MIDDLE EAST CURRENT PSYCHIATRY

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Gods never fall sick or die: dictatorship and mental health in Egypt
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Introduction
The World Health Organization defines mental health as 'a state of well being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community.'
Aim
This study reviews the impact of dictatorship on mental health of people as well as the psychology and psychopathology of dictators.
Method
Internet and PubMed searches were conducted on dictatorship with respect to the relevance of the studies selected for mental health and dictatorship.
Results
A psychiatrist is not a politician; however, he/she should be aware of the political system of the country. This political system can change many issues in the norms of the people and in the healthcare system used by them. An environment that protects and respects basic human, political, socioeconomic, and cultural rights is also fundamental to mental health promotion. It is usually easier to say that dictators are crazy but it is more difficult to know the truth about their health. Dictators are usually sane enough to rally thousands and may be millions of people behind them.
Conclusion
Countries torn by dictatorship face higher levels of distress, and yet they are most in need of productive, healthy citizens. Treating or reducing the psychological impacts of dictatorship and promoting resilience in otherwise physically healthy individuals are critical to help to rebuild thoee countries.

Keywords:
dictatorship, health, mental health, psychopathology

Introduction
At the time of the creation of the World Health Organization, in 1948, health was defined as 'a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity [1]'. Moreover, mental health is also more than the absence of mental disorders. The World Health Organization defines mental health as 'a state of well being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community [2].'
Is there a relationship between mental health and the political system that governs the country? To what extent is this relationship a strong one? Is it important for a psychiatrist to be aware by the political system of the country? These questions are difficult and studies discussing these issues are scarce.

Mental health is determined by multiple and overlapping cultural, social, psychological, and biological factors. Definitely, the political system of the country is one of these multiple factors [3]. A psychiatrist is not a politician;

however, he/she should be aware by the political system of the country. This political system can change many issues in the norms of the people and in the healthcare system used by them [4].

The aim of this review was to highlight these issues, mainly in Egypt. The review is a trial to discuss the different psychological and psychopathological aspects of dictatorship and their impact on mental health of people and on mental health services.

Methods
The investigator sought the Internet to review the literature discussing the issue of dictatorship and its relation to mental health and tried to sum up and conclude under the following headings: (i) introduction about Egypt; (ii) definition of dictatorship; (iii) impact of dictatorship on mental health of people; (iv) psychology and psychopathology of dictators; (v) impact of dictators on healthcare system; and lastly (vi) prepresidency psychological assessment.

Egypt

Egypt, officially known as the Arab Republic of Egypt, is a country situated mainly in North Africa. Egypt is a major power in the Middle East and in the Muslim world. Covering an area of approximately 1 million square kilometers, Egypt is bordered by the Mediterranean Sea to the north, by Palestine to the northeast, by the Red Sea to the east, by Sudan to the south, and by Libya to the west. Egypt is one of the most populous countries in Africa and the Middle East. The great majority of its estimated 85 million people live near the banks of the Nile River, in an area of approximately 40 000 square kilometer [5].

The economy of Egypt is one of the most developed and diversified in the Middle East, with sectors such as tourism, agriculture, industry, and service at almost equal production levels [6]. In early 2011, Egypt underwent a revolution, which resulted in the removal of the dictator of 30 years, Mohamed Hosni Mubarak. The revolution of Egypt was a peaceful clean and white one. It was a novel revolution in which the youth used Facebook and other international websites to gather each other and to unify their goals and requests. Millions of people stayed in major squares in many large cities of Egypt for 18 days until victory was achieved and Mubarak was dislodged. The revolution was described positively by many leaders from all over the world [7–9].

Dictatorship

Dictatorship is considered a description of certain types of governments or leaders who are characterized by having absolute sole power over their people, and usually this power is used in a cruel way [10]. Dictatorships may consist of a single individual, a royal family, an army, a political party, or a religious organization [11]. Moreover, the will of any dictatorship is regarded as above the will of the individuals it governs [12]. The relationship of the dictatorial state to its citizens and to other states is one of force.

Impact of dictatorship on people's mental health

To what extent people under dictatorship governments can achieve the different domains of the concept of mental health. Usually these people fail to achieve the concept and loss all domains. An environment that protects and respects basic human, political, socioeconomic, and cultural rights is also fundamental to mental health promotion. Without the security and freedom provided by these rights, it is very difficult to maintain a high level of mental health [13].

Increasing and persisting socioeconomic problems that are usually associated with dictatorship are recognized risks to mental health. In addition, the greater vulnerability of disadvantaged people in a dictatorship community to mental health disorders may be explained by factors such as the experience of insecurity and hopelessness and the risks of torture and violence against them.

People under dictatorship control are frustrated to the degree that they believe that their leaders can do everything, everywhere, and at anytime the same as Gods. People usually hope to get rid of their dictator leaders but these dictators remain for many years and people lose their hope even for natural death of these dictators as Gods never fall sick or die.

Just two or three decades ago, the personality of most of Egyptians was unique and well known all over the world. Anyone who visited Egypt observed this. Their simplicity, warm heartedness, honesty, desire to help, and bravery were characteristic features [14].

Dictators usually give priority to their safety and security and allot a great budget for this issue. President Mubarak retained his power by suppressing freedom of opposition. He created his own guards. Thousands of people worked to protect him. His secret police inspired fear and silence in those who might protest. In Egypt, these issues were a leading cause to deteriorated safety and security services for people. Police was not concerned with crime rates, traffic control, corruption, and other important issues. As a result of corruption all over the country, a gradual decline in standards of all professional ethics has occurred. There has been an increased rate of unemployment, delayed age of marriage, and increased poverty. Many Egyptians deteriorated below the poverty line and the Middle social class dissolved and was abolished. Many people tried legal and illegal immigration to other countries for work and many of them died by drowning in the Red sea and in the Mediterranean Sea. People became frustrated due to lack of any achievement in their life. This is why Egyptians started to bypass the red sign in streets, tried to get their rights by physical fights, and through hiring thugs. Moreover, thugs were hired by the police and government to control students in universities, to attack protesters, and to prevent people from going to vote in the election of parliament. Military courts replaced regular courts in any opposition. Regular courts were not supported, which is why in many cases the court took many years to reach a final decision in different crimes. The rate of achieving final court decisions had been reduced to frightening rates. Corruption became widely prevalent as many people said 'why me? Why not use some of my rights?' Many of the Egyptians became irresponsible, aggressive, manipulative, and opportunistic. Bribery and embezzlement became widely spread in Egyptian governmental companies. Moreover, Egyptians were scared to talk, hesitant to speak up, and to stand up for themselves, were desperate and exhibited traits such as pessimism and lack of initiation, of self-confidence, and of self-management. President Mubarak's dictatorial system made Egyptians always busy and dizzy, wandering for their basic physiological needs and preoccupied by subsidiary conflicts. Simply, during the dictatorship of President Mubarak, many Egyptians forgot how good a people they were.

President Mubarak as a dictator succeeded through a lot of opportunistic helpers in different associations to change the attitudes of Egyptians. They played with the Egyptian's emotions, thoughts, and behaviors in different issues during the 30 years under his dictatorship control. At many times,

Egyptians were forcibly convinced that Islamic groups are more dangerous than outside enemies. They tried to change the attitude of people toward Palestinian's crisis, Iran, and corruptors from ministers and business owners. Thieves were considered as national heroes, failed people were considered achievers, production rates and growth of economy were exaggerated and inflated. Basically, the minds of Egyptians were the ground of a big stadium for many virtual games.

Egyptians lost all dimensions of the definition of mental health as they were not in a state of well being, lost their abilities to cope with stresses of life, some of them were unproductive, and others were unemployed, unable to make any contribution to the community. Egyptians not only lost the definition of mental health but also their physical health, which deteriorated as the rate of cancers increased to a great extent due to environmental pollution. The rate of hepatitis C virus infection is higher than in other countries due to negligence and corruption, whereas the rate of anemia and malnutrition increased due to poverty and the rate of death and head injuries increased considerably due to road accidents [15].

It is also worthy to say that the dictatorship of Mubarak was not the only reason of deteriorated mental health in Egypt. There are many other reasons that played an important role in the same direction, for example globalization forces, world economic crisis, increasing world competition, international food crisis, etc.

After dislodgment of the dictator and destruction of the fear's borders, and due to many negative traits that had developed, objections and oppositions all over the country are expected to occur and this is happening in Egypt currently. These oppositions if continued will impair the production in Egypt and will endanger economic growth, which is why current oppositions should be considered a top priority for the new government.

Psychology and psychopathology of dictators
Egypt has known dictators since thousands of years. During the era of prophet Moses, Egypt had been governed by a king from Pharaohs, most commonly known as King Ramesses II [16]. King Ramesses II claimed that he was the God and was dealt with Egyptians as if this is the truth. He governed Egypt for 66 years [17]. He killed a lot of people and he took their money and lands; he wanted them to see through his vision and to obey his holy orders. His power and authority were created by his people and his helpers such as Haman and Magicians. In the end, he refused Prophet Moses's message from God and died by drowning in the sea behind Moses and his people [18]. In contrast, the last dictator of Egypt was President Mubarak. He did not claim that he was a god, but he dealt with people in the same way. Thousands of people were protecting his routes daily. Millions of people were delayed daily due to obstructed ways for his safety and security measures. He governed Egypt for 30 years. He killed thousands of people due to his negligence and lack of concern and due to corrupted people surrounding him and his family. The country lost billions of dollars and

resources under his presidency [19]. Again, he wanted people to see through his vision and to obey his holy orders. His power and authority were created by his people and his helpers mainly from security forces, tailors of law, corrupted business owners, and some corrupted media professionals [20].

President Mubarak refused to hear anything about his reduced general health due to aging, up to the extent that a new crime was invented in the Egyptian law for rumors about the president [21]. He refused to be a human being liable to sickness and death, again similar to King Ramesses II thousands of years ago.

Different dictators through the years have taken different routes to get to the top. Some were elected like President Mubarak. Some inherited the job like Kim Jong-un in North Korea. Some took over in military coups like Muammar Gaddafi. The reality is that the personality of a dictator is the same whether he or she is running a company or running a country. The dictator personality has three core priorities: 'me, me, and me'. Moreover, if he/she has added anyone else to these priorities, they usually added wife/husband, sons, and daughters. Egyptians have tried to deal with this situation as a joke, which said that 'can you imagine Egypt as a Limousine and the driver is 80 years old. He puts his son on his legs and allows him to play all the time with the driving wheel. Will you accept going anywhere with this limousine?' Not only the driver and his son as mentioned in the joke but also in most cases some of the surrounding people succeeded in attaining the chance and tried to obtain benefits from the situation. In case of King Ramsses II, Haman was the assistant of the King and succeeded in obtaining many benefits. However, in the case of President Mubarak, a lot of people played this role and corruption became increasingly prevalent. The world watched these scenarios many times.

This narcissistic personality shows itself with two abusive behaviors of every dictator. First, the dictator will do anything, anywhere, at anytime, and at any cost to retain power. Second, he /she will take advantage of people and his or her position to take whatever he/she can.

As a result of this focus on the 'me and my family' in the administration of a country, it has been observed that the outcomes of a dictator in politics are the same. For example as a result, the country's political system has descended to frightening levels of coercion, oppression, and cruelty, and eventually a revolt ensued.

Are people dictators because they are mad? Or does being a dictator make a person mad? Dictators are not born as dictators, but they are made by the surrounding persons and get powerful and stronger by the feared people. Most dictators are evils, but some are mentally ill. However, one like Muammar Gaddafi is both. It is very obvious that Gaddafi is in an unstable frame of mind and his perception of reality is distorted [22]. Having watched some of his speeches on television, his comments and speech seem very erratic. What he was saying did not make any sense and it was very incoherent. Muammar Gaddafi had lost

touch with reality. When we read or listen to what he has been saying, it is not really possible to follow his meaning, because none of it has any coherent message. From his speech and behavior, Gaddafi would be diagnosed as suffering from some kind of psychosis.

Dictators have antisocial personality traits as they lie, steal from their people, manipulate, use force against their people, and have callous emotions. Moreover, most of them have narcissistic personality traits as they believe that the world is revolving around their heads. They believe their orders are laws and their desires are orders. Some of them have borderline personality traits as they are impulsive in their decisions. Many of them have paranoid personality traits and so hire thousands of people to protect them. They give green light to security forces to arrest thousands of their imaginary enemies. Dictators usually use defensive mechanisms excessively, especially denial, rationalization, and projection.

It is usually easier to say that dictators are crazy but it is more difficult to obtain the truth about their mental health. Some dictators are abused during their childhood; for example, Hitler, who was basically living in streets after his mother died, was a loner and was subjected to abuse [23]. Saying that a dictator is mentally ill is not only insulting to people with legitimate mental illness but is an insult to every single person who was tortured or who died during the era of this dictator. The rule here is 'Dictators are usually sane enough to rally thousands and may be millions of people behind them'.

An important issue is that not all dictators are evil. Some of them try to do the right thing for the people they are making choices for and the famous example here is Francisco de Franco of Spain.

Dictatorship and healthcare system
Apart from torture, in Egypt, more sophisticated ways of abusing human rights was prevalent, especially in the way healthcare was delivered during the last three decades. The falsification of morbidity and mortality figures; not paying attention to diseases such as cancers; not talking about the hazards of environmental pollution; and the deteriorated quality of generic drugs are all products of the dictatorial system that governed the country.

As a result of corruption, a lot of business owners succeeded in registering generic antipsychotic and antidepressant drugs with limited quality of their products. These drugs replaced the original expensive drugs because of their cheaper price but at the cost of their efficacy and safety.

Under the dictatorship control and due to deteriorated professionalism of the police, policemen would abuse rights of mentally ill people as they used to arrest the mentally ill people and accused them of many crimes.

Under dictatorship in Egypt, due to the inflated budget of the safety and security of the president and due to corruption, the government had dedicated a small percentage of the budget to healthcare and a smaller percentage for mental health. This is why the Ministry of Health had failed to establish community mental health centers, was unable to secure essential pharmaceuticals, and did not develop a viable mental healthcare monitoring system [24]. Egypt serves as an example of how political culture shaped mental health programing.

Can a prejob psychiatric interview or psychological assessment predict a future dictator attaining the presidency seat?
A preemployment psychological evaluation is a specialized examination of an applicant's psychological suitability for a public position. Psychological suitability includes, at a minimum, the absence of relevant mental conditions that would reasonably be expected to interfere with safe and effective performance. A preemployment psychological evaluation should be a part of the medical examination before taking the presidency seat. Presence of physical or mental problems in the president may lead to disturbance for many others inside and outside the country. Reassuring people that their future president is physically and psychologically healthy is one of their rights. However, a simple prejob psychological interview conducted by one expert cannot exclude a future dictator to the presidency seat. Many dictators are charismatic and are geniuses and they may not be discovered through an ordinary interview. Hence, here we are talking about a complicated interview with an expert team and with objective measures. Preemployment psychological evaluation may include tests that are designed and used to measure personality traits, behaviors, or characteristics such as judgment, stress resilience, anger management, integrity, conscientiousness, teamwork, negotiation skills, and social competence. Surely if we look longitudinally to the attitudes of the presidents before the presidency job, we may find some roots for dictatorship or suspicious personality traits. To what extent can this occur in countries of the Middle East and who has the authority and the ability to tell the people that this person is suitable or not for presidency seat? Moreover, who will protect the team if the person who is not suitable takes the presidency seat? All are difficult questions and need further discussion and agreement, especially as decisions such as these are based on probability rather than on certainty.

Conclusion
Countries torn by dictatorship face higher levels of distress, and yet they are most in need of productive, healthy citizens. Treating or reducing the psychological impacts of dictatorship and promoting resilience in otherwise physically healthy individuals are critical to help to rebuild these countries. This is why new leaders and governments in Egypt should pay attention to this issue in the new era. A team of professionals should be sought to put together a plan to revert the effects of dictatorship. Negligence of this issue could repeat the same scenario observed in other countries such as Iraq.

Owing to the political changes currently occurring, we now have the means and the willingness to explore the extent of the abuse of human rights in our healthcare

system and to find those who assisted the dictatorship in the performance of its antihuman activities.

Lastly, I wish to thank all those who have helped to make our revolution a key contribution to the future of mental health in the region: the martyrdoms whose death has opened new important horizons; the military forces whose hard work and helpful insight have further sharpened and protected the message of the revolution; the media professionals who uncovered the last dictatorship of Egypt; and all professionals in Egypt whose effort will bring mental health back to Egypt.

The author has no conflict of interest to disclose.

References

1   World Health Organization (WHO). *Constitution of the World Health Organization-Basic Documents*. 45th Supplement ed. World Health Organization (WHO); 2006.
2   World Health Organization (WHO). *Promoting mental health: concepts, emerging evidence and practice. A report of the world health organization department of mental health and substance abuse in collaboration with the victorian health promotion foundation and the university of Melbourne*. Geneva: World Health Organization (WHO); 2006.
3   Chairman FR. Political systems and mental health programming. Am J Orthopsychiatry 1964; 34:201–203.
4   Nutbeam D. Health promotion glossary. Health Promotion 1986; 1:113–127.
5   Brewer D, Teeter E. *Egypt and Egyptians*. London: Cambridge University Press; 1999. pp 23
6   Mishrif A. *Investing in the Middle East: The political economy of European direct investment in Egypt*. London: Tauris Academic Studies; 2010. pp. 29–30.
7   Dreyfuss R. Obama and Egypt's revolution. 2011. Available at: *http:// www.thenation.com/blog/158533/obama-and-egypts-revolution*. Accessed on March 15th, 2011.
8   Kirkpatrick DD. Egypt Erupts in Jubilation as Mubarak Steps Down. 2011; Available: *http://www.nytimes.com/2011/02/12/world/middleeast/12egypt.html?_r=1*.
9   Buckle E. Merkel, Cameron, Sarkozy urge quick transition to broader Egypt government. 2011; Available at: *http://www.bloomberg.com/news/2011-02-03/european-leaders-demand-immediate-regime-change-amid-violence-in-egypt.html*.
10 Brooker P. *Non-democratic regimes: theory, government and politics*. New York: Palgrave Macmillan; 2000.
11 Kershaw I. *The nazi dictatorship: Problems and perspectives of interpretation*. 4th ed. London: Bloomsbury Academic; 2000.
12 Moore B. *Social origins of dictatorship and democracy: Lord and peasant in the making of the modern world*. Reprint edition ed. Boston: Beacon Press; 1993.
13 Hamid HI, Everett A. *Developing Iraq's mental health policy*. Psychiatr.Serv. 2007 Oct;58:1355-7.
14 Hemdan G. *Egyptian personality*. Egypt: Dar El Helal; 1991.
15 Khaled H. Smoking, pollution and foods behind cancers in Egypt. El Wafd 2005; 3:5.
16 Brier B. *Egyptian mummies: unravelling the secrets of an ancient art*. New York: William Morrow & Co. Inc.; 1994.
17 Brier B. *Encyclopedia of mummies*. 1st ed. New York: Facts on File; 1998.
18 Qur'an muslim's holly book. Surrah number 10: Jonah. Egypt: Dar El Salam Press; 2009.
19 Bradley JR. *Inside Egypt: The land of the pharaohs on the brink of a revolution*. Hampshire: Palgrave Macmillan Press; 2002.
20 Kim S. Egypt's Mubarak likely to retain vast wealth. 2011; Available at: *http:// abcnews.go.com/m/story?id=12821073*.
21 Eissa I. Gods never die. El Dostor 2007; 9:1.
22 Davidsson L. Gaddafi: 'He's psychotic, maybe bordering on paranoid schizophrenic'. 2011; *Available at: http://news.scotsman.com/libya/Gaddafi–39He39s-psychotic-maybe.6726935.jp*.
23 Parker L. *History's Villains - Adolf Hitler*. San Diego: Blackbirch Press; 2002.
24 Jenkins R, Heshmat A, Loza N, Siekkonen I, Sorour E. Mental health policy and development in Egypt-integrating mental health into health sector reforms 2001–9. Int J Mental Health Syst 2010; 4:17.

Psychiatric morbidity in patients with rheumatoid juvenile arthritis: a SPECT study
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Introduction
Children with chronic illness have increased rates of mental health problems and psychological difficulties. Juvenile rheumatoid arthritis (JRA) is one of the most common rheumatic diseases of children and is considered a major cause of chronic disability in children. Thirty-eight percent of patients with JRA showed some difficulties in mental flexibility.

Aim of this study
To detect psychiatric morbidity and cognitive deficit in a sample of children and adolescents with JRA, and to attempt to correlate the psychiatric and cognitive findings with concurrent cerebral perfusion abnormalities using the cerebral single photon emission computed tomography neuroimaging technique.

Method
Thirty children and adolescents with JRA included in this study were recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. These patients were subjected to full physical and psychiatric clinical interview, along with thirty healthy children and adolescents as the control group with matched age and sex. Patients and control groups were assessed using General Health Questionnaire, Wechsler Intelligence Scale, Revised Behavioral Problem Checklist, Mini kid test, Benton Visual Retention Test, and single photon emission computed tomographic imaging.

Results
Significant difference in cerebral perfusion was observed in patients compared with the control group. Behavioral and cognitive function showed significant difference in patients compared with the control group. Patients with depression showed significant perfusion differences compared with the control group, as well as the anxiety group. Therapy duration and dose showed significant difference in different brain areas.

Conclusion
Patients with JRA experience psychiatric morbidity as well as behavioral and cognitive dysfunction. The patterns of cerebral perfusion deficit are similar to those seen in depression, anxiety, and cognitive disabilities of patients.

Keywords:
juvenile arthritis, psychiatric morbidity, single photon emission computed tomography

Introduction
Juvenile rheumatoid arthritis (JRA) is one of the most common rheumatic diseases of children and is considered a major cause of chronic disability in children; it is characterized by an idiopathic synovitis of the joints associated with soft-tissue swelling and effusion [1]. Early epidemiologic studies showed that the prevalence of JRA ranges from 0.16 to 1.10/1000 and the incidence ranges from 0 to 9.2 /100 1000 in the USA [2]. In Egypt, incidence of JRA is 9.3 cases per 100 1000 per year [3].

Oligoarthritis represents the most common onset type of juvenile idiopathic arthritis in both Europe and North America, accounting for 50–75% of all cases with a meta-analysis producing an overall 58% estimate within population-based studies [4].

Although systemic onset JRA accounts for only approximately 20% of most reported series, children with systemic onset JRA are often the most difficult to treat. Many children have marked physical and emotional disability as a result of both disease and treatment-related morbidities [5].

Children with chronic illness have increased rates of mental health problems and psychological difficulties [6]. There is a decline in social and physical activities. Psychological factors may play a more active role in debilitating pediatric patients with JRA [7]. The long duration of illness is often associated with higher proportion of cases with psychiatric disorders. The diagnoses in decreasing order are depressive disorder 15%, somatoform disorder 12.5%, adjustment disorder 5%,

DOI: 10.1097/01.XME.0000398422.59986.78

and mixed anxiety and depression disorder 2.5% [8]. The strongest predictors of depression were high tension and low self-esteem, fatigue, passive coping, pain, and physical disability [9].

Previous research [10] detected some difficulties in mental flexibility in 38% of patients with JRA. These poor performances are related to hypoperfusion of the frontal and parietal lobes as detected by brain single photon emission computed tomography.

The aim of this study was to detect psychiatric morbidity and cognitive deficit in a sample of children and adolescents with JRA recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. The study also aimed to attempt to correlate the psychiatric and cognitive findings with concurrent cerebral perfusion abnormalities using the cerebral single photon emission computed tomography neuroimaging technique.

Method
Patient enrollment
Thirty children and adolescents with JRA were included in the study. These patients were recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. The diagnosis of JRA was based on clinical, laboratory, and radiological findings. These patients were subjected to full physical and psychiatric clinical interview with documentation of type of arthritis, duration, and severity of the disease. Patients of both sexes enrolled in the study were aged between 8 and 16 years, and all cases had disease duration of more than 6 months to ensure chronic disease. In addition, 30 healthy children and adolescents with matched age and sex to patients with JRA were included in the study to serve as a control group. Written informed consent was obtained from parents or care givers of both groups before enrollment in the study.

Patients and control groups were assessed using the following tests:

(1) General Health Questionnaire: this was developed as a first screening instrument for psychiatric illness to identify potential cases [11]. The version used in this study was the Arabic version of the short 28-item scale [12].
(2) Whechsler Intelligence Scale: this is the most commonly used test for children to assess intelligence quotient [13].
(3) Revised Behavioral Problem Checklist: this is a family self-rated instrument that surveys a broad range of difficulties encountered in children from preschool age through adolescence [14].
(4) Mini kid Test: this is a clinical psychiatric interview for children to detect any type of psychiatric morbidity, developed jointly for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and *International Statistical Classification of Diseases and*

Related Health Problems, 10th revision psychiatric disorders [15].
(5) Benton Visual Retention Test: this is used for assessing visual perception, visual memory, and visuo-constructive abilities [16].
(6) Single photon emission computed tomographic imaging: a dose of technetium-99m-labeled-hexamethyl propylene amine oxime is calculated according to body weight by the equation body weight × adult dose (20 mCi) and injected intravenously. A gamma camera single head was used to evaluate perfusion pattern of the brain [17].

Data obtained were tabulated and processed in a personal computer. All statistical analyses were carried out using Statistical Package of Social Science version 10 (Chicago, Illinois, USA). Independent student's *t*-test was used to evaluate the statistical differences in regional cerebral blood flow between patients and controls. We used Pearson's correlation coefficient for the bivariate correlation procedure.

Results
Demographic date
In this study, the patients' age ranged from 8 to 16 years, whereas that of the control group was from 8 to 15.8 years, thereby showing no significant difference between both groups. Of patients with JRA, 14 were boys (46.67%) and 16 were girls (53.33%), whereas eight were boys (26.67%) and 22 were girls (73.33%) in the control group. Duration of illness was 6 months–12 years (mean ± standard deviation, 3.997 ± 3.039 in years).

Family history of juvenile rheumatoid arthritis
The family history was positive in 13 patients (43.33%) and negative in 17 patients (56.67%).

Rheumatoid factor of patients with juvenile rheumatoid arthritis
Seven patients (23.33) were positive for rheumatoid factor and 23 patients were negative (76.67%) during the study.

Disease status
Twenty-two patients were in remission (73%), whereas the remaining eight patients (27%) were in relapse.

Type of arthritis
Two patients (7%) were pauciarticular rheumatoid arthritis (RA), five (17%) were systemic RA, whereas the remaining 23 patients (76%) were polyarticular RA.

Behavioral and cognitive difference in patients and control groups
Comparing behavior of patients with the control showed a significant increase in attention problem ($P = 0.000^*$), anxiety withdrawal ($P = 0.000^*$), and conduct behavior ($P = 0.000^*$), whereas cognitive functions showed a significant decrease in visual memory ($P = 0.003^*$ and $P = 0.002$) as well as total intelligence quotient ($P = 0.001^*$).

Table 1 shows a majority of patients (93%) with depressive symptoms, whereas specific phobia was 20%, social phobia and oppositional defiant disorder were 16% each, major depression, obsessive–compulsive disorder (OCD), and conduct disorder were 3% each. As a result of sample size, in further analysis, dysthymic and depression patients were included as the depression group, and specific phobia, social phobia, and OCD were included in the anxiety group.

Patient's characteristics in relation to brain perfusion
Cerebral perfusion findings in relation to juvenile rheumatoid arthritis status
Unlike the disease activity, which showed a significant decrease in left frontal lobe perfusion in patient's group ($P = 0.024^*$), the type of JRA did not have any significant correlation with brain perfusion findings.

Brain perfusion study
Perfusion studies showed a decrease with statistical difference between patients and control in right frontal ($P = < 0.001^*$) and right parietal lobes ($P = < 0.001^*$) and a statistically significant increase in left parietal ($P = < 0.001^*$) and left occipital lobes ($P = 0.003^*$).

Behavioral and cognitive function in relation to brain perfusion study
Correlating behavioral checklist items with cerebral perfusion indicated statistical differences between patients and controls in term of psychotic behavior, which showed significant difference with direct relation to left parietal perfusion ($P = 0.023$) and right occipital lobe ($P = 0.04$) brain perfusion. Although motor excess was significantly related with inverse relation to left frontal brain perfusion ($P = 0.041$), visual memory, and visual perception were significantly correlated with inverse relation to right frontal lobe brain perfusion ($P = 0.007$, $P = 0.04$, respectively).

Brain perfusion study in relation to disorder
Patients in the depressed group showed a significant decrease in right frontal ($P = 0.000^*$) and left parietal brain perfusion ($P = 0.000^*$), and a significant increase in right parietal ($P = 0.000^*$) and left occipital lobe ($P = 0.079^*$), compared with the control group. Meanwhile, the anxiety group showed a significant increase in right frontal lobe ($P = 0.000^*$) and a significant decrease

Table 1 Psychiatric morbidity in patients group

Psychiatric morbidity	Patients group N (%)
Dysthymic disorder	28 (93.33)
Specific phobia	6 (20)
Social phobia	5 (16.67)
ODD	5 (16.67)
Major depression	1 (3.33)
OCD	1 (3.33)
Conduct disorder	1 (3.33)

N, number; OCD, obsessive–compulsive disorder; ODD, oppositional defiant disorder.

in both parietal lobe ($P = 0.000^*$) cerebral perfusion compared with the control group.

Brain perfusion study in relation to therapy
Duration of therapy showed a significant difference with inverse relation to brain perfusion between corticosteroid and right parietal lobe ($P = 0.02$), and methotrexate and left parietal lobe ($P = 0.01$). Meanwhile, dose of therapy showed a significant difference with inverse relation between methotrexate and both right temporal ($P = 0.02$) and left temporal ($P = 0.04$) lobes. In addition, NSAID dose of therapy showed a significant difference with inverse relation in right temporal brain perfusion ($P = 0.04$).

Discussion
Several studies have found a direct relationship between stress (negative life events, daily hassles, and interpersonal stressors) and adjustment problems (depressed mood and behavior problems) [18]. A variety of internalizing problems and deficiencies in the social activities [7], social isolation, and sexual anxieties [19,20] have also been reported among youth with arthritis. These manifestations were evident in our patients who showed anxiety withdrawal, conduct behavior, and attention problem compared with the control group, indicating that children suffering from chronic diseases such as JRA are in need for psychiatric follow-up and therapy.

As the majority of children with arthritis were girls in previous studies, these factors may have contributed toward the higher rate of internalizing problems in their population. It has been postulated that RA shares the characteristics of being more common with depression in girls and have the diurnal variability with worsening of symptoms in the morning [21].

Previous research [22] on cognitive impairment in systemic onset JRA found that cognitive performance and social adjustment of young patients were not affected by the activity and/or duration of the disease. These findings are different from our study in terms of the study sample in which our cases were mainly polyarticular RA (76%) in whom cognitive deficit (the intelligence quotient) was a significant finding as compared with the controls. This could be explained by different sensory stimulating upbringing, the use of different cognitive assessment tool, difference in sample selection, as well as central nervous system involvement in the course of RA, which is considered to be an infrequent event. In fact, there are few surveys with conflicting results regarding the occurrence of cognitive or behavioral abnormalities [23,24].

The prevalence of psychiatric morbidity among patients with JRA was 35%, depressive disorder was 15%, somatoform disorder was 12.5%, adjustment disorder was 5%, and mixed anxiety and depressive disorder was 2.5% [8]. Another study [25] reported depressive disorder in 58–60%, anxiety disorder in 45–52%, and adjustment disorder in 28–36% of patients with JRA. In our sample,

psychiatric morbidity did not differ regarding the type or the prevalence. They were as follows in decreasing order: dysthymic disorder in 93%, specific phobia in 20%, social phobia and oppositional defiant disorder each in 16%, and finally major depression, OCD, and conduct disorder each in 3%. These findings are matching with internalizing symptoms of patients with chronic medical illness such as JRA [25].

As central nervous system involvement is infrequent but evident in RA [26], in this study we attempted to evaluate cerebral perfusion to determine whether the observed psychiatric manifestations were due to immune vacuities that may alter cerebral perfusion. Our results showed a significant decrease in right frontal and right parietal lobes, and a significant increase in left parietal and left occipital lobes in patients compared with the control group. Interestingly, these regions are known to be involved in mood regulation, anxiety, and attention span. A recent study [27] reported that depressed adolescents have abnormal hyperactivity of amygdale compared with control. Another study [28] correlated severity of depression to brain perfusion. These findings were evident in our study as the decreased perfusion of the right frontal and right parietal lobes were seen more in patients with depression compared with healthy control.

Anxiety affects amygdale perfusion [29] and another study [30] suggested that youth with generalized anxiety disorder shows hyperresonance amygdale in the absence of a compensatory increase of ventrolateral prefrontal modulation. Our results support these suggestions as the anxiety group showed increased right frontal and decreased parietal perfusion compared with the controls, which all reflects the dysfunctional brain circuit of anxiety patients.

The observed psychiatric changes in our series were influenced by the duration of intake rather than the dose of immunosuppressive drugs. These drugs are commonly used to control JRA disease activity. Of note, most cases (73%) were studied during disease remission, denoting that the observed cerebral perfusion changes were not due to disease activity and active vasculitis. These patients were maintained on very low doses of cortico-steroids (0.1–0.3 mg/kg/day). However, a significant inverse relationship was found between the right parietal perfusion and the duration of steroid intake. A similar relationship was also found between the left parietal lobe perfusion and the duration of methotrexate intake. These findings suggest that the long duration of intake of corticosteroids and other medications may alter cerebral perfusion leading to the development of depressive symptoms. Indeed, depression was reported to be more common with corticosteroid than mania during long-term therapy, as well as with a decline in working memory [31].

To conclude, this study shows that patients with JRA experience psychiatric morbidity as well as cognitive deficit. The patterns of cerebral perfusion deficit are similar to that observed in patients diagnosed with depression, anxiety, and cognitive disabilities. It is

suggested that psychiatric changes observed in our patients were due to therapy duration rather than the drug dosage.

References
1 Miller ML, Cassidy JT. Juvenile rheumatoid arthritis. In: Behrman RE, Kliegman RM, Jenson HB, editors. *Nelson textbook of pediatrics*. 16th ed. Philadelphia: Saunders; 2000. pp. 704–709.
2 Schneider R, Passo MH. Juvenile rheumatoid arthritis. Rheum Dis Clin North Am 2002; 28:503–530.
3 El Gamal Y, Mokhtar GM, Omar OH, El Sayed ZA, Mostafa GA. Bone metabolism in juvenile rheumatoid arthritis. Egypt Rheumatol Rehab 1999; 26:153–166.
4 Borchers AT, Selmi C, Cheema G, Keen CL, Shoenfeld Y, Gershwin ME. Juvenile idiopathic arthritis. Autoimmun Rev 2006; 5:279–298.
5 Adams A, Lehman TJ. Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis. Curr Opin Rheumatol 2005; 17: 612–616.
6 Glazebrook C, Hollis C, Heussler H, Goodman R, Coates L. Detecting emotional and behavioural problems in paediatric clinics. Child Care Health Dev 2003; 29:141–149.
7 Carter BD, Kronenberger WG, Edwards JF, Marshall GS, Schikler KN, Causey DL. Psychological symptoms in chronic fatigue and juvenile rheumatoid arthritis. Pediatrics 1999; 103 (**5 Pt 1**):975–979.
8 Mullick MS, Nahar JS, Haq SA. Psychiatric morbidity, stressors, impact and burden in juvenile idiopathic arthritis. J Health Popul Nutr 2005; 23: 142–149.
9 Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical and psychological predictors. J Psychosom Res 2006; 60:469–476.
10 Bartolini M, Candela M, Brugni M, Catena L, Mari F, Pomponio G, et al. Are behaviour and motor performances of rheumatoid arthritis patients influenced by subclinical cognitive impairments? A clinical and neuroimaging study. Clin Exp Rheumatol 2002; 20:491–497.
11 Goldberg DP. *The detection of psychiatric illness by questionnaire*. London: Oxford University Press; 1974.
12 Okasha A, Kamel M, Fares R, Abdel Hakiem R. An epidemiological study of depressive symptoms in rural and urban population in Egypt. Egypt J Psychiatry 1988; 11:167–181.
13 Wechsler D. *WAIS -R Manual*. New York: Psychological corporation; 1981.
14 Achenbach TM. *Manual for the Child Behavior Cheklist/4-18 and 1991 profile*. Burlington VT: Department of psychiatry, University of Vermont; 1991.
15 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 (**Suppl 20**):22–33. quiz:34–57.
16 Benton H. A visual renetion test for clinical use. Arch Neurol Psychiatry 1945; 54:212–216.
17 Van den Abbeele AD, Donohoe KJ. *Teaching atlas of nuclear medicine*. New York: Thieme Medical Publishers; 2000.
18 Sandstrom MJ, Schanberg LE. Peer rejection, social behavior and psychological adjustment in children with juvenile rheumatic disease. J Pediatr Psychol 2004; 29:29–29.34.
19 Ennett ST, DeVellis BM, Earp JA, Kredich D, Warren RW, Wilhelm CL. Disease experience and psychosocial adjustment in children with juvenile rheumatoid arthritis: children's versus mothers' reports. J Pediatr Psychol 1991; 16:557–568.
20 Wilkinson VA. Juvenile chronic arthritis in adolescence: facing the reality. Int Rehabil Med 1981; 3:11–17.
21 Chikanza IC. Neuroendocrine immune features of pediatric inflammatory rheumatic diseases. Ann N Y Acad Sci 1999; 876:71–80. discussion: 80–82.
22 Feldmann R, Weglage J, Roth J, Foell D, Frosch M. Systemic juvenile rheumatoid arthritis: cognitive function and social adjustment. Ann Neurol 2005; 58:605–609.
23 Genet F, Lapeyre E, Schnitzler A, Hausseguy A, D'Apolito AC, Lafaye de Michaux R, et al. Psychobehavioural assessment for chronic low back pain. Ann Readapt Med Phys 2006; 49:226–233.
24 Cavalcanti A, Hilário MOE, Dos Santos FH, Bolognani SAP, Bueno OFA, Len CA. Subtle cognitive deficits in adults with a previous history of sydenham's chorea during childhood. Arthritis Care Res 2010; 62:1065–1071.
25 LeBovidge JS, Lavigne JV, Donenberg GR, Miller ML. Psychological adjustment of children and adolescents with chronic arthritis: a meta-analytic review. J Pediatr Psychol 2003; 28:29–39.
26 Carbotte RM, Denburg SD, Denburg JA. Cognitive deficit associated with rheumatic diseases: neuropsychological perspectives. Arthritis Rheum 1995; 38:1363–1374.

27   Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Max JE, et al. Adolescents with major depression demonstrate increased amygdala activation. J Am Acad Child Adolesc Psychiatry 2010; 49:42–51.

28   Perico CA, Skaf CR, Yamada A, Duran F, Buchpiguel CA, Castro CC, et al. Relationship between regional cerebral blood flow and separate symptom clusters of major depression: a single photon emission computed tomography study using statistical parametric mapping. Neurosci Lett 2005; 384:265–270.

29   Guyer AE, Lau JYF, McClure Tone EB, Parrish J, Shiffrin ND, Reynolds RC, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. Arch Gen Psychiatry 2008; 65:1303–1312.

30   Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry 2008; 65:568–576.

31   Brown ES. Effects of glucocorticoids on mood, memory and the hippocampus: treatment and preventive therapy. Ann N Y Acad Sci 2009; 1179:41–55.

الملخص العربى

الأمراض النفسية المصاحبة لمرض الروماتويد عند الأطفال

دراسة بإستخدام الفوتونات المشعة لتصوير المخ

يعتبر مرض التهاب المفصلي روماتويد الصغار من الامراض المزمنه المنتشره في الاطفال والتي تحدث اعاقات نفسيه وحركيه للاطفال. وثبت بالدراسات السابقه ان حوالي 30% من الاطفال المصابيين بالتهاب المفاصل الروماتويدي يعانون من اعراض نفسيه تصل الي حد تشخيص مرض نفسي. في هذه الدراسه ثم مناظره 30 حاله التهاب مفصلي روماتويدي من الاطفال والكشف عن الاعاقات النفسيه والمعرفيه عن طريق استخدام الاختبارات النفسيه والمعرفيه اللازمه . وتم اخضاع هؤلاء الاطفال الي فحص بالاشعه المقطعيه أحاديه الفوتون علي المخ ولقد وجد فارق احصائي بين المرض والإصحاء في معامل الذكاء واختبار الذاكرة البصريه ــ كما أن المرض يعانون من نقص في الدوره الدمويه بالمخ بوجه عام مقارنة بالإصحاء وان بعض المناطق التي تعانيمن نقصفي الدوره الدمويه هي الأماكن المسؤوله عن ظهور الاعراض النفسيه ــ خاصه وانه وجد علاقه احصائية بين درجه تدفق الدم وفتره المرض ــ والعلاج بينما لم توجد هذه العلاقه مع جرعه العلاج

Attention deficit hyperactivity disorder among a sample of students from Tanta University

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Introduction
Despite growing interest in adult attention deficit hyperactivity disorder (ADHD), little is known about its prevalence, characteristics, and comorbidity, especially in Arabic countries.
Objectives
To assess the prevalence of ADHD among a sample of Egyptian college students, and to study prevalent subtypes of ADHD, comorbid psychiatric disorders, and its impact on functioning.
Patients and methods
Two thousand college students aged above 18 years were surveyed using the screener form of Adult ADHD Self-Report Scale, Version1.1. Students who had positive screening results were assessed individually using the 18-question form of this scale, the Barkley Childhood ADHD Symptom Scale, and the ADHD Current Symptom Scale. Those who proved to have ADHD and a similar number of students without ADHD were assessed using the Mini International Neuropsychiatric Interview. Both groups were compared together with regard to family history of psychiatric disorders, comorbid psychiatric conditions, and Global Assessment of Functioning.
Results
The prevalence of ADHD among college students in this study was 2.66%. Twenty-seven (69.23%) students had predominantly inattentive subtype of ADHD, whereas 12 (30.77%) students had predominantly combined type. The ratio of men-to-women was 1.4 : 1. Lifetime psychiatric comorbidity was found in 26 of 39 (66.66%) students with ADHD, in comparison with 10 of the control group (25.64%). Among these disorders, major depression, generalized anxiety, cigarette smoking, and substance abuse were significantly more in students with ADHD than in those without ADHD. Students with ADHD had significant impairment in the level of functioning as assessed by the Global Assessment of Functioning Scale. Family history of ADHD and major depression were significantly more common in students with ADHD than in control group.
Conclusion
ADHD is not uncommon among college students. It is commonly comorbid with other psychiatric disorders and impairs functioning of affected persons. Family history of psychiatric disorders is more common in families with ADHD than controls.

Keywords:
attention deficit hyperactivity disorder, adults, attention deficit hyperactivity disorder, college students, comorbidity, epidemiology, family history, functioning

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by motor hyperactivity, impulsivity, and inattention [1]. Until recently, ADHD was a diagnosis reserved for children and adolescents. New evidence, however, supports the persistence of ADHD beyond adolescence, and it is now recognized as a chronic neurobehavioral disorder in adults [2]. Estimates of ADHD prevalence averaged 3.4% (range = 1.2–7.3%) [3]. ADHD in adults frequently goes undiagnosed and untreated. This is largely associated with adults minimizing the severity of symptoms and being unaware that they actually have ADHD. Predictably, adult ADHD is associated with increased morbidity. Higher traffic violations; concomitant psychiatric disorders; and negative occupational, economic, and psychosocial functions are common findings in adults with ADHD [4–6]. More than 45% of the patients with ADHD had two or more comorbid personality disorders and nearly 60% had two or more Axis I disorders. One of the challenges is to establish whether symptoms are indeed due to ADHD and not due to another condition. These distinctions have serious implications not only for the accurate diagnosis of these conditions but also for optimal treatment and outcomes [7].

Given the increased interest in adult ADHD and the lack of epidemiological data specific to adult ADHD in Egyptian population, this study examined the prevalence of adult ADHD, prevalent subtypes of ADHD, comorbid psychiatric disorders, and its impact on functioning in a sample of college students in Tanta University, Egypt.

Patients and methods

The individuals in this study were 2000 students of six colleges of Tanta University, Egypt. Tanta University consists of 13 colleges and one institute, which includes 96 469 students. The selected faculties were Faculty of Medicine (400 students), Faculty of Science (200 students), Faculty of Pharmacy (200 students), Faculty of Commerce (400 students), Faculty of Education (200 students), and Faculty of Arts (200 students). The ratio of men-to-women was 1 : 1. The age of students participating in the study was 18 years and above. Sample recruitment was conducted in students attending colleges on Saturday, Monday, and Wednesday during the academic year 2009–2010. After receiving a full oral explanation of all study requirements and procedures, these students were surveyed face-to-face using the six-question Adult Self-Report Scale, Version1.1 Screener [8]. This screener is a subset of the WHO's 18-question Adult ADHD Self-Report Scale-Version1.1 (ASRS-V1.1), which contains the adult ADHD symptoms most predictive of having the disorder [9]. The ASRS-V1.1 is similar to the standard symptoms described in Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV) [10] with modifications in language to reflect the presentation of symptoms in adulthood. The screener has four inattention items and two hyperactivity items, which highly correlate with the full-scale ASRS. The full scale has nine inattentive and nine hyperactivity items. The items can be scaled from 0 to 4. If four or more marks appear in the darkly shaded boxes of the screener, then the patient has symptoms highly consistent with ADHD in adults.

Among the 2000 college students who were surveyed with the ASRS-V1.1 Screener, 1467 students accepted to participate in the study and completed the scale. Forty-six students had positive screening suggestive of ADHD.

Students who had positive screening results were assessed individually by both investigators of this study at the same time for the presence of core symptoms of ADHD, developmental history family history, social and educational history, and assessment if symptoms caused significant functional impairment. After evaluation, only 39 students were found to have ADHD, including 23 men and 16 women.

Symptom assessment was made using the complete version (18-question) of Adult ASRS-V1.1, the Barkley Childhood ADHD Symptom Scale, and the ADHD Current Symptom Scale [11].

The Childhood Symptom Scale focuses on the retrospective assessment of the 18 DSM-IV criteria. The ADHD Current Symptom Scale asks about adult patients' behavior in the past 6 months, using a scale of 0–3 (0 = never or rarely, 1 = sometimes, 2 = often, 3 = very often). It contains questions that correspond to the nine symptoms of inattention and to the nine symptoms of hyperactivity/impulsivity in the DSM-IV. The wording of the Current Symptoms Scale was tailored for adult self-report and observer report about an adult, instead of parent or teacher report about children.

When the diagnosis of ADHD was confirmed, the 39 students were scheduled for the second part of the assessment where the purpose was to assess for Axis I disorders, for functioning, and for family history of psychiatric disorders. A similar number of students whose screen was negative, (selected randomly, matching for age and sex) were taken as a control group for comparison.

All patients and the control group were assessed by one of the investigator of this study using the Mini International Neuropsychiatric Interview [12], which was translated into Arabic (Ghanem *et al.*, personal communication). Both groups were compared together with regard to family history of psychiatric disorders, comorbid psychiatric conditions, and global assessment of functioning using Global Assessment of Functioning (GAF) Scale [10]. The primary goal of the GAF Scale is to provide a summary score that reflects the level of a patient's overall functioning. Ratings take into account the patient's psychological, social, and occupational functioning. Impairment in functioning due to physical or environmental factors is rated.

Statistical analysis

The collected data were organized and statistically analyzed using statistical package for the social sciences statistical software, version 15.0 (SSPS Inc., Chicago, Illinois, USA). The mean and standard deviation were used for presentation of quantitative data. The Student's t-test was used for comparison between two means. For qualitative data, the number and percentage distribution were calculated and χ^2-test and Fisher's exact test were used for comparison between studied groups. Statistical significance was defined at the P value less than 0.05 level.

Results

This study was carried out on college students of medicine, pharmacy, science, education, arts, and commerce. Thus, the sample is more or less homogenous with regard to age, educational level, and socioeconomic state. All students were single and unemployed. The age of patients who had ADHD ranged from 19.2 to 21.9 years with a mean of 20.49 years. The age of students selected as control ranged from 19.2 to 21.6 years with a mean of 20.48 years ($P > 0.05$).

The response rate among those who were given the scale was 73.35%. Among the 2000 college students who were surveyed with the ASRS-V1.1 Screener, 1467 students accepted to participate in the study and completed the scale.

Among those who participated in the study, 39 students had ADHD; thus, the prevalence of ADHD among college students in this study was 2.66%. Twenty-seven (69.23%) students had a predominantly inattentive subtype of ADHD, whereas 12 (30.77%) students had a predominantly combined type.

Among the 39 ADHD students, 23 were men and 16 were women. The ratio of men-to-women was 1.4 : 1.

Lifetime psychiatric comorbidity was found in 26 of 39 (66.66%) students with ADHD, in comparison with 10 of the control group (25.64%) with statistically significant differences ($P < 0.001$). Comorbid psychiatric disorders included major depression, generalized anxiety, bipolar disorder, obsessive–compulsive disorder, cigarette smoking, and substance abuse. Among these disorders only major depression, generalized anxiety, cigarette smoking, and substance abuse were significantly more in students with ADHD than in those without ADHD ($P < 0.05$) (Table 1).

Students with ADHD had significant impairment in the level of functioning as assessed by GAF Scale, which ranged from 53 to 60 with a mean of 56.74. Scores of GAF Scale in the control group ranged from 76 to 94 with a mean of 86 ($P < 0.001$) (Table 1).

Family history of psychiatric disorders was significantly more common in students with ADHD than in the control group ($P < 0.001$). These disorders included ADHD, major depression, bipolar disorder, substance abuse, and anxiety disorders. Only ADHD and major depression were significantly more common in students with ADHD than in the control group ($P < 0.05$). Although substance abuse, bipolar disorder, and anxiety disorders were more in students with ADHD than in the control group, it did not reach statistical significance ($P > 0.05$) (Table 1).

Discussion

To our knowledge, this is the first study of adult ADHD in college students in Egypt. The prevalence rate of ADHD in this study was 2.64%. Kessler *et al.* [13] found

Table 1 Comparison between students with and without ADHD

	ADHD (N=39)	Control (N=39)	Significance
Comorbidity	26 (66.66%)	10 (25.64%)	0.000[a]
Depression	8 (20.51%)	1 (2.56%)	0.029[a]
Generalized anxiety	8 (20.51%)	1 (2.56%)	0.029[a]
OCD	2 (5.12%)	0	0.494
Cigarette smoking	19 (48.71%)	9 (23.07%)	0.033[a]
Substance abuse	12 (30.76%)	4 (10.25%)	0.047[a]
Bipolar disorder	2 (5.12%)	0	0.494
GAF Scale (mean)	56.74	86	0.000[a]
Family history	23 (58.97%)	11 (28.20%)	0.011[a]
ADHD	11 (28.20%)	2 (5.12%)	0.013[a]
Depression	9 (23.07%)	2 (5.12%)	0.047[a]
Bipolar disorder	2 (5.12%)	0	0.494
Substance abuse	7 (17.94%)	4 (10.25%)	0.517
Anxiety disorders	7 (17.94%)	4 (10.25%)	0.517

ADHD, attention deficit hyperactivity disorder; GAF, Global Assessment of Functioning; OCD, obsessive compulsive disorder.
[a]Significant.

that 4.4% of adults (age = 18–44 years) had ADHD. In a sample of prison inmates (age = 19.2 ± 2 years), the overall prevalence of ADHD was 45% [14]. Population-based studies estimated prevalence rates of ADHD at 1–7.3% using DSH-IV criteria [15]. Differences in prevalence rate of ADHD among studies may stem from the nature of the studied sample, being a representative sample of adult population or being a convenience sample such as college students in this study or prison inmates in other studies [14].

In contrast to marked sex difference frequently reported in children and adolescents with ADHD in both clinical [16,17] and community studies [18,19], this difference is less clear in this study of college students (men-to–women ratio = 1.4 : 1). Simon *et al.* [15] in their meta-analysis study arrived at the same conclusion with regard to sex difference. This more balanced sex difference may be attributed to the fact that although parents or teachers usually initiate childhood referrals, in adulthood self-referrals are common. As women with ADHD have more internalizing problems than men, this led to high self-referral in adulthood [15]. Another explanation is that more boys than girls outgrow their ADHD, leading to a decrease in the marked sex difference observed in children.

The two subtypes of ADHD detected in this study were inattentive and combined ones. Kessler *et al.* [20] found greater persistence of inattentive subtype symptoms than of hyperactive/impulsive childhood symptoms of ADHD in adulthood. This may refer to developmental difference of the disorder, whereas the hyperactivity/impulsive subtype diminishes with increasing age. Another explanation is that the diagnostic criteria of the hyperactivity/impulsive subtype became unsuitable for adults and hence cannot detect this subtype.

This study confirmed the findings of other studies of greater risk for comorbid current and past Axis I disorders in adults with ADHD. Cumyn *et al.* [6] reported that adults with ADHD, compared with those without ADHD, had higher rates of Axis I disorders (46.9 vs. 27.31%). However, the pattern of psychiatric comorbidity in adult ADHD is not consistent and differed across studies.

The higher rate of major depressive disorder seen in this study is consistent with some clinical findings [21] but not other findings [22]. Retrospective clinical studies of adults with ADHD showed a prevalence rate between 35 and 50% for depressive episodes [13,21]. Some researchers hypothesized that depression in patients with ADHD represents an adjustment disorder (i.e. a demoralizing response to chronic social and academic failure) [23].

Retrospective clinical studies of adults with ADHD showed a prevalence rate between 10 and 45% for anxiety disorders [13,21,24]. Generalized anxiety was significantly more in students with ADHD than in those without ADHD in this study. Generalized anxiety, phobia, and obsessive–compulsive disorder were inconsistently reported to be more common among ADHD patients [6,25]. In contrast, the prevalence of adult ADHD was

higher in anxiety disorder clinical samples than in the general population [26]. Biederman *et al.* [23] suggested that ADHD and anxiety disorders segregate independently in families, and that the association between anxiety disorders and ADHD may reflect reduced stress tolerance, which results in feelings of fear and emotional dysregulation.

Students with ADHD in this study had more lifetime bipolar disorder compared with the control group, but it did not reach statistical significance. Some studies of bipolar disorder revealed that lifetime ADHD is a frequent comorbid condition in adults with bipolar disorder, and it is associated with a worse course of bipolar disorder and a greater burden of other psychiatric comorbid conditions [27]. The rate of ADHD comorbidity decreases steadily as the studied population grows older [28]. The relationship between ADHD and bipolar disorder needs more research to ascertain the diagnostic boundaries and to confirm this relationship.

This study showed that nicotine dependence and drug abuse were significantly higher in students with ADHD than in those without ADHD. A robust and bidirectional comorbidity between ADHD and psychoactive substance abuse has been frequently reported in the literature [29]. The high prevalence of drug abuse in adults with ADHD was frequently reported by other studies [6,30]. Biederman *et al.* [29] explained the association between ADHD and drug dependence with the hypothesis of variable expressivity of a common risk between these disorders. Barkley *et al.* concluded that severity of ADHD creates a greater predisposition toward engaging in antisocial activities that are related to drug possession and sale, perhaps owing to the increased impulsiveness ADHD conveys. Otherwise, it may be that drug use has a disproportionate impact on those with ADHD, predisposing them toward greater antisocial activities than might be the case in the absence of ADHD [31].

The ADHD comorbidity findings raise many questions about the effect of treatment in childhood on the development of comorbidity, the effect of treatment of ADHD in adulthood on severity, and the persistence of comorbidity, in addition to diagnostic difficulties imposed by comorbidity.

This study found that students with ADHD had significantly lower level of functioning compared with those without ADHD. Other studies also found that adults with ADHD were significantly impaired in a variety of psychosocial functions (education, occupational training) [32,33]. This finding warrants increasing the awareness about the disorder to seek professional help.

Family history of psychiatric disorders, specifically ADHD, major depression, and bipolar disorder, were significantly more common in students with ADHD than in the control group. Persistent forms of ADHD are thought to have a higher familial loading than ADHD that does not persist, with increased rates of ADHD among the parents and siblings of those with persistent ADHD and with high rates of ADHD among the offsprings of parents with ADHD [34]. Approximately 20% of parents of children with ADHD will have ADHD themselves [35]. Twin and adoption studies indicate that the familiality of ADHD symptoms results from genetic factors rather than shared environmental risks, providing a further rationale for considering ADHD as a lifetime condition [36].

Family studies revealed that, relatives of children with ADHD had significantly higher rates of both ADHD and depression than did relatives of control individuals [37]. Family members of children who had ADHD and major depressive disorder had higher rates of both disorders. A common genetic factor may occur in both. ADHD and major depressive disorder may be different expressions of the same genetic factors behind the appearance of ADHD [38,39]. It is not known why some patients have one disorder, some the other, and still others have both.

In this study, relatives of students with ADHD did not have significant difference in history of bipolar disorder than did relatives of control individuals. A recent study showed that offspring of parents with bipolar disorder showed greater lifetime prevalence of ADHD [40]. The type of the sample studied may play a role in this difference.

Conclusion and recommendations
ADHD is not so rare among college students, and affects their level of functioning. ADHD is highly comorbid with other psychiatric disorders, a matter that may limit diagnosis. Attention problems should urge the clinician to screen for ADHD symptoms.

Limitations
The limitations of this study are as follows: (i) the selected sample of this study is not representative of all college students, as it is not randomly selected due to administrative difficulties and (ii) the screening tools, although commonly used in many cultures, were not standardized to the Egyptian culture.

References
1 Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005; 366:237–248.
2 Goodman DW. The consequences of attention-deficit/hyperactivity disorder in adults. J Psychiatr Pract 2007; 13:318–327.
3 Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007; 190:402–409.
4 Kessler RC, Adler L, Ames M, Barkley RA, Birnbaum H, Greenberg P, et al. The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. J Occup Environ Med 2005; 47:565–572.
5 Fried R, Petty CR, Surman CB, Reimer B, Aleardi M, Martin JM, et al. Characterizing impaired driving in adults with attention-deficit/hyperactivity disorder: a controlled study. J Clin Psychiatry 2006; 67:567–574.
6 Cumyn L, French L, Hechtman L. Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry 2009; 54:673–683.
7 Jacob CP, Romanos J, Dempfle A, Heine M, Windemuth Kieselbach C, Kruse A, et al. Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur Arch Psychiatry Clin Neurosci 2007; 257:309–317.
8 Adler L, Kessler R, Spencer T. Adult self-report scale. ASRS-V1. 1 Screener. New York: World Health Organization (WHO); 2003.

9 Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The world health organization adult ADHD self-report scale (ASRS): a short screening scale for use in the general population. Psychol Med 2005; 35:245–256.

10 American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders (DSM). 4th ed. Washington, DC: American Psychiatric Association (APA); 2000.

11 Barkley RA, Murphy KR. Attention-deficit hyperactivity disorder: a clinical workbook. 2nd ed. New York: Guilford Press; 1998.

12 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 (**Suppl 20**): 22–33. quiz:34–57.

13 Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication. Am J Psychiatry 2006; 163:716–723.

14 Rösler M, Retz W, Retz Junginger P, Hengesch G, Schneider M, Supprian T, et al. Prevalence of attention deficit/hyperactivity disorder (ADHD) and comorbid disorders in young male prison inmates. Eur Arch Psychiatry Clin Neurosci 2004; 254:365–371.

15 Simon V, Czobor P, Bálint S, Mészáros Á, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009; 194:204–211.

16 Arnold LE. Sex differences in ADHD: conference summary. J Abnorm Child Psychol 1996; 24:555–569.

17 Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry 2002; 159:36–42.

18 Gaub M, Carlson CL. Gender differences in ADHD: a meta-analysis and critical review. J Am Acad Child Adolesc Psychiatry 1997; 36: 1036–1045.

19 Ramtekkar UP, Reiersen AM, Todorov AA, Todd RD. Sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses: implications for DSM-V and ICD-11. J Am Acad Child Adolesc Psychiatry 2010; 49:217–228.

20 Kessler RC, Green JG, Adler LA, Barkley RA, Chatterji S, Faraone SV, et al. Structure and diagnosis of adult attention-deficit/hyperactivity disorder: analysis of expanded symptom criteria from the adult ADHD clinical diagnostic scale. Arch Gen Psychiatry 2010; 67:1168–1178.

21 Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, et al. Patterns of psychiatric comorbidity, cognition and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993; 150:1792–1798.

22 Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry 1996; 37: 393–401.

23 Sobanski E, Brüggemann D, Alm B, Kern S, Deschner M, Schubert T, et al. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2007; 257:371–377.

24 Sobanski E. Psychiatric comorbidity in adults with attention-deficit/ hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2006; 256 (**Suppl 1**):I/26–I/31.

25 Biederman J, Faraone SV, Keenan K, Steingard R, Tsuang MT. Familial association between attention deficit disorder and anxiety disorders. Am J Psychiatry 1991; 148:251–256.

26 Van Ameringen M, Mancini C, Simpson W, Patterson B. Adult attention deficit hyperactivity disorder in an anxiety disorders population. CNS Neurosci Ther 2010. [Epub ahead of print].

27 Tamam L, Karakus G, Ozpoyraz N. Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. Eur Arch Psychiatry Clin Neurosci 2008; 258:385–393.

28 Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 2000; 157:816–818.

29 Biederman J, Petty CR, Wilens TE, Fraire MG, Purcell CA, Mick E, et al. Familial risk analyses of attention deficit hyperactivity disorder and substance use disorders. Am J Psychiatry 2008; 165:107–115.

30 Biederman J, Wilens T, Mick E, Milberger S, Spencer TJ, Faraone SV. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. Am J Psychiatry 1995; 152:1652–1658.

31 Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 2004; 45:195–211.

32 Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry 2006; 45:192–202.

33 Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 4101 adults in the community. J Clin Psychiatry 2006; 67:524–540.

34 Faraone SV, Biederman J, Monuteaux MC. Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. Genet Epidemiol 2000; 18:1–16.

35 Faraone SV, Biederman J, Feighner JA, Monuteaux MC. Assessing symptoms of attention deficit hyperactivity disorder in children and adults: which is more valid? J Consult Clin Psychol 2000; 68:830–842.

36 Faraone SV, Doyle AE, Knoerzer JA. Heritability of attention-deficit/ hyperactivity disorder. Econom Neurosci 2001; 3:54–57.

37 Hechtman L. Families of children with attention deficit hyperactivity disorder: a review. Can J Psychiatry 1996; 41:350–360.

38 Biederman J, Faraone SV, Keenan K, Tsuang MT. Evidence of familial association between attention deficit disorder and major affective disorders. Arch Gen Psychiatry 1991; 48:633–642.

39 Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, et al. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. Arch Gen Psychiatry 1992; 49:728–738.

40 Birmaher B, Axelson D, Goldstein B, Monk K, Kalas C, Obreja M, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh bipolar offspring study (BIOS). Am J Psychiatry 2010; 167:321–330.

اضطراب قلة الانتباه و فرط الحركة فى عينة من طلبة جامعة طنطا

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مقدمة: على الرغم من الاهتمام المتزايد باضطراب قلة الانتباه و فرط الحركة عند البالغين، قلا يعرف سوى القليل عن مدى انتشاره، خصائصه، والاضطرابات النفسي المصاحبة، ولا سيما في البلدان العربية.
الهدف من البحث: تقييم مدى انتشار اضطراب قلة الانتباه و فرط الحركة لدى عينة من طلاب الجامعات المصرية، ومعرفة الأنواع الفرعية السائدة للاضطراب، الاضطرابات النفسية المصاحبة، وتأثير الاضطراب على وظيفة الفرد.
طريقة البحث: اجري هذ البحث على2000 من طلاب جامعة طنطا اكبر من 18عاما عن طريق استبيان تم توزيعه عليهم، ثم تم تقييم الأفراد الذين كانت نتيجتهم موجبة فى الاستبيان بصوره فردية عن طريق استبيانات لأعراض اضطراب قلة الانتباه و فرط الحركة الحالية و فى الطفولة. بعد ذلك تم تقييم الأطفال الذين يعانون من اضطراب قلة الانتباه و فرط الحركة بالإضافة إلى عينة مماثلة من الطلاب الذين لا يعنون من هذا الاضطراب و عمل باستخدام مقابلة ميني الدولية للأمراض العصبية والنفسية. وتمت مقارنة كلا الفريقين معا فيما يتعلق بالأداء الوظيفى، الاضطرابات النفسية المصاحبة و التاريخ العائلي للاضطرابات النفسية.
النتائج: أوضحت الدراسة ان انتشار اضطراب قلة الانتباه و فرط الحركة بين طلاب الجامعات 2,66 ٪. وكانت الأنواع الفرعية السائدة هى نوعى قلة الانتباه (69.23%) و النوع المختلط (30.77٪). وكانت نسبة الذكور إلى الإناث 1,4: 1. وجدت الدراسة أمراض نفسية مصاحبة في 26 من 39 (66.66 ٪) من الطلاب الذين يعانون من اضطراب قلة الانتباه و فرط الحركة، بالمقارنة مع عشرة من المجموعة الضابطة (25.64 ٪). ومن بين هذه الاضطرابات كان انتشار الاكتئاب النفسى الجسيم، القلق العام، تدخين السجائر وتعاطي المخدرات اكثر شيوعا عن الطلاب الذين لا يعانون من اضطراب قلة الانتباه و فرط الحركة. اوضح التاريخ العائلي للاضطرابات النفسية ان اضطراب قلة الانتباه و فرط الحركة و الاكتئاب النفسى الجسيم أكثر شيوعا لدى عائلات الطلاب الذين يعانون من اضطراب قلة الانتباه و فرط الحركة عن عائلات المجموعة الضابطة.
الخلاصة: اضطراب قلة الانتباه و فرط الحركة ليس نادرا بين طلاب الجامعات، كما انة يقلل من ادائهم الوظيفى. وتكثر الاضطرابات النفسية المصاحبة بين المصابين بهذا الاضطراب. كما ان التاريخ العائلي للاضطرابات النفسية أكثر شيوعا في أسر هؤلاء الأفراد عن الأفراد الطبيعيين.

Effect of treadmill training on activities of daily living and depression in patients with Parkinson's disease
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Introduction
Parkinson's disease is a complex neurodegenerative condition with both motor and nonmotor symptoms affecting the physical, psychological, social, and functional status of individuals. This study was conducted to assess the relationship between moderate aerobic exercise and activities of daily life and depression in Parkinson's disease.

Patients and methods
Thirty levodopa-dependent patients with Parkinson's disease, with age ranging from 49 to 70 years, represented the sample of the study. The patients were randomly assigned into two equal groups (group 1 and group 2) with matched age, height, and body weight. Computerized tomography was conducted to exclude any focal neurological disorder that may affect the gait pattern. All the patients were subjected to clinical neurological examination, which included medical past and present history; motor examination; and activities of daily living. Group 1 patients were treated by a designed physiotherapy program, in addition to 20 min of treadmill training (moderate aerobic training), whereas group 2 patients were treated only by the same designed physiotherapy program as used for group 1 patients. The Hamilton Rating Scale of Depression was used for assessment of depression.

Results
Both groups showed improvement in walking distance, walking speed, activities of daily living, and depression after the designed physiotherapy program; however, group 1 with moderate aerobic exercise showed more improvement, and the differences between the two groups were statistically significant.

Conclusion
Moderate aerobic training showed effectiveness in improving activities of daily living and in improving depressive symptoms in patients with Parkinson's disease.

Keywords:
aerobic exercise, depression, Parkinson's disease

Introduction
Parkinson's disease (PD) is a complex neurodegenerative condition with both motor and nonmotor symptoms [1]. It has substantial adverse effects on the physical, psychological, social, and functional status of the individuals [2]. The most characteristic features of PD are resting tremor, rigidity, bradykinesia, and postural instability [3]. The diagnosis of PD demands the presence of two out of the three cardinal features of bradykinesia, rigidity, and tremor, a good clinical response to levodopa, and no atypical features suggestive of another parkinsonian syndrome [4]. Depression is frequent in patients with PD. Patients with PD usually become more dependent, fearful, and hesitant. Depression has been recognized as a common feature of PD and is the most prevalent psychiatric disorder in patients with PD [5]. Limitation in functional status and activities of daily living (ADL) often result in a loss of independence and considerable decline in quality of life [6]. Depression, a disease usually accompanied by a serotonergic deficit, has been observed in approximately 40% of patients suffering from PD. It could be related to decreased serotonergic neurotransmission in untreated patients with PD. Low serotonergic activity may be related to the dopamine pathology in PD and this could be related to the high prevalence of depression in PD [7].

Physical therapy programs in conjunction with the routine medications for patients with PD could break the downward spiral of immobility [8]. Regular, 'mild or moderate' exercises could be a possible nonpharmacological form of treatment for depressive disorders [9]. Moreover, there is increasing evidence to suggest that it could be used as an alternative therapy to antidepressants and psychotherapy [10]. Physical exercise programs obtained clinically relevant outcomes in the treatment of depressive symptoms in depressed older people [11]. The aim of the study is to examine the effect of the aerobic training on alleviating the depressive symptoms in individuals with PD.

Patients and methods

Thirty levodopa-dependent patients with PD, with age ranging from 49 to 70 years, represented the sample of the study. The patients were randomly assigned into two equal groups (group 1 and group 2) with matched age, height, and body weight. The patients were diagnosed in the Neurology Department, Faculty of Medicine, Cairo University's outpatient clinic (Cairo, Egypt). Computerized tomography was performed to exclude any focal neurological disorder. The patients were referred to the outpatient clinic of Faculty of Physical Therapy, Cairo University. All the patients were subjected to clinical physical examination, which included medical past and present history; motor examination; and ADL. The Hamilton Rating Scale of Depression (HDRS) [12] was used for assessment of depression. We included patients who were able to walk independently for 6 min without interruption. The patients suffered mild-to-moderate disability according to the United Parkinson's Disease Rating Scale (UPDRS) [13] ADL/motor scores. The UPDRS is a rating scale used to follow the longitudinal course of PD. It consists of five sections: evaluation of mentation, behavior, and mood; evaluation of ADL; motor evaluation; Hoehn and Yahr stating of severity of PD; and Schwab and England ADL Scale. Worsening of symptoms increases the score. Improvement in symptoms decreases the score.

The duration of illness ranged from 3 to 5 years. Informed oral and written consents were obtained from all individuals who participated in this study. Patients with any of the following criteria were excluded from the study: severe cardiovascular disorders; neuromusculoskeletal disorder, which could potentially affect the gait; rapidly progressive motor disability; poor visuospatial abilities; epilepsy; cognitive impairment; marked rigidity; dyskinesias; anorexia; and symptomatic orthostasis. Patients who are on sedatives, tranquilizers, or sleeping aids were also excluded.

A treadmill tolerance test was first performed to assess gait safety. Those who completed six consecutive minutes of treadmill walking at 0.5 km/h proceeded to peak exercise testing. Individuals achieved adequate exercise intensities without signs of cardiopulmonary disturbances (abnormal increases in heart rate, blood pressure < 220 to $240/120$ 120 mm Hg, a significant drop in systolic pressure in response to an increasing workload, respiration not strenuous or short, lightheadedness, confusion, pallor, cyanosis, nausea) or other contraindications to training were enrolled. The walking distance and speed of the last and first sessions of each patient were recorded to be compared.

The patients in the study group (group 1) were treated by a designed conventional physiotherapy program, which was conducted by the researcher, in addition to moderate aerobic training. The designed physiotherapy program consisted of passive prolonged stretch techniques for the anterior neck, pectoralis major, hip flexors/adductors, tensor fascia latae, knee flexors, and ankle planter flexors muscles; balance training and weight shifting exercises; proprioceptive neuromuscular facilitation techniques; and graduated active exercises applied for the axial muscles to maintain/increase the muscle strength. A functional training included rolling over, standing up and sitting down, turning around using a large arc of movement or using full body movements, and traditional gait training. The patient and family were instructed to focus on maintaining long strides and adequate ground clearance during walking; on maintaining an upright posture by consciously attending to standing upright, and to reinforce physiotherapy strategies in the home and community. The moderate aerobic training included speed-dependent treadmill gait training. This training was started by 6 min of walking followed by rest. The walking speed was selected according to the patient's comfort. Individual's treadmill walking time was increased gradually from 6 to 20 min at the end of 6 weeks of training. The treatment was conducted three times a week day after day. The patients in the control group (group 2) were treated by the conventional physiotherapy program only.

Hamilton depression rating scale [12]

This scale was designed by Hamilton [12,14]. The original version consisted of 17 items and was later increased to 24 items by Klerman et al. [15]. The Scale is not meant to be a diagnostic instrument [16]. HDRS was found to distinguish between different groups of patients drawn from general practice, day-patients care, and inpatients [17]. The concurrent validity is high [18]. The inter-rater reliability of HDRS is also consistently high [12].

Data analysis and statistical methods

The coded data were entered into the computer using a database developed for data entry using Microsoft Office Excel program for Windows 2007. Data were then transferred to the Statistical Package of Social Science, version 16 (SPSS Inc., Chicago, IL, USA) for quantitative data analysis. Simple frequencies were used for data checking, whereas descriptive statistics were used for data summarization and graphs were used to illustrate simple information. Suitable statistical tests of significance were used when appropriate. Differences between studied groups were considered statistically at P value less than 0.05.

Results

There were no statistically significant differences between the two groups as regards age, sex, body weight, height, and duration of illness. This indicated that the samples were well matched and fit for the study and comparison.

In addition, there was no statistical difference between the two groups as regards the walking distance ($T = 2.25$, $P = 0.041$) before the aerobic exercise, but after the aerobic exercise the difference between the two groups was statistically significant ($T = 5.29$, $P = 0.01$) (Table 1).

Furthermore, there is no statistical difference between the two groups as regards the walking speed ($T = 1.64$, $P = 0.123$) before the aerobic exercise, but after the aerobic exercise the difference between the two groups was statistically significant ($T = 4.43$, $P = 0.001$) (Table 2).

In addition, there is no statistical difference between the two groups as regards the ADL ($T = 0.75$, $P = 0.465$) before the aerobic exercise, but after the aerobic exercise the difference between the two groups was statistically significant ($T = 6.2$, $P = 0.001$) (Table 3).

As regards the depression symptoms rated by the Hamilton Rating Scale, there is no statistical difference between the two groups before the aerobic exercise ($T = 1.98$, $P = 0.06$) and the difference was statistically significant after the aerobic exercise ($T = 8.6$, $P = 0.01$) (Table 4).

There is a positive correlation between ADL in UPDRS and the Hamilton Rating Scale of Depression after 6

Table 1 Walking distance (km) in both groups before and after moderate aerobic exercise

	Before		After		
	Mean (km)	SD (km)	Mean (km)	SD (km)	P
Group 1	0.259	0.294	0.509	0.77	0.041*
Group 2	0.087	0.012	0.346	0.08	0.01*

SD, standard deviation.
*P is statistically significant.

Table 2 Walking speed (km/hr) in both groups before and after moderate aerobic exercise

	Before		After		
	Mean (km/hr)	SD (km/hr)	Mean (km/hr)	SD (km/hr)	P
Group 1	0.9	0.13	1.28	0.1	0.01*
Group 2	0.8	0.18	1.04	0.17	0.01*

SD, standard deviation.
*P is statistically significant.

Table 3 Activity of daily living in UPDRS in both groups before and after moderate aerobic exercise

	Before		After		
	Mean	SD	Mean	SD	P
Group 1	24.8	3.09	15.6	4.2	0.01*
Group 2	25.4	2.9	22.13	4	0.01*

SD, standard deviation; UPDRS, the United Parkinson's Disease Rating Scale.
*P is statistically significant.

Table 4 Hamilton Rating Scale of Depression in both groups before and after moderate aerobic exercise

	Before		After		
	Mean	SD	Mean	SD	P
Group 1	24.27	2.7	16.06	2.29	0.01*
Group 2	25.86	3.27	22.07	3.24	0.01*

SD, standard deviation.
*P is statistically significant.

weeks of aerobic training and this was statistically significant ($R = 0.932$, $P = 0.001$).

Discussion

In our results, we found that there is an improvement in walking speed, distance, ADL, and depression after moderate aerobic exercise. The difference between the two groups before and after was statistically significant. This was supported by 14 randomized controlled trials, which supported exercise as being beneficial with regard to physical functioning, health-related quality of life, strength, balance, and gait speed for people with PD [2]. Moreover, exercise therapy was effective in improving ADL and perceived health status in patients with PD [19]. Physical exercise might represent a potential adjunctive treatment for neuropsychiatric disorders helping to delay the onset of neurodegenerative processes through neurotransmitter release, neurotrophic factor and neurogenesis, and cerebral blood flow alteration [20].

Depressive symptoms in antidepressant-naive patients with PD correlate with relatively higher serotonin binding in raphe nuclei and limbic structures, possibly reflecting lower extracellular serotonin levels. It was found that abnormal serotonergic neurotransmission plays a key role in contributing to the pathophysiology of PD depression [21]. This could help to explain how moderate aerobic exercise could be beneficial for brain health, which includes improving psychological status and cognitive function, in addition to enhancing psychological well being [21]. It is suggested that norepinephrine activation by β-adrenergic receptors may be essential for exercise-induced brain derived neurotrophic factor upregulation [22]. Furthermore, it was also suggested that physical activity and exercise probably alleviate some symptoms associated with mild-to-moderate depression and improve self-image, social skills, and cognitive functioning [23–25]. These findings could be explained by the possibility that aerobic exercise training may inhibit gray matter volume loss in the insula, and that a relationship may exist between preservation of insula gray matter and improvement of psychological well-being training [26]. The use of the treadmill for PD gait rehabilitation increased the step length and improved the gait impairment in PD [27]. It was concluded that treadmill training in patients with PD improved lower extremity functional tasks and patients' physical well being in daily life [28].

As reported previously, treadmill exercise leads to improvement of motor performance [29]; it was also demonstrated that treadmill exercise leads to increased latency to fall (improved balance). These findings suggested that treadmill exercise may, through adaptive changes of the basal ganglia and motor circuitry, lead to improvement in related motor tasks, and the beneficial effects of exercise are accompanied by differential effects on the dopaminergic system [30].

Limitations
The relatively small sample size and the short-term nature of the program are factors that limit generalizations to a broader population of individuals.

References
1 Giroux ML. Parkinson disease: managing a complex, progressive disease at all stages. Cleve Clin J Med 2007; 74:313–328.

2 Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2008; 23: 631–640.

3 Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the quality standards subcommittee of the American academy of neurology. Neurology 2006; 66:976–982.

4 Reichmann H. Clinical criteria for the diagnosis of Parkinson's disease. Neurodegener Dis 2010; 7:284–290.

5 Farabaugh A, Locascio JJ, Yap L, Growdon J, Fava M, Crawford C, et al. Cognitive-behavioral therapy for patients with Parkinson's disease and comorbid major depressive disorder. Psychosomatics 2010; 51:124–129.

6 Morris ME. Movement disorders in people with parkinson disease: a model for physical therapy. Phys Ther 2000; 80:578–597.

7 Beucke JC, Uhl I, Plotkin M, Winter C, Assion HJ, Endrass T, et al. Serotonergic neurotransmission in early Parkinson's disease: a pilot study to assess implications for depression in this disorder. World J Biol Psychiatry 2010; 11:781–787.

8 Ebersbach G, Edler D, Kaufhold O, Wissel J. Whole body vibration versus conventional physiotherapy to improve balance and gait in Parkinson's disease. Arch Phys Med Rehabil 2008; 89:399–403.

9 Sarbadhikari SN, Saha AK. Moderate exercise and chronic stress produce counteractive effects on different areas of the brain by acting through various neurotransmitter receptor subtypes: a hypothesis. Theor Biol Med Model 2006; 3. doi: 10.1186/1742-4682-3-33. Art. No. 33.

10 Kirby S. The positive effect of exercise as a therapy for clinical depression. Nurs Times 2005; 101:28–29.

11 Blake H, Mo P, Malik S, Thomas S. How effective are physical activity interventions for alleviating depressive symptoms in older people? A systematic review. Clin Rehabil 2009; 23:873–887.

12 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62.

13 Fahn S, Elton RL. Members of the UPDRS development committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent development in Parkinson's disease. 3rd ed. Florham Park, NJ: MacMillan Healthcare Information; 1987. pp. 293–304.

14 Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6:278–296.

15 Klerman GL, Lavori PW, Rice J. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. Arch Gen Psychiatry 1985; 42:689–693.

16 Preskorn SH, Fast GA. Beyond signs and symptoms: the case against a mixed anxiety and depression category. J Clin Psychiatry 1993; 54 (Suppl 1):24–32.

17 Carroll BJ, Fielding JM, Blashki TG. Depression rating scales: a critical review. Arch Gen Psychiatry 1973; 28:361–366.

18 Kearns NP, Cruickshank CA, McGuigan KJ. A comparison of depression rating scales. Br J Psychiatry 1982; 141:45–49.

19 Yousefi B, Tadibi V, Khoei A, Montazeri A. Exercise therapy, quality of life and activities of daily living in patients with Parkinson disease: a small scale quasi-randomised trial. Trials 2009; 10. Art. No. 67. Published online 11 August 2009. http://dx.crossref.org/10.1186%2F1745-6215-10-67"10.1186/1745-6215-10-67.

20 Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, et al. Exercise and mental health: many reasons to move. Neuropsychobiology 2009; 59:191–198.

21 Politis M, Wu K, Loane C, Turkheimer FE, Molloy S, Brooks DJ, et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology 2010; 75:1920–1927.

22 Ma Q. Beneficial effects of moderate voluntary physical exercise and its biological mechanisms on brain health. Neurosci Bull 2008; 24:265–270.

23 Taylor CB, Sallis JF, Needle R. The relation of physical activity and exercise to mental health. Public Health Rep 1985; 100:195–202.

24 Mota Pereira J, Silverio J, Carvalho S, Ribeiro JC, Fonte D, Ramos J. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J Psychiatr Res, article in press.

25 Arcos Carmona IM, Castro Sánchez AM, Matarán Peñarrocha GA, Gutiérrez Rubio AB, Ramos González E, Moreno Lorenzo C. Effects of aerobic exercise program and relaxation techniques on anxiety, quality of sleep, depression and quality of life in patients with fibromyalgia: a randomized controlled trial. Med Clin 2011; (in press).

26 Gondoh Y, Sensui H, Kinomura S, Fukuda H, Fujimoto T, Masud M, et al. Effects of aerobic exercise training on brain structure and psychological well-being in young adults. J Sports Med Phys Fitness 2009; 49:129–135.

27 Bello O, Sanchez JA, Fernandez del Olmo M. Treadmill walking in Parkinson's disease patients: adaptation and generalization effect. Mov Disord 2008; 23:1243–1249.

28 Kurtais Y, Kutlay S, Tur BS, Gok H, Akbostanci C. Does treadmill training improve lower-extremity tasks in Parkinson disease? A randomized controlled trial. Clin J Sport Med 2008; 18:289–291.

29 Fisher BE, Petzinger GM, Nixon K, Hogg E, Bremmer S, Meshul CK, et al. Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. J Neurosci Res 2004; 77:378–390.

30 Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, et al. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci 2007; 27:5291–5300.

الملخص العربي

دراسه العلاقه بين التمرينات الهوائيه المتوسطه و النشاطات اليوميه و الاكتئاب في مرضي باركنسون

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مقدمه : مرض باركنسون يتسبب في شذوذ مميز لنمط المشي والحاله النفسيه و كذلك النشاطات اليوميه للمريض

الهدف : دراسه العلاقه بين التمرينات الهوائيه المتوسطه و النشاطات اليوميه و الاكتئاب في مرضي باركنسون.

طريقه و أدوات البحث: أجريت هذه الدراسة على مجموعة من مرضى باركنسون المترددين على العيادة الخارجية

بكلية العلاج الطبيعي — جامعة القاهرة. تم تقسيم المرضى عشوائيا إلي مجموعتين متساويتين. تلقت إحداهما علاجا

طبيعيا تقليديا و تمرينات هوائيه متوسطه (بواسطه سير المشي الكهربائي)و تلقت المجموعة الأخرى من المرضى

البرنامج التقليدي فقط . كما تم تطبيق مقياس هاملتون للاكتئاب للمجموعتين قبل و بعد العلاج الطبيعي. **النتائج:**

أثبتت النتائج أن مرضي باركنسون في المجموعتين شهدوا تحسن في النشاطات اليوميه و الاكتئاب و لكن التحسن

كان أكثر في المجموعه التي خضعت للتمرينات الهوائيه.

An oral pathogen and psychopathology severity in a sample of Arab patients with schizophrenia

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Background
Patients with schizophrenia are known to have poor oral health and to die early from cardiovascular disease. It is also known that *Porphyromonas gingivalis* is a periodontopathogen, which is implicated in a number of systemic diseases, particularly cardiovascular disease. However, little, if any, is known about the prevalence and the quantity of this organism in the mouth of patients with schizophrenia.

Aim
To estimate the prevalence and quantity of *P. gingivalis* in saliva of patients with schizophrenia compared with nonpsychiatric controls and to correlate the quantity of *P. gingivalis* with the severity of psychopathology of schizophrenia.

Methods
Forty-three consecutive Arab attendees of the outpatient clinic of a psychiatric Hospital in Jeddah, with a diagnosis of schizophrenia, were assessed by the Positive and Negative Syndrome Scale and the Clinical Global Impression-Severity Scale. They were compared with 43 nonpsychiatric controls, in terms of the prevalence and in terms of the quantity of *P. gingivalis* in their saliva. For this purpose, anerobic culture and real-time polymerase chain reaction (PCR) with a TaqMan probe were used.

Results
In 82 (approximately 95%) participants, the real-time PCR results were matching those obtained with anerobic culture. Using real-time PCR, *P. gingivalis* was detected in 30 (approximately 70%) patients and in six (approximately 14%) controls ($P=0.000$). The *P. gingivalis* median (range) number of copies in salivary samples of patients and controls were 5.6×10^7 ($0-2.79^{10}$) and 1.9×10^5 ($0-6.84^7$), respectively ($P=0.002$). In addition, the *P. gingivalis* levels were positively correlated with the scores on all the Positive and Negative Syndrome Scale and Clinical Global Impression-Severity Scale.

Conclusion
Real-time PCR, in keeping with the results of quantitative culture, showed that (i) there is a higher prevalence and quantity of *P. gingivalis* in saliva of a sample of Arab patients with schizophrenia compared with nonpsychiatric controls and (ii) that there is a positive correlation between quantity of *P. gingivalis* cells and the severity of psychopathology of schizophrenia. Hopefully, the results of this pilot study will encourage further research into the relationships between oral microbiota and schizophrenia. Real-time PCR, as demonstrated by this study, is a promising tool in this area. It is also hoped that some preventive dental programs will become an integral part of a comprehensive psychiatric management to meet the need of this vulnerable group of population.

Keywords:
Clinical Global Impression-Severity Scale, oral health, *Porphyromonas gingivalis*, Positive and Negative Syndrome Scale, real-time PCR, saliva, schizophrenia

Introduction

Patients with schizophrenia have poor physical health and high rates of mortality [1–3]. Oral health, which is an integral part of the general health and contributes to self esteem and quality of life, may have a low priority among these patients who are, nevertheless, liable to get dental problems [4]. General self-neglect associated with mental illness, misconceptions, fear of treatment, worry about the cost of treatment, inability to access dental services, and the adverse effects of medications are among the most commonly cited barriers to dental care [5,6].

It has been estimated that more than 700 different bacterial species inhabit the human oral cavity [7].

Although the majority of oral microflora are normal/commensal bacteria, some of them are opportunistic pathogens responsible for the development of oral microbial infectious diseases such as dental caries and periodontitis [8]. One of the most pathogenic species of the entire oral flora and perhaps the most extensively studied species at the molecular level is *Porphyromonas gingivalis*. This pathogen is frequently found as a prominent component of the flora of subgingival lesions of adult patients with periodontitis [9]. However, *P. gingivalis* not only causes chronic localized oral conditions but may also increase the risk of systemic diseases, such as atherosclerotic heart disease [10].

In patients with periodontitis, *P. gingivalis* can be detected in saliva, on the dorsum of the tongue, tonsils, buccal mucosa, gingiva, and other mucous membranes [11], whereas in periodontally healthy individuals, this organism is usually absent, or if present it is in low numbers [12]. Studies suggest that periodontal disease can be minimized through maintenance of oral cleanliness [13]. However, noncompliance is a major issue [14]. Although it is a universal phenomenon, noncompliance appears to affect people with severe mental illness, such as schizophrenia, considerably more than other people [15]. In these patients, noncompliance is found to be as high with nonpsychiatric drugs as with psychiatric medications [16] and is probably related to the severity of psychopathology [17,18]. These patients are further disadvantaged not only by having higher rates of physical illnesses than those without schizophrenia but also by experiencing greater difficulty in obtaining adequate healthcare [19].

To date, however, there has been relatively little research assessing orodental status of patients with schizophrenia. Most of these studies have been published in specialty journals in the field of oral health [4] and have focused on institutionalized chronic patients (for example, [20–22]), although the majority of patients are now living outside hospital. Moreover, approaches have been mostly restricted to a clinical descriptive level using self-report questionnaires (for example, [5,23,24]) and/or clinical dental examinations (for example, [21,25–27]), with main interest centered around merely counting the number of teeth. It may be rather surprising that, despite the availability and the researchers' extensive use of various procedures to examine oral microorganisms in various populations, no previous attempts have been made, as far as we know, to detect or quantify oral opportunistic pathogens, such as *P. gingivalis*, in patients with schizophrenia. These patients are particularly prone to cardiovascular disease [28], which is the chief cause of their excess premature mortality [29]. Ironically, oral infection with *P. gingivalis* has been also strongly associated with cardiovascular disease, even after adjustment for established cardiovascular risk factors [10]. However, it is not known whether there is any relationship between *P. gingivalis* and schizophrenia, although researchers have tried, for more than a century, and still trying to find a role for infectious agents in triggering schizophrenia [30].

The aim of this study is to estimate the prevalence and quantity of *P. gingivalis* in saliva of patients with schizophrenia compared with nonpsychiatric controls and to correlate the quantity of *P. gingivalis* with the severity of psychopathology of schizophrenia. We hypothesize that the severity of oral infection in patients with schizophrenia is related to the severity of psychopathology.

Methods

A total of 43 Arab nationals were recruited from consecutive attendees of the outpatient clinic of a large private psychiatric hospital in Jeddah during the year 2010, with a diagnosis of schizophrenia [F.20 of the International Classification of Diseases tenth revision (ICD-10)]) [31]. The duration of the condition was at least 1 year. The patients' age range was 20–50 years. Patients were consistently prescribed a stable regimen of antipsychotic medication for at least 3 months before recruitment.

The control group consisted of 43 participants, individually matched for age and sex and randomly selected from companions of patients and from hospital employees and their acquaintances.

None of the participants had current febrile acute infection, acute exacerbation of a chronic infection, or an inflammatory disease, underlying hematologic, malignant, severe cardiac, liver, or renal disease. None had used antibiotics or had undergone any dental or general surgery within the previous 3 months. Participants who had missing teeth and women who were pregnant or lactating were excluded from the study. Body mass index greater than or equal to 35 or less than or equal to 18 and blood pressure of more than 150/90 were also exclusion criteria. Controls had no evidence of current or history of any psychiatric disorder. Written informed consent was obtained from each participant. Patients underwent a standardized psychiatric interview during which the ICD-10 diagnosis of schizophrenia was confirmed and two measures were administered by a trained psychiatrist: (i) the Positive and Negative Syndrome Scale (PANSS) [32]. This is a 30-item test, subdivided into three subscales: a Positive Scale composed of seven items, a Negative Scale composed of seven items, and a General Psychopathology Scale composed of 16 items. Each item is rated on a seven-point severity scale from 1 (no evidence) to 7 (extreme). (ii) The Clinical Global Impression-Severity Scale (CGIs) [33]. This subscale of CGI assesses the psychiatrist's impression of the patient's current illness state on a scale ranging from 1 (not ill at all) to 7 (extremely ill).

Saliva sampling procedure

Saliva specimens were collected by expectoration into sterile calibrated medical cups. Saliva was put into Eppendorf tubes, which were immediately frozen at -80° and stored until used in real-time polymerase chain reaction (PCR). For the detection of *P. gingivalis* by

bacterial culture, saliva samples were pooled in 1.5 ml of reduced transport fluid and were processed for cultivation under anerobic conditions within 4 h of sampling. Samples were vortexed for 2 min and split. A total of 100 µl of the sample was used for culture by 10-fold serial dilution in sterile phosphate-buffered saline solution.

Microbial culture

Serial 10-fold dilutions were prepared, and the last three dilutions were used for plating on blood agar plates (Oxoid, Basingstoke, UK) supplemented with horse blood (5%; vol/vol), hemin (5 mg/l), and menadione (1 mg/l). This was incubated anerobically in jars filled by the evacuation–replacement method with a mixture of gases (85% N_2, 10% H_2, 5% CO_2) at 37°C for 7–14 days. The isolates were identified as *P. gingivalis* on the basis of Gram staining, anerobic growth, having the typical colony color and morphology, lacking colony autofluorescence, positive hemagglutination with 3% sheep erythrocytes, production of a set of metabolic enzymes (as tested with the Rapid ID kit 32A), and having a positive indole reaction. The total number of colony forming unit of *P. gingivalis* in positive samples was determined.

Real-time polymerase chain reaction
Isolation of DNA

To extract DNA from the bacteria present in saliva, frozen suspensions were thawed and 100 µl of sample was used for automated DNA extraction and for purification with the MagNA Pure DNA Isolation Kit III (Bacteria, Fungi; Roche Molecular Diagnostics, Roche Diagnostics Corporation, Indianapolis, USA). The protocol included 1 h of pretreatment with proteinase K (20 mg/ml) at 56°C. After isolation, the DNA was eluted in 100 µl of elution buffer.

Polymerase chain reaction primers and probes

The 16S rRNA sequences of the genus *Porphyromonas* were selected. The sequence of the forward primer was 5′-GCGCTCAACGTTCAGCC-3′ (basepairs 612–628); the sequence of the reverse primer was 5′-CACGAATTC CGCCTGC-3′ (basepairs 664–679); and the sequence of the TaqMan probe was 5′-CACTGAACTCAAGCCCGG CAGTTTCAA-3′ (basepairs 634–660) The primers and probes were purchased from Applied Biosystems (Foster City, California, USA).

Quantitative polymerase chain reaction assay

PCR amplification was performed in a total reaction mixture volume of 25 µl. The reaction mixtures contained 12.5 µl of $2\times$ TaqMan universal PCR master mixture (PCR buffer, deoxynucleoside triphosphates, AmpliTaq Gold, an internal reference signal (6-carboxy-X-rhodamine), uracil *N*-glycosylase, $MgCl_2$; Applied Biosystems), *P. gingivalis*-specific primer (300 nmol/l each), *P. gingivalis*-specific probe (100 nmol/l), and 5 µl of purified DNA from plaque samples. Five microliters of the DNA extracted from *P. gingivalis* W83 was used to prepare the standard curve and as a positive control; the negative control was 5 µl of sterile H_2O. The samples were subjected to an initial amplification cycle of 50°C for

2 min and 95°C for 10 min, followed by 45 cycles at 95°C for 15 s and 60°C for 1 min.

The degradation of the probe by the DNA polymerase in each elongation step induces an increase in fluorescence that can be monitored during PCR amplification. The fluorescence signal is normalized by dividing the reporter dye emission (6-carboxyfluorescein) by the emission of the passive reference (6-carboxy-X-rhodamine). The higher the starting copy number of the nucleic acid target is, the sooner a significant increase in fluorescence is observed. Hence, this parameter can be used to compare different amplification reactions. The number of bacterial copies was calculated assuming that the genome mass is equal to 2.37 fg (femtogram = 10^{-15} g) [34].

Statistical analysis

Continuous data were expressed as mean [± standard deviation (SD)] or median (range) and were compared using Student's *t*-test, after testing for normality with a Kolmogorov–Smirnov test and after normalization by log-transformation where appropriate. Categorical data were expressed as frequencies or proportions and were analyzed with the two-tailed χ^2 test. Correlations between data were analyzed using Pearson's coefficient. Data that significantly correlated with *P. gingivalis* number of copies, after testing for potential collinearity using Pearson's correlations, were further analyzed using step-wise multivariate linear regression analysis with both forward selection and backward elimination ($P < 0.05$ for entry and $P > 0.10$ for removal). The SPSS statistical program, version 11.5 (SPSS for Windows, 2001, SPSS Inc, Chicago, Illinois, USA) was used for all statistical analyses and for sample size estimation. A two-tailed *P* value of less than 0.05 was considered significant.

Results
Background characteristics of participants

Patients and controls were not different, except that more patients were 'currently smoking' (Table 1).

Severity of psychopathology in the patient group

Mean (± SD) of scores of patients on the standard scales of PANSS and CGIs are given in Table 2.

Prevalence of salivary *P. gingivalis*

P. gingivalis was more prevalent in saliva from patients than controls. *P. gingivalis* was detected in approximately 70% (30 of 43) of the patient group but was found only in approximately 14% (six of 43) of the controls (Table 3). For either group, no relationship was found between detection of *P. gingivalis* and sex, age, or nationality. However, significant relationships were observed in both groups between *P. gingivalis* detection and being less educated, being in a lower occupational position, being unmarried, being a current smoker, and not being a Miswak user (Table 3).

Table 1 Background characteristics of participants

	Patients ($N=43$)	Controls ($N=43$)	Significance
Sex			
Male (n)	25	25	$\chi^2=0.000$; d.f.$=1$; $P=1.000$
Female (n)	18	18	
Age (years):			
Mean ($\pm$SD)	29.7 ($\pm$8.9)	30.3 ($\pm$9.0)	$T=0.361$; d.f.$=84$; $P=0.719$
Age group:			
$<$30 years (n)	28	27	$\chi^2=0.050$; d.f.$=1$; $P=0.822$
$>$30 years (n)	15	16	
Nationality:			
Saudi (n)	20	21	$\chi^2=0.047$; d.f.$=1$; $P=0.829$
Non-Saudi Arab (n)	23	22	
Education level:			
Intermediate or below (n)	33	25	$\chi^2=3.389$; d.f.$=1$; $P=0.066$
Above intermediate (n)	10	18	
Occupation:			
Higher (n)	8	15	$\chi^2=2.908$; d.f.$=1$; $P=0.088$
Lower (n)	35	28	
Marital status:			
Married (n)	21	27	$\chi^2=1.697$; d.f.$=1$; $P=0.193$
Unmarried[a] (n)	22	16	
Currently smoking			
Yes (n)	27	15	$\chi^2=6.701$; d.f.$=1$; $P=0.010$
No (n)	16	28	
Miswak[b] habitual user:			
Yes (n)	19	23	$\chi^2=0.745$; d.f.$=1$; $P=0.388$
No (n)	24	20	

[a]Never married, divorced, separated, and widowed.
[b]Tooth cleaning stick.

Number of *P. gingivalis* cells

Table 4 shows the results of absolute quantification of *P. gingivalis* cells determined in individual PCR runs. There is a significant difference between the number of *P. gingivalis* cells in salivary samples of patients and controls.

Relationship of the salivary *P. gingivalis* count with the severity of psychopathology in the patient group

The salivary levels of *P. gingivalis* were significantly positively correlated with the scores on all the PANSS subscales. The highest correlation was noted with the negative subscale. *P. gingivalis* count also positively correlated with the CGI score for severity (Table 5).

Comparison between polymerase chain reaction and culture

Results obtained with real-time PCR were matching those obtained with anerobic culture in 95.3% of cases

Table 2 Scores of patients on the Positive and Negative Syndrome Scale and Clinical Global Impression-Severity Scale

Scale	Score
PANSS	
Total	
Mean ($\pm$SD)	84.6 ($\pm$14.9)
Positive	
Mean ($\pm$SD)	23.2 ($\pm$3.2)
Negative	
Mean ($\pm$SD)	24.0 ($\pm$3.1)
General psychopathology	
Mean ($\pm$SD)	37.5 ($\pm$9.1)
CGIs	5.8 ($\pm$1.1)

CGI, Clinical Global Impression-Severity Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

(32 positive; 50 negative). A two-by-two contingency table summarizes the results (Table 6). *P. gingivalis* was cultured from 32 (37.2%) of the 86 saliva specimens. All these culture-positive samples were also positive by the real-time PCR assay. In addition, four samples were positive for *P. gingivalis* by the real-time PCR but negative by culture. These samples were thawed and recultured for 14 days. Two of these samples yielded *P. gingivalis* after this prolonged culture. All the 50 culture-negative samples were negative by the PCR assay (100% specificity). None (0%) of the PCR negatives was found to be culture positive (Table 6).

Further analyses were performed and stepwise forward multivariate regression analysis was conducted for the whole sample ($N=86$) using the logarithmically transformed number of copies of *P. gingivalis* as the dependent variable and sex, age, nationality, education level, occupation, marital status, current smoking status, Miswak habitual use, and presence/absence of schizophrenia diagnosis as independent variables. The final model that emerged from the stepwise analysis contained only three predictors. In this model, the presence of schizophrenia diagnosis remained significantly correlated with the number of copies of *P. gingivalis* (Table 7).

Discussion

We believe that this study is the first to report a higher prevalence of the oral pathogen, *P. gingivalis*, in saliva from patients with schizophrenia than matched nonpsychiatric controls, independent of sex, age, nationality, education level, occupation, marital status, current smoking status, and Miswak habitual use. We used saliva because, as an

Table 3 Prevalence of _P. gingivalis_ by real-time PCR[a]

	Real-time PCR Positive	Real-time PCR Negative	Significance χ^2 (d.f. = 1)	P
	N	N		
All participants				
Patients	30	13	27.520	0.000
Controls	6	37		
Sex				
Patients				
Male	19	6	1.100	0.294
Female	11	7		
Controls				
Male	3	22	0.190	0.663
Female	3	15		
Total				
Male	22	28	0.225	0.636
Female	14	22		
Age				
Patients				
<30 years	19	9	0.139	0.709
>30 years	11	4		
Control				
<30 years	3	24	0.488	0.485
>30 years	3	13		
Total				
<30 years	22	33	0.217	0.641
>30 years	14	17		
Nationality:				
Patients				
Saudi	12	8	1.691	0.193
Non-Saudi	18	5		
Control				
Saudi	2	19	0.671	0.413
Non-Saudi	4	18		
Total				
Saudi	14	27	1.916	0.166
Non-Saudi	22	23		
Education level:				
Patients				
Intermediate or below	28	5	15.301	0.000
Above intermediate	2	8		
Control				
Intermediate or below	6	19	5.021	0.025
Above intermediate	0	18		
Total				
Intermediate or below	34	24	20.561	0.000
Above intermediate	2	26		
Occupation:				
Patients				
Higher	1	7	15.282	0.000
Lower	29	6		
Control				
Higher	0	16	4.132	0.042
Lower	6	21		
Total				
Higher	1	23	19.435	0.000
Lower	35	27		
Marital status:				
Patients				
Married	11	10	5.882	0.015
Unmarried[a]	19	3		
Control				
Married	0	27	11.767	0.001
Unmarried[a]:	6	10		
Total				
Married	11	37	16.018	0.000
Unmarried[a]	25	13		
Current smoker:				
Patients				
Yes	24	3	12.578	0.000
No	6	10		
Control				
Yes	5	10	7.206	0.007
No	1	27		
Total				
Yes	29	13	24.931	0.000
No	7	37		

Table 3 (_continued_)

	Real-time PCR Positive	Real-time PCR Negative	Significance χ^2 (d.f. = 1)	P
	N	N		
Miswak[b]habitual user				
Patients				
Yes	10	9	4.739	0.029
No	20	4		
Control				
Yes	0	23	8.019	0.005
No	6	14		
Total				
Yes	10	32	10.991	0.001
No	26	18		

[a]Number of pareticipants with _P. gingivalis_/Number of participants tested (%).
[b]Tooth cleaning stick.

oral circulating fluid, saliva is heavily laden with bacteria (108–109 cfu/ml) [35]. Earlier, all 16S rRNA sequences of the genus _Porphyromonas_-based saliva studies had used qualitative PCR. For the detection and quantification of _P. gingivalis_ in saliva samples in this study, however, we compared the results of a quantitative anaerobic culture method with those of a real-time TaqMan PCR assay, which is, unlike conventional PCR assays, less susceptible to PCR inhibition [36] and is suggested to provide a sensitive, efficient, and reliable approach to quantitation [37]. In keeping with this suggestion, we found the sensitivity, specificity, and positive and negative predictive values of the real-time PCR to be 88.9, 100, 100, and 92.6%, respectively. Therefore, we conclude that real-time PCR confirms the results of quantitative culture of _P. gingivalis_ and offers promising advantages with respect to the rapidity and sensitivity of detection of _P. gingivalis_ in saliva samples. Until recently, however, very little attention has been given to the quantification of _P. gingivalis_ in saliva, whether of psychiatric or nonpsychiatric populations.

Our results demonstrated that in both patients and in controls _P. gingivalis_ detection was correlated with being less educated and with being in a lower occupational position. These results are consistent with previous studies, which have shown that periodontitis is more common among people with low rather than with high socioeconomic status, regardless of the indicator used [38]. Interestingly, despite the low socioeconomic level of many of our clients, they probably preferred to attend our private service over the charge-free centers available in the region. Whatever be the reason, it seems that poverty, which raises the risk of schizophrenia, especially deficit schizophrenia [39], might have preferentially reduced the chance of receiving adequate dental care and hence could partly explain our results. However, this study has also shown in the nonpsychiatric controls a somewhat similar trend of association between high prevalence of oral _P. gingivalis_ and low educational and occupational levels.

Our finding that the _P. gingivalis_ detection was more frequent among unmarried than married people in both patients and controls is also consistent with other studies

Table 4 Number of copies (median and range values) of *P. gingivalis* in salivary samples of patients and controls assessed by real-time PCR absolute quantification.

	Patients	Controls	Significance[a]
Median (range)	$5.6 \times 10^7 (0{-}2.79^{10})$	$1.9 \times 10^5 (0{-}6.84^7)$	$t=3.136$; d.f.$=84$; $P=0.002$

[a]After normalization using logarithmic transformation.

Table 5 Correlation coefficients between number of copies of *P. gingivalis* in salivary samples of patients and scores on the PANSS and CGIs ($N=43$)

Scale	r	P
PANSS scale		
Total	0.437	0.003
Positive	0.328	0.032
Negative	0.484	0.001
General psychopathology	0.393	0.009
CGIs	0.453	0.002

CGI, Clinical Global Impression-Severity Scale; PANSS, Positive and Negative Syndrome Scale.

Table 6 Detection of *P. gingivalis* by real-time PCR and anerobic culture

	Real-time PCR result[a]		
Anerobic culture result	Positive (n)	Negative (n)	Total (N)
Positive (n)	32	0	32
Negative (n)	4	50	54
Total (n)	36	50	86

[a]Sensitivity$=88.9\%$; specificity$=100.0\%$; positive predictive value$=100.0\%$; negative predictive value$=92.6\%$.

Table 7 Stepwise multiple regression analysis of variables significantly related to number of copies of *P. gingivalis* among total participants ($N=86$)

Variable	B	SE	β	t	P
Constant	14.790	2.093		7.065	0.000
Smoker	3.802	1.145	0.373	3.321	0.001
Schizophrenia diagnosis	3.097	0.890	0.304	3.479	0.001
Education	2.467	1.195	0.227	2.065	0.042

Regression analysis included sex, age, nationality, education level, occupation, marital status, current smoking status, Miswak habitual use, and schizophrenia diagnosis. B$=$raw (unstandardized) regression coefficient for the association between stated variables and number of copies of *P. gingivalis*.
Adjusted $R^2=0.411$; $F=20.753$; $P=0.000$.
SE, standard error.

symptoms such as lack of initiative (PANSS: N2), apathy, anergy, or avolition (PANSS: N4), etc. would likely lead to reduced self-care and poor dental health, far worse than that of members of the general population [5]. However, a cause and effect relationship between severities of the negative or other symptoms of schizophrenia and quantities of the oral pathogen should not be claimed by this pilot study, at least because of the limitation of its cross-sectional design.

Among participants those with evidence of cardiovascular disease were excluded from the study. However, this variable would have been important and interesting to investigate when relating to both *P. gingivalis* and schizophrenia. Moreover, the study was limited by not reporting some rather relevant data such as details of medication history, general and dental clinical and radiographic examination findings. We did not assess the cognitive functions, although the central role of cognitive dysfunction in schizophrenia has been increasingly appreciated [45], whereas there have been some suggestions that cognitive impairment may be associated with periodontal disease [46,47]. Moreover, the endocrine and metabolic status of the participants, despite relevance to both schizophrenia and oral infections with a possible confounding role, were not evaluated. One more limitation is the relatively small sample size.

showing higher susceptibility to various infections among single, widowed, and separated individuals rather than married individuals, independent of other demographic factors [40].

In addition, in keeping with other studies, which have indicated that smoking significantly increases the risk for the development of extensive and severe oral infections [41], we found significant correlation between *P. gingivalis* detection and current smoking in both patients and in controls. In the final model of regression analysis, we found that being a current smoker was the most predictive variable for the level of *P. gingivalis* in saliva.

Interestingly, habitual use of 'Miswak' (the chewing stick or the traditional toothbrush commonly used in Saudi Arabia and many Islamic countries) was negatively associated in this study with *P. gingivalis* detection. This should lend support to the few previous studies, which have suggested that regular use of Miswak is associated with good oral health [42–44].

Correlation coefficients of the salivary levels of *P. gingivalis* with scores on PANSS and CGIs were determined in this study. The results showed that *P. gingivalis* levels were significantly associated with the severity of schizophrenia psychopathology as expressed by scores of both instruments, with negative symptoms presenting the strongest correlation. The achieved results were not unexpected, considering that negative symptoms, which include

Conclusion
Within the limits of this study, we conclude that the real-time PCR has confirmed the results of quantitative culture and has demonstrated significantly higher prevalence and quantity of *P. gingivalis* in the saliva of patients with schizophrenia compared with nonpsychiatric controls. Both real-time PCR and quantitative culture have also confirmed a positive correlation between quantity of *P. gingivalis* cells and severity of psychopathology of schizophrenia. This pilot study may be the first to

report such findings. It is hoped, however, that the results will encourage further research into the relationships between oral microbiota and schizophrenia. Real-time PCR, with its capacity to produce both qualitative and quantitative results, is a promising tool in this area. We should also hope that the need of the mentally ill for more dental care will be appreciated by all concerned and that some preventive dental programs will become an integral part of comprehensive psychiatric management to meet the need of this vulnerable group of population.

There is no conflict of interest to declare.

References

1 El Mallakh P, Howard PB, Evans BN. Medical illnesses in people with schizophrenia. Nurs Clin North Am 2010; 45:591–611.

2 Pack S. Poor physical health and mortality in patients with schizophrenia. Nurs Stand 2009; 23:41–45.

3 Von Hausswolff Juhlin Y, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. Acta Phychiatr Scand Suppl 2009; 438:15–21.

4 Arnaiz A, Zumárraga M, Diez Altuna I, Uriarte JJ, Moro J, Pérez Ansorena MA. Oral health and the symptoms of schizophrenia. Psychiatry Res 2010; [Epub ahead of print].

5 McCreadie RG, Stevens H, Henderson J, Hall D, McCaul R, Filik R, et al. The dental health of people with schizophrenia. Acta Psychiatr Scand 2004; 110:306–310.

6 Mirza I, Day R, Phelan M, Wulff Cochrane V. Oral health of psychiatric in-patients: a point prevalence survey of an inner-city hospital. Psychiatr Bull 2001; 25:143–145.

7 Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. J Clin Microbiol 2005; 43:5721–5732.

8 Marsh PD, Percival RS. The oral microflora–friend or foe? Can we decide? Int Dent J 2006; 56 (4 Suppl 1):233–239.

9 Loos BG, Dyer DW, Whittam TS, Selander RK. Genetic structure of populations of Porphyromonas gingivalis associated with periodontitis and other oral infections. Infect Immun 1993; 61:204–212.

10 Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease. Clin Microbiol Infect 2007; 13 (Suppl 4):3–10.

11 Van Winkelhoff AJ, Van der Velden U, Clement M, De Graaff J. Intra-oral distribution of black-pigmented bacteroides species in periodontitis patients. Oral Microbiol Immunol 1988; 3:83–85.

12 Griffen AL, Becker MR, Lyons SR, Moeschberger ML, Leys EJ. Prevalence of Porphyromonas gingivalis and periodontal health status. J Clin Microbiol 1998; 36:3239–3242.

13 Ciancio S. Improving oral health: current considerations. J Clin Periodontol 2003; 30 (Suppl 5):4–6.

14 Miyamoto T, Kumagai T, Jones JA, Van Dyke TE, Nunn ME. Compliance as a prognostic indicator: retrospective study of 505 patients treated and maintained for 15 years. J Periodontol 2006; 77:223–232.

15 Surguladze S, Timms P, David AS. Teaching psychiatric trainees 'compliance therapy'. Psychiatr Bull 2002; 26:12–15.

16 Dolder CR, Lacro JP, Jeste DV. Adherence to antipsychotic and nonpsychiatric medications in middle-aged and older patients with psychotic disorders. Psychosom Med 2003; 65:156–162.

17 Rettenbacher MA, Hofer A, Eder U, Hummer M, Kemmler G, Weiss EM, et al. Compliance in schizophrenia: psychopathology, side effects and patients' attitudes toward the illness and medication. J Clin Psychiatry 2004; 65:1211–1218.

18 Stanković Z, Britvić D, Vuković O, Ille T. Treatment compliance of outpatients with schizophrenia: patient's attitudes, demographic, clinical and therapeutic variables. Psychiatr Danub 2008; 20:42–52.

19 Sartorius N. Physical illness in people with mental disorders. World Psychiatry 2007; 6:3–4.

20 Gurbuz O, Alatas G, Kurt E, Issever H, Dogan F. Oral health and treatment needs of institutionalized chronic psychiatric patients in Istanbul, Turkey. Community Dent Health 2010; 27:151–157.

21 Chu KY, Yang NP, Chou P, Chiu HJ, Chi LY. Factors associated with dental caries among institutionalized residents with schizophrenia in Taiwan: a cross-sectional study. BMC Public Health 2010; 10:482.

22 Zusman SP, Ponizovsky AM, Dekel D, Masarwa AE, Ramon T, Natapov L, et al. An assessment of the dental health of chronic institutionalized patients with psychiatric disease in Israel. Spec Care Dentist 2010; 30:18–22.

23 Hede B, Petersen PE. Self-assessment of dental health among Danish noninstitutionalized psychiatric patients. Spec Care Dentist 1992; 12:33–36.

24 Persson K, Axtelius B, Söderfeldt B, Ostman M. Oral health-related quality of life and dental status in an outpatient psychiatric population: a multivariate approach. Int J Ment Health Nurs 2010; 19:62–70.

25 Gowda EM, Bhat PS, Swamy MM. Dental health requirements for psychiatric patient. MJAFI 2007; 63:328–330.

26 Lewis S, Jagger RG, Treasure E. The oral health of psychiatric in-patients in South Wales. Spec Care Dentist 2001; 21:182–186.

27 Rekha R, Hiremath SS, Bharath S. Oral health status and treatment requirements of hospitalized psychiatric patients in Bangalore city: a comparative study. J Indian Soc Pedod Prev Dent 2002; 20:63–67.

28 Callaghan RC, Boire MD, Lazo RG, McKenzie K, Cohn T. Schizophrenia and the incidence of cardiovascular morbidity: a population-based longitudinal study in Ontario, Canada. Schizophr Res 2009; 115:325–332.

29 Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J 2005; 150:1115–1121.

30 Yolken RH, Torrey EF. Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry 2008; 13:470–479.

31 World Health Organization. The ICD-10 classification of mental and behavioural disorders. Geneva: WHO; 1992.

32 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276.

33 Guy W. ECDEU assessment manual for psychopharmacology. U.S. National Institute of Health; 1976.

34 Nelson KE, Fleischmann RD, DeBoy RT, Paulsen IT, Fouts DE, Eisen JA, et al. Complete genome sequence of the oral pathogenic bacterium Porphyromonas gingivalis strain W83. J Bacteriol 2003; 185:5591–5601.

35 Gu F, Li Y, Zhou C, Wong DT, Ho CM, Qi F, et al. Bacterial 16S rRNA/rDNA profiling in the liquid phase of human saliva. Open Dent J 2009; 3:80–84.

36 Layton A, McKay L, Williams D, Garrett V, Gentry R, Sayler G. Development of bacteroides 16S rRNA gene TaqMan-based real-time PCR assays for estimation of total, human and bovine fecal pollution in water. Appl Environ Microbiol 2006; 72:4214–4224.

37 Lyons SR, Griffen AL, Leys EJ. Quantitative real-time PCR for Porphyromonas gingivalis and total bacteria. J Clin Microbiol 2000; 38:2362–2365.

38 Borrell LN, Burt BA, Neighbors HW, Taylor GW. Social factors and periodontitis in an older population. Am J Public Health 2004; 94:748–754.

39 Jones BJ, Gallagher BJ III, Pisa AM, McFalls JA Jr. Social class, family history and type of schizophrenia. Psychiatry Res 2008; 159:127–132.

40 Seymour CW, Iwashyna TJ, Cooke CR, Hough CL, Martin GS. Marital status and the epidemiology and outcomes of sepsis. Chest 2010; 137:1289–1296.

41 Shchipkova AY, Nagaraja HN, Kumar PS. Subgingival microbial profiles of smokers with periodontitis. J Dent Res 2010; 89:1247–1253.

42 Al Otaibi M, Zimmerman M, Angmar Mansson B. Prevailing oral hygiene practices among urban Saudi Arabians in relation to age, gender and socio-economic background. Acta Odontol Scand 2003; 61:212–216.

43 Asadi SG, Asadi ZG. Chewing sticks and the oral hygiene habits of the adult Pakistani population. Int Dent J 1997; 47:275–278.

44 Darout IA, Albandar JM, Skaug N. Periodontal status of adult Sudanese habitual users of miswak chewing sticks or toothbrushes. Acta Odontol Scand 2000; 58:25–30.

45 Nuechterlein KH, Green MF, Kern RS. Schizophrenia as a cognitive disorder: recent approaches to identifying its core cognitive components ti aid treatment development. Adv Schizophr Res 2009; 4:267–282.

46 Kaye EK, Valencia A, Baba N, Spiro A III, Dietrich T, Garcia RI. Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc 2010; 58:713–718.

47 Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. J Neurol Neurosurg Psychiatry 2009; 80:1206–1211.

الملخص العربي

جرثومة بالفم وشدة السيكوباثولوجيا في عينة من مرضى عرب لديهم فصام

مقدمة: من المعروف أن مرضى الفصام يتمتعون بصحة فم سيئة، و أنهم يموتون مبكرا بأمراض القلب والأوعية الدموية. من المعروف أيضا أن بكتريا (*P. gingivalis*) هي جرثومة مسببة لأمراض بالفم ومتورطة في عدد من الأمراض الجهازية، و على الأخص أمراض القلب والأوعية الدموية. لكنه من غير المعروف مدى انتشار وكمية هذه الجرثومة في فم مرضى الفصام. **الهدف:** تقدير مدى انتشار بكتريا (*P. gingivalis*) بين مرضى الفصام وتحديد كميتها في لعاب هؤلاء المرضى مقارنة بعينة ضابطة غير مريضة نفسيا، ودراسة ارتباط كمية (*P. gingivalis*) بشدة الأعراض المرضية-النفسية (السيكوباثولوجية). **الطرق:** أجري تقييم لثلاثة وأربعين عربيا من المترددين المتتاليين على عيادة خارجية بمستشفى نفسية بجدة ولديهم فصام، و ذلك باستخدام المقاييس (PANSS) و (CGIs)، كما تم مقارنتهم بثلاثة وأربعين شخصا (مجموعة ضابطة) من حيث مدى انتشار بكتريا (*P. gingivalis*) لديهم و تحديد كمية هذه البكتريا باللعاب باستخدام المزارع اللاهوائية و (real-time PCR). **النتائج:** في ٨٢ شخصا (نحو 95%) من كل المشاركين تطابقت نتائج ال (real-time PCR) مع المزارع اللاهوائية، و تم اكتشاف بكتريا (*P. gingivalis*) في ٣٠ (نحو 70%) من المرضى و ٦ (نحو 14%) من الأشخاص الضابطين (p=0.000). و كان مقدار الوسيط (و مدى) عدد نسخ البكتريا في عينات لعاب المرضى و الأشخاص الضابطين [(2.79^{10} -0) $5.6x10^7$] و [(6.84^7 -0) $1.9x10^5$] على الترتيب (p=0.002). كما كانت كميات بكتريا (*P. gingivalis*) مرتبطة ايجابيا بالدرجات على مقاييس (PANSS) جميعها و (CGIs). **الخلاصة:** أظهرت نتائج ال (real-time PCR) المتمشية مع المزارع اللاهوائية أن (أ) انتشار بكتريا (*P. gingivalis*) بين عينة من مرضى عرب مصابين بالفصام، وكمياتها في لعاب هؤلاء المرضى، كانا أعلى منهما في العينة الضابطة، و أن (ب) هناك علاقة ايجابية بين كمية بكتريا (*P. gingivalis*) و شدة السيكوباثولوجيا في الفصام. إننا نأمل أن تشجع نتائج هذه الدراسة الرائدة المزيد من البحث في العلاقات بين المجهريات الفمية والفصام. و كما اظهرت الدراسة الحالية فإن ال (real-time PCR) هي أداة واعدة في هذا المجال. نأمل أيضا أن تدخل بعض البرامج الوقائية للأسنان كجزء لا يتجزأ من الرعاية الطب-نفسية الشاملة لتلبية حاجة هذه الفئة من ضعفاء القوم.

Depressive symptoms and hopelessness among patients with cancer: role of religiosity

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Introduction
Patients suffering from cancer may be more vulnerable to depressive symptoms and suicidality. These symptoms may be affected by the degree of religiosity and faith.
Aim
The objective of this study was to assess the depressive symptoms, hopelessness, and suicidality among patients suffering from cancer and to study the role of religiosity and how it affects depressive symptoms, hopelessness, and suicidality in this group of patients.
Materials and methods
This is a cross-sectional study among a sample of patients with cancer. They were subjected to sociodemographic sheets and self-report questionnaires (Beck Depression Inventory (BDI), Beck Hopelessness Scale, Religious Orientation Scale-Revised (internal–external religiosity).
Results
Most of the patients (97.5%) expressed depressive symptoms (BDI > 10) with different severities: mild (10.3%), moderate (76.9%), and severe (12.5%). The highest severity was among patients suffering from breast cancer. The majority (77.9%) of patient scores in hopelessness were estimated to be mild. There was an indirect relationship between BDI scores and scores of external and internal religiosity. The study revealed an indirect relationship between hopelessness scores and external religiosity scores. However, the relationship was statistically nonsignificant.
Conclusion
This study revealed that Egyptian patients who are suffering from cancer experience a high frequency of depressive symptoms. However, hopelessness and suicidality are expressed in low frequency.

Keywords:
cancer, depression, hopelessness, religiosity, suicidality

Introduction
The term 'malignancy' refers to cancerous cells that usually have the ability to spread, invade, and destroy tissue. Malignant cells tend to have fast, uncontrolled growth due to changes in their genetic makeup. There are more than 100 different types of cancer. Most cancers are named for the organ or the type of cell in which they start. The leading cancers in Egyptian patients are of the urinary bladder (32.67%), gastrointestinal tract (22.24%), breast (13.15%), and lymphoma (9.8%) [1].

Several studies have also studied hopelessness and depression in terminally ill and oncology patients; it revealed that hopelessness at the time of an index psychiatric assessment is a significant predictor of eventual completed suicide [2]. This evidence suggests that there is a relatively consistent association between hopelessness and suicide that cannot be explained by depression alone. Weishaar and Beck [3] concluded that hopelessness serves as an important intervening variable that mediates the relationship between depression and

suicide. Chochinov et al. [4] confirm the relevance of the construct of hopelessness for understanding suicidal ideation and behavior.

Religiosity is a complex phenomenon that has a profound impact on the daily lives of human beings and is related to aspects of individual subjective experience such as meaning, personal happiness, and the effects of traumatic life events [5]. Spilka et al. [6] applied the general-attribution theory to the psychology of religion, in which it could be suggested that the religious framework serves as a source for explaining various life events. Moreover, James and Wells [5] hypothesized that religiosity mediates behavioral–cognitive mechanisms as it affects mental health perception.

Studying the relation between religiosity, depression, and hopelessness in terminally ill patients is of increasing importance. Different studies on patients with cancer and their families revealed that religion has an effect on their psychological well being and coping abilities [7,8]. There is a growing body of evidence that religiosity can

buffer depression and support the healing process [9]. Moreover, a positive relationship had been found between religiosity, psychological well being, and adaptive coping for patients with cancer [10,11]. In contrast, negative religious coping was associated with significantly poorer functioning on almost all outcomes: depression, distress, mental health, pain, and fatigue [12].

This study hypothesized that patients with cancer suffer from depressive and suicidal symptoms. Religiosity decreases the intensity of these symptoms.

The aim of this study was to assess the depressive symptoms, hopelessness, and suicidality among patients suffering from cancer and to study the role of religiosity and how it affects depressive symptoms, hopelessness, and suicidality in this group of patients.

Patients and methods
Study type
This is a cross-sectional study.

Site of the study
Clinical data were collected from patients seeking medical services at the Hospital of Electricity. This hospital is located in Eastern Cairo; however, it serves workers and employees of the 'Ministry of Electricity and Energy' in all cities and in governorates of the whole country of Egypt.

Study population
The participants of the study were selected from patients with cancer seeking medical advice at the above-mentioned hospital during a period of 3 months from June to September 2010. Patients fulfilling the inclusion criteria were contacted personally, and informed consent was obtained from those who agreed to participate after explaining the purpose of the study, the interview process, and the use of the collected data. Eighty out of 97 selected patients agreed to participate in the study.

Inclusion criteria included (i) patients having the clinical diagnosis of cancer in any stage of treatment or remission, (ii) patients who can read and write, and (iii) patients who signed the informed consent. Exclusion criteria included (i) patients with a known psychiatric disorder discovered before the appearance of cancer, (ii) illiterate patients, and (iii) patients who refused to participate in the study.

Sociodemographic and illness characteristics were collected and included age, sex, marital status, educational level, employment, religion, number of chemotherapy cycles, and radiotherapy sessions. Sociodemographic sheets and self-report questionnaires were distributed and collected from patients after approximately 1 h, when they finished filling them.

Depressive symptoms were detected by the Beck Depression Inventory II (BDI-II). This is a 21-item self-report instrument that assesses the severity of depressive symptomatology in adults. It is a revised version of the original BDI [13], updated to correspond to criteria from the *Diagnostic and Statistical Manual of Mental Disorders* [14]. Each of the 21 items measures the presence and the severity of a somatic or cognitive symptom of depression, rated on a four-point scale ranging from 0 to 3. The ratings are summed, yielding a total score that can range from 0 to 63. Severity scores are interpreted as follows: 0–9, minimal; 10–16, mild; 17–29, moderate; and 30–63, severe. The BDI-II has been validated as a sensitive, specific, and predictive tool for measuring depression [15]. Despite the fact that the somatic symptoms of pre-existing medical conditions may overlap those of depression, studies have shown that the somatic items do not interfere with the discriminative capacity of the BDI-II in primary-care settings [16]. The BDI-II has also been shown to be sensitive and specific at any phase of a depressive disorder [17].

Hopelessness and suicidality were measured by the Beck Hopelessness Scale (BHS). This is a self-report questionnaire with 20 items. The patient must rate each of them as a True or False statement. The severity of hopelessness is calculated by summing scores for the 20 items, the total score ranging from $0 =$ no hopelessness to $20 =$ maximum hopelessness. Scores ranged from $0–3 =$ minimal hopelessness; $4–8 =$ mild; $9–14 =$ moderate; and $15–20 =$ severe hopelessness. The BHS is positively associated with an elevated risk of an eventual suicide attempt or suicide completion. A high score indicates that the treatment of the patient must be rigorous and constant [13]. The English version of BHS has been translated to Arabic and then translated back into English separately.

Religiosity was measured by the Religious Orientation Scale-Revised (internal–external religiosity) [18], which has strong psychometric properties and is considered the best current measure of religious orientation [19] with reliability for internal being 0.83 and for external being 0.65 [20]. The validity of the Religious Orientation Scale is generally well supported, but due to the value-laden nature of the scale and to the evolving definition of internal and external over time, specifically what it measures has been open to a great deal of discussion. The revised version of the Religious Orientation Scale, the internal–external religiosity [18], was created as a response to the analysis of the original created by Kirkpatrick [21]. The Arabic version was used in this study by El Behairy and Demerdash [22].

Ethical consideration
The participation was entirely on a voluntary basis. All patients were guaranteed confidentiality. The study was approved by the Research Ethics Committee.

Statistical analysis
Data were transferred to a personal computer. Analysis was carried out using Statistical Package for Social Sciences version 10 (SPSS Inc., USA). The Pearson's χ^2-test was used for comparison between qualitative variables. Linear regression was performed for independent variables of depression. P value was used to indicate

the level of significance ($P \leq 0.05$ is considered significant, $P \leq 0.01$ is highly significant, $P \leq 0.001$ is very highly significant).

Results

This study aimed to assess the severity of depression and hopelessness in patients with different types of malignancy and to investigate their relationship with religious orientation. The study was conducted on 14 patients with lung cancer, 10 patients with colon cancer, 22 patients with breast cancer, 10 patients with leukemia, 10 patients with liver cancer, and 14 patients with urinary bladder cancer (Table 1).

The mean scores of religiosity (internal and external) BDI and BHS are illustrated in Table 2. A very high statistically significant relationship ($P = 0.000$) was observed between the external religiosity and type of cancer; highest external religiosity was associated with liver, lung, and urinary bladder cancers.

The highest mean scores of hopelessness and depression were observed in patients with breast cancer, followed by colon cancer and then lung cancer. It was observed that depressive symptoms were encountered in all patients with different percentages (Table 3). Mild depression was found in 40% of patients suffering from leukemia and in 28.6% of patients suffering from urinary bladder cancer. Moderate depression occurred in all of the patients suffering from lung cancer and in those suffering from liver cancer, in 80% of patients suffering from colon cancer, in 71.4% patients suffering from urinary bladder

cancer, in 63.6% of patients suffering from breast cancer, and in 40% of patients suffering from leukemia. Severe depression occurred in 27.3% of patients suffering from breast cancer, in 20% of patients suffering from colon cancer, and in 20% of patients suffering from leukemia.

According to BHS (Table 4) mild hopelessness was found in all patients suffering from liver cancer, in 85.7% of patients with lung cancer, in 51.7% of patients with urinary bladder cancer, in 50% of patients with breast cancer, and in 40% of patients with leukemia. Moderate hopelessness was seen in 51.7% of patients with urinary bladder cancer, in 22.7% of patients with breast cancer, in 20% of patients with colon cancer, in 14% of patients with lung cancer, and in 10% of patients with leukemia. Severe hopelessness was found in 18.2% of patients with breast cancer, and in 10% of patients with leukemia. In contrast, no hopelessness was detected in 42.9% of patients with bladder cancer, in 40% of patients with leukemia, and in 9% of patients with breast cancer.

Direct relationship was observed between severity of depression and severity of hopelessness, with a very high statistical significance ($P = 0.000$). Meanwhile, there was an indirect relationship between BDI scores and scores of external and internal religiosity. The study revealed an indirect relationship between hopelessness scores and external religiosity scores. However, the relationship was statistically nonsignificant.

Discussion
Cancer as a stress

Anxiety, worry, and fear are certainly common emotional responses to the threat of a disease and particularly to the threat of metastases and death associated with the diagnosis of cancer. Several reports have indicated that screenings, investigations, announcements, and treatment of cancer may induce or precipitate a series of psychological disorders, including transient anxiety at one extreme and elevated rate of depression and suicide at the other [23–25].

This study explored the symptoms of depression and hopelessness among a group of patients suffering from

Table 1 Age and sex of patients

| Group | Number | Sex | | Age (years) |
		Male	Female	Mean ± SD
Lung cancer	14	14	0	55.29 ± 6.318
Colon cancer	10	8	2	58.80 ± 6.713
Breast cancer	22	0	22	51.64 ± 7.081
Leukemia	10	8	2	56.40 ± 17.122
Liver cancer	10	10	0	58.60 ± 10.276
UB cancer	14	12	2	57.57 ± 9.329

SD, standard deviation; UB, urinary bladder.

Table 2 Mean scores of BDI, BHS, and ROS

Group (*n*)	BDI Mean ± SD	BHS Mean ± SD	E-ROS Mean ± SD	I-ROS Mean ± SD
Lung cancer (14)	24.57 ± 3.502	6.29 ± 1.939	36.86 ± 2.033	31.14 ± 3.697
Colon cancer (10)	24.60 ± 3.918	6.70 ± 3.917	33.00 ± 1.633	30.20 ± 1.814
Breast cancer (22)	25.09 ± 6.316	8.23 ± 5.014	34.18 ± 3.319	30.00 ± 3.147
Leukemia (10)	21.80 ± 4.826	5.80 ± 5.266	35.20 ± 2.348	27.40 ± 2.366
Liver cancer (10)	23.80 ± 1.814	4.90 ± 0.994	37.80 ± 2.348	30.60 ± 6.096
UB cancer (14)	21.57 ± 4.071	3.93 ± 2.464	36.43 ± 2.209	29.29 ± 3.625
Test used	ANOVA			
f value	1.492	2.584	6.036	1.452
P value	0.203	0.033	0.000	0.216
	NS	Significant	VHS	NS

ANOVA, analysis of variance; BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; E-ROS, External Religious Orientation Scale; I-ROS, Internal Religious Orientation Scale; NS, not significant; ROS, Religious Orientation Scale; SD, standard deviation; UB, urinary bladder; VHS, very highly significant.

Table 3 Distribution of depressive symptoms as measured by BDI

Group (n)	BDI				χ^2	d.f.	P value
	Minimal	Mild	Moderate	Severe			
Lung cancer (14)	0	0	14	0	38.26	15	0.001HS
Colon cancer (10)	0	0	8	2			
Breast cancer (20)	2	0	14	6			
Leukemia (10)	0	4	4	2			
Liver cancer (10)	0	0	10	0			
UB cancer (14)	0	4	10	0			
Total (80)	2	8	60	10			

BDI, Beck Depression Inventory; d.f., degree of freedom; HS, highly significant; SD, standard deviation; UB, urinary bladder.

Table 4 Distribution of hopelessness as measured by BHS

Group (n)	BHS				χ^2	d.f.	P value
	None	Mild	Moderate	Severe			
Lung cancer (14)	0	12	2	0	0.002	15	0.000 VHS
Colon cancer (10)	0	8	2	0			
Breast cancer (20)	2	11	5	4			
Leukemia (10)	4	4	1	1			
Liver cancer (10)	0	10	0	0			
UB cancer (14)	6	8	0	0			
Total (80)	12	53	10	5			

BHS, Beck Hopelessness Scale; d.f., degree of freedom; UB, urinary bladder; SD, standard deviation.

different types of cancer. Only two patients expressed minimal depressive symptoms and did not score in hopelessness scale; they were married women in the late fifties (58 and 57 years), with relatively long duration of breast cancer surviving (2 years) moderate religiosity scores with no discrepancy between external and internal religiosity.

Research suggests that most patients with cancer maintained high levels of hope when they were in remission, and interestingly the degree of hope actually increased as the illness progressed [25].

Depressive symptoms among patients with cancer

Depression is common in the general population and in adults and children with cancer and frequently coexists with anxiety and pain [26]. Depression is one of the most common psychiatric disorders seen in patients with advanced cancer [27]. Diagnostic and treatment challenges faced by healthcare professionals in this area remain considerable. These challenges include a distinct lack of adequate supporting evidence and a host of common misconceptions (Irving and Lloyd-Williams, 2010). Owing to the lack of recognized criteria, prevalence estimates vary widely from 5 to 26% for major depression and from 7.2 to 25.7% for minor depression in those patients with advanced cancer [28–31].

In this study, most of the patients (97.5%) expressed depressive symptoms (BDI > 10) with different severities: mild (10.3%), moderate (76.9%), and severe (12.5%). Even if we exclude the number of patients suffering from mild depression, the percentage of Egyptian patients suffering from cancer and expressing depressive symptoms remains the highest among recent studies addressing the same issue [28–31].

A number of psychological factors promoting depression have been associated with advanced cancer. These include the emotional impact of cancer diagnosis, medication side effects, and the progression of cancer-associated disability [32]. Moreover, lifestyle changes, financial concerns, pain, fear of death, and the stigma of being a patient with cancer add to the patient's stresses [33]. The Egyptian society suffers from most of these factors, especially financial concerns, stigma, disability, and side effects.

This study revealed that depressive symptoms were highest in severity among patients suffering from breast cancer; this result could be understood when taking into consideration the effect of physical disfigurement after mastectomy and its perceived relationship to femininity and sexuality. A review of the literature revealed important attributions to these results. Women's sexuality can be especially complex after breast cancer [34]. The impact of sexual changes can last for many years after successful treatment [35,36]. It is often associated with serious physical and emotional side effects [37,38] and is unlike other types of cancer assessed in this study, in which no evident physical disfigurement occurs after surgical intervention.

Hope and hopelessness with cancer and role of religiosity

The experience of hope is important in everyday life and especially while coping with a highly stressful life event such as cancer [39,40]. Hope is related to quality of life and well being, both in the general population and for persons coping with various illnesses [41,42]. Snyder *et al.* [43] defined hope as a set of cognitive beliefs with two added components: 'agency', related to goals (determination in meeting goals), and 'pathways', to these goals (sense of ability in meeting goals). Within this perspective, hope is not a single response to an event, but rather involves a more general orientation to the future [25].

According to this, people with advanced cancer do have goals they wish to meet. They may possess the determination and the sense of ability to achieve their goals. The content of some of their goal might be specifically related to coping with cancer. For example, patients with cancer might wish for cure, for not suffering, for spending time

with loved ones, or for coping better with their illness [44]. Depression is associated with a desire to hasten death in terminally ill patients with cancer [45,46]. Recent studies have gone on to suggest that depression in patients with advanced cancer is not only associated with an increased interest in assisted suicide but is also associated with an instability of this interest. It follows that when confronted with a request for patient-assisted suicide the possibility of depression should be considered [47].

Assessment of hopelessness scores was found to be related to the tendency for suicidality. This study revealed hopelessness in 85% of patients: severe (7.4%), moderate (14.7%), and mild (77.9%). Although moderate depressive symptoms were the most encountered in the studied group, the majority of patient scores in hopelessness were estimated to be mild, which means that suicidal tendency in this group is low despite of the high frequency of depressive symptoms. This result can be explained by the assumption that the idea of suicide is strongly prohibited religiously and is a totally unacceptable idea among the majority of population in the Egyptian community. This was commonly observed while interviewing patients and attitudes were assessed while performing the BHS.

In contrast, the inclination to religion during severe stress, especially the stress encountered during severe and chronic illnesses, is usually accompanied by the increase in religious activities as a way of relieving stress associated with illness.

Hopelessness was most severe among patients with breast cancer. These women experience a range of serious negative emotional changes as a result of disturbances to their sexuality, including fear of loss of fertility, negative body image, feelings of sexual unattractiveness [35], loss of femininity [48], depression and anxiety [49], as well as alterations to their sexual self [50].

Other studies suggested an increased rate of suicide in patients with cancer. Llorente *et al.* [51] have conducted a population-based, retrospective cohort review of men aged 65 or more, residing in South Florida. The average annual incidence of suicide for men was 55.3 per 100 000 people, but for men with cancer, the rate was 274.7 per 100 000 people. The risk of suicide in men with prostate cancer was 4.24 times that of an age-specific and sex-specific cohort. Bill-Axelson *et al.* [52] presented their investigation of the suicide rate in the Swedish population. In total, 128 suicides were reported among 77 439 patients with cancer .

Does religiosity play a role in enhancing hope?
The relationship between religion and mental health has been debated for centuries. History shows that religious organizations were often the first to offer compassionate care to the vulnerable groups. The first hospitals for patients with mental health problems established in the fourteenth century were church-sponsored and priest-managed [53].

In Egypt, similar to most Arab countries, Islamic beliefs and practices deeply affect lifestyle. The Koran teaches the value of pity, humility, and compassion toward human beings and underlines the importance of patience, loyalty, integrity, and control of impulses and desires [54]. The welfare of all members is vital to the community mental health, and professionals can encourage the patient to take care of himself as the body is God's gift and should not be abused [55,56].

This study revealed an indirect relationship between BDI scores and scores of external and internal religiosity and an indirect relationship (statistically nonsignificant) between hopelessness scores (including suicidality) and external religiosity. Herth [57] found a positive relationship between coping, religion, and hope in three settings: in patients undergoing chemotherapy, in outpatients, and in those in the home setting. Fehring *et al.* [58] found that religiosity, hope, and positive mood states were all positively-related. Stanton *et al.* [59] found that turning to religion as a coping style is effective for less hopeful women. Van Ness and Larson [60] in their review of the literature on hope and religion at the end-of-life of elderly persons, examined whether hope may serve as a mediator for the positive outcome effect of religiosity. They concluded that the role of hope as a mediator between religiosity and mental health is not well established and that more research is needed.

Study on the impact of religion on suicide has not yielded consistent results. Some investigators have argued for a model based on the alternative conception of religious commitment (e.g. religiosity *per se*) as a prophylactic against suicide [61]. Durkheim's [62] theory of religious integration serves as a point of departure for sociological study on suicide. The key dimension of integration is the sheer number of shared beliefs and practices. The more numerous and strong these beliefs and practices are, the greater the integration, and the lesser the risk of suicide. In all cases, however, theoretical arguments are often based on individual-level processes involving how religion promotes meaning for individuals and thereby lowers the risk of suicide [61].

Belief in an afterlife as a reward for persevering through life crises, such as divorce, unemployment, and death, probably lowers suicide risk far more than many other religious beliefs such as the Virgin Birth [63]. Belief in an afterlife, of course, might lead some individuals to commit suicide to hasten attainment of this state. As a consequence, most religions have prohibitions against suicide to discourage people from deciding on this tactic [64].

In Eastern culture, religion plays an important role as a deterrent of suicide; however, studies are still scarce in this domain. Research pointed out that many people who were not religious previously might turn to religion for comfort [65,66]. This often involves beliefs in a living and caring God, private religious activities, reading religious scriptures for direction and encouragement, or looking for support from pastors or members of faith community. In fact, many studies commonly reported that religiousness

is a powerful resource of hope, meaning and purpose in life, comfort, and solace. These protective and beneficial effects are particularly strong in people with illness and disability [67–71].

For this, Braam *et al.* [72] explained that: 'Religion may offer a frame of reference toward questions of life, sufferings, and death, and may help to accept a decrease in physical functioning in light of religious and spiritual values'. In Islam, meditation and prayer are very supportive when experiencing difficulties and they can be used in therapy; for instance, if a patient requests to pray in front of the therapist, such a request should be fulfilled. The lack of desire for praying can be seen as a symptom of distress and can come along with a deep sense of guilt [55,56].

Clinical implications
We need to conduct further studies on the impact of religiosity on the survival and the prognosis of the depressed patients with cancer. General practitioners and oncologists would be guided to the best way to detect psychiatric illness and to differentiate it from the normal reaction to stress of cancer. Diagnosis through the clinical guidelines suggested an assessment of mood through review of patients with cancer, and finally multidisciplinary care can improve outcomes for patients with cancer and should be considered throughout management and treatment.

Limitations
A more comprehensive study would include psychiatric history and examination, which was difficult to perform in this study due to unwillingness from the part of most patients to be examined by a psychiatrist while they are in the medical ward, for fear of embarrassment and stigma. Moreover, other scales to examine suicidality should be included in the study; however, available rating scales required a direct interview with the patients, which was quite difficult especially when talking directly about death and dying. This sensitive issue is easier written than said. This study would better be conducted as a case–control study, but it was quite difficult to find a number of control individuals from patients with cancer not experiencing any psychiatric manifestations.

References
1 Dey S, Zhang Z, Hablas A, Seifeldein IA, Ramadan M, El-Hamzawy H, Soliman AS. Geographic patterns of cancer in the population-based registry of Egypt: possible links to environmental exposures. Cancer Epidemiology 2011; 35:254–264.

2 Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. Am J Psychiatry 1985; 142:559–563.

3 Weishaar ME, Beck AT. Hopelessness and suicide. Int Rev Psychiatry 1992; 4:177–184.

4 Chochinov HM, Wilson KG, Enns M, Lander S. Depression, hopelessness and suicidal ideation in the terminally ill. Psychosomatics 1998; 39: 366–370.

5 James A, Wells A. Religion and mental health: towards a cognitive-behavioural framework. Br J Health Psychol 2003; 8 (**Pt 3**):359–376.

6 Spilka B, Shaver P, Kirkpatrick LA. A general attribution theory for the psychology of religion. J Sci Study Religion 1985; 24:1–20.

7 Soothill K, Morris SM, Harman JC, Thomas C, Francis B, McIllmurray MB. Cancer and faith. Having faith–does it make a difference among patients and their informal carers? Scand J Caring Sci 2002; 16:256–263.

8 Ramondetta LM, Sills D. Spirituality and religion in the 'art of dying'. J Clin Oncol 2003; 21:4460–4462.

9 Aukst Margetic B, Jakovljevic M, Margetic B, Biscan M, Samija M. Religiosity, depression and pain in patients with breast cancer. Gen Hosp Psychiatry 2005; 27:250–255.

10 Musick MA, Koenig HG, Larson DB, Matthews D. Religion and spiritual beliefs. In: Holland JC, editor. *Psycho-oncology*. New York: Oxford University Press; 1998. pp. 780–789.

11 Gall TL, Cornblat MW. Breast cancer survivors give voice: a qualitative analysis of spiritual factors in long-term adjustment. Psychooncology 2002; 11:524–535.

12 Sherman AC, Simonton S, Latif U, Spohn R, Tricot G. Religious struggle and religious comfort in response to illness: health outcomes among stem cell transplant patients. J Behav Med 2005; 28:359–367.

13 Beck AT, Steer RA. *Manual for the beck depression inventory*. San Antonio, TX: The Psychological Corporation; 1993.

14 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

15 Osman A, Downs WR, Barrios FX, Kopper BA, Gutierrez PM, Chiros CE. Factor structure and psychometric characteristics of the Beck Depression Inventory-II. J Psychopathol Behav Assess 1997; 19:359–376.

16 Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the beck depression inventory-II with primary care medical patients. Health Psychol 2001; 20:112–119.

17 Viinamaki H, Tanskanen A, Honkalampi K, Koivumaa Honkanen H, Haatainen K, Kaustio O, et al. Is the beck depression inventory suitable for screening major depression in different phases of the disease? Nord J Psychiatry 2004; 58:49–53.

18 Gorsuch RL, McPherson SE. Intrinsic/extrinsic measurement: I/E-revised and single-item scales. J Sci Study Religion 1989; 28:348–354.

19 Hill PC. Measurement in the psychology of religion and spirituality. In: Paloutzian RF, Park CL, editors. *Handbook of the psychology of religion and spirituality*. New York: Guilford Press; 2005. pp. 43–61.

20 Hill PC. Religious Orientation Scale-revised. In: Hill PC, Hood RW, editors. *Measures of religiosity*. Birmingham, AL: Religious Education Press; 1999. pp. 154–156.

21 Kirkpatrick LA. A psychometric analysis of the Allport-Ross and Feagin measures of intrinsic-extrinsic religious orientation. In: Lynn ML, Moberg DO, editors. *Research in the social scientific study of religion*. Greenwich CT: JAI Press; 1989. pp. 1–31.

22 El Behairy A, Demerdash A. *Religious Orientation Scale*. Cairo, Egypt: El Nahda El Masreya Library; 1988.

23 Awsare NS, Green JSA, Aldwinckle B, Hanbury DC, Boustead GB, McNicholas TA. The measurement of psychological distress in men being investigated for the presence of prostate cancer. Prostate Cancer Prostatic Dis 2008; 11:384–389.

24 Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology 2001; 10:19–28.

25 Hasson Ohayon I, Braun M, Galinsky D, Baider L. Religiosity and hope: a path for women coping with a diagnosis of breast cancer. Psychosomatics 2009; 50:525–533.

26 Massie MJ. Prevalence of depression in patients with cancer. Journal of the National Cancer Institute Monographs No. 32; 2004.

27 Minagawa H, Uchitomi Y, Yamawaki S, Ishitani K. Psychiatric morbidity in terminally ill cancer patients: a prospective study. Cancer 1996; 78: 1131–1137.

28 Wilson KG, Chochinov HM, Graham Skirko M, Allard P, Chary S, Gagnon PR, et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage 2007; 33:118–129.

29 Grabsch B, Clarke DM, Love A, McKenzie DP, Snyder RD, Bloch S, et al. Psychological morbidity and quality of life in women with advanced breast cancer: a cross-sectional survey. Palliat Support Care 2006; 4:47–56.

30 Kadan Lottick NS, Vanderwerker LC, Block SD, Zhang B, Prigerson HG. Psychiatric disorders and mental health service use in patients with advanced cancer: a report from the coping with cancer study. Cancer 2005; 104:2872–2881.

31 Hotopf M, Chidgey J, Addington Hall J, Ly KL. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. Palliat Med 2002; 16:81–97.

32 Greer S, Silberfarb PM. Psychological concomitants of cancer: current state of research. Psychol Med 1982; 12:563–573.

33 Chapple A, Ziebland S, McPherson A. Stigma, shame, and blame experienced by patients with lung cancer: qualitative study. BMJ 2004; 328:1470. Doi: 10.1136/bmj.38111.639734.7C. PMCID: PMC428516.

34 Thomas MacLean R. Beyond dichotomies of health and illness: life after breast cancer. Nurs Inq 2005; 12:200–209.

35 Bertero C, Chamberlain Wilmoth M. Breast cancer diagnosis and its treatment affecting the self: a meta-synthesis. Cancer Nurs 2007; 30: 194–202. quiz 203–204.

36 Andersen BL. In sickness and in health. Maintaining intimacy after breast cancer recurrence. Cancer J 2009; 15:70–73.

37 Langellier KM, Sullivan CF. Breast talk in breast cancer narratives. Qual Health Res 1998; 8:76–94.

38 Emilee G, Ussher JM, Perz J. Sexuality after breast cancer: a review. Maturitas 2010; 66:397–407.

39 Snyder CR. *Coping: the psychology of what works*. New York: Oxford University Press; 1999.

40 Yates P. Towards a reconceptualization of hope for patients with a diagnosis of cancer. J Adv Nurs 1993; 18:701–706.

41 Miller WR, Thoresen CE. Spirituality, religion and health: an emerging research field. Am Psychol 2003; 58:24–35.

42 Elliott TR, Uswatte G, Lewis L, Palmatier A. Goal instability and adjustment to physical disability. J Counsel Psychol 2000; 47:251–265.

43 Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, Sigmon ST, et al. The will and the ways: development and validation of an individual-differences measure of hope. J Pers Soc Psychol 1991; 60:570–585.

44 Sullivan MD. Hope and hopelessness at the end of life. Am J Geriatr Psychiatry 2003; 11:393–405.

45 Van der Lee ML, Van der Bom JG, Swarte NB, Heintz AP, De Graeff A, Van den Bout J. Euthanasia and depression: a prospective cohort study among terminally ill cancer patients. J Clin Oncol 2005; 23:6607–6612.

46 Chochinov HM, Wilson KG, Enns M, Mowchun N, Lander S, Levitt M, et al. Desire for death in the terminally ill. Am J Psychiatry 1995; 152:1185–1191.

47 Emanuel EJ, Fairclough DL, Emanuel LL. Attitudes and desires related to euthanasia and physician-assisted suicide among terminally ill patients and their caregivers. JAMA 2000; 284:2460–2468.

48 Archibald S, Lemieux S, Byers ES, Tamlyn K, Worth J. Chemically-induced menopause and the sexual functioning of breast cancer survivors. Women Ther 2006; 29:83–106.

49 Garrusi B, Faezee H. How do Iranian women with breast cancer conceptualize sex and body image? Sex Disabil 2008; 26:159–165.

50 Wilmoth MC. The aftermath of breast cancer: an altered sexual self. Cancer Nurs 2001; 24:278–286.

51 Llorente MD, Burke M, Gregory GR, Bosworth HB, Grambow SC, Horner RD, et al. Prostate cancer: a significant risk factor for late-life suicide. Am J Geriatr Psychiatry 2005; 13:195–201.

52 Bill-Axelson A, Garmo H, Lambe M, Bratt O, Adolfsson J, Nyberg U, et al. Suicide risk in men with prostate-specific antigen-detected early prostate cancer: a nationwide population-based cohort study from PCBaSe Sweden. Eur Urol 2010; 57:390–395.

53 Alexander FG, Selesnick ST. *The history of psychiatry: an evaluation of psychiatric thought and practice from prehistoric times to the present*. New York: Harper; 1966.

54 Caroppo E, Muscelli C, Brogna P, Paci M, Camerino C, Bria P. Relating with migrants: ethnopsychiatry and psychotherapy. Ann Ist Super Sanita 2009; 45:331–340.

55 Carter DJ, Rashidi A. East meets West. Integrative psychotherapy approaches for muslim women. Holist Nurs Pract 2004; 18:152–159.

56 Carter DJ, Rashidi A. Theoretical model of psychotherapy: eastern Asian-Islamic women with mental illness. Health Care Women Int 2003; 24:399–413.

57 Herth KA. The relationship between level of hope and level of coping response and other variables in patients with cancer. Oncol Nurs Forum 1989; 16:67–72.

58 Fehring RJ, Miller JF, Shaw C. Spiritual well-being, religiosity, hope, depression and other mood states in elderly people coping with cancer. Oncol Nurs Forum 1997; 24:663–671.

59 Stanton AL, Danoff Burg S, Huggins ME. The first year after breast cancer diagnosis: hope and coping strategies as predictors of adjustment. Psychooncology 2002; 11:93–102.

60 Van Ness PH, Larson DB. Religion, senescence and mental health: the end of life is not the end of hope. Am J Geriatr Psychiatry 2002; 10: 386–397.

61 Stack S. Religiosity, depression and suicide. In: Schumaker J, editor. *Religion and mental health*. New York: Oxford University Press; 1992. pp. 87–97.

62 Durkheim E. *Suicide*. New York: Free Press; 1966.

63 Stack S. Religion and suicide: a reanalysis. Soc Psychiatry 1980; 15:65–70.

64 Lester D. Spiritualism and suicide. Omega 1981; 12:45–49.

65 Koenig HG. Religion and medicine II: religion, mental health and related behaviors. Int J Psychiatry Med 2001; 31:97–109.

66 Koenig HG, Larson DB. Religion and mental health: evidence for an association. Int Rev Psychiatry 2001; 13:67–78.

67 Ehman JW, Ott BB, Short TH, Ciampa RC, Hansen Flaschen J. Do patients want physicians to inquire about their spiritual or religious beliefs if they become gravely ill? Arch Intern Med 1999; 159:1803–1806.

68 King DE, Koenig HG. *Faith, spirituality and medicine: towards the making of the healing practitioner*. 1st ed. London, United Kingdom; Routledge; 2000.

69 Koenig HG, George LK, Peterson BL. Religiosity and remission of depression in medically ill older patients. Am J Psychiatry 1998; 155: 536–542.

70 Koenig HG, George LK, Titus P. Religion, spirituality and health in medically ill hospitalized older patients. J Am Geriatr Soc 2004; 52:554–562.

71 Mueller PS, Plevak DJ, Rummans TA. Religious involvement, spirituality and medicine: implications for clinical practice. Mayo Clin Proc 2001; 76:1225–1235.

72 Braam AW, Hein E, Deeg DJH, Twisk JWR, Beekman ATF, Van Tilburg W. Religious involvement and 6-year course of depressive symptoms in older Dutch citizens: results from the longitudinal aging study Amsterdam. J Aging Health 2004; 16:467–489.

أعراض الاكتئاب واليأس بين مرضى السرطان : دور التدين

مقدمــة: وجـد أن مرضـى السـرطان مـن أكثـر المرضـى الـذين يعـانون مـن أعـراض الاكتئـاب وفقـدان الأمـل و الرغبـة فـي الأنتحـار.و قـد تتـأثر هـذه الأعـــــــــراض بدرجـــــــــة التـــــــــدين والإيمـــــــــان. **الـهـدف** مـن هـذه الدراسـة هـو تقيـيم أعـراض الاكتئـاب، واليـأس والانتحـار بـين المرضـى الـذين يعـانون مـن السـرطان، ودراسـة دور التـدين وكيفيـة تـأثيره علـى أعـراض الاكتئـاب ، واليـأس والانتحـار فـي هـذه الفئـة مـن المرضـى **طـرق البحـث :** هـذه الدراسـة مقطعيـة لـدى عينـة مـن مرضـى السـرطان. و تـم عمـل اسـتبيان لتحديـد الخصـائص الاجتماعيـة والديموغرافيـة و مقيـاس بيـك للاكتئـــاب ،مقيـــاس بيـــك اليـــأس،و مقيـــاس التوجـــه الـــديني المـــنقح **النتـائج :** وجـد أن معظـم المرضـى (97.5 ٪) لـديهم أعـراض الاكتئـاب مـع اخـتلاف درجاتـه : خفيـف (10.3 ٪) متوسـطة (76.9 ٪) والشـديد (12.5 ٪) وكـان أعلـى مسـتوى فـي شـدة الأكتئـاب بـين المريضـات اللاتـي يعـانين مـن سـرطان الثـدي. وقـدرت الغـالبيـة (77.9 ٪) مـن المرضـى بمقيـاس بيـك لليـأس إلـى أن تكـون خفيفـة. كانـت هنـاك علاقـة غيـر مباشـرة بـين دراجـات مقيـاس بيـك لليـاس ومقـاييس التـدين الخارجيـة والداخليـة. وكشـفت الدراسـة وجـود علاقـة طرديـة بـين شـدة اليـأس و التـدين الخـارجي. **الخلاصـة :** بينـت هـذه الدراسـة أن المرضـى المصـريين الـذين يعـانون مـن السـرطان،لديهم درجـة عاليـة مـن أعـراض الاكتئـاب. بينمـا يـتم التعبيـر عـن اليـأس والانتحـار بصـور أقل.

Relationship between blood-level folic acid deficiency and depression in patients with refractory epilepsy

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Introduction
Depression is common in patients with epilepsy, resulting in lack of response to antiepileptic drugs. Antiepileptic drugs are found to reduce folic acid level. Depression is a common symptom of folate deficiency. This study was undertaken to assess the relationship between serum folate levels and depression in patients with refractory epilepsy.

Patients and Methods
The study included 37 patients with refractory epilepsy, attending the neuropsychiatric outpatient clinic in the Suez Canal University hospital after giving written informed consent. We included adult male and female patients with age ranging from 18–40 years. Patients were subjected to clinical history, examination, serum folate level, and Hamilton Depression Rating Scale.

Results
According to the Hamilton Depression Scale, 62.2% were estimated to have mild, moderate, and severe depression. Half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) were having low normal values. There was significant association between severe depression and low folic acid level (<3.5). Longer duration of the disease was found to be associated with lower folic acid levels and higher depression scale score with significant difference. There was no significant association between received drugs and the severity of depression or low serum folic acid.

Conclusion
Depression was higher in patients with refractory epilepsy. Low serum folic acid was considered as a risk factor for depression and its severity in patients with refractory epilepsy, particularly in patients receiving polytherapy.

Keywords:
depression, folic acid, refractory epilepsy

Introduction
Depression is the most common psychiatric disease in patients with epilepsy with average incidence of 30–40% [1]. Depression has been associated with lack of response to AEDs, and thereby with the likelihood of developing pharmacoresistant or intractable epilepsy [2]. Refractory epilepsy is defined as two or more seizures per month for a period of 2 years or more despite supervised trials (6 months each twice with monotherapy and once with polytherapy) [3].

Several antiepileptic drugs (AEDs), such as carbamazepine, valproic acid, phenytoin, oxcarbazepine, and lamotrigine have been reported to reduce folic acid absorption in humans [4,5]. Serum and red blood cell folate are reduced in up to 90% patients receiving phenytoin, carbamazepine, or barbiturates [6]. Depression is a common symptom of folate deficiency [7].

The aim of this study was to assess the relationship between serum folate levels and depression in patients with refractory epilepsy attending the neuropsychiatry outpatient clinic in the Suez Canal University hospital.

Patients and methods
The study included 37 patients with refractory epilepsy attending the neuropsychiatric outpatient clinic in Suez Canal University hospital after giving written informed consent. Both adult male and female patients with age ranging from 18 to 40 years old were included. We excluded patients who did not experience epileptic seizures for at least 2 weeks, patients receiving folic acid supplementation, patients known to be mentally retarded, patients with psychotic symptoms, patients with chronic organic diseases, patients with family history of depression, patients with substance abuse, and female patients in premenstrual or postmenopausal periods.

Patients fulfilling the inclusion and exclusion criteria were subjected to clinical history, examination, serum

folate level in which the normal range of folate levels is 3.5–16.1 ng/ml (3.5 ng/ml–7.7 ng/ml will be considered to be in the low normal range) [8], and the Hamilton Depression Rating Scale in which a multiple-choice questionnaire was used to detect and to rate the severity of a patient's depression [9].

Data were imported into the Statistical Package for the Social Sciences (latest available version of SPSS, SPSS Inc., Chicago, Illinois, USA) software for analysis. According to the type of data, the following tests were used to test differences for significance: χ^2 and paired t-test. The assessment of odds ratio was used to test the relationship between different dependent and independent variables. P value was set at a value of less than 0.05 for significant results and less than 0.01 for highly significant results. An informed consent was taken from all the patients before taking any data or conducting any investigations.

Results

Of the 37 patients, 20 of them (54.1%) were women and 17 of them (45.9%) were men. The age of the studied patients was found to be ranging from 22 to 38 years.

According to the received medications and duration of disease, no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three drugs. Carbamezapine and phenytoin were received by 28 patients for each drug (75.7%). Valporic acid was received by 24 patients (64.86%). The mean duration of the disease was 12.1 years with most of the patients (56.8%) having been diagnosed for 10–15 years.

According to the Hamilton Depression Scale, 14 patients (37.8%) were not depressed. Ten patients (27.1%) were estimated to have mild depression, whereas eight (21.6%) had severe depression (Table 1).

Approximately half of the patients (48.7%) were estimated to have low levels of folic acid, with nine of them (24.3%) having low normal values (Table 2). There was significant association between severe depression and low folic acid level (< 3.5). There is significant association between patients with no depression (13.5%) and high normal level of folic acid (Table 3).

Longer duration of the disease was found to be associated with lower folic acid levels with significant difference (Table 4). There was significant difference between longer duration of the disease and higher depression scale score (Table 5).

Table 1 Severity of depression according to Hamilton Depression Scale

Depression scale	Number	Percentage (%)
No depression (0–6)	14	37.8
Mild depression (7–17)	10	27.1
Moderate depression (18–24)	5	13.5
Severe depression (>24)	8	21.6
Total	37	100

Table 2 Folic acid level among the studied patients

Folic acid level	Number	Percentage (%)
Low (<3.5)	18	48.7
Low normal (3.5–7.7)	9	24.3
Medium normal (7.8–11.9)	5	13.5
High normal (12–16)	5	13.5
Total	37	100

There was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 6). There was also no significant association between received drugs and low serum folic acid, although most of the patients with low serum folic acid were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid (Table 7).

Discussion

Depression is the most common psychiatric disease in patients with epilepsy [1]. An average incidence of 30–40% is, however, assumed [10]. Hitiris et al. [2] reported that depression due to the reduction in serum folate, which is associated with the induction of enzymes by AEDs, has been associated with lack of response to AEDs and thereby with the likelihood of developing pharmacoresistant epilepsy.

Hence, more important is that if the depression is not detected the epilepsy is actually harder to control, again probably for biological reasons [11]. Schuele and Lüders [12] found that emotional and psychosocial difficulties are disproportionately high in people with refractory epilepsy.

In this study, the prevalence of depression among the studied patients with refractory epilepsy was found to be 62.2%. This finding agrees with the findings by Gilliam et al. [13], Victoroff et al. [14], and Jones et al. [15], as they reported that 50–58% of the patients with refractory epilepsy were identified as having depression. O'Donoghue et al. [16] also noted that depression occurred more frequently in patients with higher seizure frequency compared with seizure-free patients.

In contrast, Attarian et al. [17] reported that patients with epilepsy have a higher prevalence of depression than the general population, but the intractability of the seizure disorder does not seem to be an independent risk factor for the occurrence of depression. This contrast may be due to using of the Beck Depression Inventory in that study to evaluate depressive symptoms. Depression in epilepsy is multifactorial in nature and has been shown to be influenced by a number of factors, which includes neurobiological, psychosocial, and pharmacological factors [18].

In this study, 48.7% were estimated to have low levels of folic acid (< 3.5), in addition to 24.3% having low normal values (3.5–7.7 ng/ml). This finding is agreed with Hermann et al. [19] as they found in 46 patients with chronic epilepsy,

Table 3 Relationship between folic acid level and depression scale

Folic acid level	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	P value
Low (<3.5)	3 (8.1%)	4 (10.8%)	4 (10.8%)	7 (18.9%)	0.01[a]
Low normal (3.5–7.7)	3 (8.1%)	4 (10.8%)	1 (2.7%)	1 (2.7%)	0.6 (NS)
Medium normal (7.8–11.9)	3 (8.1%)	2 (5.4%)	0 (0%)	0 (0%)	0.4 (NS)
High normal (12–16)	5 (13.5%)	0 (0%)	0 (0%)	0 (0%)	0.02[a]

NS, not significant.
[a]Statistically significant difference (*P* value <0.05).

Table 4 Relationship between folic acid level and duration of disease

	Low (<3.5)	Low normal (3.5–7.7)	Medium normal (7.8–11.9)	High normal (12–16)	P value
Mean±SD	16.89±2.3	13.6±4.1	12.5±5.3	11.8±3.9	0.01[a]

SD, standard deviation.
[a]Statistically significant difference (*P* value <0.05).

Table 5 Relationship between depression scale and duration of disease

	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	P value
Mean±SD	9.1±2.9	11.6±3.4	13.6±4.9	17.5±7.6	0.02[a]

SD, standard deviation.
[a]Statistically significant difference (*P* value <0.05).

Table 6 Relationship between combination therapy and depression

Drugs	No depression (0–6)	Mild depression (7–17)	Moderate depression (18–24)	Severe depression (>24)	P value
Valporic acid, carbamezapine, phenytoin	0 (0%)	1 (2.7%)	2 (5.4%)	3 (8.1%)	0.05 (NS)
Carbamezapine, valporic acid	5 (13.5%)	4 (10.8%)	0 (0%)	0 (0%)	0.1 (NS)
Phenytoin, valporic acid	5 (13.5%)	2 (5.4%)	1 (2.7%)	1 (2.7%)	0.8 (NS)
Carbamezapine, phenytoin	4 (10.8%)	3 (8.1%)	2 (5.4%)	4 (10.8%)	0.6 (NS)

NS, no statistically significant difference (*P* value >0.05).

Table 7 Relationship between combination therapy and folic acid level

Drugs	Low (<3.5)	Low normal (3.5–7.7)	Medium normal (7.8–11.9)	High normal (12–16)	P value
Valporic acid, carbamezapine, phenytoin	4 (10.8%)	1 (2.7%)	1 (2.7%)	0 (0%)	0.6 (NS)
Carbamezapine, valporic acid	2 (5.4%)	3 (8.1%)	2 (5.4%)	2 (5.4%)	0.3 (NS)
Phenytoin, valporic acid	2 (5.4%)	3 (8.1%)	1 (2.7%)	3 (8.1%)	0.1 (NS)
Carbamezapine, phenytoin	10 (32.4%)	2 (5.4%)	1 (2.7%)	0 (0%)	0.07 (NS)

NS, no statistically significant difference (*P* value >0.05).

folate serum level was below the normal range limit in 21.7% of patients with chronic epilepsy, of the remaining patients 45.6% had a low normal folate level.

In this study, there was significant association between depression and low serum folic acid level. Fifteen (40.5%) of the studied patients were found to have depression (ranging from mild, moderate, and severe depression) and low folic acid level (< 3.5). Seven (18.9%) of the studied patients were found to have severe depression and low folic acid level (< 3.5). Most of the patients with no depression (29.7%) were estimated to have normal levels of folic acid (ranging from low normal to high normal levels) and 13.5% of the patients with no depression were estimated to have high normal level of folic acid, which was a statistically significant difference.

This agreed with the findings by and Froscher *et al.* [20], who reported that in patients with psychiatric disorders, patients with epilepsy have a lower folate serum level than controls, and Kishi *et al.* [21] found that the reduction in serum folate is associated with the induction of enzymes by AEDs. Hermann and Whitman [22] in their study found that patients with minor depression had a significantly lower serum folate level than patients without depression. A serum folate level below 7.5 ng/ml was significantly associated with a pathological score on the Self-Rating Depression Scale.

In this study, longer duration of the disease was found to be associated with higher depression scale score. The mean duration of the disease was 12.1 years with most of the patients having been diagnosed for 10–15 years now (56.8%). This finding is consistent with most of the studies that found correlation between seizure frequency, longer duration of epilepsy, and depression [17,23]. This is in contrast with Glosser et al. [24], Oguz et al. [25], Baki et al. [26], and Kim et al. [27] who found that, however, the age, age of onset, duration of illness, religion, education, and multidrug therapy were not related to the severity of depression. The reasons for inconsistencies between these results and other studies are possibly due to difference in study groups, as other studies evaluate temporal lobe epileptic patients with hippocampal atrophy or hippocampal sclerosis, whereas this study evaluated patients with refractory epilepsy and used a different scale for evaluating depression.

In present study, there is no monotherapy was received, most commonly drugs were used in combination (polytherapy) of two or three of drugs among the studied patients, were carbamezapine and phenytoin were received by twenty eight of the patients for each drug (75.7%). Valporic acid was received by 24 patients (54.1%). This finding is nearly similar to the study conducted by Meneses et al. [28], who found that the most frequently used AEDs were phenytoin, valproic acid, carbamazepine, clobazam, and primidone.

In this study, there was no significant association between received drugs and the severity of depression. However, most of the patients with severe depression were receiving carbamezapine and phenytoin as part of their therapy either alone or in combination with valporic acid. This finding agrees with the study by Meneses et al. [28] and Mensah et al. [29], as they reported that depression was not associated with monotherapy or polytherapy. In contrast, Nemeroff and Owens [4] reported that carbamazepine, phenobarbital, phenytoin, and vigabatrin can contribute to depression and memory impairment.

Ogawa et al. [6] found that some AEDs are at risk for low levels of serum and red blood cell folic acid. This finding is in contrast to this study as there was no significant association between received drugs and the low serum folic acid. However, most of the patients with low serum folic acid were receiving carbamezapine and phenytoin as part of their therapy, either alone or in combination with valporic acid.

There is no conflict of interest to declare.

References

1 Barry JJ, Lembke A, Huynh N. Affective disorders in epilepsy. In: Ettinger AB, Kanner AM, editors. Psychiatric issues in epilepsy: a practical guide to diagnosis and treatment. Philadelphia: Lippincott Williams & Wilkins; 2001. pp. 45–71.

2 Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007; 75:192–196.

3 Venkitaraman S, Girthi SP. Recent advances in the management of refractory epilepsy. Neurosci Today 2003; 7:183–188.

4 Nemeroff CB, Owens MJ. Treatment of mood disorders. Nat Neurosci 2002; 5 (Suppl):1068–1070.

5 Van Praag HM, De Kloet ER, Van Os J. Stress, the brain and depression. Cambridge University Press; 2004.

6 Ogawa Y, Kaneko S, Otani K, Fukushima Y. Serum folic acid levels in epileptic mothers and their relationship to congenital malformations. Epilepsy Res 1991; 8:75–78.

7 Young SN, Ghadirian AM. Folic acid and psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13:841–863.

8 Collegium Internationale Psychiatriae Scalarum. Internationale skalen fur psychiatrie. Beltz Test; 4., uberarbeitete und erw; 1996.

9 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62.

10 Kanner AM, Nieto JC. Depressive disorders in epilepsy. Neurology 1999; 53 (5 Suppl 2):S26–S32.

11 Kanner AM, Dunn DW. Diagnosis and management of depression and psychosis in children and adolescents with epilepsy. J Child Neurol 2004; 19 (Suppl 1):S65–S72.

12 Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. Lancet Neurol 2008; 7:514–524.

13 Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health and function in epilepsy. Epilepsy Behav 2003; 4 (Suppl 4):S26–S30.

14 Victoroff JI, Benson F, Grafton ST, Engel J Jr, Mazziotta JC. Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. Arch Neurol 1994; 51:155–163.

15 Jones JE, Hermann BP, Barry JJ, Gilliam F, Kanner AM, Meador KJ. Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. J Neuropsychiatry Clin Neurosci 2005; 17:172–179.

16 O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract 1999; 49:211–214.

17 Attarian H, Vahle V, Carter J, Hykes E, Gilliam F. Relationship between depression and intractability of seizures. Epilepsy Behav 2003; 4: 298–301.

18 Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? Neurology 2002; 58 (8 Suppl 5):S27–S39.

19 Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences and treatment of major depression. Epilepsia 2000; 41 (Suppl 2):S31–S41.

20 Froscher W, Maier V, Laage M, Wolfersdorf M, Straub R, Rothmeier J, et al. Folate deficiency, anticonvulsant drugs and psychiatric morbidity. Clin Neuropharmacol 1995; 18:165–182.

21 Kishi T, Fujita N, Eguchi T, Ueda K. Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. J Neurol Sci 1997; 145:109–112.

22 Hermann BP, Whitman S. Psychosocial predictors of interictal depression. J Epilepsy 1989; 2:231–237.

23 Reuber M, Andersen B, Elger CE, Helmstaedter C. Depression and anxiety before and after temporal lobe epilepsy surgery. Seizure 2004; 13:129–135.

24 Glosser G, Zwil AS, Glosser DS, O'Connor MJ, Sperling MR. Psychiatric aspects of temporal lobe epilepsy before and after anterior temporal lobectomy. J Neurol Neurosurg Psychiatry 2000; 68:53–58.

25 Oguz A, Kurul S, Dirik E. Relationship of epilepsy-related factors to anxiety and depression scores in epileptic children. J Child Neurol 2002; 17: 37–40.

26 Baki O, Erdogan A, Kantarci O, Akisik G, Kayaalp L, Yalcinkaya C. Anxiety and depression in children with epilepsy and their mothers. Epilepsy Behav 2004; 5:958–964.

27 Kim DS, Kim OJ, Lee BI. Beck Depression Inventory in temporal lobe epilepsy with hippocampal atrophy: relation to lesion laterality. J Korean Neurol Assoc 1999; 17:478–485.

28 Meneses RF, Pais Ribeiro J, Martins da Silva A, Giovagnoli AR. Portuguese hospital anxiety and depression scale (HADS): usefulness in focal epilepsy. Internet J Mental Health 2008; 5:1531–2941.

29 Mensah SA, Beavis JM, Thapar AK, Kerr M. The presence and clinical implications of depression in a community population of adults with epilepsy. Epilepsy Behav 2006; 8:213–219.

الملخص العربي

العلاقة ما بين نقص مستوى حمض الفوليك بالدم و مرض الاكتئاب فى مرضى الصرع المستعصي

هدف البحث: إن مرض الاكتئاب هو من أكثر الأمراض شيوعا بين مرضي الصرع. و قد وجدت الأبحاث أن 30-40% من مرضي الصرع غير المستجيبين للعلاج والذي يسمي في هذه الحالة مرض الصرع المستعصي. كما أشارت الأبحاث أن نسبة الاكتئاب بين مرضي الصرع المستعصي تتراوح من 50-58%. وأثبتت الدراسات أن التشنجات الصرعية ذاتها تقلل من نسبة حمض الفوليك في الدم و يعد الاكتئاب من أكثر الأمراض شيوعا في حالات نقص حمض الفوليك بالجسم. تهدف هذه الدراسة إلي تحديد العلاقة بين نسبة حمض الفوليك بالدم وظهور الاكتئاب بين مرضي الصرع المستعصي. **طريقة البحث:** و قد تمت الدراسة على سبعة و ثلاثون مريضا يعانون من الصرع المستعصي ويتعرضون لعدد من النوبات الصرعية لا تقل عن نوبة صرعية بالشهر في خلال سنتين بالرغم من انتظامهم علي أكثر من نوعين من الأدوية المضادة للصرع التقليدية. وتم أخذ التاريخ المرضي والفحص الإكلينيكي الشامل وتم عمل رسم مخ و أخذ عينة من الدم لتحديد نسبة حمض الفوليك. كما خضعت لتطبيق سلم هاملتون لتقييم الاكتئاب. **نتائج البحث:** وجدت الدراسة أن معدل انتشار الاكتئاب بين مرض الصرع المستعصي 62.2% و معدل نقص نسبة حمض الفوليك بالدم 48.7%, و قد تبين أن هناك علاقة قوية بين نقص نسبة حمض الفوليك بالدم و بين ظهور الاكتئاب بل وحدته أيضا. كما أثبتت هذه الدراسة أن هناك علاقة قوية بين عدم وجود تغيرات أو بؤر صرعية في رسم المخ وعدم ظهور الاكتئاب بين مرضي الصرع. **الاستنتاج:** معظم المرضي المستخدمين لعقار الكارامازبين وعقار الفينيتوين معا يعانون من اكتئاب و نقص نسبة حمض الفوليك إلا أن هذه النسبة ليست ذات قيمة إحصائية.

N-acetyl aspartate concentration is correlated with severity of generalized anxiety disorder
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Introduction
This study used proton magnetic resonance spectroscopy to assess concentrations of N-acetyl aspartate in patients with generalized anxiety disorder (GAD).

Materials and methods
Brain metabolite resonance was measured in the left and right dorsolateral prefrontal cortex in 20 drug-naive patients with GAD and 20 age-matched and sex-matched healthy volunteers. Correlation studies were conducted between brain metabolites and scores in the Hamilton Anxiety Rating Scale and in the Taylor's Manifest Anxiety Scale.

Results
The only statistically significant difference between the patients with GAD and their matched comparison individuals was in right N-acetyl aspartate and in right N-acetyl aspartate/creatine. There were direct correlations between either right N-acetyl aspartate or N-acetyl aspartate/creatine and the scores in the Hamilton Anxiety Scale and Taylor's Manifest Anxiety Scale in patients with GAD, but not in the control group.

Conclusion
GAD is associated with asymmetric increases in the N-acetyl aspartate and N-acetyl aspartate/creatine ratio, which are directly correlated with the severity of GAD by psychometric scales.

Keywords:
coping, prefrontal cortex, psychometric scales, stress

Introduction
Anxiety disorders, which are among the most prevalent psychiatric disorders, afflict up to 25% of the US population at some point during their life and 17% experience an anxiety disorder during a given year [1,2]. Moreover, a recent and large study by the Mental Health in General Population database found that the overall prevalence of anxiety disorders was estimated to be 21.6%, with generalized anxiety disorder (GAD) being the most prevalent one (12.8%) [3]. In contrast, epidemiological studies are quite rare in the Arab world [4].

GAD is a disorder characterized by continuous symptoms of anxiety and vegetative hyperarousal associated with extreme and exaggerated sorrows. Sorrows may be about family harm, financial, or occupational issues. Patients are aware that their fear is not realistic and that their sorrows are exaggerated [5].

There has been an enormous increase in studies on anxiety disorders implying neuroimaging procedures [6], leading to growing evidence that brain areas involved in the stress response, including the prefrontal cortex [5,7–12], hippocampus, and amygdale [10], play a role in the symptoms of anxiety.

The dorsolateral prefrontal cortex (DLPC), together with other connected areas, is assumed to be important in working memory and in executive function, including the regulation of thinking and action. Damage to this region might impede commitment in relationships, as manifested by performance on working memory tasks, and might be associated with impaired self-efficacy, which in turn can compromise commitment [13]. It is also involved in learning how two events are associated with each other and how individuals might compare [14] or contrast these items. The right DLPC is especially likely to be involved in the memory of information that is personally meaningful. For example, when this area is anesthetized, individuals cannot readily identify a picture of their own face [15]. In contrast, the DLPC is involved in both risky and moral decisions. For example, when individuals need to decide how to distribute limited resources, representing a moral decision, the DLPC is activated. Also, this region is especially active when the costs and benefits of each alternative are weighed [16] and so it has an important role in facing stress and in managing it. Patients with major depressive disorder show low levels of activity in the left DLPC but elevated activity in the right one in response to emotional judgments. However, the elevated levels in the right DLPC transpired only when the emotional stimuli were expected [17], indicating that this region might be associated with emotional appraisal. Furthermore, in a study by Monk et al. [18], it was found that patients with GAD manifested greater right prefrontal cortex activation to trials containing angry faces. Moreover, Etkin et al. [10] found that activity in

dorsomedial and DLPC reflects the amount of emotional conflict, when a coping strategy seems not to be directly available. Engel *et al.* [5] found an increased cerebral blood flow in the right DLPC in a state of anticipatory anxiety before public speaking.

Magnetic resonance spectroscopy (MRS) use in anxiety disorders is still modest, particularly social phobia and generalized anxiety [19]. To our knowledge very few proton MRS (^{1}H-MRS) studies [7,20] of GAD have been reported. The hypothesis at the beginning of this study was that N-acetyl aspartate (NAA)/creatine ratios in DLPC is increased and may be or may not be correlated to the severity of anxiety as measured by psychometric tests. This study was approved by the Scientific and Ethics Committee of Mansoura Faculty of Medicine (Egypt).

Materials and methods
Twenty adult patients with Diagnostic and Statistical Manual of psychiatric disorders 4th edition GAD [nine men and 11 women; mean age = 35.43 years, standard deviation (SD) = 6.33] and 20 healthy volunteers (mean age = 35.27 years, SD = 7.58) were recruited through the Mansoura University Hospital Outpatient Psychiatric Clinic,. Healthy volunteers (relatives of patients in the Medicine Outpatient Clinic in the same hospital, negative family history of any psychiatric disorders, no family relationship to these study patients) were prospectively pair-matched with respect to age and sex (Table 1). Exclusion criteria included all other psychiatric disorders including substance abuse, significant medical or neurological disorders, mental retardation, head accident or trauma, patients with manifest congenital disorders, language or hearing difficulties, and patients with drugs or hormonal (contraceptive piles, etc.) induced GAD. Inclusion criteria required that all patients should be drug naive. Healthy participants had no history of axis I disorder, either personally or in first degree relatives. All participants had unremarkable urine toxicology, urine analysis, complete blood count, blood chemistry, and electrocardiography results. Timing of scans in female participants was matched relative to their menstrual phase (1 week after onset of menstruation). Groups did not differ in ethnic composition, educational level, intelligence quotient, height, or weight.

Table 1 Demonstrate the demographic data

	GAD		Control		Significant
	Mean	SD	Mean	SD	*P*
Age (years)	35.43	6.33	35.27	7.58	0.943
Age of onset	17.05	2.395	0	0	–
Duration of illness	8.95	4.79	0	0	–
IQ	91.35	6.74	92.24	7.47	0.692
Education (years)	11.6	1.66	12.19	2.58	0.475
Height (cm)	165.5	6.13	166.85	6.747	0.278
Weight (kg)	75.75	5.22	77.57	7.62	0.380
Hamilton Anxiety Rating Scale	21.50	4.71	1.52	2.13	0.000
Taylor's Manifest Anxiety Scale	35.50	8.53	2.28	2.93	0.000

GAD, generalized anxiety disorder; IQ, intelligence quotient; SD, standard deviation.

Patients had screening and day-of-scan scores of at least 15 in the Hamilton Anxiety Rating Scale [21] (mean = 21.5, SD = 4.7) and at least 21 on the Arabic version of Taylor's Manifest Anxiety Scale (mean = 35.5, SD = 8.5) [22,23]. Scores of healthy participants were substantially lower and did not overlap with those of patients (Hamilton Anxiety Scale mean = 1.5, SD = 2.1; Taylor's Manifest Anxiety Scale mean = 2.2, SD = 2.9). This study was approved by the Mansoura University Faculty of Medicine, Psychiatric Department; all volunteers provided written informed consent before participation.

Scans were taken using conventional magnetic resonance imaging and MRS on 1.5 T unit (Magnetom Symphony, Siemens, Version VA 12A, Wittelsbacher Platz, Munchen, Germany) using a head coil. Magnetic resonance imaging protocol using the single-voxel ^{1}H-MRS imaging sequence, including axial T1-WI [time repetition (TR)/echo time (TE) = 500–600/14–15 ms], sagittal T2-WI (TR/TE = 4450/86 ms), and coronal fluid attenuation inversion recovery image (9000/14/2500 ms), was acquired. The slice thickness was 6 mm, the matrix was 156 × 256, and the field of view was 230 mm.

Single-voxel ^{1}H-MRS imaging was performed using a spin-echo mode sequence (TR/TE = 1500/30). Water suppression was achieved with chemical shift selective. Two voxels (15 × 15 × 15) were placed on the right DLPC and on the left DLPC in control and patient groups (Fig. 1).

Preprocessing included the following steps: noise filtering (– 2 Hz exponential multiplication) and elimination of the first three signal points to prevent artifacts in the spectrum baseline. Spectra were decomposed into major resonance and a residual. Metabolites ratios were measured by a fitting. After fitting, the spectral results were screened both by automatic analysis and by a blind manner manual inspection of eliminated bad spectral fits on the basis of poor data quality (arising because of excessive noise, patient motion, etc.). Seven spectra were rejected. In addition, ^{1}H-MRS was preprocessed to perform automatic removal of the residual water and lipid. The spectra were processed with an Hankel singular value decomposition-matched filter [24]. Signal processing was performed by time domain analysis, quantifying the resonances of interest with an iterative nonlinear method (advanced method for accurate robust and efficient spectral fitting) [25].

The raw data were transferred to an off-line workstation and were postprocessed automatically using a spectroscopic analysis package of 1.5 T (Signa; Simens, Wittelsbacher Platz, Munchen, Germany) equipped with head coil. The metabolites were identified including NAA at 2.0 part per mint (ppm), creatine at 3.0 ppm, and choline at 3.2 ppm. The integral value of each peak was dimensionless and represented relative measurement of concentration of each metabolite. The peak ratios were calculated from the integration of the single peak including NNA/creatine, NAA/choline, and choline/creatine.

Statistical analysis
Data were summarized using mean and standard deviation (quantitative data). The statistically significant

Figure 1
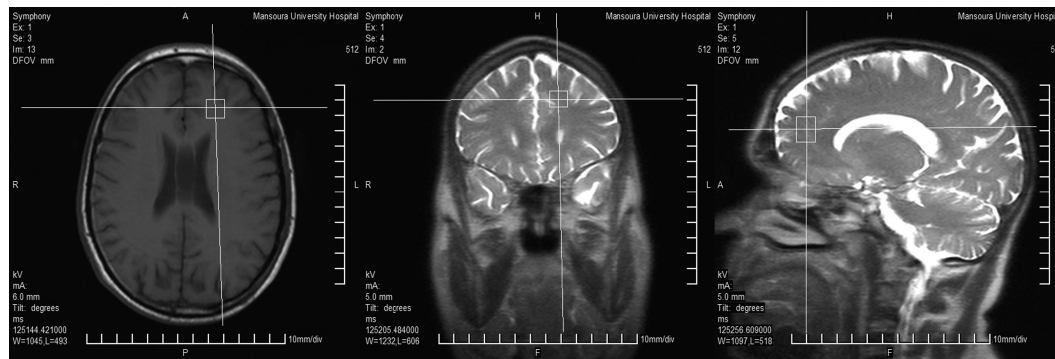
Shows the localization of single-voxel magnetic resonance spectroscopy on the dorsolateral prefrontal cortex.

difference between patient and control groups was tested using the *t*-test. The correlation between psychometric scales and MRS metabolites was assessed using the Pearson's correlation test. The results were computed on an IBM compatible personal computer using Statistical Package for Social Sciences for Windows 15 (SPSS Inc., Chicago, Illinois, USA).

Results

The following brain metabolites were examined: N-acetyl aspartate (NAA), NAA/creatine, NAA/choline, choline, and choline/creatine in right and right DLPCs (Fig. 2). The only statistically significant differences between the patients with GAD and their matched control individuals were in right NAA (GAD, mean = 13.61, SD = ± 1.75; control, mean = 8.45, SD = ± 3.09; P = 0.000) and in right NAA/creatine (GAD, mean = 1.68, SD = ± 0.43; control, mean = 1.29, SD = ± 0.23; P = 0.001) (Table 2). The correlation study was conducted between right NAA and the score in the Hamilton Anxiety Scale and in Taylor's Manifest Anxiety Scale and between NAA/creatine and the

score in the Hamilton Anxiety Scale and in Taylor's Manifest Anxiety Scale. Table 3 shows that there was a direct correlation between right NAA and the Hamilton Anxiety Scale (r = .850) (P = 0.000), right NAA and Taylor's Manifest Anxiety Scale (r = 0.880) (P = 0.000) in patients with generalized anxiety, but not in the control group (Hamilton Anxiety Scale r = 2.64, P = 0.248; Taylor r = 0.134, P = 0.564). Moreover, NAA/creatine was directly correlated with the Hamilton Anxiety Scale (r = 0.769, P = 0.000) and Taylor's Manifest Anxiety Scale (r = 0.763, P = 0.000) in patients with generalized anxiety, but not in the control group (Hamilton Anxiety Scale r = 0.371, P = 0.098; Taylor r = 0.217, P = 0.345). The correlations between the scores on anxiety scales and right NAA or right NAA/creatine ratio were also statistically significant in both sexes (Table 4).

Discussion

This study shows that there were statistically significant increases in right DLPC NAA and in right NAA/creatine,

Figure 2
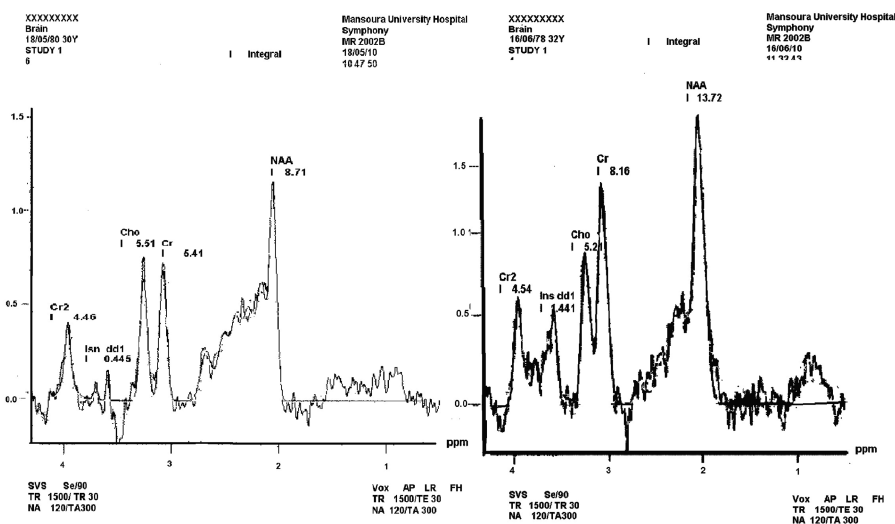
Shows magnetic resonance spectroscopy spectrum curve in a control individual on the right side and the magnetic resonance spectroscopy curve of a generalized anxiety patient on the left side. Cho, choline; Cr, creatine; NAA, N-acetyl aspartate.

Table 2 Brain metabolites in control and anxiety groups

	GAD	Mean	SD	P
Left choline/NAA	GAD	0.47385	0.187109	638
	Control	0.44686	0.177149	
Right choline/NAA	GAD	0.39310	0.121718	625
	Control	0.41149	0.117186	
Left choline	GAD	4.41900	1.335810	784
	Control	4.29476	1.539125	
Right choline	GAD	5.11700	1.782160	0.146
	Control	4.38429	1.361652	
Left NAA	GAD	10.72850	3.113256	0.649
	Control	10.33429	2.362199	
Right NAA	GAD	13.61850	1.754916	0.000
	Control	8.45429	3.099341	
Right NAA/creatine	GAD	1.68735	0.431282	0.001
	Control	1.29171	0.233850	
Left NAA/creatine	GAD	2.26330	1.283955	0.117
	Control	1.77819	0.515117	
Left choline/creatine	GAD	0.58725	0.170211	0.401
	Control	0.53975	0.187404	
Right choline/ creatine	GAD	0.79315	0.612822	0.866
	Control	0.76620	0.382722	

GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.

Table 3 Describes correlation between brain metabolites and anxiety scales

			#1	#2
Control	Right NAA	Pearson's correlation	0.264	0.134
		[significant (two-tailed)]	0.248	0.564
GAD	Right NAA	Pearson's correlation	0.850[a]	0.880[a]
		[significant (two-tailed)]	0.000	0.000
Control	Right NAA/creatine	Pearson's correlation	0.371	0.217
		[significant (two-tailed)]	0.098	0.345
GAD	Right NAA/creatine	Pearson's correlation	0.769[a]	0.763[a]
		[significant (two-tailed)]	0.000	0.000

Note: #1=Hamilton Anxiety Scale; #2=Taylor's Manifest Anxiety Scale.
GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.
[a]Correlation is significant at the 0.01 level (two-tailed).

a measure of neuronal viability, in patients with GAD than in the control group. This increase in concentration was directly correlated with the severity of anxiety symptoms as measured by the Hamilton Anxiety Scale and the Taylor's Manifest Anxiety Scale.

The neurobiological bases of GAD are poorly characterized. Hypermetabolism in prefrontal cortical regions [26] and neuronal hypertrophy in limbic structures [27] have been observed. ^{1}H-MRS studies in related disorders have found topographic reductions (or no change) in prefrontal cortical or hippocampal measures of NAA, an amino acid considered as a marker of neuronal viability [28]. Similarly, decreases in NAA/creatine ratios were found in prefrontal cortical regions of adult nonhuman primates who had undergone adverse rearing conditions as infants approximately 10 years earlier, suggesting possible trauma-related neurotoxicity [29].

The results of this study are consistent with Mathew *et al.* [7], who recently described that patients with GAD had a 16.5% higher NAA/creatine ratio, a suggested marker of neuronal viability, in right DLPC compared with healthy controls.

The increase in NAA and NAA/creatine ratio could reflect an increase in the number of neurons in DLPC. This increase in number of neurons may be an adaptive mechanism to stress, which needs further studies to confirm this assumption. The direction of NAA/creatine abnormality in GAD is potentially consistent with findings suggesting prefrontal cortical hypermetabolism in GAD [26] and increased cerebral blood flow in the right DLPC in persons with social phobia anticipating public speaking [30].

The adaptive mechanism to stress could be explained as follows; there are evidences to suggest that the developing brain organizes in response to the pattern, intensity, and nature of sensory perceptual and affective experience of events during childhood [31,32]. Therefore, stress

Table 4 Illustrates correlation between brain metabolites and scores on anxiety scales according to sex

Sex	Brain metabolites/anxiety scales score	Control				GAD			
		Mean	SD	R	Significant	Mean	SD	R	Significant
Male	Right NAA	8.43	3.20	0.273	0.345	14.28	1.90	0.800[b]	0.002
	Hamilton Anxiety Scale	1.28	1.72			23.75	4.45		
	Right NAA	8.43500	3.20	−0.113	0.701	14.28	1.90	0.858[b]	0.000
	Taylor's Manifest Anxiety Scale	2.5000	2.90			39.83	7.56		
	Right NAA/creatine	1.29557	0.25	0.402	0.154	1.87	0.37	0.637[a]	0.026
	Taylor's Manifest Anxiety Scale	2.5000	2.90			39.83	7.56		
	Right NAA/creatine	1.29557	0.25	0.611	0.107	1.87	0.37	0.698a	012
	Hamilton Anxiety Scale	1.2857	1.72			23.75	4.45		
Female	Right NAA	8.49	3.11	0.27	0.54	12.61	0.85	0.842[b]	0.009
	Hamilton Anxiety Scale	2.0	2.88			18.12	2.74		
	Right NAA	8.49	3.11	0.197	0.673	12.61	0.85	0.873[b]	0.005
	Taylor's Manifest Anxiety Scale	1.85	3.18			29.00	5.20		
	Right NAA/creatine	1.28400	0.20	−0.225	0.628	1.40	0.36	686[a]	0.040
	Taylor's Manifest Anxiety Scale	1.8571	3.18			29.00	5.20		
	Right NAA/creatine	1.28400	0.20	0.303	508	1.40	0.367	0.850[b]	0.000
	Hamilton Anxiety Scale	2.0000	2.88			18.12	2.74		

GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.
[a]Correlation is significant at the 0.05 level (two-tailed).
[b]Correlation is significant at the 0.01 level (two-tailed).

responses can affect the development of the brain by altering neurogenesis, migration, synaptogenesis, and neurochemical differentiation [33,31]. Hence, the brains of traumatized children develop to be hypervigilant and are potentially related to threat. These children are in a persistent state of arousal, and therefore experience persistent anxiety [33]. Other studies suggest that early exposure to consistent, daily stress can later result in more adaptive behavior and resiliency, whereas exposure to unpredictable stress can result in deficits. Predictability and control can make events much less destructive or traumatic [34]. Although these adaptive changes in the brain make a child better suited to sense, to perceive, and to act on threats in their world, these 'survival tactics' ill-serve the child when the environment changes (e.g. in school, peer relationships) [34].

A similar condition is described by Whiteside *et al.* [35] who observed higher glutamate + glutamine/creatine and NAA/creatine in the orbitofrontal cortex of patients with obsessive compulsive disorder. The investigators suggested that this increase in NAA could reflect an increase in the number of neurons, which is consistent with neurobiological models of obsessive compulsive disorder that have postulated higher activity in the cortex or with neurodevelopmental theories involving inefficient neuronal pruning in this disorder.

In contrast, the scores in Taylor's Manifest Anxiety Scale and in the Hamilton Anxiety Scale, which examine the severity of anxiety, were directly correlated to right NAA and NAA/creatine. This means that the severe the anxiety the more the need for neuronal activity to compensate it and to prepare the individual to combat the stress. Hence, an increase in NAA, which is a neuronal viability marker, is observed. This may also support this study assumption that there may be an adaptive way for the brain to face stress that appeared clinically as GAD. This study may open new areas for research on the adaptive function of brain to stress according its severity. In addition, it also puts forth some questions for further studies 'Is the brain of a patient with GAD not same for all patients depending on the degree of stress each one faces? And if it is true, is it wise to have the same treatment for all patients?'

Conclusion
This study found that there were increases in right DLPC NAA and right NAA/creatine in patients with GAD than in the control group. These increases in concentrations were directly correlated with the severity of anxiety symptoms. From this finding, an assumption can be made that there may be a special way of adaption to stress and GAD may be present. Further studies are needed to confirm or to refuse this assumption.

References
1 Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National comorbidity survey. Arch Gen Psychiatry 1994; 51:8–19.

2 Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, et al. The cross-national epidemiology of panic disorder. Arch Gen Psychiatry 1997; 54:305–309.

3 Leray E, Camara A, Drapier D, Riou F, Bougeant N, Pelissolo A, et al. Prevalence, characteristics and comorbidities of anxiety disorders in France: results from the 'Mental Health in General Population' Survey (MHGP). Eur Psychiatry 2011. the article in press http://dx.doi.org/10.1016/j.eurpsy. 2009.12.001.

4 Tanios CY, Abou Saleh MT, Karam AN, Salamoun MM, Mneimneh ZN, Karam EG. The epidemiology of anxiety disorders in the Arab world: a review. J Anxiety Disord 2009; 23:409–419.

5 Engel K, Bandelow B, Gruber O, Wedekind D. Neuroimaging in anxiety disorders. J Neural Transm 2009; 116:703–716.

6 Bremner JD. Brain imaging anxiety disorders. Exp Rev Neurotherap 2004; 4:275–284.

7 Mathew SJ, Mao X, Coplan JD, Smith EL, Sackeim HA, Gorman JM, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton magnetic resonance spectroscopic imaging study. Am J Psychiatry 2004; 161:1119–1121.

8 Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. Neuroreport 2004; 15:2261–2265.

9 Schienle A, Schafer A, Walter B, Stark R, Vaitl D. Brain activation of spider phobics towards disorder-relevant, generally disgust- and fear-inducing pictures. Neurosci Lett 2005; 388:1–6.

10 Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 2006; 51:871–882.

11 Kilts CD, Kelsey JE, Knight B, Ely TD, Bowman FD, Gross RE, et al. The neural correlates of social anxiety disorder and response to pharmaco therapy. Neuropsychopharmacology 2006; 31:2243–2253.

12 Straube T, Mentzel HJ, Miltner WH. Neural mechanisms of automatic and direct processing of phobogenic stimuli in specific phobia. Biol Psychiatry 2006; 59:162–170.

13 Petrican R, Schimmack U. The role of dorsolateral prefrontal function in relationship commitment. J Res Personality 2008; 42:1130–1135.

14 Murray LJ, Ranganath C. The dorsolateral prefrontal cortex contributes to successful relational memory encoding. J Neurosci 2007; 27: 5515–5522.

15 Keenan JP, Nelson A, O'Connor M, Pascual Leone A. Self-recognition and the right hemisphere. Nature 2001; 409:305.

16 Greene JD, Sommerville RB, Nystrom LE, Darley JM, Cohen JD. An fMRI investigation of emotional engagement in moral judgment. Science 2001; 293:2105–2108.

17 Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry 2008; 63:369–376.

18 Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry 2006; 163:1091–1097.

19 Trzesniak C, Araújo D, Crippa JAS. Magnetic resonance spectroscopy in anxiety disorders. Acta Neuropsychiatr 2008; 20:56–71.

20 Coplan JD, Mathew SJ, Mao X, Smith EL, Hof PR, Coplan PM, et al. Decreased choline and creatine concentrations in centrum semiovale in patients with generalized anxiety disorder: relationship to IQ and early trauma. Psychiatry Res 2006; 147:27–39.

21 Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55.

22 Taylor JA. A personality scale of manifest anxiety. J Abnorm Soc Psychol 1953; 48:285–290.

23 Fahmi M, Ghali M, Meleka K. Arabic version of the personality scale of manifest anxiety. Egypt Psychiatry 1977; 11:119–126.

24 Van den Boogaart A, Van Ormondt D, Pijnapel WWF, De Beer R, Ala Korpela M. Removal of the water resonance from 1H magnetic resonance spectra. In: McWhirter JG, editor. *Mathematics in processing III*. Oxford: Clarendon Press; 1994. pp. 175–195.

25 Vanhamme L, Van Den Boogaart A, Van Huffel S. Improved method for accurate and efficient quantification of MRS data with use of prior knowledge. J Magnet Reson 1997; 129:35–43.

26 Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. Biol Psychiatry 1991; 29:1181–1199.

27 De Bellis MD, Casey BJ, Dahl RE, Birmaher B, Williamson DE, Thomas KM, et al. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol Psychiatry 2000; 48:51–57.

28 Lyoo IK, Renshaw PF. Magnetic resonance spectroscopy: current and future applications in psychiatric research. Biol Psychiatry 2002; 51: 195–207.

29 Mathew SJ, Shungu DC, Mao X, Smith EL, Perera GM, Kegeles LS, *et al.* A magnetic resonance spectroscopic imaging study of adult nonhuman primates exposed to early-life stressors. Biol Psychiatry 2003; 54: 727–735.

30 Tillfors M, Furmark T, Marteinsdottir I, Fredrikson M. Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. Biol Psychiatry 2002; 52:1113–1119.

31 Perry BD. Neurobiological sequelae of childhood trauma: post traumatic stress disorders in children. In: Murburg M, editor. *Catecholamine function in post traumatic stress disorder: Emerging concepts.* Washington, DC: American Psychiatric Press; 1994. pp. 253–276.

32 Perry BD, Pollard RA, Blakley TL, Baker WL, Vigilante D. Childhood trauma, the neurobiology of adaptation and 'use-dependent' development of the brain: how 'states' become 'traits'. Infant Mental Health J 1995; 16:271–291.

33 Lauder JM. Neurotransmitters as morphogens. Prog Brain Res 1988; 73:365–387.

34 Perry BD. *Neurodevelopmental adaptations to violence: how children survive the intragenerational vortex of violence. Violence and childhood trauma: understanding and responding to the effects of violence on young children.* Cleveland, Ohio: Gund Foundation Publishers; 1996. pp. 67–80.

35 Whiteside SP, Port JD, Deacon BJ, Abramowitz JS. A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. Psychiatry Res 2006; 146:137–147.

الآلية التكيفية لاضطراب القلق العام: دراسة بواسطة الرنين المغنطيسي الطيفي

المقدمة: استعملت الدراسةُ الحاليةُ بروتون الرنينُ المغناطيسي الطيفي لقياس تركيز إن أسيتيل اسبرتات في مرضى القلق العام. **الطريقة:** تم قياس طيف التمثيل الايضي للمخ في الجانبين الأيمن و الأيسر من الفص الأمامي الخلف جانبي للمخ في 20 من المرض بالقلق العام الذين لم يسبق أن تعاطوا أدوية نفسية سابقا و مثلهم مجموعة مقارنة من الأصحاء. كما تم إجراء دراسة ارتباط بين تركيز ناتج التمثيل الايضي للمخ و درجة القلق علي مقياس هامليتون و علي تيلور للقلق الظاهر. **النتيجة:** لم يتبين وجود أي اختلاف ذو دلالة إحصائية بين ناتج التمثيل الايضي للمخ للمرضي و الأصحاء معدا بالنسبة ان استيل اسبرتات علي الفص الأيمن للمخ و كان هناك ارتباط ذو دلالة إحصائية بين هذه الزيادة و القياس علي مقياس هامليتون للقلق و مقياس تيلور للقلق الظاهر. **الاستنتاجات:** اضطراب القلق العَامّ يتميز بزيادة غير مُتَناظرِةٍ في تركيز إن أسيتيل اسبرتات و نسبة إن أسيتيل علي كرياتين مع وجود علاقة ارتباط طردية بينهما و شدَّةِ اضطراب القلق العام الذي يمكن تفسيرة كنوع من الآلياتَ التكيفية لمواجه الضغوط النفسية.

Cognitive dysfunction in children presented with behavioral disorders

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Background
Executive function impairments have been proposed to be implicated in a wide range of childhood neuropsychiatric disorders.

Objectives
The primary aim of this study is to directly examine the similarities and differences in executive functioning among attention deficit hyperactivity disorder (ADHD), disruptive behavior disorder (DBD), and pediatric bipolar disorder (BD) and to determine whether a distinct cognitive profile exists for each.

Patients and methods
A sample of 92 children were selected from the psychiatric outpatient clinic of Mansoura University Hospitals, who were diagnosed according to diagnostic and statistical manual 4th ed. text revision as having one of the following childhood psychiatric disorders: ADHD, DBD, or BD. They were subjected to seven executive function tasks (adopted from Van der Sluis S et al., 2007) to assess specifically shifting, inhibition, and updating. Cases were compared with a control group of 45 children with minor dermatological problems and free psychiatric history. They were with the same age range, sex percentage and educational and cultural background of patients' sample.

Results
Children with BD (manic episode), specifically, have significant deficits in the shifting ability. Meanwhile, children with ADHD show significant impairment in updating function. However, impairment in inhibition was detected in ADHD, DBD, and BD.

Conclusion
The differences in executive functions may be used to establish a specific cognitive profile for different disorders that provides a more objective means of differential diagnosis among them when they are not reliably distinguished by clinical diagnostic methods. Moreover, these could propose a cognitive dimension for such disorders.

Keywords:
attention deficit hyperactivity disorder, bipolar disorder, disruptive behavior disorder, executive functions

Introduction

Impairment in executive functions (EF) has been consistently linked to criminality, delinquency, physical aggression, conduct disorder, psychopathy, and antisocial personality disorder [1]. These impairments have also been implicated in a range of neuropsychiatric and medical disorders, including schizophrenia, major depression, alcoholism, structural brain disease, diabetes mellitus, and normal aging [2]. EF impairments are not unique to specific childhood psychiatric disorders and have been linked to a range of clinical disorders, including attention deficit hyperactivity disorder (ADHD), substance-use disorders, autism spectrum disorders, schizophrenia, and bipolar disorder (BD) [3,4]. Impairment in the neuropsychological processes of executive functioning (EF), which includes the cognitive functions necessary for self-regulation and the regulation of socially appropriate behavior, has received considerable research attention.

In this context, EF impairment has been established, impairing the ability to anticipate behavioral consequences, to assess punishment and reward, and impairing abilities to generate socially appropriate behavior in challenging contexts [5,6]. EF is an umbrella term encompassing a diverse range of cognitive processes and behavioral competencies to facilitate the initiation, planning, regulation, sequencing, and achievement of complex goal-oriented behavior and thought [2]. No overarching or widely accepted conceptual framework of EF has been developed and there continues to be disagreement about the processes thought to be involved in EF [2,7,8]. Within this profusion of terms, three EFs are generally acknowledged as important because they are supposedly implicated in the performance of most executive tasks and are relatively well defined: shifting, inhibition, and updating [8–10]. Shifting, attention switching, or cognitive flexibility refers to the ability to switch rapidly back and forth between multiple tasks, mental sets, and

operations [8,11]. It has been estimated that this ability emerges in children between the ages of 3 and 5 years when using simple switching tasks. As the task rules increase in complexity, however, the child will show more errors in flexibility [12]. This ability improves considerably between the ages of 7 and 9 years and continues to improve until adolescence [13]. Inhibition is defined by Morris and Jones [14] as the ability to suppress dominant, automatic, or prepotent responses in favor of a more goal-appropriate one. Failure to inhibit in children might result in behaviors such as responding before the task is understood, answering before sufficient information is available, and allowing attention to be captured by irrelevant stimuli, that is, distractibility or failing to correct obviously inappropriate responses [15]. Studies found that the greatest period of development inhibition occurred between the ages of 6 and 8 years, as cited by Passler *et al.* [16]. They further suggested that by age 10 the child's ability to inhibit attention to irrelevant stimuli, as well as to avoid preservative errors, was complete with mastery of these skills evident at the age of 12 years. However, younger children had more variability in their responding rates and showed slower response times overall than did either older children or adults. Miyake *et al.* [8] mentioned that updating refers to the updating and monitoring of representations held in working memory. These processes involve the monitoring and coding of incoming information that is relevant to the task at hand, followed by the revision of item held in working memory and a replacement of old irrelevant information with new relevant information. Updating thus concerns the dynamic, goal-directed manipulation of memory content. Hughes and Graham [17] have identified several difficulties in the accurate assessment of executive functions in children, the most important of which is the child's limited language ability. When task instructions are complex, verbal comprehension in the child is taxed engaging nonexecutive skills.

In pediatric populations, there is considerable overlap between some psychiatric disorders such as ADHD, disruptive behavior disorder (DBD), and BD as there are shared symptoms such as inappropriate actions and verbal responses in social situations, lack of inhibition, and distractibility [18]. Behavioral disinhibition could be considered as a marker of motivational or emotional dysregulation that might predispose a child to develop one of several dysregulatory disorders such as ADHD, DBD, or BD [19]. However, there is limited research on the relation between impairment in EF and behavioral problems in children, despite the shared developmental timetable [20] and despite the increasing evidence for the underlying neural mechanisms in common [21]. Accordingly, this study hypothesizes the role of executive functions as a core process in such disorders with behavioral disinhibition. The aim of this study is to examine three facets of executive functions (shifting, inhibition, and updating) in children diagnosed as having one of the following disorders: ADHD, DBD, and BD. These disorders have behavioral disinhibition in common that may interfere with the cognitive task performance. This might further help the diagnostic

accuracy by uncovering the similarities and differences in executive functions and might help to compare the cognitive profiles among these disorders.

Patients and methods

The study was conducted at the outpatient clinic (OPC) of Psychiatry Department, Mansoura University Hospitals. The OPC presents its services to several governorates, mainly ElD akahlia, Demietta, Portsaid, and their surrounding countryside. The study was conducted during the period from March 2009 to August 2010. This is a case–control study in which 92 children fulfilled the inclusion and exclusion criteria during the period of the study. Children included in this study were of both sexes, aged from 6 to 12 years with an intelligence quotient (IQ) equal to or more than 80, with attendance of at least one parent, and diagnosed as having one of the following childhood psychiatric disorders: ADHD, DBD, and BD. Children with an IQ below 80, with general medical condition, organic mental disorders, or epilepsy, under medical or psychiatric treatment, with comorbidity of the different disorders, and/or those who refused to join the study (child or parental causes) were excluded from this study. Exclusion criteria such as IQ being below 80 was considered given the complex nature of higher order processing of executive function that is markedly reliant on other nonexecutive processes such as language, calculation, or visuospatial processing.

A control group of 45 children was recruited randomly from the OPC of the Dermatology Department of the Mansoura University Hospitals (Egypt). They had the following criteria: complaint of minor dermatological problems with free psychiatric history, matched with cases for age, sex, education, and cultural background, and not receiving centrally acting medical agents, for example, antihistamines, which may interfere with the psychiatric assessment.

Parental consent was obtained for 137 children (92 cases, 45 controls) to participate in this study. All children were subjected to an extensive clinical history and physical and psychiatric semistructured interview guided by the Child Mental Status Examination [22]. The latter is a set of observations that provide a detailed description of the child's behavior during the diagnostic interview. The interview is used to collect basic information about the personal, physical, and psychiatric histories, complaints, mental status evaluation, and investigations if needed. In addition, they were subjected to physical and neurological examination to exclude any general medical condition, which may interfere with the performance of the child during assessment of executive functions. Those diagnosed as having one of the following pure childhood psychiatric disorders were selected. These disorders include ADHD, DBD (conduct disorder and oppositional defiant disorder), and BD. Diagnoses were confirmed by at least two senior staff according to the diagnostic and statistical manual 4th ed. text revision criteria [23]. Data were collected by two independent psychiatrists with at

least a Master's degree and a minimum of 5 years of training in the Children and Adolescent Unit of the Psychiatric Department at the Mansoura University Hospitals.

Neuropsychological assessment was made using the following tools: Wechsler Intelligence Scale for Children [24], Arabic Version [25], designed for application on children from ages of 5–15 years, was used to assess the IQ of the children. It consists of 12 items, six for the verbal scale and the other six for the performance scale. These are used for the calculation of verbal IQ, performance IQ, and total IQ. Assessment of executive functions was made using a battery of seven tasks adopted for children to assess shifting, inhibition, and updating as the main components of executive functions. These tasks were obtained by interpersonal communication with Van der Sluis *et al.* [26]. Three measures of inhibition were administered namely quantity inhibition task, object inhibition task, and numerical size inhibition task. For quantity inhibition, children were presented with a set of similar digits; they had to name the number of stimuli within the set, for example, if the set '444' was presented, the correct answer was '3'. In object inhibition, children were instructed to name the smaller, less obtrusive object, that is, to ignore the larger, prepotent figure in favor of the smaller, less noticeable one. In numerical size inhibition, the children had to name the numerically largest digit of a pair, which was always the physically smallest, that is, they had to ignore the larger, more prepotent digit in favor of the smaller one. Furthermore, three measures of shifting were administered namely object shifting, symbol shifting, and place shifting. For objects shifting, depending on the color of the stimulus, children were to name either the object (when blue) or the digit (when yellow). For symbol shifting, depending on the color of the stimulus, children were required to name the letter (when blue) or the digit (when yellow). For place shifting, a letter and a digit were presented in pairs in one of the corners of a square. Children were to name the letter when the pair was printed in one of the top corners, and the digit when the pair was printed in one of the bottom corners. Meanwhile, one measure of updating was administered namely to keep track in which the children were instructed to name all pictures in the series and to keep track of the target categories. At the end of a series, they were asked to name the last picture that they had seen of each of the target categories. Scores of all these tasks are proportionate to the correct answers (1 for correct or 0 for wrong item's response). Inhibition and shifting task scores measure from 0–40 for each task. Updating task scores measure from 0–28.

Translation and back translation of executive function tasks and validity were performed through the cooperation with the Department of Educational Psychology, Faculty of Education, Mansoura University. Reliability was examined by the test–retest method with Cronbach alpha coefficient (0.87) through the cooperation with the Department of Community, Faculty of Medicine, Mansoura University. This study is now in process for publication. Arabic Version Wechsler Intelligence Scale

for Children [24] was applied by a professional psychologist with a minimum of 5 years experience. Assessment of executive functions was made by psychiatrist with a Master's degree with more than 5 years of training in the Children and Adolescent Unit of the Psychiatric Department at the Mansoura University Hospitals. This was preceded after supervised evaluation of a prestudy training.

The statistics of data was calculated using excel program and Statistical Package for Social Science program version 10 (SPSS Inc., Chicago, Illinois, USA). To test the normality of data distribution, the Kolmogrov–Smirnov test was conducted. The data description was carried out in the form of frequency and proportion for qualitative data and in the form of mean and (± standard deviation) for quantitative data. The analysis of the data was performed to test statistically significant difference between groups. The χ^2-test was used for qualitative data. For quantitative data, the Student's *t*-test was used to compare between two groups. The one-way analysis of variance test compares more than two groups, followed by the post-hoc least significant difference test for intragroup comparisons. Correlation coefficiency was calculated to detect association between variables. Significance levels are reached when *P* value is less than or equal to 0.05 at a confidence interval of 95%.

Results

The mean age in the patient group was 9.1 ± 2 years, the majority were boys (60; 65.2%), and 70 patients were from urban area (76.1%). Meanwhile, among the control group the mean age was 9.1 ± 1.8 years with the majority being boys (25; 55.6%) and 35 were from urban area (77.8%). Table 1 shows that the highest mean of age is present in patients with BD than other disorders with statistical difference. Furthermore, sex difference is present in ADHD as more boys (80%) were found to have the disorder. In Table 2, significant difference in IQ between cases (88.16) and control (95.37) was found. In addition, the lowest mean of scores of IQ is present in ADHD inattentive type in comparison with the other disorders ($P = 0.026$). In Table 3, the comparison between cases and the control groups across the selected executive functions (shifting, inhibition, and updating) represents significant differences ($P < 0.001$) in all measures of executive functions. Table 4 shows that shifting function (total) has the highest mean of scores in conduct disorder (27.72), followed by ADHD hyperactive, oppositional defiant, ADHD inattentive, and ADHD combined, respectively. Then, the lowest mean of scores was bipolar (14.159) with statistically significant difference ($P < 0.001$). Table 5 shows that the highest mean of scores in the total inhibition function was present in ADHD inattentive (35.95), then in oppositional defiant, ADHD hyperactive, conduct disorder, bipolar, and finally ADHD combined (27.18). With regard to updating function in the different disorders, the lowest mean of scores is present in ADHD inattentive type (13.57) followed by ADHD hyperactive and ADHD combined (15.86). Higher scores with slight differences are present in

Table 1 Sociodemographic distribution of the patients in different disorders

Patients	N (%)	Age (years)	Sex		Residence	
			Male	Female	Urban	Rural
ADHD inattentive	14 (15.21)	8.17±1.8	9 (64.3%)	5 (35.7%)	10 (71.4%)	4 (28.6%)
ADHD hyperactive	15 (16.30)	8.9±2.07	12 (80%)	3 (20%)	13 (86.7%)	2 (13.3%)
ADHD combined	15 (16.30)	8.2±1.4	12 (80%)	3 (20%)	12 (80%)	3 (20%)
Conduct disorders	24 (26.8)	9.9±1.8	16 (66.7%)	8 (33.3%)	17 (70.8%)	7 (29.2%)
Oppositional defiant	13 (14.13)	8.1±1.9	6 (46.2%)	7 (53.84%)	11 (84.6%)	2 (15.4%)
Bipolar disorders	11 (11.95)	11.1±0.7	5 (45.5%)	6 (54.5%)	7 (63.6%)	4 (36.4%)
Significance		F(6.63); P<0.001	χ^2(6.89); P=0.229		χ^2(3.03); P=0.694	

ADHD, attention deficit hyperactivity disorder.

bipolar, oppositional defiant, and conduct disorder, respectively (Table 6).

Discussion

Impairment of EF generally does not present in isolation, but is a component of a larger constellation of psychological, emotional, and behavioral problems, including physical and mental health issues, substance use, and poor academic functioning [27]. Research that assists in identifying or supporting a particular executive process as underlying the behaviors of psychiatric disorders in children may help our understanding of these disorders [28]. In this study, it is suggested that finding out relationships between the behavioral symptoms detected in children and executive functions may later on help clinicians with improved diagnoses and particularly with differential diagnoses and with the designing and implementation of interventions.

Sociodemographic data of the studied groups show that the highest age mean was detected in BD; this is similar to Birmaher et al. [29]. More boys were identified as having ADHD. This sex difference is consistent with epidemiological studies of ADHD [30]. Moreover, IQ level showed significant difference between cases and control and between the different disorders. ADHD inattentive type has the lowest mean of IQ scores than did other groups. This is similar to the results of Nigg [31] and Mahone et al. [32]. This could be to the psychopathological effect of the disorders.

Assessment of shifting
This study's results show that children with ADHD do not have a specific deficit in shifting with no variations among ADHD subtypes compared with other groups. These results were similar to that of Nigg et al. [33] and

Table 2 Intelligence quotient level of the studied groups

Groups	IQ	Significance
Cases	88.16±4.73	t (−8.52); P<0.001
Control	95.37±4.48	
ADHD inattentive	84.85±1.95	F (2.68); P=0.026
ADHD hyperactive	89.86±6.27	
ADHD combined	86.73±2.96	
Conduct disorders	88.62±5.63	
Oppositional defiant	89.76±4.65	
Bipolar disorders	89.09±2.16	

ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient.

Alloway et al. [34]. In contrast, Tripp et al. [35] and Willcutt et al. [3] found considerable deficit in shifting among ADHD children. In these findings, there is a deficit in the shifting ability (symbol, object, and place) among the BD group. In agreement with this study, other studies [36–38] showed a significant difference in shifting from the control group.

Assessment of inhibition
These results revealed the presence of greater difficulty with inhibition measures in ADHD combined type in comparison with other ADHD subtypes. These results are similar to those of other studies [39–41]. In contrast, Willcutt et al. [3] found no differences between subtypes of ADHD. Furthermore, it is found that there is similarity between ADHD combined and BD in inhibition measures. This is consistent with the study of Passarotti et al. [42], which directly compared inhibition in each of these disorders. The finding in this study might add to the interpenetration and to the overlap of the concepts of disinhibition. Hence, it could be suggested that both ADHD combined and BD have add-on effects of two types of inhibitory dysfunction. Behavioral disinhibition, as a novelty seeking and approach of unfamiliar stimuli and the impairment in executive inhibition, as a defect in the process of suppression of a response for goal direct behavior, might be implicated in the impairment of EF.

Assessment of updating
This study shows a greater deficit in updating in ADHD inattentive type. This confirms the results of Nigg et al. [39], Chhabildas et al. [43], Sergeant et al. [44], and Happé et al. [45]. Meanwhile, Willcutt et al. [3] found no impairment in working memory among ADHD subtypes. However, according to the results of this study, it appears that updating may differentiate between ADHD and BD as it is more impaired in ADHD. These results are similar to those of Nigg et al. [39], Barkley et al. [46], Dickstein et al. [47]. Accordingly, the updating task is not secondary to the behavioral disinhibition. Furthermore, it could be in favor of the working memory as a core or primary deficit in ADHD that results in difficulty in paying attention.

Executive functions in disruptive behavior disorders
In these results, no deficit in EF could be considered to be specific to the pure DBD. Clark et al. [48] and Oosterlaan et al. [49] concluded that impairment in EF

Table 3 Comparison between cases and control groups across executive functions

Executive function tasks	Cases (N=92) (mean ± SD)	Control (N=45) (mean ± SD)	Significance
Updating task	16.86 ± 2.79	22.75 ± 1.46	t (− 13.25); $P < 0.001$
Symbol shifting task	26.63 ± 6.64	34.91 ± 1.76	t (− 8.20); $P < 0.001$
Object shifting task	26.44 ± 6.79	34.8 ± 1.96	t (− 8.06); $P < 0.001$
Place shifting task	26.04 ± 6.97	34.55 ± 1.92	t (− 8.02); $P < 0.001$
Shifting (total)	23.99 ± 5.09	31.75 ± 1.61	t (− 9.95); $P < 0.001$
Quantity inhibition task	31.14 ± 4.93	37.71 ± 1.76	t (− 8.64); $P < 0.001$
Object inhibition task	30.38 ± 5.12	37.46 ± 1.79	t (− 8.99); $P < 0.001$
Numerical size inhibition task	31.57 ± 5.08	38.31 ± 1.85	t (− 8.60); $P < 0.001$
Inhibition (total)	31.03 ± 4.75	37.82 ± 1.69	t (− 9.28); $P < 0.001$

SD, standard deviation.

Table 4 Assessment of shifting in different disorders[a]

Disorders	N	Symbol shifting task Mean ± SD	Object shifting task Mean ± SD	Place shifting task Mean ± SD	Shifting (total) Mean ± SD
ADHD inattentive	14	28.92 ± 3.95	26 ± 3.16	24.42 ± 3.41	23.23 ± 1.76
ADHD hyperactive	15	27.80 ± 5.68	29.86 ± 2.09	29.86 ± 2.58	25.80 ± 2.35
ADHD combined	15	24.93 ± 5.18	25.80 ± 5.25	24.33 ± 4.22	22.73 ± 3.39
Conduct	24	30.45 ± 3.65	30.70 ± 4.51	30.95 ± 4.72	27.72 ± 3.66
Oppositional defiant	13	28.30 ± 5.42	27.61 ± 5.62	28.15 ± 4.94	25.63 ± 4.52
Bipolar	11	14.09 ± 2.70	12.54 ± 1.29	12 ± 1.41	14.15 ± 1.21
Significance		F(21.96); $P < 0.001$	F(32.94); $P < 0.001$	F(40.44); $P < 0.001$	F(30.68); $P < 0.001$

ADHD, attention deficit hyperactivity disorder; SD, standard deviation.
[a]Scoring of shifting tasks = 0–40.

Table 5 Assessment of inhibition in different disorders[a]

Disorders	N	Quantity inhibition task Mean ± SD	Object inhibition task Mean ± SD	Numerical size inhibition task Mean ± SD	Inhibition (Total) Mean ± SD
ADHD inattentive	14	36.21 ± 1.25	34.78 ± 1.36	36.85 ± 1.95	35.95 ± 1.06
ADHD hyperactive	15	33.86 ± 1.84	31.33 ± 3.79	33.33 ± 3.71	32.84 ± 2.71
ADHD combined	15	28.00 ± 6.05	26.06 ± 5.96	26.0 ± 6.02	26.68 ± 5.53
Conduct	24	29.41 ± 4.85	30.41 ± 4.72	31.50 ± 3.84	30.44 ± 4.23
Oppositional defiant	13	32.76 ± 2.12	32.92 ± 3.09	33.30 ± 2.68	33.0 ± 2.53
Bipolar	11	27.09 ± 3.64	26.27 ± 4.51	28.18 ± 3.18	27.18 ± 3.60
Significance		F(11.88) $P < 0.001$	F(9.21) $P < 0.001$	F(14.37) $P < 0.001$	F(13.16) $P < 0.001$

ADHD, attention deficit hyperactivity disorder; SD, standard deviation.
[a]Scoring of inhibition tasks = 0–40.

Table 6 Assessment of updating in different disorders

Disorders	N	Updating Mean ± SD
ADHD inattentive	14	13.57 ± 1.94
ADHD hyperactive	15	15.66 ± 1.91
ADHD combined	15	15.86 ± 1.88
Conduct	24	18.79 ± 2.60
Oppositional defiant	13	18.46 ± 2.40
Bipolar	11	18.00 ± 1.00
Significance		F(14.48); $P < 0.001$

ADHD, attention deficit hyperactivity disorder; SD, standard deviation.

found in children with DBD was due to the presence of comorbid ADHD. The association between DBD and EF deficits did not remain significant, when the effect of ADHD was partialled out. However, other finding suggests that DBD could be associated with EF impairment after controlling for ADHD [46,48]. Hence, this association between DBD and EF should be questioned because of the finding suggesting that the association can be explained by comorbidity of these disorders with ADHD, which has been associated with EF impairments.

Conclusion

This study provides evidences that the primary deficit in BD is present in shifting ability, whereas updating function is specifically impaired in ADHD. However, the findings indicate that inhibition impairment is present in ADHD, DBD, and BD. In addition, differences in executive function performance are found among ADHD subtypes as deficits in inhibition are more specific to the ADHD combined type, whereas impairment in updating is more specific to the ADHD inattentive type. These differences may suppose a specific cognitive profile for each disorder that provides more objective means of differential diagnosis among these disorders when they are not reliably distinguished by clinical diagnostic methods.

Limitations of the study

This study is a preliminary examination of executive function profiles in different childhood psychiatric disorders. The first limitation is the wide age range (6 years to 12 years of age) that may result in systematic differences between children in different stages of development of EF. Second, the sample size was relatively small. The use of variable analysis to investigate processes involved in different disorders is better to be pursued with larger samples. Third, the available measures may not assess 'pure' EF tasks as they mostly measured more than one EF. Tapping pure EF is conceptually not feasible because almost every task requires an individual to keep rules in mind and thus addresses working memory next to the EF, which was aimed to be measured.

Recommendations

Further research could examine the interaction of age and development on executive functions in normal versus disordered children. Moreover, it is recommended to compare the inhibitory tasks of large samples of boys and girls separately to clarify the effect of sex differences on EF. This would be helpful in understanding better these developmental processes. Lastly, this study addressed the pure forms of the disorders. Hence, future studies considering the impact of comorbidity between the childhood disorders may enhance further understanding of the psychopathology involved.

Acknowledgements

References

1 Morgan AB, Lilienfeld SO. A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. Clin Psychol Rev 2000; 20:113–136.

2 Royall DR, Lauterbach EC, Cummings JL, Reeve A, Rummans TA, Kaufer DI, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the committee on research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2002; 14:377–405.

3 Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry 2005; 57:1336–1346.

4 Schug RA, Raine A. Comparative meta-analyses of neuropsychological functioning in antisocial schizophrenic persons. Clin Psychol Rev 2009; 29:230–242.

5 Esther Strauss E, Sherman EMS, Spreen O. Compendium of neuropsychological tests: administration, norms and commentary. 3rd ed. USA: Oxford University Press; 2006.

6 Seguin JR. The frontal lobe and aggression. Eur J Dev Psychol 2009; 6:100–119.

7 Burgess PW. Theory and methodology in executive function research. In: Rabbitt P, editor. Methodology of frontal and executive function. Hove, UK: Psychology Press; 1997. pp. 81–116.

8 Miyake A, Friedman N, Emerson MJ, Witzki A, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex 'Frontal Lobe' tasks: a latent variable analysis. Cognit Psychol 2000; 41:49–100.

9 Baddeley A. Exploring the central executive. Q J Exp Psychol 1996; 49:5–28.

10 Clair-Thompson HL St, Gathercole SE. Executive functions and achievements in school: shifting, updating, inhibition and working memory. Q J Exp Psychol 2006; 59:745–759.

11 Monsell S. Control of mental processes. In: Bruce V, editor. Unsolved mysteries of the mind: tutorial essays in cognition. UK: Erlbaum; 1996. pp. 93–148.

12 Espy KA. The Shape school: assessing executive function in preschool children. Dev Neuropsychol 1997; 13:495–499.

13 Zelazo PD, Frye D. Cognitive complexity and control: II. The development of executive function in childhood. Curr Dir Psychol Sci 1998; 7:121–126.

14 Morris N, Jones DM. Memory updating in working memory: the role of the central executive. Br J Psychol 1990; 81:111–121.

15 Schachar R, Logan GD. Impulsivity and inhibitory control in normal development and childhood psychopathology. Dev Psychol 1990; 26:710–720.

16 Passler M, Issac W, Hynd GW. Neuropsychological development of behavior attributed to frontal lobe functioning in children. Dev Neuropsychol 1985; 1:349–370.

17 Hughes C, Graham A. Measuring executive functions in childhood: problems and solutions. Child Adolesc Ment Health. 2002; 7:131–142.

18 Geller B, Zimerman B, Williams M, DelBello MP, Bolhofner K, Craney JL, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002; 12:11–25.

19 Séguin JR, Zelazo PD. Executive function in early physical aggression. In: Tremblay RE, Hartup WW, Archer J, editors. Developmental origins of aggression. 1st ed. New York: The Guilford Press; 2005. pp. 307–329.

20 Zelazo PD, Cunningham W. Executive function: mechanisms underlying emotion regulation. In: Gross JJ, editor. Handbook of emotion regulation. New York: The Guilford Press; 2007. pp. 135–58.

21 Nigg JT. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychol Bull 2000; 126:220–246.

22 Barry N. Diagnostic counter for children and adolescents. In: Ebert M, Loosen P, Nurcombe B, Leckman J, editors. Current diagnosis treatment psychiatry. 2nd ed. NY, London, Madrid: McGraw-Hill Companies; 2008. pp. 56–66.

23 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Pub; 2000.

24 Wechsler D. Wechsler intelligence scale for children. San Antonio: The Psychological Corporation; 1949.

25 Ismael MM. The wechsler intelligence scale for children (WISC) the Arabic version. Cairo: The Egyptian Anglo library; 1993.

26 Van der Sluis S, De Jong PF, Van der Leij A. Executive functioning in children and its relations with reasoning, reading and arithmetic. Intelligence 2007; 35:427–449.

27 Odgers CL, Caspi A, Broadbent JM, Dickson N, Hancox RJ, Harrington H, et al. Prediction of differential adult health burden by conduct problem subtypes in males. Arch Gen Psychiatry 2007; 64:476–484.

28 Rapport MD, Chung KM, Shore G, Isaacs P. A conceptual model of child psychopathology: implications for understanding attention deficit hyperactivity disorder and treatment efficacy. J Clin Child Adolesc Psychol 2001; 30:48–58.

29 Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006; 63:175–183.

30 Doyle AE, Biederman J, Seidman LJ, Weber W, Faraone SV. Diagnostic efficiency of neuropsychological test scores for discriminating boys with and without attention deficit-hyperactivity disorder. J Consult Clin Psychol 2000; 68:477–488.

31 Nigg JT. Is ADHD a disinhibitory disorder. Psychol Bull 2001; 127:571–598.

32 Mahone EM, Hagelthorn KM, Cutting LE, Schuerholz LJ, Pelletier SF, Rawlins C, et al. Effects of IQ on executive function measures in children with ADHD. Child Neuropsychol 2002; 8:52–65.

33 Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJS. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? Biol Psychiatry 2005; 57:1224–1230.

34 Alloway TP, Gathercole SE, Holmes J, Place M, Elliott JG, Hilton K. The diagnostic utility of behavioral checklists in identifying children with ADHD and children with working memory deficits. Child Psychiatry Hum Dev 2009; 40:353–366.

35 Tripp G, Ryan J, Peace K. Neuropsychological functioning in children with DSM-IV combined type attention deficit hyperactivity disorder. Aust N Z J Psychiatry 2002; 36:6–771.

36 Meyer SE, Carlson GA, Wiggs EA, Martinez PE, Ronsaville DS, Klimes-Dougan B, et al. A prospective study of the association among impaired executive functioning, childhood attentional problems and the development of bipolar disorder. Dev Psychopathol 2004; 16:461–476.

37 Olvera RL, Semrud-Clikeman M, Pliszka SR, O'Donnell L. Neuropsychological deficits in adolescents with conduct disorder and comorbid bipolar disorder: a pilot study. Bipolar Disord 2005; 7:57–67.

38 Walshaw PD, Alloy LB, Sabb FW. Executive function in pediatric bipolar disorder and attention-deficit hyperactivity disorder: in search of distinct phenotypic profiles. Neuropsychol Rev 2010; 20: 103–120.

39 Nigg JT, Blaskey LG, Huang-Pollock CL, Rappley MD. Neuropsychological executive functions and DSM-IV ADHD subtypes. J Am Acad Child Adolesc Psychiatry 2002; 41:59–66.

40 Hinshaw SP, Carte ET, Sami N, Treuting JJ, Zupan BA. Preadolescent girls with attention-deficit/hyperactivity disorder: II. neuropsychological performance in relation to subtypes and individual classification. J Consult Clin Psychol 2002; 70:1099–1111.

41 Huang-Pollock CL, Nigg JT, Halperin JM. Single dissociation findings of ADHD deficits in vigilance but not anterior or posterior attention systems. Neuropsychol 2006; 20:420–429.

42 Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. Psychiatr Res Neuroimaging 2010; 181:36–43.

43 Chhabildas N, Pennington BF, Willcutt EG. A comparison of the neuropsychological profiles of the DSM-IV subtypes of ADHD. J Abnorm Child Psychol 2001; 29:529–540.

44 Sergeant JA, Geurts H, Oosterlaan J. How specific is a deficit of executive functioning for Attention-Deficit/Hyperactivity Disorder? Behav Brain Res 2002; 130:3–28.

45 Happé F, Booth R, Charlton R, Hughes C. Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. Brain Cognit. 2006; 61:25–39.

46 Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L. Executive functioning, temporal discounting and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). J Abnorm Child Psychol 2001; 29:541–556.

47 Dickstein DP, Treland JE, Snow J, McClure EB, Mehta MS, Towbin KE, *et al.* Neuropsychological performance in pediatric bipolar disorder. Biol Psychiatry 2004; 55:32–39.

48 Clark C, Prior M, Kinsella GJ. Do executive function deficits differentiate between adolescents with ADHD and oppositional defiant/conduct disorder? A neuropsychological study using the six elements test and hayling sentence completion test. J Abnorm Child Psychol 2000; 28:403–414.

49 Oosterlaan J, Scheres A, Sergeant JA. Which executive functioning deficits are associated with AD/HD, ODD/CD and comorbid AD/HD + ODD/CD? J Abnorm Child Psychol 2005; 33:69–85.

الملخص العربى

اختلال الوظائف المعرفية فى الاطفال فى وجود الاضطرابات السلوكية

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يفترض وجود خلل فى الوظائف التنفيذية فى معظم الأضطرابات النفسية فى الأطفال.

و تهدف هذه الدراسة لفحص أوجه التشابه والاختلاف فى الوظائف التنفيذية بين بعض الأضطرابات النفسية فى الأطفال وتحديدا فى اضطراب نقص الانتباه وفرط الحركة واضطراب السلوك المناوئ والاضطراب الوجدانى ثنائى القطب وذلك كمحاوله لتحديد ما إذا كان هناك منظور معرفى محدد لكل من تلك الضطرابات.

ولقد أخذت عينه من 92 طفلا من عيادة لأمراض النفسية بمستشفيات المنصوره الجامعيه حيث تم تشخيصهم بإحدى الاضطرابات السابقه طبقا للدليل التشخيصى والاحصائى الامريكى الرابع للاضطرابات النفسية. وقد تم تطبيق اختبارات الوظائف التنفيذية للأطفال (صوفى فان دير سلويس) حيث تم تحديد ثلاثة من هذه الوظائف التنفيذية (القدرة على التثبيط، القدرة على التحول، والقدرة على التتبع) لدراسة مدى اختلال هذه الوظائف. وتمت مقارنتهم بعينه ضابطه من 45 طفل.

وخلصت الدراسة الى أن الأطفال ذوى الاضطراب الوجدانى يعانون من خلل واضح فى القدرة على التحول و أن أطفال اضطراب فرط الحركة ونقص الانتباه يعانون من ضعف القدرة على التتبع. وأن القدرة على التثبيط بها اختلال فى جميع الأمراض المذكورة.