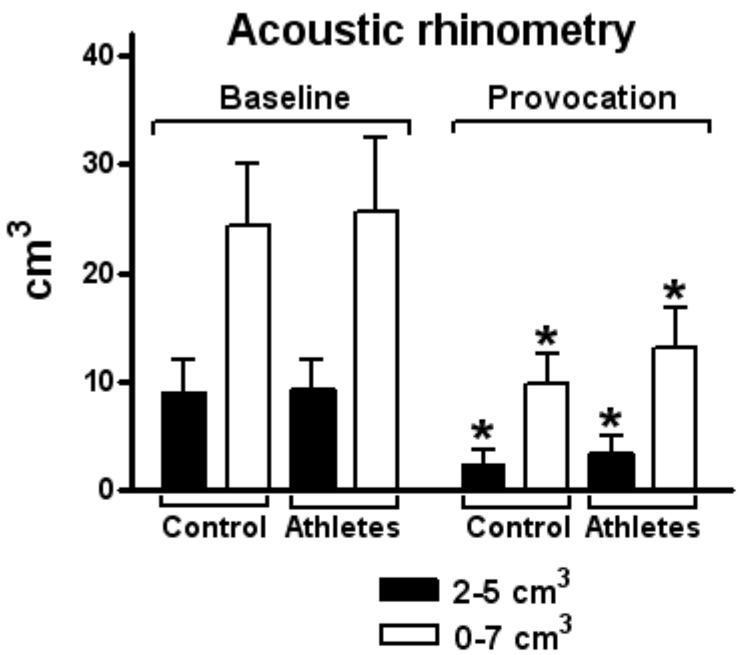


Figure 7. Results of acoustic rhinometry (AR vol. 2–5, nasal cavity volume from 2 to 5 cm3; AR vol. 0–7, nasal cavity volume from 0 to 7 cm3) of allergic athletes and non-athletes. There was no significant difference between the groups before or after provocation. After provocation the nasal respiratory indicators decreased significantly in both ranges (vol. 2–5 cm3, vol. 0–7 cm3) in both groups. The error bars in the figure indicate the standard error.
*: significant difference vs. the baseline ($p<0.05$).

The two groups showed similar results for NIPF, because NP caused severe swelling of the nasal mucosa that blocked nasal airflow totally in both groups following NP **(Fig 8)**.

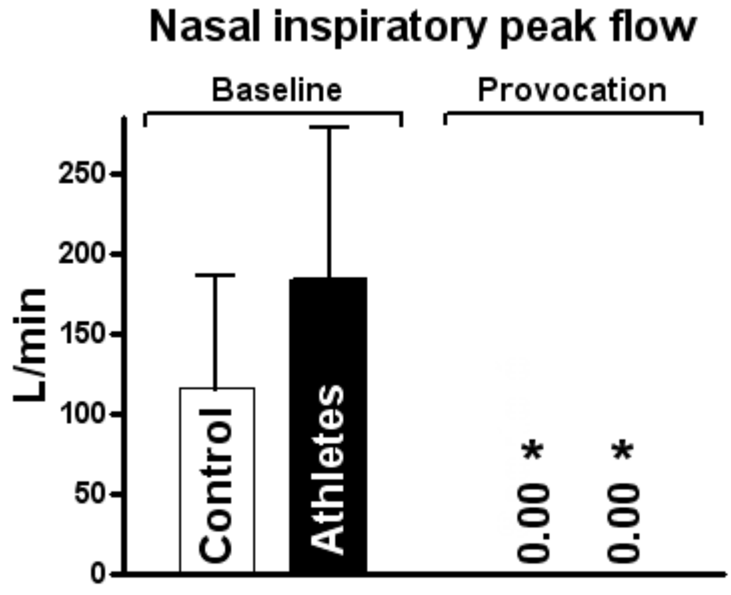


Figure 8. Nasal inspiratory peak flow (NIPF) of allergic athletes vs. non-athletes. There was no significant difference between the groups before provocation. After provocation NIPF dropped to zero in both groups. The error bars in the figure indicate the standard error.
*: significant difference vs. the baseline ($p<0.05$).

Assessment of physical fitness in the two groups following NP revealed that the average value of the fitness index is significantly higher in the athlete group **(Fig. 5)**.

No significant differences were found between the two groups in the results of letter fluency tests that measure executive functions. Letter fluency tests revealed a tendency difference in the error rate of the two groups, as athletes made errors while no errors were made in the control group **(Table I)**. Of all tests assessing the components of the working memory, only the results of the backward digit span test (measuring complex working memory capacity) showed a significant difference in favor of the athletes **(Fig. 9)**. However, following NP, both groups scored the same result on the digit span test that measures verbal short-term memory. The Corsi Block Test, which assessed the visual component of short-term memory, also failed to provide significant differences between the two groups **(Fig. 9)**.

STAI test revealed no significant differences between the two groups either for state or trait anxiety levels **(Table I)**.

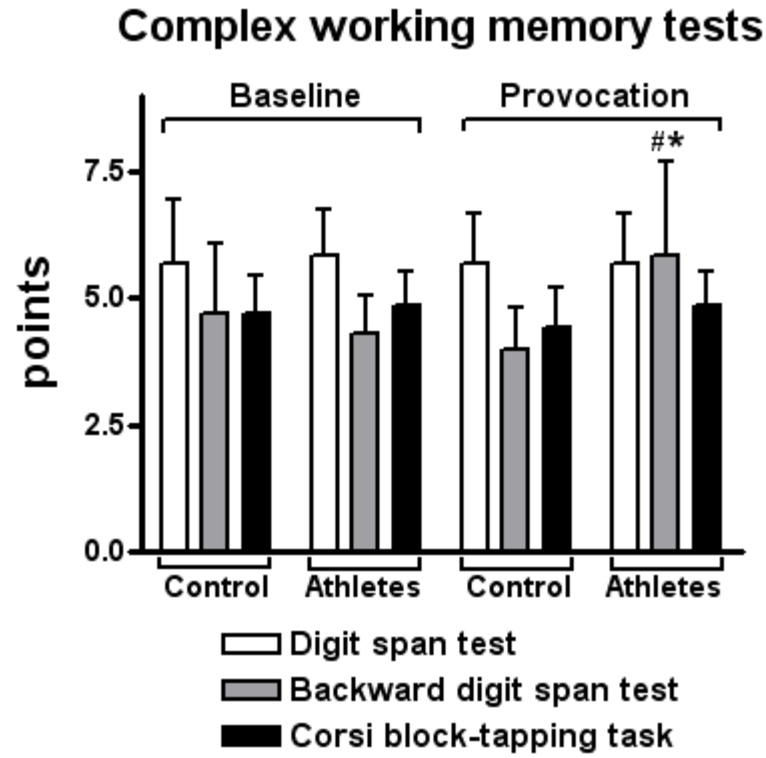


Figure 9. Results of complex working memory tests of allergic athletes and non-athletes. There was a significant difference between the groups in favor of athletes in the post provocation results of the backward digit span test. Intragroup analysis revealed a significant difference between the two measurement sessions in the group of athletes with allergy, indicating better performance in the backward digit span test following provocation. The error bars in the figure indicate the standard error. #: significant difference vs. the control ($p<0.05$); *: significant difference vs. the baseline ($p<0.05$).

4.2.3. Performance of the groups before and after provocation

The athlete group showed significant differences in the values of nasal respiration indicators (AR vol. 2–5; vol. 0–7 **(Fig. 7)**; NIPF **(Fig. 8)**) measured in the first and second session. This indicates that provocation caused nasal congestion. There were no significant differences in lung capacity or fitness parameters between measurements at baseline or after NP. As for cognitive indicators, significant differences between the two sessions were only found for semantic fluency (the total number of all words) **(Fig. 10)** and the performance of complex working memory (backward digit span) **(Fig. 9)** with the athletes performing better following provocation in both tests.

Comparison of results from the two sessions showed no additional significant differences for the remaining cognitive function tests, or tests for anxiety levels. Comparison of control group values measured in the first and second session revealed significant differences in the same parameters as in the athlete group: in the rate of AR **(Fig. 7)** in both ranges and NIPF. **(Fig 8)**. There were no significant differences in lung capacity **(Table I, Fig. 6)**, fitness index **(Fig. 5)** or cognitive functions **(Table I, Fig. 9, Fig. 10)**.

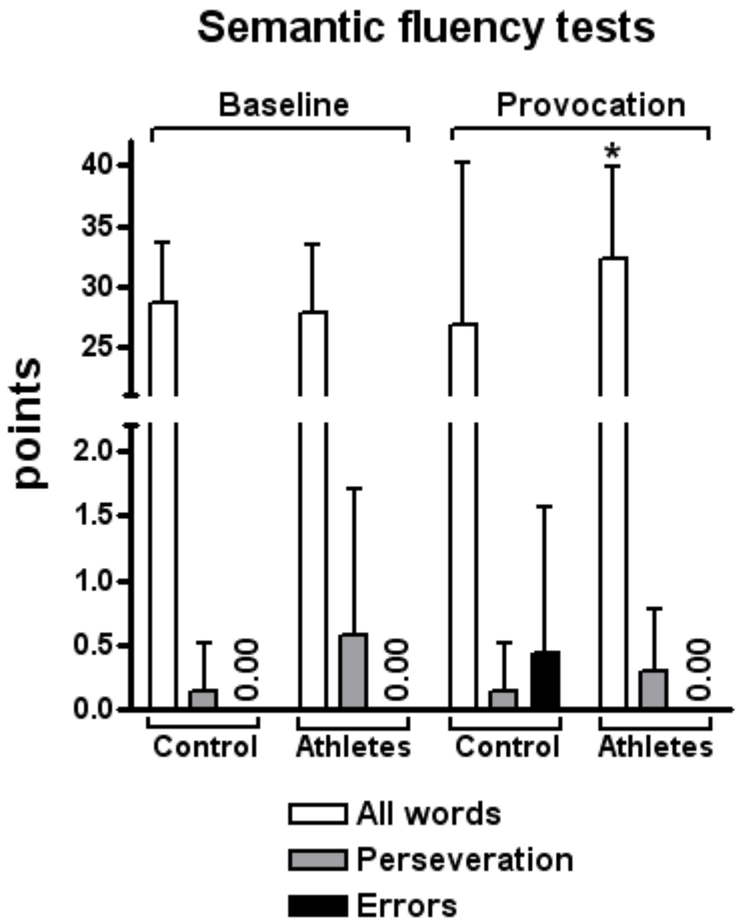


Figure 10. Results of semantic fluency tests of allergic athletes and non-athletes. Intergroup analysis did not reveal significant differences before or after provocation. Intragroup analysis revealed that allergic athletes performed better in the number of all words after provocation. The error bars in the figure indicate the standard error.

*: significant difference vs. the baseline ($p<0.05$).

4.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

4.3.1. The results of explicit memory – story retelling

4.3.1.1. Basic measurement – comparison of groups

At the first measurement time, we did not reveal any significant differernces between the groups on the Rivermead Behavioral Memory Test during the immediate recall **(Fig. 11)** [t(12)=–0.51, p=0.62; athlete group 8.14±2.27 point; control group 8.71±1.93 point]. In the delayed recall **(Fig. 12)** we also found no significant difference between the groups [t(12)= 1.14, p=0.39; athlete group 7.64 ± 2.85; control group 6.5 ± 1.87].

4.3.1.2. Nasal allergic provocation

After provocation, we found a significant difference between the two groups during the immediate recall of explicit memory processes **(Fig. 11)**, [t(12)=2.48, p=0.03), the athlete group (12.07 ± 3.03) showed better performance than the control group (8.64 ± 2.06). A significant difference appeared between the groups at the delayed recall **(Fig. 12)** as well [t(12)=2,21, p=0.047], the athlete group performed better (10.93 ± 3.27) than the control group (7.43 ± 2.62).

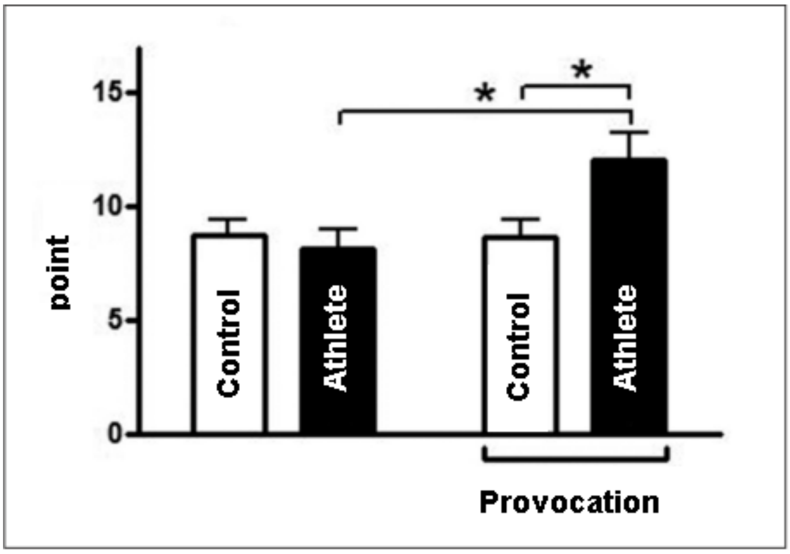


Figure 11. Results of The Rivermead test in terms of immediate recall: the performance of athlete and control group did not alter from each other during the basic measurement in terms of immediate recall, but the athletes performed significantly better compared to the control group and themselves as well, after provocation. The error bars in the figure indicate the standard error. *: a significant difference, $p<0.05$.

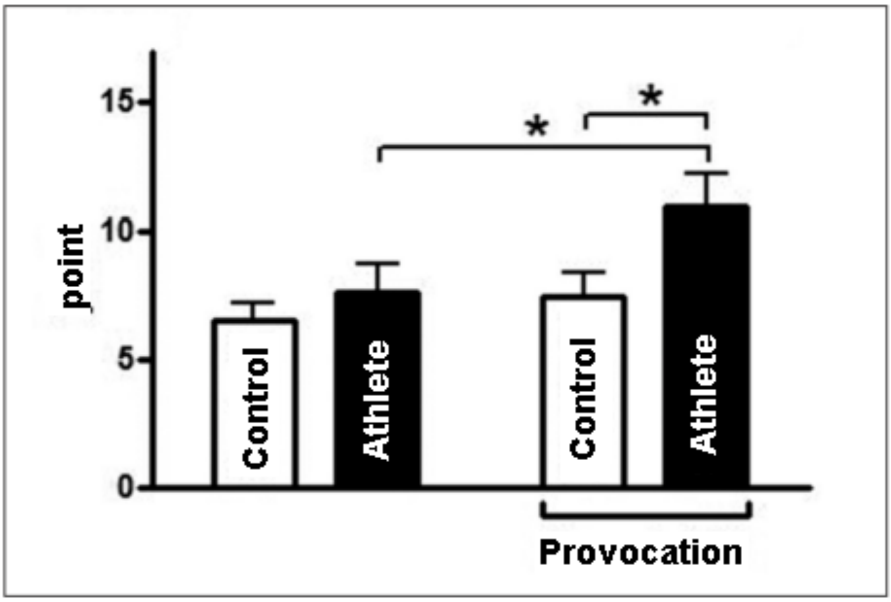


Figure 12. Results of The Rivermead test in terms of delayed recall: the performance of athlete and control group did not alter from each other during the basic measurement in terms of delayed recall, but the athletes performed significantly better compared to the control group and themselves as well, after provocation. The error bars in the figure indicate the standard error. *: a significant difference, p<0.05.

4.3.1.3. Comparison of the control group results at the two measurement times

The control group showed no significant difference between the two session in the explicit memory test either at the immediate recall **(Fig. 11)** [t(6)=0.09, p=0.93; 8.71 ± 1.93 vs. 8.65 ± 2.06] or at the delayed recall **(Fig. 12)** [t(6)=-1.24, p=0.26; 6.50 ± 1.87 vs. 7.43 ± 2.62].

4.3.1.4. Comparison of the athlete group results at the two measurement times

In the Rivermead Behavioral Memory Test, athletes' responses showed a significant difference in the immediate recall **(Fig. 11)** between the two times, compared to themselves [t(6)=- 2.81, p=0.03; 8.14 ± 2.26 vs. 12.07 ± 3.03]. In the case of delayed recall **(Fig. 12)**, we also found a significant difference between the two measurement times in favor of the second measurement [t(6)=–3.13, p=0,02; 7.64±2.85 vs. 10.93±3.72]. The explicit memory performance of athletes significantly improved during the period of provocation compared to the results of the asymptomatic period in both immediate and delayed recall **(Fig. 11, 12)**.

4.3.2. Results of the implicit memory – Alternating Serial Reaction Time task

4.3.2.1. Basic measurement – comparison of groups

When comparing the results of the athletes and the control group at the first test, we found a significant improvement in sequence-specific learning with the progress of the task, which is indicated by the TRIPLET main effect [F(1.12)=12,53 ηp^2=0.511, p<0.004]. The subjects responded faster to high frequency triplets than to the ones with low frequency. There was no significant difference between the athlete and the control group in the sequence specific learning [TRIPLET X GROUP interaction: F(1.12)=0.88 ηp^2=0.07, p=0.37]. There was no general skill learning which was demonstrated by the EPOCH main effect [F(3.36)=2.32 ηp^2=0.16, p=0.09], with the progress of the task there was no significant reduction in response time to the appearing stimuli, the participants did not significantly accelerate during the course of the task. We did not find any significant difference between the two groups in this case either [EPOCH X GROUP interaction: F(3.36)=0.13 ηp^2=0.01, p=0.94].

The TRIPLET X EPOCH interaction [F(3.36)=0.36 ηp^2=0.03, p=0.79], and the TRIPLET X EPOCH X GROUP interaction [F(3.36)=0.61 ηp^2=0.05 p=0.61] is not significant, which means that the learning pattern of these two groups were the same. There was no significant difference between the athlete and control group, in the general reaction time [GROUP main effect: F(1.12)=0.08 ηp^2=0.007, p=0.78] **(Fig. 13.A)**.

4.3.2.2. Comparison of groups after provocation

During the second test of the athletes and control group, in the comparison of their results after provocation, we found significant improvement in sequence-specific learning with the progress of the task, which is demonstrated by the main effect of TRIPLET [F(1.12)=41.29 ηp^2=0.78, p<0.00], the test subjects responded faster to high frequency triplets, than to the low frequency ones. We did not find any significant difference between the athlete and control group in terms of sequence specific learning [TRIPLET X GROUP interaction: $F(1.12)=3.24$ $\eta p^2=0.21$, $p=0.09$].

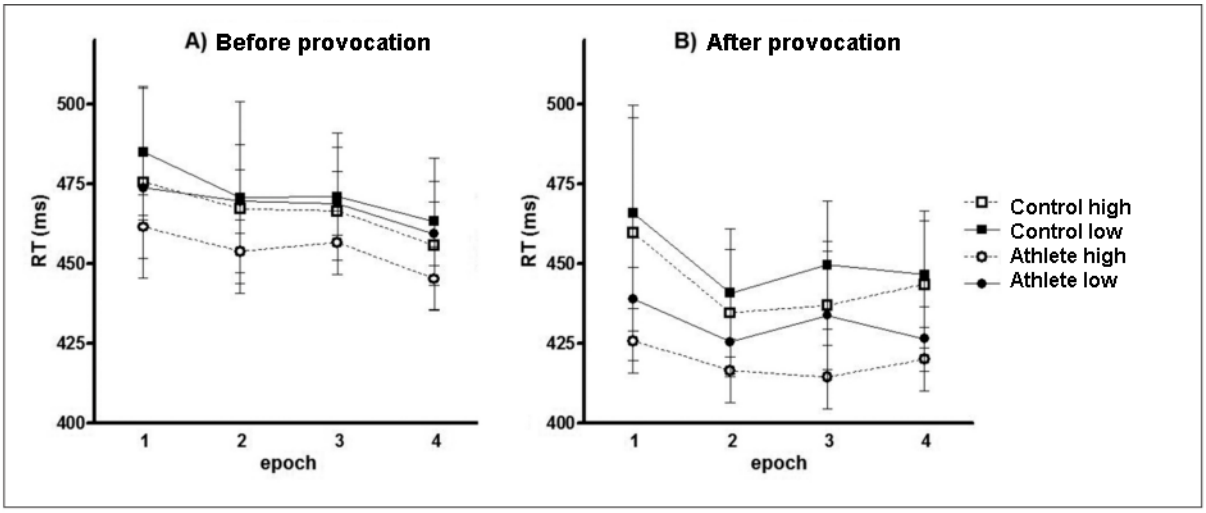


Figure 13. Sequence-specfic and general skills learning before (A) and after (B) provocation: The response time of the athlete group has decreased both in terms of low and high frequency triples. The difference between the response time to the two triple types did not increase gradually during the task. The response time of the control group also decreased with the progress of the task in the case of low and high frequency triplets as well. There is no noticeable gradual increase in reaction time to the two types of triplets, nor before (A) neither after (B) provocation. There was no significant difference in the learning pattern of the two groups. The error bars in the figure indicate the standard error.

There was no general skill learning during thetask demonstrated by the main effect of EPOCH [$F(3.36)=2.46$ $\eta p^2=0.17$, $p=0.078$]. During the the task, both groups showed a tendency in reduction of response time to stimuli, but we did not find any significant difference between the two groups [EPOCH X GROUP interaction: $F(3.36)=0.39$ $\eta p^2=0.03$, $p=0.76$].

The TRIPLET X EPOCH interaction were not significant [$F(3.36)=1.44$ $\eta p^2=0.11$, $p=0.25$], meaning that the learning pattern of the two groups are the same [TRIPLET X EPOCH X GROUP interaction: $F(3.36]=0.005$ $\eta p^2=0.00$ $p<0.99$]. There was no significant difference between the athlete and control group in the general response time [GROUP main effect: $F(1.12)=0.793$ $\eta p^2=0.06$, $p=0.39$] **(Fig. 3.B)**.

4.3.2.3. Comparison of the control group results at the two measurement times

When comparing the response times measured during the two test sequences of the control group, the test subjects demonstrated significant improvement in sequence specific learning, which is indicate by the main effect of TRIPLET [$F(1.12)=11.97$, $\eta p^2=0.49$, $p=0.005$]. Thus, their reaction time was lower for high frequency triplets than for the low frequency triplets. We did not find significant difference between the two measurement times in sequence specific learning [TRIPLET X SESSION interaction: $F(1.12)=0.04$ $\eta p^2=0.003$, $p=0.85$]. In the case of general skill learning, we revealed in trend demonstrated by the main effect of EPOCH [$F(3.36)=2.28$ $\eta p^2=0.16$, $p=0.096$]. During the task, the response time to stimuli changed in trend. There was no significant difference between the two measurement times [EPOCH X SESSION interaction: $F(3.36)=0.41$ $\eta p^2=0.33$, $p=0.74$].

The TRIPLET X EPOCH interaction was not significant [$F(3.36)=0.39$ $\eta p^2=0.03$, $p=0.76$] which shows, that the reaction time did not improve on average during the task. There was no difference between the the two session [TRIPLET X EPOCH X SESSION interaction: $F(3.36)=0.98$ $\eta p^2=0.08$ $p=0.41$] **(Fig. 14.A)**.

4.3.2.4. Comparison of the athlete group results at the two measurement times

For the athlete group, when comparing reaction times measured during the two tests, we found that patients showed significant improvement in sequence specific learning, which is demonstrated by theTRIPLET main effect [$F(1.12)=30.69$, $\eta p^2=0.72$, $p < 0.001$], thus, the reaction time of athletes was lower in high frequency triplets, compared to low frequency triplets during the task. There was no significant difference between the two session in sequence specific learning [TRIPLET X SESSION interaction: $F(1.12)=0.16$ $\eta p^2=0.01$, $p=0.69$].

We did not find any significant general skill learning, demonstrated by the EPOCH main effect [$F(3.36]=2.24$ $\eta p^2=0.16$, $p=0.101$]. During the task , the response time to stimuli did not change, so the athletes did not speed up during the task. Theres was no significant differences between the two session [EPOCH X SESSION interaction: $F(3.36)=0.34$ $\eta p^2=0.03$, $p=0.797$].

The TRIPLET X EPOCH interaction was not significant [$F(3.36)=0.67$ $\eta p^2=0.05$, $p=0.57$], that the reaction time did not improve generally, during the task. There was no difference between the two session [TRIPLET X EPOCH X SESSION interaction: $F(3.36)=0.55$ $\eta p^2=0.04$ $p=0.65$] **(Fig. 4.B).**

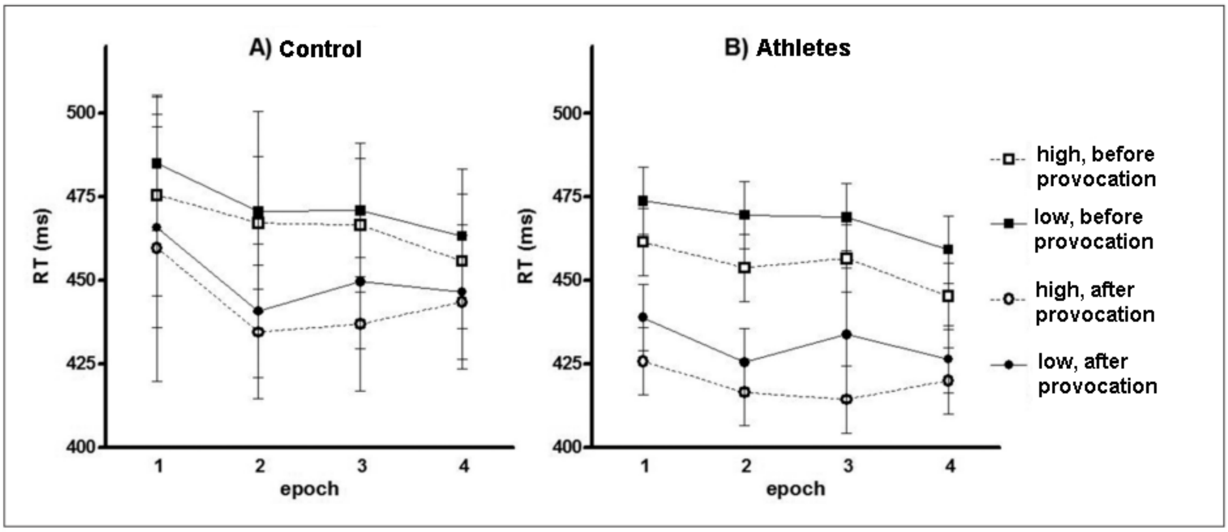


Figure 14. Sequence specific and general skills learning in control (A) and athlete (B) groups: In both groups the reaction time decreased with the progress of the task, both for low and high frequency triples. There was no observable steady increase in response time in either group while responding to the two types of triplets. There was no significant difference between the two measurement times, so the mean response time of control subjects (A) and athletes (B) was not significantly different after the allergic provocation compared to the performance at the first test. The error bars in the figure indicate the standard error.

5. DISCUSSION

5.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY AFTER NASAL PROVOCATION TEST

During our investigations, we were investigated the effect of phototherapy on the symptoms of single-, high-dose, sudden and intense nasal reactions in ragweed allergic patients. For this purpose, patients with intranasal RL phototherapy and untreated allergic patients were compared. Based on our results there was no difference between the two groups in the initial parameters. After NP, significant symptomatic worsening was observed in both groups compared to the M0 period. NP induced nasal congestion, sneezing, rhinorrhea, itching nose (TNS), and itching throat, itchy, watery eyes and coughing (TSS). The volume of nasal cavity and the parameters' of nasal airflow significantly reduced to NP-M10 and NP-M30, then in the eight-hour period's measurement the symptoms gradually retracted. After the second provocation (V2), similar results were obtained.

NP results increase of eosinophils in the tissues, increases the rapid growth of Th2 cytokines in the cells, and increases Th2 transcription factors in T cells[97]. The growth of T cells in the nasal mucosa is high compared to healthy individuals due to the excessive response of Th2[98]. In the IgE-sensitized individuals, after a sudden allergen release, within minutes, symptoms such as sneezing and itching nose appear, that are usually followed by rhinorrhea and nasal congestion, and within 1 hour the symptoms are reduced. These reactions are derived from the complexes of crosslinked and sensitized IgE allergen, on the surface of mast cells and basophils resulting in the release of histamine and tryptase. Histamine induces itching through the H1 receptors, affecting the end of the sensory nerves leading to systemic reflex, such as sneezing attack[99,100]. Leukotrienes, the prostaglandin D2 and vascular endothelial growth factors (VEGF) cause leakage derived from blood vessels leading to edema in large venous sinuses, and enhancing glandular mucus secretion, all of which may contribute to sensation of nasal congestion[99,100].

In human NP studies with cat hair and weed allergens, the kinetics of local and systemic responses were studied, in the mucous membrane allergen exposure[101,102]. It has been shown that levels of tryptase and histamine of the mucus fluid peak within 5 minutes, indicating that local mast cells are activated immediately after exposure to allergen followed by further proliferation on surface activating markers such as the CD63 on circulating basophils.

Phototherapy was used to reduce single high dose allergen-induced symptoms. Based on our results, among the placebo and the RL group there was no difference between the measured values during the repeated provocation after the (mUV/VIS) Rhinolight therapy. The Szeged RL Group[30,28,29,79,27] reports in a number of articles on the efficacy off RL phototherapy treatment in allergic rhinitis. However, recent studies have been conducted in ragweed allergic season, which means significantly smaller but sustained allergen exposure. Allergic inflammation is associated with a change in the cytokine balance with Th2-dominance[103]. Numerous data indicate that Th2 cytokines (IL-5 and IL-4) are present in an increased number of nasal mucosa in patients with allergic rhinitis[104,103]. IL-5 is a cytokine that promotes the maturation, activation and prolonged survival of eosinophils, which are the main effector cells in the allergic rhinitis[80]. Suppression of effector cells is a potential therapeutic strategy to reduce the symptoms of allergic rhinitis. Irradiation of the nasal mucosa can significantly reduce the major source of local IL-5 and the T lymphocytes. Thus, after phototherapy, the apoptosis of these cells can be the basis for the decreased IL-5 production mechanism. Memory T cells play an important role in the length and maintenance of the allergic process.

The apoptosis of these cells by phototherapy (programmed cell death) may be beneficial in the long-term. Phototherapy reduced the number of eosinophilic cells and ECP levels in the nasal wash fluid[27]. This is due to the direct proapoptotic effect of Rhinolight in eosinophilic cells and the reduction of IL-5 local levels. Similar results have been observed in eosinophil, ECP and IL-5 levels and well-known allergic rhinitis therapies for T lymphocytes such as local glucocorticoids or immunotherapy[105,104,106,107]. In the case of allergic rhinitis, the IL-4 level also increased in the nasal mucosa. IL-4 is essential for the production of T-cell precursors, the Th2 cytokines, and activates IgE isotype B cells[108]. However, the role of IL-4 in the change of survival and function of eosinophilic is not yet fully clarified. There was no late reaction after the NP in our study.

5.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

The aim of this study was to assess the effects of allergic rhinitis on respiration parameters, fitness and cognitive functions, and also to see whether regular exercise helps develop resistance against the symptoms. To address these questions we compared the performance of athletes to non-athletes. The results show a significant difference in fitness indicators and lung capacity between the group of athletes with allergy and the allergic control group before NP. The athletes performed better in the fitness test and showed higher lung capacity values than the control group. Following NP, the athletes also showed significantly better lung capacity and fitness indicator values than the control group. In terms of cognitive functions, the only significant difference was measured in the performance of the complex working memory with higher scores seen in the group of athletes.

Our results show that the allergic athletes scored higher for fitness indicators and lung capacity in both assessment sessions, which is probably explained by the fact that they are in better physical condition. The two groups showed no differences in cognitive functions before NP, therefore this sample does not confirm the claim of Hotting et al.[109] that regular physical exercise has a beneficial effect on cognitive functions. Our results are similar to Jacobson and Mattheaus's[110] findings, who could not detect differences in executive functions, general intelligence and the mental processing speed between athletes and non-athletes.

No decline in performance was found in either group following NP, which are in line with studies that also found no differences in cognitive functions with or without allergic symptoms[1,2,44]. Hartgerink-Lutgens et al.[1] explain this by stating that the idea of people with allergy experiencing a decline in their performance is subjective, but this decline cannot be confirmed by objective testing. Our results, however, are in contrast with previous research that indicated a decline in the performance of people with allergy in reaction time, short-term memory performance and divided attention tasks [32,35,33,34,36,37]. However, these studies compared the performance of healthy controls to the performance of those with allergy. The differences in methodology may also account for our different results.

The two measuring sessions unsurprisingly revealed a difference in the level of nasal cavity restriction when the two groups were individually compared. NP led to blockage in the nasal cavity, which restricted respiration, but provocation caused no decline in lung capacity. These findings are in contrast with the study of Price et al.[111] who showed that inflammation of upper and lower airways are in close correlation; inflammation of the nose may lead to bronchial hyperresponsiveness and in turn, a reaction in the lungs may lead to inflammation in the nose[112]. In some studies, patients with allergic rhinitis seemed to be free from bronchial hyperresponsiveness, but signs of allergic inflammation were found in the airways in the form of sputum induction.

Our results suggest that the allergic athlete group performed better compared to both the control and to itself following NP in executive functions and complex working memory tests. This may be explained by findings from previous studies[113-115], which have shown that regular exercise correlates with resilience, thus improves stress resistance. This is why people doing regular exercise tend to perform better under stress. This study involved athletes who are exposed to stress regularly during preparation for international competitions and during competitions themselves. Adaptation to such stress may explain the improved physical and cognitive performance following NP compared to baseline.

5.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

During our investigation, we were looking for how allergic rhinitis affects the explicit and implicit memory, and investigate if regular sports influence explicit and implicit memory? In order to do that, we compared allergic athletes with allergic persons who do not sports. There is no such study in the literature, which studied memory factors for allergic rhinitis athletes. The only similar study was to research the quality of life of athletes suffering from hayfever, with the help of „Quality of Life" questionnaire, and they concluded the beneficial effect on allergic symptoms of the nasal spray called Budesonide[116].

Based on our results, the athlete and the control group performed similarly in the asymptomatic period, including tests of explicit and implicit memory. However, athletes achieved better results in post-provocation measurement regarding explicit memory on immediate and delayed memory recall tests. Our test results confirmed the results of Fletcher et al.[113], who demonstrated at Olympic athletes that stressors influence psychical factors -

such as positive personality, motivation, and confidence - to the extent that they significantly contribute to achieving optimal sports performance. In another study[117], examining university students, it was found that physical activity has a significantly good effect on mental health and interacts with the level of trait anxiety. The relationship between resilience, mental health and sport performance was observed in athletes with the help of the Connor-Davidson Resilience Scale, and they concluded that the level of resilience could „predict" sport performance and mental health[118].

These three studies[113,117,118] proved, that doing sports regularly is related to the resilience level, thus increasing the resistance to stress, which can be developed with positive psychological factors[113], adequate mental health[117,118], and in team sports with positive conformity[119]. Therefore, those who do sports on a regular basis, are more likely to be able to perform well, under greater pressure, as well. Our results, however, are contrary to those studies where it has been shown that stress did not affect[77] or impaired explicit memory performance[78].

The allergic group of athletes achieved better results compared to itself as a result of provocation in explicit memory, but there was no change in the measurement of implicit memory compared with baseline measurements. Our results contradict previous studies where performance deterioration was found in patients with explicit memory performance. However, our findings confirm the results of the same studies where no deviation was found in the implicit memory function[70-76]. According to Hartgerink-Lutgens et al.[1] allergic patients only experience subjective degradation, but this deterioration does not appear on objective tests.

In the control group, there was no change in the performance of explicit or implicit memory after the provocation compared to the asymptomatic period.

The limitation of our study was the low sample size since we found few people in the same sport who are allergic athletes, aged 30-50 and undertook the uncomfortable NP.

6. CONCLUSIONS

6.1. EFFICIENCY OF THE "RHINOLIGHT" PHOTOTERAPY AFTER NASAL PROVOCATION

Data from the Szeged RL Group[30,28,29,79,27]suggest that the quantitative relationship between inflammation-induced IL-4 and IL-5 may determine the apoptosis rate of eosinophils at the site of allergic inflammation. Similar results have been reported after local glucocorticoid therapy of allergic rhinitis[120]. Reduction of IL-5 in the oral mucosa after phototherapy with persistence of IL-4 may provide further support for light therapy-induced eosinophil apoptosis[104,103].

High dose allergen exposure means "over-threshold stimulus". As a result, cytokine outflow reaches such a level, which can not be compensated for by the administered dose RL phototherapy’s eosinophil and T cell apoptosis and histamine degranulatory inhibitor effect. There was no late reaction after the NP in our study[27].

The aim of our study is to investigate whether (mUV/VIS) phototherapy is suitable for preventive treatment, if it has preventive effect. It has been shown that phototherapy did not produce significant effects on symptoms caused by a single-, high-dose allergen on the non-inflamed nasal mucosa. So far, (mUV/VIS) light therapy has not yet been used for prevention, only for therapeutic purposes[30,28,29,79,27]. Based on the results of our research, the use of phototherapy does not encourage the use as prophylaxis. Additional quantitative studies are required to determine the therapeutic threshold.

6.2. PHYSICAL AND COGNITIVE PERFORMANCE OF PATIENTS WITH RAGWEED ALLERGY

In summary, NP did not influence significantly the cognitive and physical performance of the control group of people with allergy and the group of allergic athletes, in fact, improved results were recorded for certain functions. Disturbing elements caused by NP, such as swollen nasal mucosa, sneezing and watering eyes did not hinder cognitive functions in people with allergy. One explanation may be the competitive spirit of athletes. In sum, this study indicates that exposure to a single, high dose of allergen may result in increased focus in patients with allergy.

6.3. EXPLICIT AND IMPLICIT MEMORY OF PHYSICALLY ACTIVE AND INACTIVE PATIENTS WITH RAGWEED ALLERGY

NP with a single high dose allergen causes serious allergic symptoms in patients with sensitized allergens, which may result in an increased concentration on the athletes. Nasal symptoms caused by provocation, such as nasal congestion, rhinorrhea, sneezing, and lachrymation did not impair memory functions. The improvement of increased explicit functions that can be observed in athletes point to a high level of concentration potential in a stressed state.

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9. APPENDIX

A questionnaire for distinguishing between rhinitis and allegic rhinitis can also be used in family practice practice[17].

Nátha és AR elkülönítése

Az alábbi validált kérdőív használata javasolt (www.globalfamilydoctor.com). Az első kérdéscsoportban a „nem" válaszok, míg a második kérdéscsoportban az „igen" válaszok jellemzőek AR-re.

a) Rendelkezik-e Ön az alábbi tünetekkel?

– Féloldali orrpanaszok?	Igen	Nem
– Sűrű, zöld- vagy sárga színű orrváladék?	Igen	Nem
– Hátsó garatfalon lecsorgó nyák és nincsen vizes orrfolyás?	Igen	Nem
– Arcfájdalom?	Igen	Nem
– Ismétlődő orrvérzések?	Igen	Nem
– Szaglásvesztés?	Igen	Nem

b) Rendelkezik-e Ön az alábbi tünetekkel naponta legalább egy órán keresztül vagy a legtöbb napon egy adott szezonban, ha a panaszai szezonálisak?

– Vizes orrváladékozás	Igen	Nem
– Tüsszögés, rohamokban	Igen	Nem
– Orrdugulás	Igen	Nem
– Orrviszketés	Igen	Nem
– Kötőhártya-gyulladás (vörös, viszkető szem)	Igen	Nem