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The Role of Mental and Physical Activities against Development of Alzheimer's Disease in Socialized and Isolated Rats

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder; lifestyle changes may slow its onset. Mental and physical activities have been related to better cognitive function in older adults. Cognitive engagement and physical activities have been associated with decreased risk of AD. Social isolation refers to a complete absence of or insufficient contact with other members of society and can exacerbate memory deficits.

Objective: To study the influence of mental and physical activities in normal socialized conditions as well as to evaluate their role in social isolated conditions on normal and AD rat models.

Methods: Rats were divided into two main groups; Group I socialized and Group II isolated. Both socialized and isolated groups were subdivided into four subgroups; two received saline and served as control, while two served as AD subgroups and received $ALCl_3$ (70 mg/kg IP) every day for four weeks. One of the control and AD subgroups was exposed to mental and physical activities but the other not exposed. Mental and physical activities were performed using Swimming test and Y-maze (each for one time/week) during four weeks. Isolated rats were housed individually in cages covered with black plastic while socialized rats randomly paired and housed in transparent covered cages. Histopathological changes in different brain regions and biochemical changes in Aβ, ACHE, brain monoamins (DA, NE, 5-HT), inflammatory mediators (TNF-α, IL-1β), oxidative parameters; (MDA, SOD, TAC) as well as brain derived neurotrophic factor (BDNF) were also measured for all groups. **Results:** Brain neurological damage characterizing isolation was more pronounced in isolation-associated AD rats. Mental and physical activities significantly decreased Aβ, ACHE, MDA, TNF-α, IL-1β together with increased SOD, TAC, DA, NE, 5-HT and BDNF. The protective effect of mental and physical activities against brain neuronal degenerations was more marked in isolated rats especially in isolated-associated AD rats. These results were confirmed by histopathological examinations of different brain regions.

Conclusion: Mental and physical activities can protect from brain neuronal degenerations either induced by isolation or that associated with AD in both socialized and isolated rat models. The protection using mental and physical activities is more pronounced in isolation-associated AD model.

Keywords: Alzheimer's disease; Isolation; Mental and physical activities; Rats

Introduction

Aluminum (Al) is the third most abundant element in the earth's crust [1,2]. It is increasingly taken into the body through food, water, air and drugs [3]. Al is also added as alum to drinking water for purification purposes [4,5]. It is considered as a potential factor in etiology of Alzheimer's disease (AD) [6,7]. Excessive Al intake leads to deposition of β- amyloid (Aβ) and overexpression of β- amyloid precursor protein (APP) in central nerve cells [8,9]. Al neurotoxicity is also associated with oxidative stress [10] as well as generation of Reactive Oxygen Species (ROS) that can damage the neuronal membrane and nucleic acids. Acetylcholinesterase (AChE) together with Aβ promotes the formation of Aβ-AChE complex which is more toxic [11]. Moreover, AD is characterized also by extracellular deposits of amyloid Aβ as well as intracellular aggregation of tau protein and consequently neuronal death [12].

Stress has potent modulating effects on both learning and memory processes, chronic stress negatively impacts both of them [12,13]. Social isolation (SI) as a major source of psychosocial stresses is associated with high prevalence of neurological diseases. Moreover, chronic stress that induced by SI is considered as a risk factor for development of AD [14]. Indeed, in both health and disease conditions cognition is highly susceptible to the influence of different social stressors. Low level of social engagement or SI has been identified as risk factor for AD and dementia, they increase the risk of cognitive impairment in old age [15,16]. On tests of cognitive functions, individuals with more social engagement demonstrate greater scores as compared to those with lower social engagement [17,18]. In addition, SI alters normal brain functions as well as structure. Indeed, social engagement has been linked to larger brain volumes [19]. Consequently, individuals who engage in affiliative interaction are more resistant to develop AD and dementia [16].

On the other hand, SI may cause inflammation and induce cell damage as the sympathetic nervous system and the hypothalamo-pituitary-adrenal axis shift towards a pro-inflammatory state. Chronic stressors as well as SI also exacerbate the oxidative stress-mediated damage in AD patients [20]. It is shown that stress and hypothalamo-pituitary-adrenal axis activity are associated with increased oxidative damage [21]. Both inflammation and oxidative stress can reduce total neural substrate and brain reserve in isolated AD patients, thus allowing clinical symptoms to occur at early stages of neuropathology [16]. Consequently, memory decline effectively increased with SI than

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with socially integrated rat model [22]. Moreover, levels of Aβ-40 as well as Aβ-42 in the hippocampus were increased. However, precise mechanism by which SI causes increase in Aβ is still not clear. Indeed, the beginning of cognition decline associated AD development is correlated well with Aβ and stress levels [14,23]. Furthermore, stress induced by SI is associated with the hippocampus as well as the frontal cortex related neuron circuits. It is well known that SI can damage both hippocampus and frontal cortex of animals [24] thus leading to abnormal neurotransmission function [25], synaptic plasticity [26], apoptosis [27], potassium ion channel currents change [28] and accumulation of oxidative products [24] as well as regeneration [26]. However, the mechanisms by which SI stress causing cognitive deficits is not very clear. However, social engagement, enough social connections and participation in different social activities can prevent cognitive decline [29,30].

It has been demonstrated that socially and physically active people have a reduced risk of cognitive impairment [31,32]. Several observational studies have reported that people who engaged in mentally stimulating activities such as learning, reading or playing games either at younger ages [33] or at older ages [34] are less likely to develop dementia compared with others who do not engage in any activities. According to the scientific researches, social relationships as well as mental and physical activities are important factors in maintaining memory. The effect of these factors on memory is attributed to the increase of partial blood flow and promote neurogenesis due to production of new nervous cells [35,36]. Furthermore, cognitive reserve hypothesis postulated that social and physical activity can increase the ability to tolerate brain pathology through enhanced synaptic activity and the efficient brain recovery [37].

Many clinical trials have been conducted to examine whether physical and mental activities can improve cognitive function in healthy adults. Some found that they improve cognitive function while others failed to show marked beneficial effects. Thus, the purpose of this study was to evaluate the effectiveness of mental and physical activities in improving cognitive function in normal socialized conditions as well as in social isolated conditions for both normal rats as well as for AD rat models. In addition, the study aimed to illustrate the role of social isolation in aggravating the progression of AD in rats.

Materials and Methods

Animals

Sprague Dawley male rats obtained from the Egyptian Nile Company were used; their weight ranged from 270-290 g. Rats were kept at standardized and adequate conditions regarding housing cages (stainless-steel), temperature (25°C ± 1°C), diet (standard pellets), water (ad-libitum) as well as all others experimental conditions. Isolation was induced for four weeks to all rats of the isolated groups by housing each rat individually in a stainless-steel cage with black plastic cover. On the other hand, socialized rats were paired randomly and housed in stainless-steel cages with transparent covers. The work was conducting according to the ethical guidelines prepared by Faculty of Pharmacy in accordance with the international guidelines and was approved from Al-Azhar University in Egypt.

Drugs and chemicals

For induction of AD in rats model, hydrated aluminum chloride was used ($AlCl_3.6H_2O$). It was obtained from Sigma Chemical Company (USA) and was prepared freshly every day by dissolving 70 mg/kg of it in distilled water. Moreover, all other chemicals and solvents were purchased of the highest commercially available grades.

Experimental design

Eight groups of rats were used each contain 8 rats. Four groups were maintained on program of both mental as well as physical activities while the other four groups were never exposed. Mental and physical activities were performed using Swimming test and Y-maze (each test for one time/each week) during the four weeks of the experiment. Rats were daily received intra-peritoneal injections which were classified as follows.

Control socialized group

In which socialized rats were injected with 1 ml/kg normal saline.

Control socialized group exposed to mental and physical activities

In which socialized rats were injected with 1 ml/kg normal saline and were exposed to both mental as well as physical activities.

Control isolated group

In which isolated rats were injected with 1 ml/kg normal saline.

Control isolated group exposed to mental and physical activities

In which isolated rats were injected with 1 ml/kg normal saline and were exposed to both mental as well as physical activities.

AD socialized group

In which socialized rats were injected with 70 mg/kg $AlCl_3$.

AD socialized group exposed to mental and physical activities

In which socialized rats were injected with 70 mg/kg $AlCl_3$ and were exposed to both mental as well as physical activities.

AD isolated group

In which isolated rats were injected with 70 mg/kg $AlCl_3$.

AD isolated group exposed to mental and physical activities

In which isolated rats were injected with 70 mg/kg $AlCl_3$ and were exposed to both mental as well as physical activities.

After four weeks of experiments; all rats were sacrificed and brain tissues were quickly removed and washed with saline (ice-cold) and immediately stored at –80°C for the biochemical analysis. After homogenization, the saline homogenates were prepared for evaluation of the content of β-amyloid (Aβ) and the activity of acetylcholine esterase (ACHE). In addition, brain tissue homogenate was used for assessment of brain derived neurotrophic factor (BDNF). Oxidative markers as malondialdehyde (MDA) and total antioxidant capacity (TAC) as well as the activity of superoxide dismutase (SOD) were also evaluated. Tumor necrosis factor-alpha (TNF-α) and Interleukin 1β (IL-1β) which represent the inflammatory mediators were also estimated. The content of brain monoamines was also evaluated for Dopamine (DA) and Norepinephrine (NE) as well as for Serotonin (5-HT). Moreover, two brains from each group were kept for further histopathological examinations (in 10% formaldehyde solution).

Biochemical Parameters

Assessment of Aβ content

According to the kit manufacturer's instructions, Aβ content was

measured in brain homogenate. The ELISA kit which provided by MyBioSource, Inc., USA in a Product Number (MBS702915) was used.

Assessment the activity of ACHE

The activity was measured in the brain using the commercially available kit which obtained from Sigma-Aldrich Company at St. Louis, USA in a Product Number (MAK119) depending on the previously described method [38].

Assessment of BDNF

By using ELISA kit depending on the previously described method [39], BDNF was evaluated in the brain. The kit provided by MyBioSource, Inc., USA in a Product Number (MBS494147).

Oxidative markers (MDA, SOD, TAC) assessment

In the brain homogenate lipid peroxidation was determined by evaluating thiobarbituric acid reactive substances (TBARS) level which evaluated as MDA [40]. However, the activity of SOD was measured depending on enzyme ability to reduce phenazine methosulphate which mediated the decrease in the dye of nitroblue tetrazolium [41] where increase in the absorbance (at 560 nm) for five min was measured. Finally, the antioxidants reactions with exogenously provide H_2O_2 (defined amount) was used for TAC assessment. The remaining H_2O_2 was measured colourimetrically,

Assessment of inflammatory mediators in the brain (IL-1β, TNF-α)

By using ELISA kit**,** TNF-α was measured in brain homogenate. The kit Product Number was RTA00, SRTA00, and PRTA00, it was used depending on the method which previously described [42]**.** According to the instructions of the manufacturer, IL-1β was also determined in brain homogenate by using ELISA kit. The kit was obtained from RayBiotech, Inc., USA with Number ELR-IL1b.

Assessment of DA, NE and 5-HT

Rats were rapidly sacrificed with minimum disturbance by decapitation to avoid changes in concentrations of brain monoamines which may occur in few minutes [43]. Serotonin was fluorometrically assayed while DA and NE were evaluated in the brain homogenate using the method which previously described by [44].

Behavioral Experiments

Two behavioural experiments were used as an integrative testing battery to allow measuring the most behavioural changes associated with both mental as well as physical activities.

Y-Maze test for assessment of spatial working memory

Measured parameters: The percentage spontaneous alternation was calculated as (actual alternations/maximum alternations) × 100.

Rats were tested in the Y-maze test which previously described [45]. The measured parameter reflected spatial working memory which is form of short-term memory. The test was used for measuring the willingness of rodents to explore the new environment. Rats preferred to investigate the new arm of the maze rather than returning to the arm that was previously visited. Different brain parts as hippocampus, basal forebrain, septum and prefrontal cortex were involved in Y-maze task [46,47]. It is evident that rat must remember which arm it had entered on a previous occasion to enable the alternation of its choice on the following trial. Therefore, spontaneous alternation has been embraced by behavioral pharmacologists as a quick and relatively simple test of spatial working memory, devoid of fear and reinforces [48].

The used apparatus is made of black wood and consisted of three arms of equal size, labeled as A, B, and C respectively. Each arm of the maze was 12 cm wide, 40 cm long, had 35 cm high walls with a 120° angle between two adjacent arms. During the test, each rat was placed at the centre of the maze and the sequence of entries into the three arms was noted over a period of 8 min. An arm entry was counted when the hind paws of the rat were completely within the arm. The ability to alternate requires remembering which arms have already been visited. Measured parameters were the total number of arm entries and the spontaneous alternation score calculated as the number of alternations divided by the total possible of alternations and multiplied by 100. Before the next animal was tested, the maze was cleaned and dried to avoid olfactory cues [49].

Swimming test for assessment of motor coordination

The swimming test was carried out following the method previously described [50-52] and modified [53]. The apparatus consists of a glass tank 91.4 cm × 91.4 cm × 30.5 cm. It was filled with water to its half and temperature was adjusted (26°C to 27°C) by using thermostat. The ramp was stabilized at the middle of one side of the apparatus while the swimming starting point was at the middle of the opposite side. Rats were taken to the test situation one hour before the test; they were placed individually at the starting point and observed until reaching the ramp for maximal 3 minutes. The behavior of rats in the swimming apparatus was evaluated by the following parameters:

Swimming time: It was measured in seconds using a stopwatch; it is the time from starting swimming till reaching the ramp with forepaws.

Swimming direction score: It ranged from (0-4):

i. Animal is given score (4) when swims directly from the starting point to the ramp.

ii. Animal is given score (3) when reaches the ramp through either right or left direction.

iii. Animal is given score (2) when reaches the ramp through both right and left directions.

iv. Animal is given score (1) when swims in all directions and in the middle but finally reaches the ramp during the 3 minutes.

v. Animal is given score (0) when swims in all directions, floats passively in the water but cannot reach the ramp within 3 minutes.

The measured parameters were recorded as index of muscular strength, neuromuscular coordination as well as awareness and vigilance.

Brain Histopathological Examinations

After fixed brain specimens in 10% formalin for 24 hours, they were washed with tap water. Brain specimens were also prepared and stained for light microscopy examinations [54]. Serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene embedded in paraffin at 56°C in hot air oven for 24 h. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by microtome. The obtained tissue sections were collected on glass slides and deparaffinized. After that, sections were stained with Hematoxylin and Eosin stain for routine histological examination.

Statistical Analysis

Data are expressed as mean ± SEM and multiple comparisons were done using one-way ANOVA followed by Tukey Kramer as a post hoc test and two-way ANOVA followed by Bonferroni post- tests. All statistical analysis and graphs were constructed using GraphPad Prism (ISI®, USA) software (version 5).

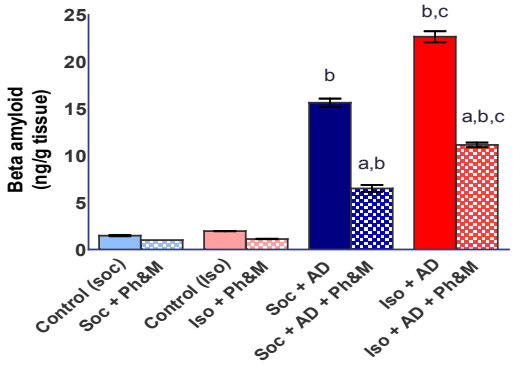
Results

Brain β-amyloid (Aβ) content

As illustrated in Figure 1, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain Aβ content to 41.64% and 49.2% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant elevation in brain Aβ content to 1054.62% and 1151.93% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain Aβ content to 641.7% and 993.8% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain Aβ content to 144.94% and 171.2% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

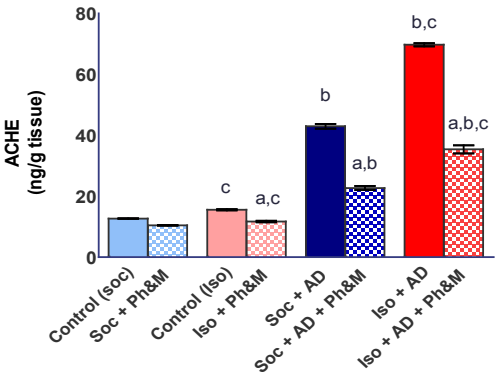
Brain Acetylcholine Esterase (ACHE) activity

As shown in Figure 2, control isolated rats with mental and physical activities showed significant reduction in the brain ACHE activity to 75.2% as compared to corresponding control isolated group. Additionally, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain ACHE activity to 52.83% and 50.7% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant elevation in the brain ACHE activity to 338.9% and 448.13% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain ACHE activity to 216.8% and 302.6% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, control isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain ACHE activity to 122.75% and 111.75% as compared to corresponding control socialized groups either alone or in combination with mental and physical activities respectively. Also, AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain ACHE activity to 162.3% and 155.95% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.



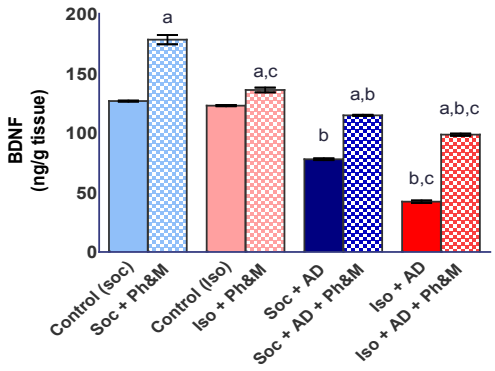
Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph and M activity and corresponding control or AD groups at p<0.05.
b: Significant difference from corresponding AD groups at p<0.05
c: Significant difference between isolated and corresponding socialized (control, AD or Ph and M activity) groups at p<0.05.

Figure 1: Effect of mental and physical activities on brain β-amyloid (Aβ) content in socialized and isolated rats.



Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph and M activity and corresponding control or AD groups at p<0.05.
b: Significant difference from corresponding AD groups at p<0.05
c: Significant difference between isolated and corresponding socialized (control, AD or Ph and M activity) groups at p<0.05.

Figure 2: Effect of mental and physical activities on brain acetylcholine esterase (ACHE) activity in socialized and isolated rats.



Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph and M activity and corresponding control or AD groups at p<0.05.
b: Significant difference from corresponding AD groups at p<0.05
c: Significant difference between isolated and corresponding socialized (control, AD or Ph and M activity) groups at p<0.05.

Figure 3: Effect of mental and physical activities on brain derived neurotrophic factor (BDNF) in socialized and isolated rats.

Brain Derived Neurotrophic Factor (BDNF)

As illustrated in Figure 3, control socialized and isolated rats with mental and physical activities showed significant elevation in the brain BDNF to 140.73% and 110.66% as compared to corresponding control socialized and isolated groups respectively. Additionally, AD

socialized and isolated groups with mental and physical activities showed significant elevation in the brain BDNF to 147.4% and 233.3% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in the brain BDNF to 61.47% and 34.4% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain BDNF to 64.4% and 72.4% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, control isolated group with mental and physical activities showed a significant reduction in the brain BDNF to 76.3% as compared to corresponding control socialized group with mental and physical activities. Also, AD isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain BDNF to 54.22% and 85.82% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

Brain Oxidative Stress Markers (MDA, SOD and TAC)

As shown in Figures 4a-4c control socialized and isolated rats with mental and physical activities showed significant reduction in brain MDA content to 51.48% and 94.06% as compared to corresponding control socialized and isolated groups respectively. Additionally, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain MDA content to 26.7% and 38.7% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant elevation in brain MDA content to 1486.8% and 1179.2% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain MDA content to 769.93% and 485.2% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, control isolated group with mental and physical activities showed a significant elevation in brain MDA content to 270.8% as compared to corresponding control socialized group with mental and physical activities. Also, AD isolated group with mental and physical activities showed a significant elevation in brain MDA content to 170.63% with respect to their corresponding AD socialized group with mental and physical activities.

Moreover, control socialized and isolated rats with mental and physical activities showed significant elevation in brain SOD activity to 123.45% and 112.9% as compared to corresponding control socialized and isolated groups respectively. Additionally, AD socialized and

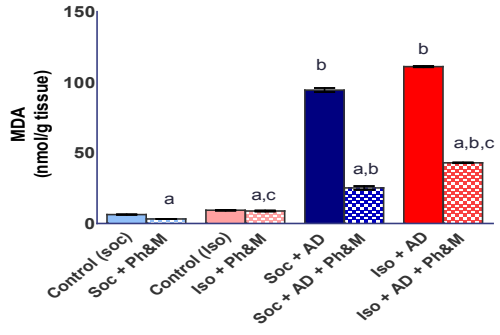


Figure 4a: Effect of mental and physical activities on brain oxidative stress markers Malondialdehyde (MDA) content in socialized and isolated rats.

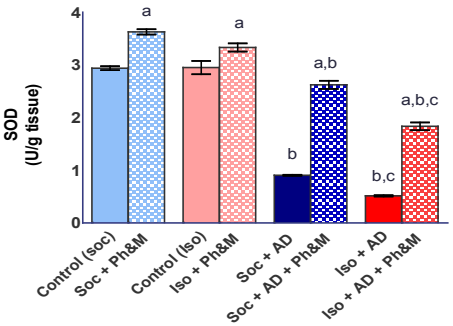
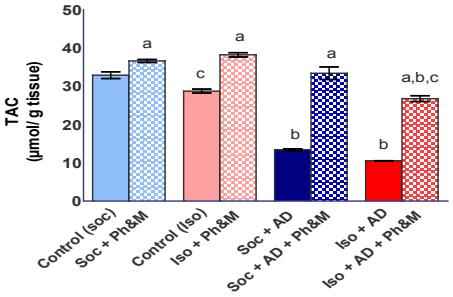


Figure 4b: Effect of mental and physical activities on brain oxidative stress markers Superoxide Dismutase (SOD) enzyme activity in socialized and isolated rats.



Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph andM activity and corresponding control or AD groups at $p<0.05$.
b: Significant difference from corresponding AD groups at $p<0.05$
c: Significant difference between isolated and corresponding socialized (control, AD or Ph andM activity) groups at $p<0.05$.

Figure 4c: Effect of mental and physical activities on brain oxidative stress markers total antioxidant capacity (TAC) in socialized and isolated rats.

isolated groups with mental and physical activities showed significant elevation in brain SOD activity to 289.3% and 356.3% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in brain SOD activity to 30.9% and 17.46% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain SOD activity to 72.32% and 55.07% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, AD isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain SOD activity to 56.8% and 69.95% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

Additionally, control socialized and isolated rats with mental and physical activities showed significant elevation in brain TAC to 111.27 and 132.94% as compared to corresponding control socialized and isolated groups respectively. Additionally, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain TAC to 249.1% and 255.04% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in brain TAC to 40.77% and 36.52% with respect to their corresponding control groups respectively. Also, AD isolated group with mental and physical activities showed significant reduction in brain TAC to 70.07% with respect to their corresponding isolated group with mental and

physical activities respectively. Finally, control isolated group showed a significant reduction in the brain TAC to 87.33% as compared to corresponding control socialized group. Also, AD isolated group with mental and physical activities showed a significant reduction in the brain TAC to 80.11% with respect to their corresponding AD socialized group with mental and physical activities.

Brain inflammatory mediators (IL-1β and TNF-α)

As illustrated in Figures 5a and 5b control isolated group with mental and physical activities showed significant reduction in brain IL-1β to 76.15% as compared to corresponding control isolated group. Additionally, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain IL-1β to 48.32% and 56.84% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant elevation in brain IL-1β to 355.8% and 334.13% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain IL-1β to 204.4% and 249.4% with respect to their corresponding socialized and isolated groups with mental and physical activities respectively. Finally, AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain IL-1β to 106.54% and 125.31% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

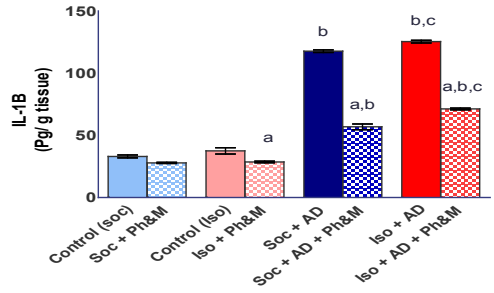
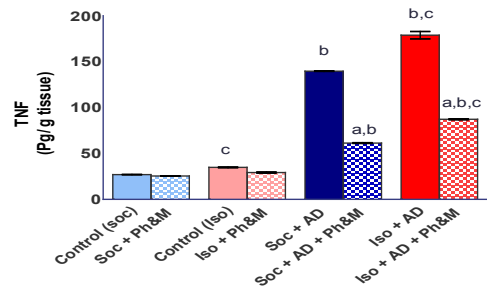


Figure 5a: Effect of mental and physical activities on brain inflammatory mediators (IL-1β) in socialized and isolated rats.



Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph andM activity and corresponding control or AD groups at p<0.05.
b: Significant difference from corresponding AD groups at p<0.05
c: Significant difference between isolated and corresponding socialized (control, AD or Ph andM activity) groups at p<0.05.

Figure 5b: Effect of mental and physical activities on brain inflammatory mediators (TNF-α) in socialized and isolated rats.

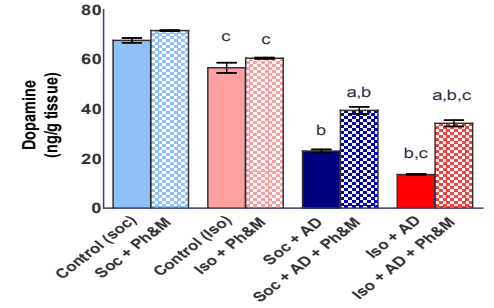


Figure 6a: Effect of mental and physical activities on brain monoamines Dopamine (DA) in socialized and isolated rats.

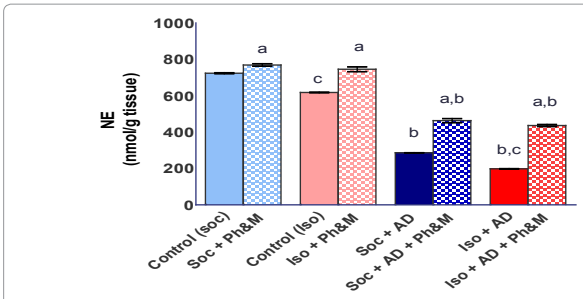
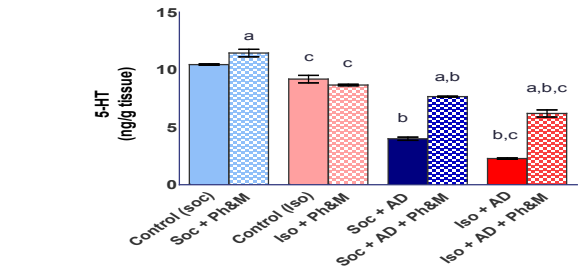


Figure 6b: Effect of mental and physical activities on brain monoamines Norepinephrine (NE) in socialized and isolated rats.



Data expressed as Mean ± SEM (n=8)
a: Significant difference between Ph and M activity and corresponding control or AD groups at p<0.05.
b: Significant difference from corresponding AD groups at p<0.05
c: Significant difference between isolated and corresponding socialized (control, AD or Ph and M activity) groups at p<0.05.

Figure 6c: Effect of mental and physical activities on brain monoamines Serotonin (5-HT) in socialized and isolated rats.

Moreover, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain TNF-α to 43.944% and 48.81% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant elevation in brain TNF-α to 516.3% and 512.3% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain TNF-α to 240.93% and 298.3% with respect to their corresponding control socialized and isolated groups with mental and physical activities respectively.

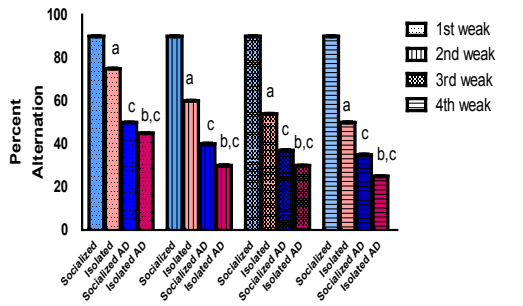
Finally, control isolated group showed a significant elevation in the brain TNF-α to 129.04% as compared to corresponding control socialized group. Also, AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain TNF-α to 128.1% and 142.3% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

Brain neurochemical parameterss

As shown in Figures 6a-6c, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain DA content to 171.21% and 252.03% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in brain DA content to 34.04% and 23.97% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain DA content to 55.1% and 56.56% with respect to their corresponding control socialized and isolated groups with mental and physical activities respectively. Finally, control isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain DA content to 83.7% and 84.5% as compared to corresponding control socialized groups either alone or in combination with mental and physical activities respectively. Also, AD isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain DA content to 58.92% and 86.74% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.

Additionally, control socialized and isolated rats with mental and physical activities showed significant elevation in brain NE level to 106.2% and 120.71% as compared to corresponding control socialized and isolated groups respectively. Additionally, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain NE level to 161.7% and 219.8% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in brain NE level to 39.6% and 32.1% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain NE level to 60.23% and 58.5% with respect to their corresponding control socialized and isolated groups with mental and physical activities respectively. Finally, control isolated group showed a significant reduction in the brain NE level to 85.34% as compared to corresponding control socialized group. Also, AD isolated group showed significant reduction in the brain NE level to 69.22% with respect to their corresponding AD socialized group.

Moreover, control socialized rats with mental and physical activities showed significant elevation in brain 5-HT level to 109.5% as compared to corresponding control socialized. Additionally, AD socialized and isolated groups with mental and physical activities showed significant elevation in brain 5-HT level to 191.6% and 272.52% with respect to their corresponding AD socialized and isolated groups respectively. In contrast to, AD socialized and isolated groups showed significant reduction in brain 5-HT level to 38.3% and 24.83% with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant reduction in brain 5-HT level to 66.93% and 71.54% with respect to their corresponding control socialized and isolated groups with mental and physical activities respectively. Finally, control isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain 5-HT level to 87.88% and 75.7% as compared to corresponding control socialized groups either alone or in combination with mental and physical activities respectively. Also, AD isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain 5-HT level to 56.9% and 80.91% with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively.



Data expressed as Mean ± SEM (n=8)
Significant difference at p<0.05 between:
a: Control isolated and socialized
b: AD isolated and socialized
c: AD and the corresponding control either socialized or isolated

Figure 7: Effect of mental and physical activities on spatial working memory performance in the Y-maze test of socialized and isolated rats.

Behavioral Experiments

Y-maze test

As shown in Figure 7, in the first week, it was found that social isolation for a long period caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 83.3% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant decrease in the percentage of spontaneous alternations to 90.0% as compared to corresponding AD socialized group. Additionally, AD socialized and isolated groups showed also significant impairment in spatial working memory as evidenced by a significant decrease in the percentage of spontaneous alternations to 55.55% and 60% with respect to their corresponding control groups respectively.

In the second week, it was found that social isolation for a long period caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 66.7% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant decrease in the percentage of spontaneous alternations to 75% as compared to corresponding AD socialized group. Additionally, AD socialized and isolated groups showed also significant impairment in spatial working memory as evidenced by a significant decrease in the percentage of spontaneous alternations to 44.44% and 50% with respect to their corresponding control groups respectively.

In the third week, it was found that social isolation for a long period caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 60% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant decrease in the percentage of spontaneous alternations to 81.1% as compared to corresponding AD socialized group. Additionally, AD socialized and isolated groups showed also significant impairment in spatial working memory as evidenced by a significant decrease in the percentage of spontaneous alternations to 41.11% and 55.55% with respect to their corresponding control groups respectively.

In the fourth week, it was found that social isolation for a long period caused a significant impairment in spatial working memory, as

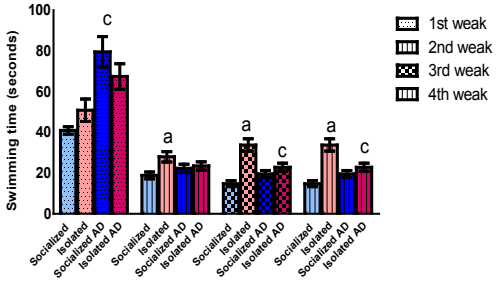
evidenced by a significant decrease in the percentage of spontaneous alternations reaching 55.6% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant decrease in the percentage of spontaneous alternations to 71.4% as compared to corresponding AD socialized group. Additionally, AD socialized and isolated groups showed also significant impairment in spatial working memory to 38.9% and 50% with respect to their corresponding control groups respectively.

Additionally, it was found that socialized group did not significantly change the spatial working memory in the second week as compared to the first week, in the third week as compared to the second week and in the fourth week as compared to the third week. However, it was found that social isolation for a long period caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 80% in the second week as compared to the first week, to 90% in the third week as compared to the second week and to 92.6% in the fourth week as compared to the third week. Additionally, it was found that AD socialized caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 80% in the second week as compared to the first week, to 92.5% in the third week as compared to the second week and to 94.6% in the fourth week as compared to the third week. Finally, it was found that AD isolated caused a significant impairment in spatial working memory, as evidenced by a significant decrease in the percentage of spontaneous alternations reaching 66.7% in the second week as compared to the first week, while did not significantly change the spatial working memory in the third week as compared to the second week, however it significantly decreases the percentage of spontaneous alternations to 83.33% in the fourth week as compared to the third week.

Swimming test (Swimming time)

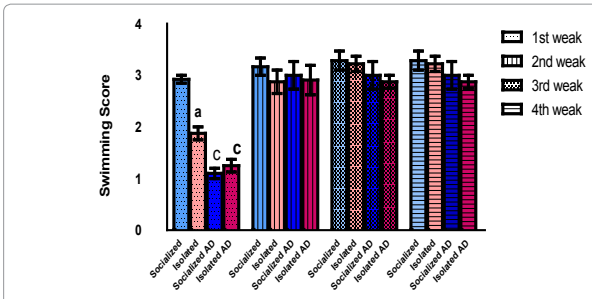
As shown in Figure 8, in the first week, it was found that AD socialized group showed a significant elevation in swimming time to 194.33% with respect to their corresponding control group. In the second week, it was found that social isolation for a long period caused a significant elevation in swimming time to 148.4% as compared to the corresponding control socialized group.

In the third week, it was found that social isolation for a long period showed a significant elevation in swimming time to 228.11% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant reduction in swimming time to 67.6% with respect to their corresponding control group.



Data expressed as Mean ± SEM (n=8)
Significant difference at p<0.05 between:
a: Control isolated and socialized
b: AD isolated and socialized
c: AD and the corresponding control either socialized or isolated

Figure 8: Effect of mental and physical activities on swimming time of socialized and isolated rats.



Data expressed as Mean ± SEM. (n=8)
Significant difference at p<0.05 between:
a: Control isolated and socialized
b: AD isolated and socialized
c: AD and the corresponding control either socialized or isolated

Figure 9: Effect of mental and physical activities on swimming direction score of socialized and isolated rats.

In the fourth week, it was found that social isolation for a long period showed a significant elevation in swimming time to 228.12% as compared to the corresponding control socialized group. Also, AD isolated group showed a significant decrease in swimming time to 67.6% with respect to their corresponding control group. It was found that socialized group showed a significant decrease in swimming time to 46.1% in the second week as compared to the first week. Also, it was found that social isolation for a long period caused a significant decrease in swimming time to 55.03% in the second week as compared to the first week. Additionally, it was found that AD socialized showed a significant decrease in swimming time to 28.15% in the second week as compared to the first week. Finally, it was found that AD isolated showed a significant decrease in swimming time to 34.85% in the second week as compared to the first week.

Swimming test (direction score)

As shown in Figure 9, in the first week, it was found that social isolation for a long period caused a significant decrease in direction score to 64.15% as compared to the corresponding control socialized group. Additionally, AD socialized and isolated groups showed also a significant decrease in direction score to 37.63% and 66.7% with respect to their corresponding control groups respectively. It was found that socialized group did not significantly change direction score in the second week as compared to the first week, in the third week as compared to the second week and in the fourth week as compared to the third week. However, it was found that social isolation for a long period caused a significant increase in direction score to 153.33% in the second week as compared to the first week. Additionally, it was found that AD socialized caused a significant increase in direction score to 272.72% in the second week as compared to the first week. Finally, it was found that AD isolated caused a significant increase in direction score to 232.72% in the second week as compared to the first week.

Histopathological Alterations in the Brain

Histopathological alterations in the brain specimens from different treated groups are shown in Figure 10a-10h and Table 1. Brain specimens from control socialized rats either alone or in combination with mental and physical activities showed normal histological structure and no histopathological alteration in all areas. On the other hand, brain specimens of control isolated group showed focal nuclear pyknosis as well as degeneration in the neuronal cells of cerebral cortex

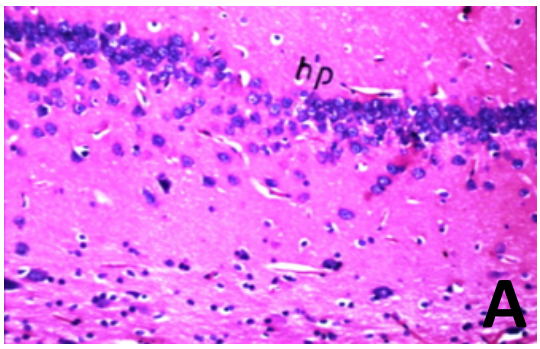


Figure 10a: Representative photomicrograph (magnification 40X) of brain section stained by Hematoxylin and Eosin: Section taken from brain of control socialized group showed normal histological structure of the hippocampus (hp).

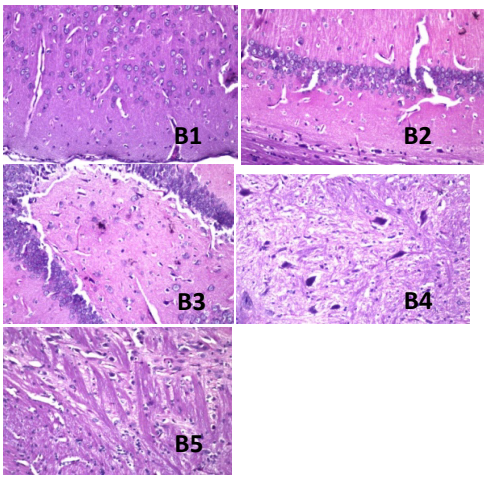


Figure 10b: Representative photomicrographs (magnification 40X) of brain sections stained by Hematoxylin and Eosin: Sections taken from brain of control socialized group with Ph and M activities showed no histopathological alteration in all areas (B1, B2, B3, B4, B5).

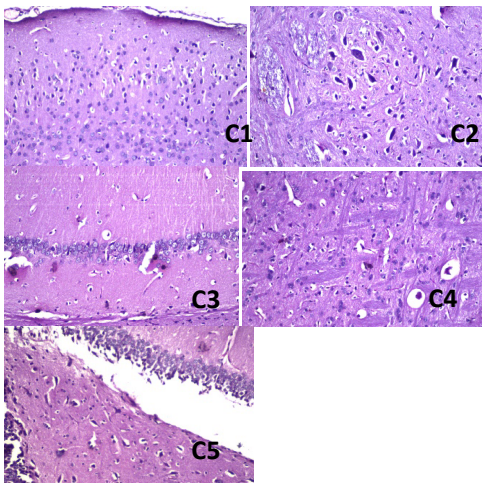


Figure 10c: Representative photomicrographs (magnification 40X) of brain sections stained by Hematoxylin and Eosin: Sections taken from brain of control isolated group showed focal nuclear pyknosis and degeneration in the neuronal cells of cerebral cortex (C1), atrophy in some neurons of the substantia nigra (C2) but no histopathological alteration in the hippocampus (C3, C4) as well as in the striatum (C5).

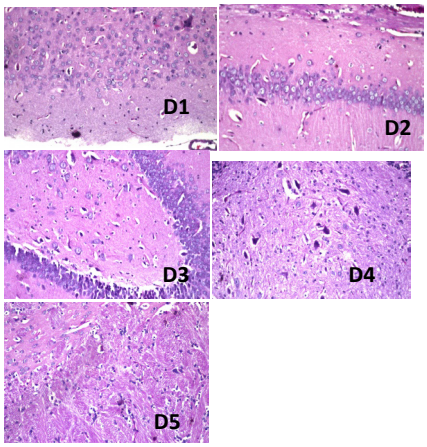


Figure 10d: Representative photomicrographs (magnification 40 X) of brain sections stained by Hematoxylin and Eosin: Sections taken from brain of control isolated group with Ph and M activities showed no histopathological alteration in all areas (D1, D2, D3, D4, D5).

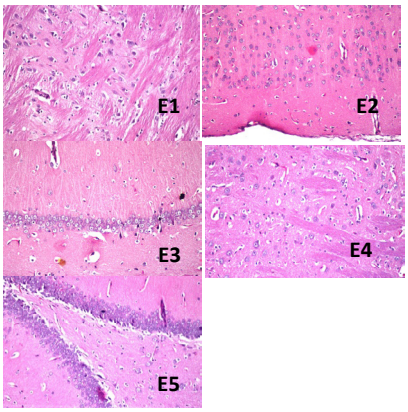


Figure 10e: Representative photomicrographs (magnification 40X) of brain sections stained by Hematoxylin and Eosin: Section taken from brain of AD socialized group showed normal histological structure in the striatum (E1) while showed nuclear pyknosis and degeneration in the neurons of cerebral cortex (E2) and hippocampus (E3, E4). Atrophy was observed in some neurons of the substantia nigra (E5).

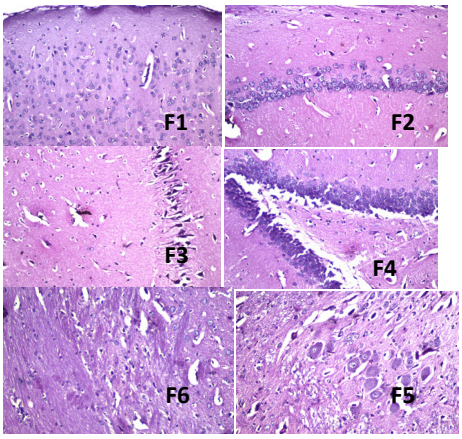


Figure 10f: Representative photomicrographs (magnification 40 X) of brain sections stained by Hematoxylin and Eosin: Section taken from brain of AD socialized group with Ph and M showed no histopathological alteration in the all areas of the brain except the nuclear pyknosis and degeneration in few neurons of the pyramidal cells in the hippocampus (Fig. F1, F2, F3, F4, F5, F6).

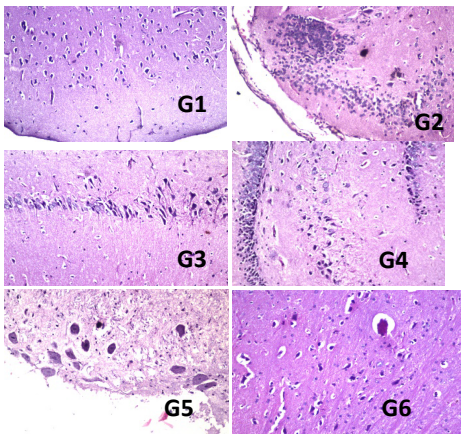


Figure 10g: Representative photomicrographs (magnification 40X) of brain sections stained by Hematoxylin and Eosin: Section taken from brain of AD isolated group showed nuclear necrosis and degeneration in cerebral cortex (G1) associated with focal gliosis (G2). Hippocampus as well as neurons of the fascia dentate, striatum and substantia nigra showed nuclear pyknosis and degeneration with congestion in the blood vessels (G3, G4, G5, G6).

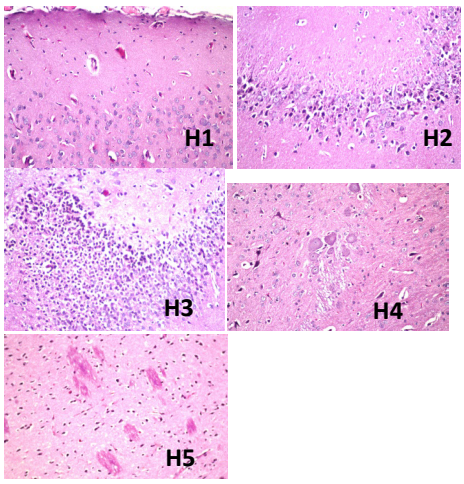


Figure 10h: Representative photomicrographs (magnification 40X) of brain sections stained by Hematoxylin and Eosin: Section taken from brain of AD isolated group with Ph and M showed no histopathological alteration in cerebral cortex (H1), Nuclear pyknosis and degeneration in subiculum and fascia dentate in the hippocampus (H2, H3), few focal eosinophilic plagues formation in striatum (H4). There was loss of the nissels granules in some neurons of the substantia nigra (H5).

associated with atrophy in some neurons of the substantia nigra but no histopathological alteration in the hippocampus as well as in the striatum.

While brain specimens of control isolated group with Ph and M activities showed no histopathological alteration in all areas. Additionally, brain specimens of AD socialized group showed normal histological structure in the striatum while showed nuclear pyknosis and degeneration in the neurons of cerebral cortex and hippocampus associated with atrophy in some neurons of the substantia nigra. While brain specimens of AD socialized group with Ph & M showed no histopathological alteration in the all areas of the brain except the nuclear pyknosis and degeneration in few neurons of the pyramidal cells in the hippocampus. However, brain specimens of AD isolated group showed sever pathological changes indicated by nuclear necrosis and degeneration in cerebral cortex associated with focal gliosis. Also, it is clear that, hippocampus as well as neurons of the fascia dentate, striatum and substantia nigra in AD isolated group showed nuclear pyknosis and degeneration with congestion in the blood vessels. Finally, brain specimens of AD isolated group with Ph and M showed no histopathological alteration in cerebral cortex. Nuclear pyknosis and degeneration in subiculum and fascia dentate in the hippocampus was observed, few focal eosinophilic plagues formation in striatum associated with was loss of the nissels granules in some neurons of the substantia nigra. Consequently, it is clear that Ph and M improved brain neurological damage induced by social isolation and AD disease.

Discussion

Alzheimer's disease is a fatal neurodegenerative disorder marked by cognitive and memory decline, neuronal death, behavioral disturbances, reduction in daily living activities and neuropsychiatric symptoms. Therefore, it was supposed that AD represents the major cause of dementia in the world [55,56]. Aluminum is known as environmental pollutant that causes neuropathological, neurochemical and neurobehavioral changes which are similar to AD [57]. Additionally, Al was reported to accelerate extracellular Aβ production and aggregation [58]. An alteration of the cholinergic activity is also preceded by the cholinotoxic activity of Al which is a key event in the neurochemistry of AD [59]. In addition, Al was reported to produce ROS that causes lipids and proteins damage altering neuronal membrane integrity as well as the antioxidant defence status [60]. In a previous study, it has been suggested that physical activity and exercise can maintain and even enhance cognition and brain function as well as reduce the risk of age-associated neurological disorders. However, the role of other factors such as intellectual engagement and social interactions may also have higher beneficial effects on cognition and brain functions [61].

Histopathological alterations	Control socialized	Control socialized + PhandM	Control isolated	Control isolated + PhandM	AD socialized	AD socialized + Ph and M	AD isolated	AD isolated + Ph and M
Degeneration and pyknosis in hippocampus neurons	-	-	-	-	-	+	+++	+
Eosinophillic plaque formation in striatum	-	-	-	-	-	-	+++	+
Gliosis	-	-	-	-	-	-	+++	-
Focal nuclear pyknosis and degeneration in neuronal of cerebral cortex	-	-	+	-	++	-	+++	-
Atrophy in some neurons of the substantia nigra	-	-	+	-	+	-	+++	+
+++: Severe; ++: Moderate; +: Mild; -: Nil								

Table 1: Effect of mental and physical activities on the severity of brain histopathological alterations in socialized and isolated rats.

Social isolation has been reported to negatively affect brain development and adult behaviour [62]. Social isolation leads to long term effects on mood behaviour, neuromorphology and neurotransmitters functions [63,64]. These effects has been clearly shown in the present study as AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain Aβ content with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively. This could be explained as, SI for a long period resulted in brain neurological damage indicated by significant elevation in the brain Aβ content as compared to control socialized group. These findings are in agreement with [65]. SI increases neuronal oxidative stress [66], which consecutively can stimulate β- and γ-secretase activity [67], resulting in Aβ elevation and cognition deficits, also stress promotes APP processing along the amyloidogenic pathway [65]. Social isolation can also exaggerate the inflammatory processes [68].

Alzheimer socialized and isolated groups with mental and physical activities showed a significant reduction in the brain Aβ content with respect to their corresponding AD socialized and isolated groups respectively, this may be attributed to the effect of physical and mental activities that is correlated with a reduced rate of the atrophy of hippocampus, responsible for learning and memory, as well as, their ability to slow the rate of mental and cognitive deficits in older individuals, Moreover, they are often referred as brain or cognitive reserve due to their protective effect against development of dementia or cognitive decline [69].

There are a number of mechanisms by which social engagement could reduce the risk of dementia. In a previous animal studies, environmental complexity and richness slow down cognitive decline [70] and enhance neurogenesis [71]. Cognitive reserve hypothesis suggests that physical and social activity may increase the ability to tolerate brain pathology through improved synaptic activity and more efficient brain repair [72,73]. Social experiences influence a wide range of biologic systems and may also diminish the risk of dementia through stress reduction or through reduction of cardiovascular disease risk factors that are also associated with brain disease [74]. Glucocorticoids and corticosteroids hormones are associated with the stress response and brain function, particularly in the hippocampus [75]. The level of these hormones may have altered by be social engagement leading to stress reduction.

Several studies demonstrate that SI stress can lead to cognitive deficits [76]. It has been widely known that cognition decline resulted from SI stress is associated with the hippocampus and frontal cortex related neuron circuits. Social isolation can damage hippocampus and frontal cortex of animals [77] leading to abnormal function of neurotransmission [78], synaptic plasticity [79], apoptosis [27] potassium ion channel currents change [28], the accumulation of oxidative products [24], regeneration [79], and the dysfunction of HPA axis [80]. However, the mechanisms of cognitive deficits created by SI stress and the improvement from the re-socialization are not completely clear. Cognitive decline can be prevented by social engagement including enough social connections and participation in social activities [29,30].

On the other hand, AD socialized and isolated groups showed significant elevation in brain Aβ content with respect to their corresponding control groups respectively. Also, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain Aβ content with respect to their corresponding control socialized and isolated groups with mental and physical activities, respectively. This gives an indication for a neuroprotective effect of mental and physical activities which lead us to one conclusion that they could delay and probably reverses neurotrophic abnormalities [81,82].

Physical exercise has been considered as an established and effective first-line treatment in mild to moderate depression and individuals who were at risk of AD and dementia showed improved cognition after modest physical exercise [83]. The role of physical exercise in AD and depression have been attributed to its impact on changing certain neurobiological mechanisms including monoamine metabolism, HPA axis function, neurotrophic factors, neurogenesis, and neuroinflammation [83]. As a result of these valuable effects of physical exercise in psychiatric conditions, a suggestion that physical exercise can be used as a non-pharmacological therapy for providing protection from neurodegenerative diseases, stress and depression [84,85].

Results of the present study showed that both control isolated, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain ACHE as compared to their corresponding control isolated group and AD socialized and isolated groups, respectively. On the other hand, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain ACHE with respect to their corresponding socialized and isolated groups with mental and physical activities, respectively. Also, isolated or AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain ACHE activity as compared to corresponding control socialized and AD socialized groups either alone or in combination with mental and physical activities respectively. ACHE activity can be increased by Al exposure and this leads to pathological deterioration related to the development of AD [86-88]. Elevation of AChE activity can describe that Al interacts with the cholinergic system, acting as a cholinotoxin [2,89]. Aluminum contributes to pathological processes in AD leading to learning and memory deficits by interference with cholinergic projection functions [90]. Besides the fact that Al is a cholinotoxin agent, its neurotoxic effects could be exerted by further mechanisms including the generation of oxidative stress [5]. The increased production of the AChE may be due to a direct action of Aβ, which binds to nicotinic receptors or overexpression of APP and consequently Aβ induced by Al results in the increased activity of AChE within and around Aβ plaques [2,91].

It has been shown that SI induced significant elevation in the brain ACHE activity as compared to control socialized group which was evidenced to be paralleled to learning and memory impairment. It is well recognized that individuals with more social engagement have a reduced rate of cognitive decline with aging [17]. Furthermore, the rate of memory decline effectively doubles with SI [92]. By focusing primarily on the hippocampus, physical and mental exercise can influence brain structure from increased neurogenesis and angiogenesis to greater dendritic complexity, It is more obvious that a central mechanism is exercise-dependent peripheral and central regulation of growth factors, which operate in unique cascades to arrange structural and functional change. Mechanisms that interfere with growth factor signalling, specifically inflammation as it has been evidenced that inflammatory response connected with the presence of plaques is secondary to accumulation of Aβ and is involved in neuronal damage and in the progression of AD [93]. All these mechanisms can lead to neurodegeneration and cognitive deficits which can be modulated by

exercise. Finally, exercise reduces peripheral risk factors for cognitive deficits and neurodegeneration by reduction of inflammation [94]. Research of Colcombe et al. [95] demonstrated that physical activity is associated with increased blood perfusion of brain regions that modulate attention. Finally, it can be concluded that the increased activity was due to physical activity stimulated synaptogenesis, increased blood supply, and unspecified cholinergic effects.

It has been shown that BDNF protects neurons from stress-induced damage, promotes neurogenesis in the hippocampus, and is supposed to be an important for synaptic plasticity, learning, and modulation of depression [8]. Brain of AD patients exhibits low expression of BDNF [96,97]. In the current study, socialized and isolated rats with mental and physical activities showed significant elevation in the brain BDNF as compared to corresponding control socialized and isolated groups respectively. Additionally, AD socialized and isolated groups with mental and physical activities showed significant elevation in the brain BDNF with respect to their corresponding AD socialized and isolated groups respectively. It is clear that, exercise modulates both plasticity and various supporting systems that participate in maintaining brain function and health. Additionally, exercise was found to increase BDNF gene expression in hippocampal neurons [98]. Consequently, common mechanisms could mediate the varied effects of exercise on learning, depression and neurogenesis, as well as on overall brain health [99]. However, exercise increases brain availability of BDNF that modulate most of the neuronal functions [100].

On the other hand, AD socialized and isolated groups with mental and physical activities showed significant reduction in the brain BDNF with respect to their corresponding socialized and isolated groups with mental and physical activities, respectively. Also, isolated or AD isolated groups either alone or in combination with mental and physical activities showed a significant reduction in the brain BDNF activity as compared to corresponding control socialized groups and AD socialized groups either alone or in combination with mental and physical activities respectively. It was found that neurogenesis was significantly decreased in isolated group as compared to socialized one. It is quite evident that neurogenesis can improve brain function in AD [101]. Decreased BNDF levels have been linked to faster cognitive decline and poor memory performance in AD [102]. These results are in accordance with Rothmanr and Mattson [103]. Moreover, SI can cause apoptosis of hippocampal cells and cognitive decline [104].

Adverse stress and aging have been consistently shown to decrease the expression of neurotrophic factors. For example, animals subjected to chronic immobilization stress and SI have been shown to decrease BDNF levels in the hippocampus [105], chronic social stress during adolescence in mice results in reduced hippocampal BDNF levels and cognitive impairment when the animals are older, suggesting that adverse stress during early life cause danger to the brain during aging [106]. It is possible that changes in basal BDNF expression that occur in the hippocampus in normal aging and AD render brain cells susceptible to the adverse effects of chronic stress on neuroprotective signalling pathways. Specifically, BDNF mediates the formation of memories via long-term potentiation. Physical exercise and social activities has been found to increase BDNF levels and to improve learning and memory deficits in animal models of AD, associated with consistent up-regulation of BDNF expression [107,108].

Animals subjected to physical exercise exhibit increased neurogenesis and acquisition and memory retention, effects that are mediated by increases in BDNF in response to exercise [109]. It is well known that BDNF synthesis is centrally mediated and activity dependent and that exercise enhance BDNF transcription in the brain [110]. In addition, exercise induces brain uptake of IGF-1, which is necessary for the elevation in BDNF mRNA expression [111]. However, the regions within the brain responsible for the production of BDNF are not known. Physical exercise increases circulating BDNF levels in healthy peoples [112]. Besides, BDNF is considered as an important modulator of many other neuronal functions such as neurotransmitter release [113] and synaptic plasticity. It has been shown to regulate neurotransmitters including cholinergic and dopaminergic systems. In contrast, animals subjected to chronic adverse stress display reduced levels of BDNF in hippocampal neurons [106], suggesting an adverse effect chronic stress on the ability of neurons to protect themselves against injury and disease. The stress response would improve by administration of BDNF; it increases cognitive performance and decreases synapse loss as well as restores learning and memory in animal models of AD [114].

Aluminum administration increased the production of ROS which induces membrane lipid peroxidation and damages the function of membrane resulting in membrane depolarization. The brain is an organ that is especially vulnerable to peroxide damage because of several factors, such as its high lipid content, high oxygen turn over, low mitotic rate as well as low antioxidant concentration. However, increased production of ROS was reported during Al exposure, which is attributed to electron leakage and increased electron chain activity [2,8]. Subsequently ROS attack most cell components including membrane lipids producing lipid peroxidation [115]. Therefore, oxidative stress can be hypothesized to be one of the contributing factors for Al-induced central nervous disorders [116]. This explains the increased brain lipid peroxidation levels in Al-intoxicated rats in the present study. Further oxidation reaction and lipid peroxidation processes can lead to abnormal mitochondria respiratory chain reaction and inflammation and finally to the generation of AD [117]. Also, it has been found that SI increases oxidative stress markers in the brain, including lipid peroxidation, protein carbonyls, and nitrite levels [106].

The present study revealed that, socialized and isolated rats with mental and physical activities showed significant improvement in oxidative stress markers as seen in significant reduction in brain MDA as well as significant elevation in SOD and TAC as compared to corresponding control socialized and isolated groups respectively. Also, AD socialized and isolated groups with mental and physical activities as compared to their corresponding AD socialized and isolated groups respectively. It is well recognized that regular exercise has favourable influence on brain function, including better memory and increased capillarization [118], brain plasticity [85] and up-regulation of the antioxidant system [119], and thus preventing the neuronal degenerative effects of SI and AD which subsequently, increase ROS and lipid peroxidation of neuronal cell membrane [14,16]. These findings are in agreement with other results of [119]. Also, it has been found in a previous study that immobilization-induced oxidative stress in the brain and impaired memory were attenuated by exercise, and regular exercise has been shown to decrease the level of reactive carbonyl derivative, a marker of oxidative protein damage, and to prevent the age-related learning and memory impairment [120].

On the other hand, AD socialized and isolated groups with mental and physical activities showed significant elevation in MDA and significant reduction in the brain SOD and TAC with respect to their corresponding socialized and isolated groups with mental and physical activities, respectively. Also the same in isolated groups or AD isolated groups either alone or in combination with mental and

physical activities as compared to corresponding control socialized and AD socialized groups either alone or in combination with mental and physical activities respectively. SOD is known as natural anti-oxidant enzymes represent the first line of defence against free radical damage under oxidative stress conditions [117].

There are different mechanisms by which exercise improves cognitive function. One hypothesis is that exercise is neuroprotective possibly via its ability to decrease oxidative stress and protect the brain from damage and neurodegenerative diseases [85,121]. In rats, age-related oxidative damage can be reduced by exercise, mainly lipid oxidation in the cerebellum [122]. Another possible mechanism is that exercise appears to facilitate learning via improved long term potentiation [123]. Physical activity may also result in neurogenesis within the hippocampus [124]. Further studies confirmed the importance of exercise in older rats, benefits that included not only improved memory and neurogenesis but also reduced apoptosis in the hippocampus [125]. Another hypothesis is that exercise upregulates growth factors, such as BDNF [126], associated with energy metabolism and homeostasis, which in turn lead to cognitive benefits.

BDNF in particular may be important to inducing neurogenesis [127], and has been linked to hippocampal plasticity, learning, and memory in animal models as well as, growth factors, serotonin levels may increase with exercise while also reducing levels of corticosteroids [95]. Alternatively, exercise may exert its positive cognitive influence more indirectly via impact on other risk factors such as diabetes and/or hypertension, which may also be mediated by the above mentioned upregulation of growth factors and ultimately reduction in inflammation [85]. Finally, exercise may also counteract some genetic risk factors for dementia.

In the present study, it has been found that Al exposure significantly increased the levels of TNF-α and IL-1β both in hippocampus and frontal cortex. The increase in the level of TNF-α observed in this study can lead to the activation of glial cells. The proinflammatory cytokine TNF-α can be synthesized and released in the brain by astrocytes, microglial, and some neurons [128]. TNF-α and IL-1β have been suggested to be elevated in various models of nervous system injury and are thought to contribute to the pattern and severity of the response [129]. In agreement with the present results, previous studies indicate that Al can stimulate the production of proinflammatory cytokine [130]. The levels of activated NFκB, an immune related factor, were found to be significantly increased in the brains of mice treated with Al [131]. Activated NFκB has been shown to increase TNF-α synthesis [129]. These findings indicate that Al may cause neurodegeneration by two potentially interrelated mechanisms, immune-mediated and increased oxidative stress mediated neuronal death. Also, it has been found that SI increases oxidative stress and inflammatory reaction. Also, Barrientos et al. [132] demonstrated that rats subjected to SI showed significant elevation of IL-1ß protein levels in the hippocampus. Moreover, inflammatory markers associated with isolation can be increased in AD patients [133] together with increased the rate of cognitive deficits [134].

Results of the present study also showed that, either control isolated or AD socialized and isolated with mental and physical activities showed significant reduction in the brain IL-1β and TNF-α as compared to their corresponding groups without mental and physical activities. These results may be attributed to the valuable effects of exercise that regulates many classes of proteins, in addition to, growth factors are regulated by exercise including those involved in metabolism, inflammation and synaptic plasticity which all correlate with cognitive decline, furthermore, exercise might counteract the negative effects of this inflammation by reducing circulating pro-inflammatory cytokines which impair BDNF signalling in neurons leading to cognitive impairment [135]. Exercise also could attenuate levels of pro-inflammatory cytokine in the brain of AD individuals by reducing the load of Aβ, which itself has pro-inflammatory effects [136].

On the other hand, AD socialized and isolated groups showed significant elevation in brain IL-1β and TNF-α with respect to their corresponding control groups respectively. Finally, AD isolated groups either alone or in combination with mental and physical activities showed a significant elevation in the brain IL-1β and TNF-α with respect to their corresponding AD socialized groups either alone or in combination with mental and physical activities respectively. As revealed in the study of Helmy et al. [133], IL-1 plays an essential role in the process of neuroinflammation and in the pathogenesis of AD, in addition, TNF-α is one of the major proinflammatory response regulators in the brain that could increase the neurotoxicity and resulted in cellular damage and cognitive decline in AD. It was documented also that, inflammatory markers associated with SI can be increased markedly in AD patients leading to increase the rate of cognitive deficit [137].

In the present study AD, socialized and isolated groups with mental and physical activities showed significant elevation in brain neurotransmitters DA, NE and 5-HT with respect to their corresponding AD socialized and isolated groups respectively. Neurotoxicity of Al is linked, to deficiencies of these neurotransmitters. It was observed that altered production of neurotransmitters produces severe neurological illness [138]. Social isolation has been found to decrease noradrenergic and serotonergic neurons in the brain. Frontal cortex and hippocampus of animals have been injured by SI leading to abnormal function of neurotransmission, additionally previous studies have reported that SI elicits a variety of behavioral abnormalities which may be ascribed to deficiency in the brain neurotransmitters as NE, 5-HT or DA as neurotransmitter systems are also affected by exercise. Serotonin levels are increased throughout the brain in exercising rats [113]. Chronic wheel running increased basal levels of 5-HT [139]. Furthermore, 5-HT has been shown to enhance neuron proliferation, whereas its depletion decreases neuron proliferation [140].

Exercise may also act through noradrenergic system. Basal levels of noradrenalin may be increased wheel running [113] and mRNA for the noradrenalin modulator [141]. The same type of exercise blunted the release of noradrenalin in the frontal cortex and its depletion in the locus coeruleus, hippocampus and amygdala in response to stress [142]. It was shown that exercise can reverse age-related cognitive declines through an increased dopamine receptor density in the striatum [113]. Animal studies [143] suggested that exercise may be a potential intervention for reduction of the onset rate or incidence of Parkinson disease, based on the observation that treadmill running resulted in an attenuation of dopamine depletion in the striatum of hemi-Parkinsonian rats. Acetylcholine level and muscarinic receptor density are increased in the hippocampus of adult exercising rats [113]. Along with a direct effect of physical activity on ACh, a large body of evidence supports the idea that an ACh-mediated mechanism regulates BDNF gene expression in the hippocampus [144], in a study in culture, have shown that recombinant human BDNF (rhBDNF) stimulates development of basal forebrain cholinergic neurons and increases dopamine uptake in mesencephalic cultures.

Noteworthy to mention that physical and mental activities ameliorate that level of brain neurotransmitters since they can provide neuroprotective effect through decreasing oxidative stress,

inflammation, Aβ accumulation and AChE level leading finally to neuronal survival and cognitive improvement. In addition, the effects of exercise on neurotransmission should be explored in a multidimensional way because there is a constant interaction between neurotransmitters and their receptors during locomotion [145]. From all the previous explanations behavioral alterations were observed in the current study when perfuming Y-maze and swimming tests, as physical and mental activities, indicating working memory, cognitive alterations, general motor activity and motor coordination in AD, isolated or AD isolated rats as compared to socialized and AD socialized rats. In addition, histopathological examinations have confirmed the biochemical results.

Remarkably, exercise reduces all of these peripheral risk factors, improving cardiovascular health, lipid–cholesterol balance, energy metabolism, glucose use, insulin sensitivity and inflammation [146]. Exercise is thus uniquely positioned to improve brain health and function by reducing the peripheral (indirect) risk factors for cognitive decline and, in parallel, by directly enhancing brain health and cognitive function [147]. Several lines of evidence have emphasized the neuroprotective and anti-inflammatory effects of physical activity in animal models, possibly via the overproduction of circulating neurotrophic factors and modulation of synaptic plasticity [27]. Human studies have shown neuroprotective effects of exercise, which can reduce the risk of cognitive impairment, depression, dementia, and neurodegenerative disorders [85]. Thus, reduced physical activity in socially isolated animal after SI may play a role in anatomical and functional deficits observed in this study.

Conclusion

Data from the present study provides further evidences for the neurodegenerative effects of SI which represents a major risk factor in AD development as well as for the influence of SI on neurotoxicity of Al in a rat model of AD. It also evidences the role of physical and mental training for increasing memory and cognitive activities in rats and attenuating the neurodegenerations caused by AD and/or SI. Mental and physical activities targets many aspects of brain functions and had broad effects on learning and memory as well as on brain health particularly during AD development. They also stimulate neurogenesis and are considered as important intervention technique for improving brain function and enhancing its resistance to neurodegenerative diseases. Consequently, mental and physical exercises are recommended together with other pharmaceutical medications for treating AD or delaying its progression.

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