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To cite this article: Soran Rajabi, Esha'q Keshavarz, Yoosef Dehghani, Maryam Keshavarz & Khadije AliMoradi (2017): Comparing executive functions between patients with chronic asthma and healthy subjects, Journal of Asthma, DOI: [10.1080/02770903.2017.1337786](https://doi.org/10.1080/02770903.2017.1337786)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1337786>



Published online: 14 Jul 2017.



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Comparing executive functions between patients with chronic asthma and healthy subjects

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ABSTRACT

Objective: Allergic diseases have different levels of prevalence all over the world. Among them, asthma is the most common chronic disease. Up to now, little attention has been paid to the impact of this chronic disease on people's executive functions. The present study aimed at comparing the executive functions in patients with chronic asthma and healthy subjects. **Methods:** The study population was patients with chronic asthma who were referred to Al-Zahra hospital in Isfahan Province and their visitors who were assigned as the control group. Thirty patients with chronic asthma and 30 patient visitors were enrolled in this study, and three software programs (Wisconsin, Stroop, and Continuous Performance Tests) were used. **Results:** The results of multivariate variance analysis showed that there is a significant difference between patients with chronic asthma and healthy subjects in terms of set shifting, inhibition, and attention performance. **Conclusions:** This study revealed that the executive functions of patients with chronic asthma have significant defects.

ARTICLE HISTORY

Received 3 February 2017
Revised 18 May 2017
Accepted 29 May 2017

KEYWORDS

Attention; chronic asthma;
executive function;
inhibition; preservation

Introduction

Allergic diseases have different levels of prevalence all over the world. Among them, asthma is the most common chronic disease [23]. According to published studies, the prevalence of allergic diseases, such as asthma, has been increasing in recent decades.

Asthma is more common in children than adults, in women than men, and in blacks than Hispanics. This allergic disease is almost 33% more common in women than men (This pattern is reversed in children). According to the report of global burden of asthma in 2003, the prevalence of asthma in Iranian children was estimated to be 10 percent (Masoli, Fabian, Holt, Beasley, 2004). In Iran, the prevalence of asthma symptoms in children varied across the country between 2.7 and 5.43%. There are no adequate studies on the prevalence of asthma symptoms in adults in Iran. This wide range of prevalence in different parts of Iran is due to climatic variation, life style, vegetation, and air pollution in different cities. Unfortunately, because of the lack of studies with standard methods and the lack of care for asthma at the national level, the evaluation of these patients is extremely difficult in Iran. Meanwhile, in the second report of the Committee after 6 years and in 2004, the prevalence of asthma symptoms in Iranian children was estimated 13/2%,

which implies an annual increase of 0/17% prevalence of asthma symptoms [6]. Generally, the prevalence of asthma symptoms in the country seems to be higher than international estimates [6]. Based on the calculations and considering sub-groups of Iran population, the estimated number of patients with asthma symptoms is close to 49,50,000, which is much higher than expected.

The National Heart, Lung, and Blood Institute of the National Institutes of Health that initiated a formal data repository in 2000 to facilitate the sharing of data from clinical trials and observational studies with the general scientific community has summarized asthma in this way: chronic inflammatory disease of the airways in which cells or cellular elements play a role. This inflammation causes recurrent episodes of wheezing, shortness of breath, and coughing [14]. Asthma is more common in children than adults and in blacks than whites and Hispanics [46]. The primary cause of asthma is airway inflammation.

The high incidence of asthma in the young population and the prolonged treatment with anti-inflammatory drugs to contain the symptoms and avoid deadly apnea episodes make this disease a serious clinical condition for the patients and a significant economic burden for the health care providers. Furthermore, secondary effects of breathlessness on blood oxygenation can have

long-term consequences on brain function. Indeed, asthmatic children are at risk of developing intermittent hypoxia and sleep apnea, which have been seen to correlate with lower IQ scores and are at risk of developing attention deficit disorder [8]. Interestingly, Guo and colleagues in this issue of *Experimental Neurology* have shown that ovalbumin-induced bronchial asthma has a direct effect on synaptic plasticity, neurogenesis, memory, and brain inflammation [29]. It is established that blood oxygenation is critical for brain function. Hypoxia is considered one of the main causes of brain damage and cognitive impairment. In addition, dyspnea episodes during life are considered a major risk factor for developing neurodegenerative disease [15]. Early studies from the group of Gozal have shown that obstructive sleep apnea, without interfering with the sleep pattern, leads to spatial memory impairment, neuronal cell death, and gliosis in adult [28] and immature rats [50].

Chronic asthma often leads to serious problems in patients and affects all aspects of their life. Patients may be depressed, not enjoy their daily tasks, and even feel helpless about their illness. In these patients, it is possible that attention, concentration, abstract reasoning, the ability to change and inhibit impulsive responses, and cognitive flexibility may be impaired, their response to environmental stimuli diminished, their resistance to intervening external stimuli reduced, and their memory function impaired. In such cases, these problems, in turn, can lead to issues related to quality of life, such as cognitive problems and reduction of social interactions. Patients with chronic asthma show varying degrees of cognitive impairment. In research studies that have been conducted over the years, it has been shown that these patients have depression, anxiety, impaired cognitive processing and, in general, more cognitive disorders than non-asthmatic people [3,11]. Given the long-term evolution of asthma and also due to the fact that the onset of this disease is often from childhood, it is expected that various aspects of cognitive performance would be affected [5].

The human understanding about the relationship between the brain and mind can have a significant impact on an individual's life, because, undoubtedly, human and social life is dependent on brain functions. It is through the use of cognitive skills that each person is able to establish meaningful relationships, self-care, solves everyday problems, and enjoys a useful life. In contrast, cognitive deficits reduce a person's independence and sense of security and performance efficiency by affecting his/her personal, social, and professional functions; therefore, improving these functions increases a person's independence [12].

Executive functions are a set of distinct cognitive processes, which is responsible for controlling cognition and behavior and reside in the parietal and prefrontal

cortex. When problems occur in cognitive functions, behavior control is decreased and individual performance is affected [12]. In categories offered by Miyake and Friedman [43] and Miyake et al. [42], there are three executive functions: inhibition, switching between tasks, and updating working memory; response inhibition and interference control are considered as two types of inhibition.

Many findings have confirmed that chronic diseases over time affect cognitive functions. For example, in conducted research studies, it has been confirmed that cognitive disorders can be followed by cerebrovascular diseases [58,38,1], chronic kidney disease [34,20,52], multiple sclerosis [31,41,32], and chronic obstructive pulmonary disease [18,33,27].

Executive functions are a set of functions that people use in situations that require cognitive processes to reach optimal performance. This term applies to a set of cognitive processes that people use to succeed in a purposeful, adaptive, new behavior. Elements such as goal setting, planning, organizing behavior, flexibility, memory and attention systems; problem solving; and scanning are necessary during an assignment [21].

Conventionally, executive functions are considered equivalent to frontal lobe (forehead). In some research studies, "frontal functions" are used as a synonymous of "executive functions" and problems with executive functions are discussed in the name "frontal lobe syndrome" (Stuss & Alexander, 2000). It can be said that executive functions are a set of processes related to distinct areas of frontal lobes, especially prefrontal cortex.

Impairment in executive functions of the brain makes many problems, such as difficulties in organizing, remembering assignments, starting an activity and completing it, recalling the rules, performing complex mathematical tasks, completing time-consuming activities, being punctual, controlling emotions, and planning for future. Due to the fact that brain continues to develop until adulthood, executive functions are formed by physical changes, as well as on-going experiences. Prompt attention to problems with executive functions may help the individual in offsetting weaknesses [4]. Patients with chronic asthma show varying degrees of cognitive impairments [3,11].

In 2005, Moss et al. conducted studies about cognitive disorders in patients with chronic obstructive pulmonary disease and asthma; they concluded that these patients have lower oxygen saturation levels and significantly poorer cognitive functions than healthy people [44].

Creer [13], by studying six processes of goal setting, data collection, data interpretation, decision-making, performance, and self-efficacy, found that these functions are impaired in patients with asthma, and this in turn

causes mismanagement and lack of improvement in these patients [13].

Using the Montreal Cognitive Assessment, Caldera-Alvarado et al. (2013) studied 1380 patients over 55 years old through to investigate the relationship between asthma and cognitive impairment. They concluded that there is a strong relationship between asthma and cognitive disorders [5].

Alan Frol et al. [26], by studying patients with asthma, pointed out that although chronic asthma causes cognitive impairments, the effect of corticosteroids prescribed for treatment of this disease should not be ignored in the development of these disorders. They found that in this disease, subjective cognitive assessment is impaired more than goal recognition [26].

Albéri [3], during his studies about asthma, found that this disease, in addition to creating inflammatory symptoms, has a significant impact on cognitive processing through disrupting synaptic flexibility, and asthma should be considered as a secondary neurological disease [3].

Considering the importance of cognitive functions in patients with chronic asthma, and because few studies have been conducted in this regard, the aim of this study was to investigate whether cognitive functions are impaired in patients with chronic asthma.

Methodology

This research method is a causal-comparative, case-control type. The sample consisted of 30 patients with chronic asthma, with an average age of 34 and standard deviation of 9.23. Eighty percent of these patients had the history of corticosteroid usage. Inclusion criteria consisted of patients with at least 5-year history of asthma, and without any other chronic disease (chronic obstructive pulmonary disease, cardiovascular and cerebrovascular disease, and chronic kidney disease). Also, 30 patient visitors, with an average age of 26 and standard deviation of 4, were selected as the comparison group. In order to gather information, three software programs [Wisconsin, Stroop, and Continuous Performance Tests (CPTs)], all designed by Sina Cognitive Sciences Institute, were used to measure cognitive functions, and their validity and reliability have been confirmed.

Wisconsin Card Sorting Test

The initial version of the Wisconsin Card Sorting Test (WCST) was designed by Berg et al. [10] ([19]). This test was designed for measuring abstract reasoning and the ability to adapt cognitive strategies to environmental challenges. For this reason, it is believed that the WCST

measures a complex range of executive functions including planning, organizing, abstract reasoning, concept formation, maintaining cognitive rules, and the ability to change and inhibit impulsive responses [37].

This test was designed for measuring cognitive flexibility and the ability to change the set based on abstract thinking. In terms of reliability, Ekssler and colleagues reported the reliability between scores, and the internal validity scores were found to be 0.92 and 0.94, respectively. Lezak et al. (1995) has reported the validity of this test for measuring cognitive deficits after brain injury to be 0.86. The validity of this test based on agreement coefficient of evaluators in the study of Spearman and Strauss has been reported as 0.83 (Abidizadegan et al., 2008).

Stroop Test

The Stroop Test was designed in 1935 by Ridley Stroop in order to measure and evaluate selective attention, cognitive flexibility, resistance to external intervening stimuli, and creativity. This test is comparatively efficient in measuring the severity and type of mental reaction toward environmental stressors, neurological disorders, and inhibition control. This test is applied for the diagnosis of a number of disorders, including Attention deficit hyperactivity disorder/Attention deficit disorder (ADHD/ADD), Oppositional defiant disorder (ODD), frontal lobe disorders, brain dysfunction, and psychiatric applications.

Today, this test can be used for children up to 6 years and for adults up to 80 years. Performing this test requires little space, a quiet environment, and sufficient explanation for the subjects. MacLeod (1991), in an article about the Stroop test, states that this test has offered interesting points about various aspects of “attention” and “cognitive processes” in the field of psychology.

The reliability of the Stroop test is reported to be 0.88 for the first and second cards, and 0.80 for the third and fourth cards [17]. In general, its reliability by the test-retest method has been reported to be from 80 to 91% [7,39,40,37]. The Stroop test is not a unit test, and its different forms have been prepared for educational purposes.

Continuous Performance Test

The CPT was developed by Rosvold et al. [49] in 1956. This is a visual-motor test and measures sustained attention, care, alertness, and focused attention. To the present, various forms of CPT have been developed for research and therapeutic purposes, and in all these forms, subjects have to apply their attention to a relatively simple set of audio or visual stimuli for a time, and when the target stimulus is presented, they are required to push a key

for response. In terms of the reliability, HadianFard et al. [30] reported test–retest reliability in a range of 0.59–0.93. The test was validated by the criterion validity method by comparing a non-asthmatic group (30 schoolboys) and a group with attention deficit hyperactivity disorder (25 schoolboys).

Research procedure

After selecting the sample and test and explaining its goals for patients who were referred to the emergency department, they were told that this test is voluntary and for personal knowledge, and there is no obligation to participate. After obtaining the consent of participants, executive function tests, including the WCST, Stroop test, and CPT, were carried out. The mean time for collection of the data was 6 months.

Patients with at least 5-year history of asthma and without any other chronic disease (chronic obstructive pulmonary disease, cardiovascular and cerebrovascular disease, chronic kidney disease), with an age range of 1 to –60, from both genders were enrolled in this research.

Data analysis method

In this study, the frequency, percentage, mean, standard deviation, and multivariate analysis of variance (MANOVA) statistical test were used. Data were analyzed using SPSS version 24 software. Meanwhile, the level of significance for testing the hypothesis was considered to be 0.05.

Findings

The results in Table 1 indicate that of a total of 60 people that participated in this study, 30 were patients with asthma (50%), and 30 were healthy subjects (50%). Forty percent of patients were single and 60% were married. Among non-asthmatic participants, 76.6% were married and 23.3% were single. Of both asthmatics and non-asthmatic subjects, 3.3% had less than a high school diploma, 6.7% of asthmatics and 10% of non-asthmatic individuals had a high school diploma, 26.7% of asthmatics and 3.3% of non-asthmatic subjects had an associate degree, 36.7% of asthmatics and 60% of non-asthmatic subjects had a bachelor's degree, 23.3% of asthmatics, and 20% of non-asthmatic subjects had an MA degree, and 3.3% of subjects of both groups had a PhD. Of asthmatics, 10.0% were women, and 63.3% were men. Fifty percent of non-asthmatic subjects were women, and 50% were men. Non-asthmatic participants were more likely than those with asthma to report not having made any health care

Table 1. Frequency and percentage of demographic characteristics in each group (asthmatics and non-asthmatic subjects).

	Asthmatics	Non-asthmatic
Gender		
Male	19 (63.3%)	15 (50.0%)
Female	11 (36.7%)	15 (50.0%)
Total	30 (50.0%)	30 (50.0%)
Marriage		
Single	12 (40%)	7 (23.3%)
Married	18 (60%)	23 (76.6%)
Education		
Under diploma	1 (3.3%)	1 (3.3%)
Diploma	2 (6.7%)	3 (10.0%)
Associate degree	8 (26.7%)	1 (3.3%)
Bachelor	11 (36.7%)	18 (60.0%)
MA	7 (23.3%)	6 (20.0%)
PHD	1 (3.3%)	1 (3.3%)
Health care access		
Number of health care in past year		
None	3 (10.0%)	23 (76.6%)
1–3	21 (70%)	6 (20.0%)
≥4	6 (20.0%)	1 (3.3%)
Routine pattern of health care utilization		
No place	2 (6.67%)	15 (50.0%)
Emergency room	10 (33.3%)	3 (10.07%)
Publicly funded care	5 (16.67%)	8 (26.7%)
Private care	13 (43.3%)	4 (13.3%)

visits in the past year (76.6% versus 10.0%) and not having a place to visit for routine health care (50.0% versus 6.67%).

The results in Table 2 indicate that there is a significant difference between the two groups in terms of the component number of categories of the Wisconsin test “as a definitive of set shifting” ($F_{(8,51)} = 4.96$, *Wilks' Lambda* = 0.64; *partial eta squared* = 0.079, $p = 0.05$). This means that asthmatics have a lower average in terms of the number of classes compared with non-asthmatic subjects. Also, there is a significant difference between the two groups in terms of preservation error, total number of errors, total number of tries, and other errors. Therefore, there is a significant difference between asthmatics and non-asthmatics in terms of set shifting.

However, there is no significant difference between the two groups in terms of the correct number, duration, conceptual level, failure, the percentage of conceptual level responses, and the total number of trials and errors.

The results of Table 3 indicate that there is a significant difference between the two groups in terms of the number of correct responses of the Stroop test in the second stage “as an indicator of inhibition” ($F_{(8,51)} = 9.67$, *Wilks' Lambda* = 0.65; *partial eta squared* = 0.14, $p = 0.03$). This means that asthmatics have a lower average in terms of the number of correct answers or, to be more precise, have less inhibition compared with non-asthmatic subjects. Therefore, there is a significant difference between asthmatics and non-asthmatics in terms of response inhibition. Also, there is a significant difference between asthmatics and

Table 2. Using multivariate variance analysis (MANOVA) to compare the results of the Wisconsin test between two groups of patients with asthma and healthy subjects.

Source	Dependent variable	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared
Group	Number of categories	6.667	1	6.667	4.962	.030	.079
	Preservation error	60.000	1	60.000	11.500	.001	.165
	Total number of corrects	.417	1	.417	.037	.848	.001
	Total number of errors	442.817	1	442.817	12.888	.001	.182
	Total number of tries	470.400	1	470.400	13.662	.000	.191
	Other errors	176.817	1	176.817	10.007	.002	.147
	Time test	897.067	1	897.067	.237	.629	.004
	Conceptual level	.150	1	.150	.200	.656	.003
	Fail main	.067	1	.067	.406	.527	.007
	Percent of conceptual level	43.350	1	43.350	.210	.649	.004

Table 3. Use of multivariate variance analysis (MANOVA) to compare the results of the Stroop test between two groups of patients with asthma and healthy subjects.

Source	Dependent variable	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared
Group	Reaction time01	481.667	1	481.667	5.508	.022	.087
	Number of errors01	1.067	1	1.067	1.954	.168	.033
	No reply01	20.417	1	20.417	7.748	.007	.118
	Number of corrects01	.150	1	.150	.004	.952	.000
	Time record01	150100.017	1	150100.017	4.211	.045	.068
	Reaction time02	564.267	1	564.267	4.300	.043	.069
	Number of errors02	256.267	1	256.267	12.625	.001	.179
	No reply02	50.417	1	50.417	3.558	.064	.058
	Number of corrects02	286.017	1	286.017	3.659	.061	.059
	Time record02	145533.750	1	145533.750	3.234	.077	.053
	Result test	299.267	1	299.267	9.673	.003	.143

non-asthmatics in terms of number of errors and reaction time in the second stage.

The results of Table 4 indicate that with respect to *F*, there is a significant difference in terms of attention between the two groups ($F_{(8,51)} = 9.35$, *Wilks' Lambda* = 0.75; *partial eta squared* = 0.14, $p = 0.003$). This means that asthmatics have a considerably lower average in terms of attention compared with non-asthmatic subjects. Therefore, there is a significant difference between asthmatics and non-asthmatics in terms of attention. There is no significant difference between the two groups in terms of omission error.

Discussion and conclusion

This study aimed at evaluating and comparing executive functions in patients with chronic asthma and a non-asthmatic group. The results of multivariate analysis showed that asthmatics differed significantly compared

with non-asthmatic subjects in terms of executive functions (set shifting, inhibition, and attention). These findings are consistent with the research results of Moss and colleagues in 2005 that showed that executive functions in patients with asthma are much worse than those of non-asthmatic people.

During an asthma attack, the small airways are inflamed and swollen, and muscles around the airways are constricted and respiratory secretions are increased. This process greatly restricts the airways, and oxygen entry and exit and carbon dioxide excretion are disrupted. On the other hand, exchange surfaces of the airways (alveoli) are also filled with secretion, and pulmonary capillary blood circulation disorder occurs. This process plays a major role in the exchange of oxygen and carbon dioxide. In total, less oxygen is exchanged and enters the bloodstream through the alveoli, and elimination of carbon dioxide is disrupted. When the severity of asthma is great, the deterioration of these problems is also higher.

Table 4. Use of multivariate variance analysis (MANOVA) to compare the results of the continuous performance test between two groups of patients with asthma and healthy subjects.

Source	Dependent variable	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared
Group	Commission error	20.417	1	20.417	9.356	.003	.139
	Omission error	33.750	1	33.750	1.125	.293	.019
	Correct	81.667	1	81.667	.207	.651	.004
	Reaction time	1255128.067	1	1255128.067	7.889	.007	.120

When insufficient oxygen enters into the blood, the individual suffers from lack of oxygen in the brain, which is the most sensitive organ to hypoxia. As a result, in the early stages of disease, the patient's consciousness and cognitive functions are disrupted, which presents itself as restlessness, memory impairment, anxiety, aggression, and lack of awareness of time, place, and person, and in the final stages causes loss of consciousness. High levels of carbon dioxide (hypercapnia) also directly affect brain function, which causes loss of consciousness in the form of carbon dioxide narcosis.

Another point is that allergic diseases result in sleep apnea and disturb person's nocturnal sleep. Man approximately needs 8 hours of sleep to have efficient function. Even short-term sleep deprivation may result in impaired daytime cognitive performance [56,24]. These patients have problems in attention and concentration tests, visual scanning, hand-eye coordination, and mental set flexibility. These tests require information to be stored in working memory, while new information is assimilated and responses are made.

Cognitive and behavioral problems in patients with asthma are due partly to the adverse effects of therapeutic interventions. Many therapeutic interventions used for asthma cause side effects, such as restlessness, sleep disorders (prolongation of going to sleep), headaches, and mood disorders, and undermine self-management (White & Sander, 1999; Rachelefsky, Wo, & Adelson et al., 1986, cited by Saricoban et al. [51]). For example, the use of corticosteroids in children impairs their school performance and learning capacity (Stein & Lerner, 1993; cited by Lavoie et al. [35]). The reason for this process is not entirely clear, but it seems that the use of these drugs shrinks the hippocampus volume [26].

When the brain chronically is exposed to glucocorticoids, neuro-psychotic, neuro-physiological, and structural changes occur (Sapolsky et al., 1985, 1986; cited by Frol et al. [26]). Many of these changes, especially ventricular enlargement and atrophy of the brain, are associated with cognitive impairment (McEwen, 1988; cited by Belanoff et al. [9]).

Patients who received regular corticosteroid therapy had relatively better performance compared with patients who did not receive this treatment. A possible explanation is that regular and simultaneous treatment with corticosteroids and long-acting bronchodilators (drugs that widen the airways) gradually reduce the inflammation of small airways and improve alveolar gas exchange and generally reduce the frequency of asthma attacks. To explain these findings, it can be said that oxygen is a key ingredient in the metabolism of nerve cells in the brain and other parts, and these cells need oxygen and glucose for their performance. Whenever one of these two

materials is not available for cells, their function is disrupted. Researchers have found that physical activity and diet or a combination of these two can greatly improve reactivity of the airways and memory function. These cognitive effects alter learning capacity and weaken academic performance (Stein, Lerner; cited by Lavoie et al. [35]).

Also, several studies demonstrated that negative emotions are associated with decreased lung function in asthma patients [47,48, 54, 55]. People with asthma and comorbid psychiatric disorders have more impaired functioning in both emotional and physical arenas than persons with disease alone with poorer control of asthma [2, Siddique et al., 2000]. This association could occur through disorganization of self-care behavior or by direct psychological effect of anxiety on autonomic and immune system. Elevated anxiety and depression have been found to be positively related to asthma severity in children [45] but not in adults [2]. However, empirical data to whether and how negative emotions precipitate or exacerbate asthma attacks are inconsistent [36].

Limitations

Medical condition of patients and complexity of tests prevented proper performance of participants.

Confounding factors such as fatigue, treatment stress, and hospital conditions interfered in performance of participants.

Recommendations for future studies

In this research, the role of sleep problems, corticosteroid drugs, and hypoxia disorder in executive functions of patients with asthma have not been investigated separately; these items can be considered in future studies.

Also, we studied executive problems in adult patients. It is recommended that further research works be conducted on pediatric patients.

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