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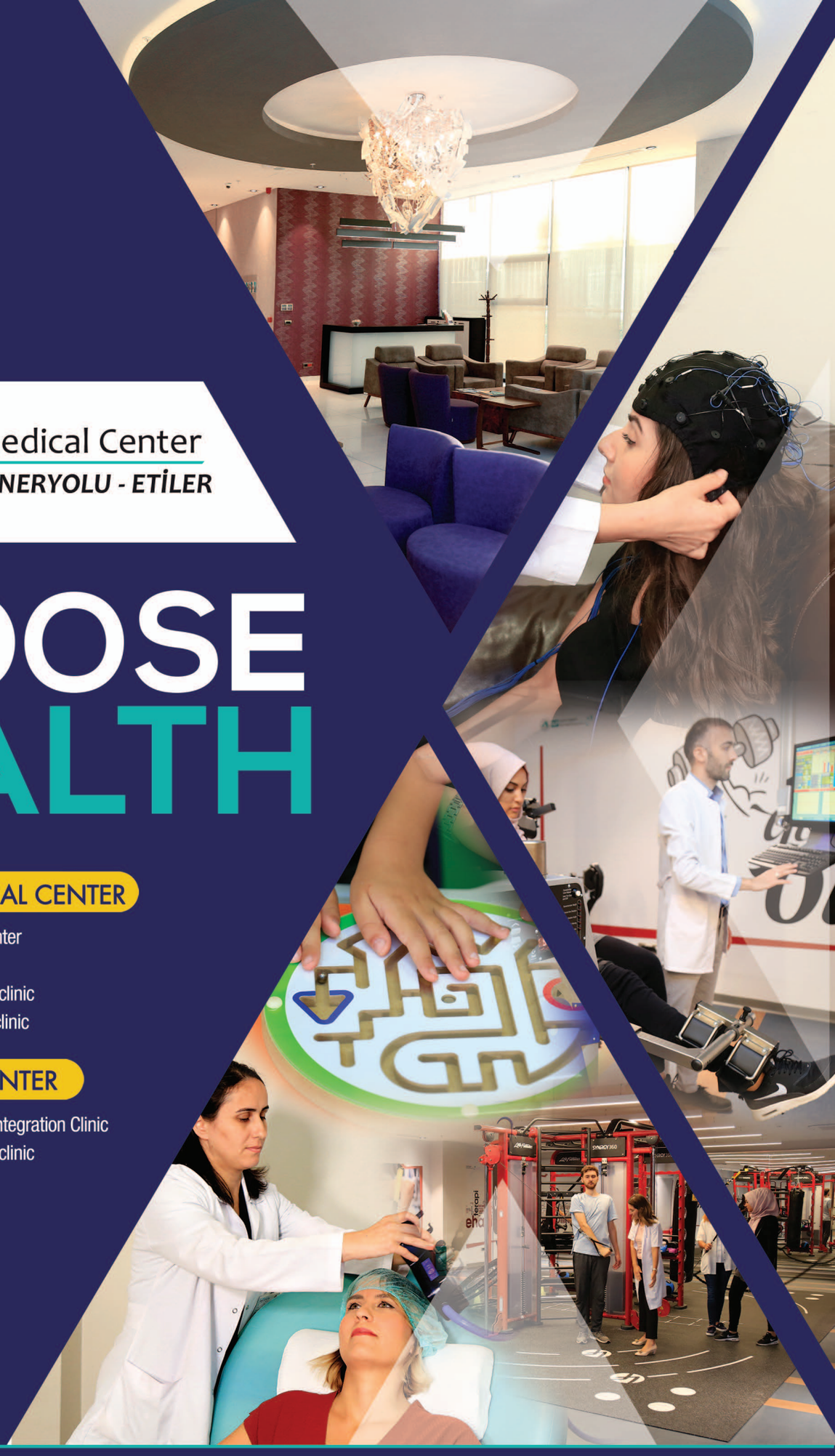

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JNBS (J. Neuro. Behav. Sci) is a comprehensive scientific journal in the field of behavioral sciences. It covers many disciplines and systems (eg neurophysiological, neuroscience systems) with behavioral (eg cognitive neuroscience) and clinical aspects of molecules (eg molecular neuroscience, biochemistry), and computational methods in health.

The journal covers all areas of neuroscience with an emphasis on psychiatry and psychology as long as the target is to describe the neural mechanisms underlying normal or pathological behavior. Pre-clinical and clinical studies are equally acceptable for publication. In this context; the articles and treatment results of computational modeling methods of psychiatric and neurological disorders are also covered by the journal.

JNBS emphasis on psychiatric and neurological disorders. However, studies on normal human behavior are also considered. Animal studies and technical notes must have a clear relevance and applicability to human diseases. Case Reports including current neurological therapies or diagnostic methods are generally covered by JNBS.

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We strongly encourage you to use MathType (third-party software) or Equation

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According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

The Reference Section:

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Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998;55(5):697-701. doi: 10.1016/s0006-2952(97)00515-7.

Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

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The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

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The Journal of Neurobehavioral Sciences

Volume 9 ¦ Issue 1 ¦ January-March 2022

Contents

Review Article

Motor Function Test Protocol for Parkinsonian Triad in Rodent Model of Parkinson's Disease

Abstract

Over the years, there has been an increase in research on parkinsonism in basic and translational neuroscience. Parkinson's disease (PD) is a progressive neurodegenerative disorder vehemently associated with motor function deficits and other unique features collectively called the Parkinsonian triad, which slightly differs from other movement disorders such as Wilson's disease, tardive dyskinesia, chorea, and athetosis. Parkinsonian triad combines three major motor phenotypes of PD including bradykinesia, rigidity, and resting tremors. Hence, there is a need to review motor deficits protocols to create a set of behavioral protocols that critically address the parkinsonian triad's quantification in PD models. Literature search on Medline and PubMed was conducted to access the articles on the motor function test in a rodent model of Parkinsonism. Search terms include parkinsonism, parkinsonian triad, bradykinesia, rigidity, resting tremors, stepping test, parallel bar test, pole test, and cylinder test. This review shows that bradykinesia characterized by difficulty in movement initiation could be assessed using a stepping test by measuring stepping length and time taken to initiate movement on a wooden ramp. It can also be assessed using a parallel bar test by measuring the time taken to make 90° turn. This turning hesitation is one of the critical features of akinesia. Rigidity is associated with an increase in muscle tone; it is assessed by using a pole test to measure the time taken for the rodent to slide down a smooth pole. Resting tremors is an involuntary, oscillatory movement of the distal part of the upper limb when not performing an action. It could be graded using a cylinder test when the rodent suspends its forelimb on the air in an attempt to climb the wall of the cylinder. In conclusion, the examinations and quantifications of the Parkinsonian triad are required to diagnose parkinsonism in rodent models.

Keywords: *Cylinder test, bradykinesia, parallel bar test, parkinsonian triad, parkinsonism, pole test, resting tremors, rigidity, stepping test*

Mujittapha Umar Sirajo[1], Kauthar Murtala[2], John Chukwuma Oyem[3], Azeez Olakunle Ishola[4], Lukman Femi Owolabi[1,5]

[1]Department of Anatomy, Bayero University, Kano, [2]Department of Medical Laboratory, Ahmadu Bello University, Zaria, [3]Department of Anatomy, University of Port Harcourt, Rivers State, [4]Department of Anatomy, AfeBabalola University Ado-Ekiti, Nigeria, [5]Department of Medicine, College of Medicine, University of Bisha, Bisha, Kingdom of Saudi Arabia

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Orcid
Mujittapha Umar Sirajo {ORCID: 0000-0002-6896-5285}
Kauthar Murtala{ORCID: 0000-0002-0467-5748}
John Chukwuma Oyem{ORCID: 0000-0001-9378-7858}
Azeez Olakunle Ishola{ORCID: 0000-0001-9509-1440}
Lukman Femi Owolabi{ORCID: 0000-0002-8669-9558}

Address for correspondence:
Dr. Mujittapha Umar Sirajo, Department of Anatomy, Faculty of Basic Health Sciences, Bayero University, PMB 3011, Kano, Nigeria.
E-mail: mujittaphasurajo@gmail.com

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Introduction

Parkinson's disease (PD) is a chronic and progressive brain disorder associated with many motor and nonmotor deficits.[1,2] These deficits result from progressive degeneration of dopamine neurons in the substantia nigra pas compacta (SNc), leading to loss of dopamine in the basal ganglia.[3-5] In most cases, PD occurs sporadically and is proposed to result from a complex interaction between environmental and genetic factors.[6,7]

For an excellent research to be carried out on parkinsonism using an animal model, it should fulfill the following criteria;[8] first, face validity criterion; the animal model should express major and most common phenotypes of human PD, otherwise known as the parkinsonian triad. Second, constructive validity criterion; the model should be created with a sound scientific rationale, and finally, the predictive validity criterion, which indicates that the model should have the propensity to respond to therapy comparably to clinical therapy.

Parkinsonian Triad

Parkinsonian triad is the combination of bradykinesia, rigidity, and resting tremor, which are the three main phenotypes of PD.[8,9] These three phenotypes are collectively called Parkinsonism or Parkinsonian syndrome.[10] The diagnoses of Parkinsonism can be made with the clinical manisfestations of at least two of the triad.[10,11]

How to cite this article: Sirajo MU, Murtala K, Oyem JC, Ishola AO, Owolabi LF. Motor function test protocol for parkinsonian triad in rodent model of Parkinson's disease. J Neurobehav Sci 2022;9:1-6.

Ethics committee approval: There is no need for ethics committee approval.

Bradykinesia

Bradykinesia means slow movement; it is the most common feature of Parkinsonism attributed to basal nuclei disorders.[11] Bradykinesia encompasses difficulty planning, initiating [as seen in Figure 1a-d], and executing movement, decreasing facial expression, including the rate of eye blink and sometimes the inability to perform sequential and simultaneous tasks effectively.[12] It is hypothesized that bradykinesia results from the disruption in motor cortex activity mediated by reduced dopaminergic function and in some cases, bradykinesia presents itself in the form of akinesia, a sudden and transient inability to move for about 10 s.[13,14] This is also called freezing or motor block; its features include start hesitation, turn hesitation, hesitation in narrow or tight quarters, destination hesitation, and open space hesitation.[15]

Resting Tremors

Resting tremor is an involuntary, rhythmic muscle movement involving oscillatory movement prominently in the distal part of the upper limb [as observed in Figure 2a and b] at a frequency of about 4−6 Hz when not performing an action.[9,10] The tremors tend to stop when the hand is in action, such as in a flexed grip.[16] Drug-induced Parkinsonism is less likely to be associated with tremor, although it can sometimes present with a tremor.[16,17]

Rigidity

Rigidity refers to increased resistance, stiffness, and inflexibility of the body's proximal part, such as the neck, shoulders, hips, and distal part of the body such as wrists and ankles [as seen in Figure 3b and c].[18] Rigidity is accompanied by the "cogwheel" phenomenon, especially when associated with an underlying tremor present throughout the range of passive movement of a limb (flexion, extension, or rotation about a joint).[18,19]

Protocols for Motor Function Deficit Test

Several different behavioral tests are imperative in assessing PD in rat models, each providing slightly different results. For the protocols reviewed in this paper, the rodents should be trained during the treatment phase of the designed experiment.[19]

Tests for Bradykinesia

Stepping test

Stepping tests could be designed to detect motor activities' speed including hyperkinesia, normal motor activities, bradykinesia, or akinesia.[20] The stepping test is conducted on a wooden ramp that is 1 m long connected to the rodent cage of 0.3 m height [as seen in Figure 1a and b]. The rodent is gently placed on the wooden ramp with their heads pointing towards the cages.[21] The time taken for each rat to initiate stepping by its four limbs is used to determine the difficulty of initiating movement. The distance covered by the rodent on the wooden ramp divided by the number of steps made by the rodent on the wooden ramp could be used to determine stepping length.[21] Note that experimentally, the time the rodents use to reach their

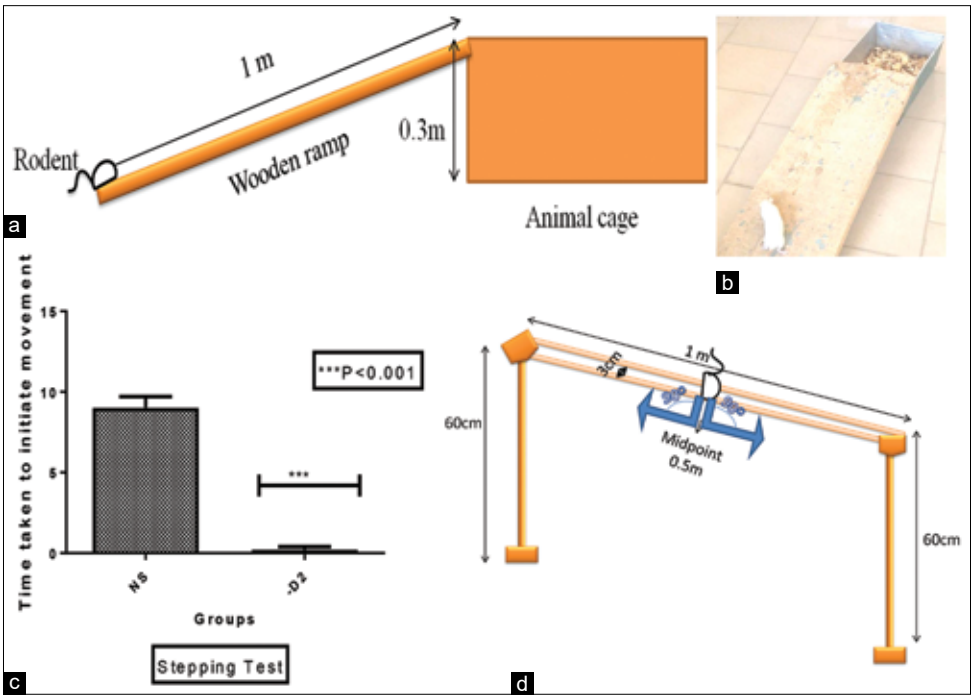

Figure 1: Diagrammatic and graphical interpretation of bradykinesia using the stepping test and parallel bar test. (a) Diagramatic illustration of stepping test set-up. (b) A pictorial representation of a wistar rat demonstrating the stepping test. (c) Stepping test result shows a significant ($P < 0.001$) increase in time taken to initiate steps by the four limbs of the dopamine-2 receptor knockout model parkinsonism.[17] (d) Diagrammatic illustration of parallel bar test set-up

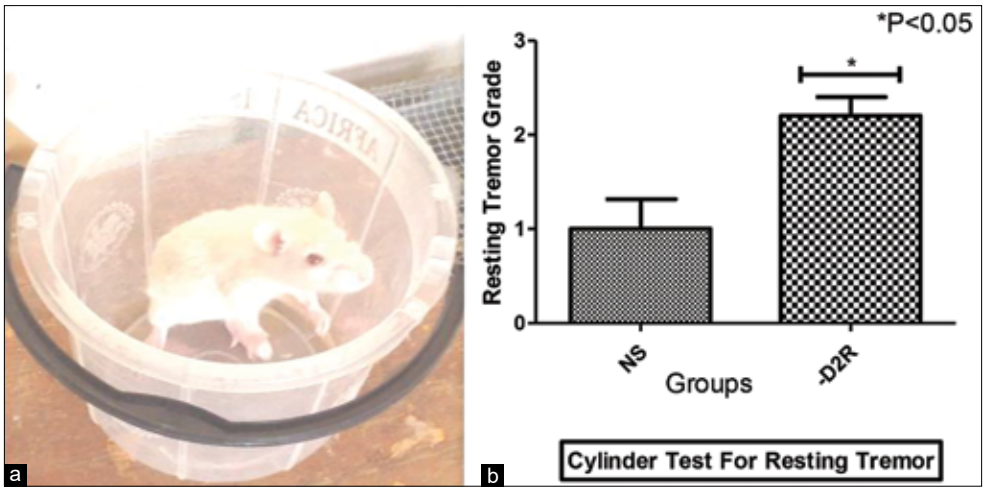

Figure 2: Diagrammatic and graphical interpretation of resting tremor using the cylinder test. (a) A pictorial representation of a parkinsonian rat exhibiting resting tremors in a cylinder test set up. (b) Cylinder test result shows a statistically significant (*P* < 0.05) increase in resting tremor in the dopamine-2 receptor knockout model of parkinsonism[17]

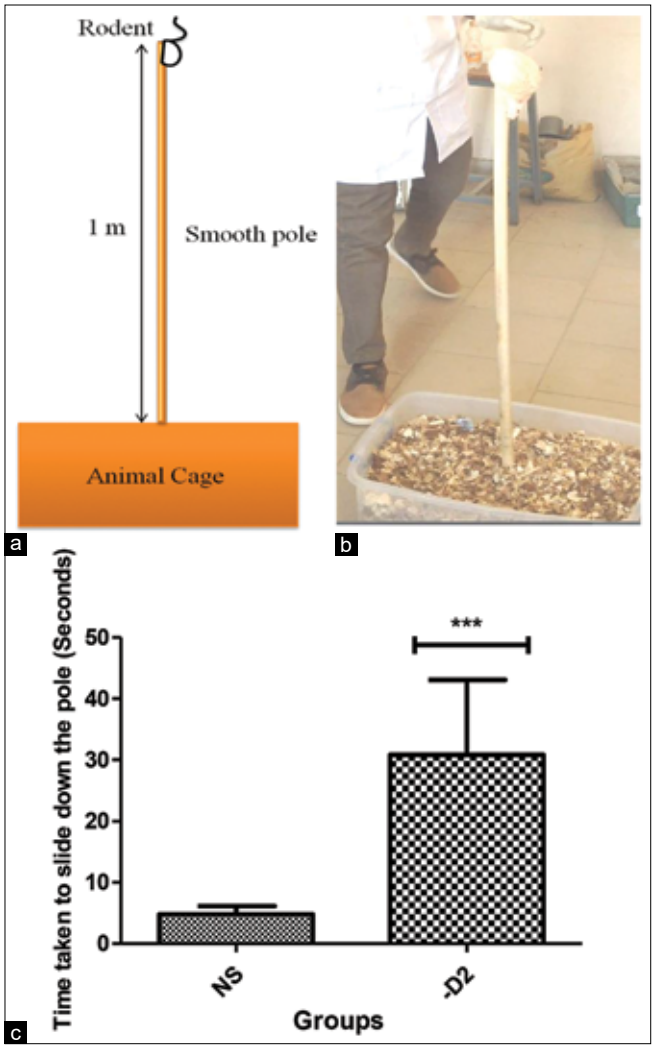

Figure 3: Diagrammatic and graphical interpretation of rigidity using the pole test. (a) Diagrammatic illustration of pole test set-up. (b) Pictorial representation of the pole test set-up. (c) Pole test result shows a significant increase in time taken to slide down the pole by the dopamine-2 receptor knockout model of parkinsonism[17]

cage cannot be used to determine bradykinesia because the rodents tend to be distracted, exploring the edges of the wooden ramp.

Parallel bar test

A parallel bar test can be designed to assess bradykinesia, using the time taken to make 90° turns.[17] As seen in the apparatus comprises two wooden frames of 60 cm height connected by two 1 m long plans and 1 mm thick parallel bars 3 cm apart [as seen in Figure 1d]. The test is conducted by placing the animal at the center of the two parallel bars (0.5 m), with its forelimb and hind limb on different bars, and allowed to roam freely on the bar. The time taken for the animal to make a 90° turns (latency of turn) is used to assess bradykinesia.[22] In addition, the time taken to move from the center of the bars to either ends is used in assessing bradykinesia.[22-24]

Protocols for Resting Tremors

Cylinder/beaker test

Three scientists experienced in laboratory animal research are needed for accurate assessment of resting tremors using the cylinder test. This is to reduce misapprehension during the study. The volume and dimension of the cylinder to be used depends on the size of the rodent. Each animal should be placed in a transparent cylinder or beaker with an open top and allowed to explore the cylinder walls with its forelimbs while standing on the two hind limbs [as seen n Figure 2a]. As the animal raises it forelimb attempting to climb the container's wall, the three or more scientists conducting the test should grade the degree of resting tremors on a scale of 1–5 while the rodent suspends its forelimb on air during climbing attempts. Moreover, the number of times the animal places its forelimb against the container's wall can also be used to measure motor function deficit.[25,26]

Protocol for Rigidity

Pole test

Pole test is designed to assess rigidity. Sirajo *et al*., who used the pole test to assess rigidity in a Wistar rat model of Parkinsonism, previously reported the use of pole test to assess rigidity.[17] The Pole test is conducted on a smooth wooden pole of 1 m in length and 3 cm in diameter fixed in the middle of an empty cage [as seen in Figure 3a]. The rodent is placed facing downward, at the top of a wooden pole. The time taken for the Wistar rats to move down the Pole is used to assess rigidity.[17,24]

Procedures

For all the behavioural tests, the rodents should be familiarized with the behavioural test room 72 h before thecommencement of the tests.

Bradykinesia

Stepping test

1. Clean the wooden ramp with methylated spirit and cotton wool before putting each rodent on the wooden ramp.

For movement initiation

1. Hold the rodent by the tail and gently place it on the lowest height of the wooden ramp, with its face facing the direction of the cage
2. Start a stopwatch immediately after placing the rodent on the wooden ramp
3. Pause the stopwatch immediately the rodent makes steps with each of its four limbs
4. Record time read by the stopwatch.

For stepping length

1. Stain the tail of the rodent with a cleanable ink
2. Place the rodent on the wooden ramp and carefully count the number of steps made by the rodent in 3 min
3. Use a thread to trace the distance covered by the rodent
4. Measure the length of the thread with a ruler
5. Divide the length of the thread/distance covered by the rodent in 3 min over the number of steps made by the rodent in 3 min.

Parallel bar test

1. Hold the rodent by the tail and gently place the rodent at the midpoint (0.5 m mark) on the parallel bars with it fore paws on the posterior pole and it hind paws on the anterior pole.

For turning hesitant

1. Start a stopwatch immediately after placing the rodent on the parallel bars
2. End the stopwatch immediately after the animal turn completely to the right or to the left
3. 180 s is the maximum time allowed (cut-off time) for each rodent, terminate the experimentif the animal exceeds 180 s without making 90° turn
4. Record the time read by the stopwatch.

For bradykinesia

1. Start a stopwatch immediately after placing the rodent on the parallel bars
2. End the stop watch when the rodent reaches the extreme end of the parallel bar
3. Record the time read by the stopwatch.

Resting tremors

Cylinder/beaker test

1. Clean the container with methylated spirit and cotton wool before putting each rodent inside it
2. Set a stopwatch for 3 min (Duration of each experiment)
3. Hold the rodent by the tail and gently put it vertically inside the container with the rodent facing downward
4. The 3 laboratory scientist should grade the resting tremor of the rodent during attempt to climb the wall of the container.

Rigidity

Pole test

1. Hold the animal by the tail and place it at the peak of the wooden pole
2. Immediately after placing the animal, start a stopwatch
3. End the stop watch immediately the rodent reaches the ground/it cage
4. Read and record the time taken for the rodent to reach it cage.

Discussion

In this article, we reviewed research protocols for quantifying and assessing parkinsonian triad in a Wistar rat model of PD. This review is relevant to basic and translational neuroscience researchers in developing countries who lacks funding for innovative research and whose research focus on designing therapeutic strategies for the management of PD.

Parkinsonian triad tests are designed to assess the degree of dopamine system damage in a rodent model of parkinsonism.[26] It could also be used to assess a proposed therapeutic strategiy in rescuing damages in the dopamine system.[27]

Parkinsonism leads to loss of motor coordination.[28] Unfortunately, several other extrapyramidal syndromes manifest loss of motor coordination.[28] However, loss of motor coordination in parkinsonism slightly differs from other motor functions diseases; in parkinsonism, the motor phenotypes are collectively called the Parkinsonian triad, a group of three major symptoms of

PD (Bradykinesia, Rigidity and Resting tremor).[28,29] These symptoms lead to a loss of overall motor coordination.[29]

Bradykinesia is the main clinical feature of parkinsonism.[30,31] The diagnosis of PD is based on the manifestation of bradykinesia and at least one of the two other phenotypes of parkinsonian triad.[32,33] Bradykinesia leads to an increase in time taken to initiate movement or increase in time taken to complete a voluntary movement. Bradykinesia can be presented in akinesia, a complete inability to initiate movements for a few seconds. The stepping test provides a window for detecting both akinesia and bradykinesia. Akinesia is assessed by measuring time taking to initiate movement, and bradykinesia by measuring stepping length. Significant ($P < 0.001$) increase in bradykinesia was seen in dopamine-2 receptor knockout model Parkinsonism when tested on a wooden ramp [as seen in Figure 1c].[23,34]

Although the brain circuitry that generates tremor is not well understood, tremor is regarded as an abnormal involuntary rhythmic and oscillatory movement.[35] Tremors can be classified into resting tremors and action tremors. Resting tremors are associated with an involuntary activity. The examples of such tremors include PD tremor, physiological tremor, essential tremor, medication-induced tremor, lesional tremor, dystonic tremors, other neurodegenerative tremors, and psychogenic tremors.[36] In PD, resting tremor occurs when the forelimb is not in contact with any object. Action tremors are associated with voluntary movements. Postural, kinetic, intention, task-specific, and isometric action tremors can be observed in mice when holding them by the tail, with their head facing downward. Tremor is often challenging to quantify and distinguish from other motor abnormalities in animals and this pose a major challenge in research.[37] In this study, we showed that resting tremor can be quantified by observing and grading its frequency, amplitude, and phase. Our reviewed experimental result showed a less significant increase in resting tremors in the cylinder test [As seen in Figure 2b].[17] A less significant increase in resting tremor reaffirms the previous findings that drug-induced parkinsonism is less likely to be associated with resting tremors.[17,38]

Rigidity is associated with increased muscle tone, leading to stiffness, muscle's inflexibility, and a degree in the range of motion.[35-38] It is usually presented when the muscles are rapidly stretched.[38] This phenotype has been evaluated using the pole test by measuring time taken to slide down a smooth wooden pole. Increased muscle tone tends to decrease the speed of sliding down [As shown in Figure 3c].[17]

Conclusion

The characteristic motor function deficits observed in PD slightly differ from other movement disorders. The diagnosis of PD is based on the Parkinsonian triad, which can be effectively demonstrated using the stepping test, modified cylinder test, and pole test. Hence, these tests should be adopted to assess motor function deficits associated in PD, especially in developing laboratories that lacks advanced techniques for quantifying motor functions deficits.

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There are no conflicts of interest to declare.

Author contribution subject and rate

- Sirajo Mujittapha Umar (35%): Design the research, data collection and analyses and wrote the whole manuscript.
- Kauthar Murtala (20%): Organized the research and supervised the article write-up.
- John C. Oyem (15%): Contributed with comments on manuscript organization and write-up.
- Ishola Olakunje Azeez (15%): Contributed with comments on research design and interpretations of the behavioural testing.
- Lukman Femi Owolabi (15%): Contributed with comments on research design and interpretations of the behavioural testing.

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Original Article

The Mind − Brain Problem from the Perspective of Agency

Abstract

Aim: In this article, it is argued that the elusive mind qualifies as an active agent which works through the brain rather than the brain creating the subjective mind or acting as the mind itself. **Materials and Methods:** This article relies on observation-based reasoned arguments and thus it is philosophical in nature. **Discussion:** We seem to be living in a virtual reality interwoven of subjective experiences of sights, sounds, tastes, smells, colors, pain, and pleasure, all rendered by the enigmatic mind. The mind cannot be reduced to physical existence such as the sporadic electrical activity of the brain since no electrical activity has ever produced such cohesive subjective experience, the same way that the laws of physics cannot be reduced to matter and energy that comprise the physical existence. **Conclusion:** Unlike properties, agencies differ from emergent quantities in that agencies more than passively qualify matter; they actively control and rule matter. Agencies are characterized by causal power, and thus the capacity to cause changes. Several agencies can be identified in nature. The agency of physics is associated with the physical realm and is comprised of the universal laws and forces of physics. Life qualifies as a purposive agency which is comprised of the laws and influences of life. Even quantum fields act like virtual mechanisms and thus qualify as active agents associated with the production of the fundamental particles of physics with a fixed set of properties out of quanta of energy.

Keywords: *Active agents, agencies, brain, emergent qualities, mind, perceptions*

Yunus A. Çengel

Department of Mechanical Engineering, University of Nevada, Reno, NV, USA

Introduction

Despite remarkable developments in science and technology during the past century, there is still widespread ambiguity and confusion about the human mind and the associated faculties such as intelligence, consciousness, emotions, desires, and free will. We are nowhere close to reaching a consensus in understanding these traits. Perhaps, this is not surprising since we are dealing with invisible subjective qualities the existence of which is highly controversial. Although we tend to confirm their presence innately, we cannot pinpoint them physically. The nonphysical mind is a fertile ground for a variety of opinions, ideologies, and beliefs to flourish and individual prejudices to form. There is not even an agreed upon methodology for the investigation of the matters of the mind.

The prevailing neuroscientific view the human brain is that it is a mystifying biological machine and that fundamentally every thought and feeling we experience is simply the flickers of the billions of neurons. It is generally believed that our thoughts and our understanding of ourselves and our world are somehow produced by these crackling connections between brain cells, although nobody has the faintest idea how those brain cells composed of inept molecules can possibly do this. Despite the decades of neurological research by the best minds in the field and major U. S. government initiatives on brain research such as the "Decade of the Brain" in the 1990s and the "BRAIN Initiative" launched in 2013 and involved the collaboration of hundreds of researchers around the globe, the human brain still remains largely a puzzle.[1] We are nowhere close to understanding its mysteries. Clearly, there is a need to think out of box and develop new perspectives.

From a physiological point of view, the wondrous brain is merely a meat which involves random electric signals through the movement of charged particles such as sodium and potassium ions. However, functionally, the material brain is said to be planning, coordinating, and overseeing all our physical and mental activity. Such difficult acts are feats that no piece of meat,

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Orcid
Yunus A. Çengel {ORCID: 0000-0002-8057-5036}

Address for correspondence:
Prof. Yunus A. Çengel, Department of Mechanical Engineering, University of Nevada, Reno, NV, USA. E-mail: yunus.cengel@yahoo.com

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with or without electric signals, can perform. Hence, the notion that the electrical activity in the brain produces the kind of mastermind that has the knowledge, intelligence, will, and the skill to coordinate and direct all internal and external human bodily functions does not seem plausible. No electrically active matter such as the batteries or microprocessors in smartphones has ever produced anything close to such subjective qualities or a trace of those skills. Therefore, the brain is still associated with deep mystery, and researchers have expressed doubt whether we ever will be able to unlock this mystery.

Many researchers and scientists firmly subscribe to the materialistic worldview when it comes to brain. At best, they accept the existence of subjective entities such as intelligence and consciousness, but only as products of brain activity. At worst, they deny their existence altogether, proclaiming that the mind is simply the brain and the exhibition of neurophysiological activities in the brain.

Hard-line materialists insist that all subjective qualities such as consciousness, emotions, life, and free will stem from matter and are reducible to matter. The origin of this contention, it seems, is simply the materialistic worldview that these thinkers subscribe to, as there is no compelling evidence or justification for this hard stance. The presumption that "existence is limited to physical things only and all apparently nonphysical things are merely the outcome of physical interactions" is simply an ideological view since it cannot be tested. Therefore, the notion that 'the sources of all subjective things like consciousness and free will are physical things' is just an opinion or hypothesis, and not an indisputable scientific fact. The opposing notion that "subjective qualities do not need to originate from physical realm" is an equally valid view. All such views should be judged by their own merits on the basis of reason, logical consistency, and conformity with observations, without prejudice. Also, care should be exercised to avoid drawing wrong conclusions from the right observations.

Those who subscribe to the Cartesian dualist perspective, on the other hand, view the physical body and the nonphysical mind as the perfectly harmonious cooperation of two distinct and separate entities,[2] and thus the name "duality." The word "mind" is used in a broad sense which includes everything other than the physical body. Dualists posit that the mind must be distinct from the body, irreducible to the physical realm, for it to be able to assert influence over the body. Other theories borrow and merge some aspects of these two opposing worldviews.

The advocates of emergent theories, for example, reject as baseless the idea that subjective qualities can be reduced to the physical realm, but they do not subscribe to the idea of a nonphysical mind distinct from the physical body. They maintain that the mind is a phenomenon which emerges on the assembly of brain out of nowhere. There is an abondance of literature on existence, notably by Goldstein,[3] Corning,[4] O'connor and Wong,[5] and Çengel[6] on emergence, and Davidson[7] and Schlosser[8] on agency.

In this article, we challenge the prevailing strict materialist worldview that matter is everything and everything is matter, and the reductionist approach that all subjective qualities are illusions and that they can be reduced to matter, as these contentions do not conform with common observations. In fact, all objective observations refute both notions. We demonstrate these refutations with examples, analogies and compelling arguments showing that inept matter, including the nerve cells in the brain, which are not much different than other nerve cells in the rest of the body, cannot possibly be the generator of subjective human traits such as consciousness, emotions, and free will.

Emergent Quantities and Agencies

Emergence is described as the phenomenon of a quality appearing out of nothing on a physical entity during its formation, and disappearing into nothingness when the entity is taken apart. Emergent qualities are the properties of physical entities that appear out of nowhere, and disappear into nothingness when the physical thing is broken down into its constituents.[6] That is, emergent qualities do not originate from the physical constituents of an entity, assembly, or organization.[9]

The appearance of emergent qualities is contingent upon the existence of the physical entities on which they emerge. This sets the stage for the perfect illusion that emergent qualities originate from the physical entity. However, *intimacy* should not be confused with *causality*. Recurrent intimacy is not a valid reason for causality. Unless a *causal mechanism* is identified and replicated, the claim that emergent qualities originate from physical entities themselves remains an unsubstantiated supposition.

The phrases *agent*, *active agent*, and *agency* are commonly used within the context of causation. Agencies are characterized by *causal power*, and thus the capacity to cause change. An agency is said to be *purposive* or *goal oriented* if its activity is aimed at realizing an objective. Life, for example, qualifies as a *purposive agency* since all living beings are goal oriented. The laws and forces of physics, on the other hand, qualify as a *non-purposive agency* since they exert the same pull or push effect of certain magnitude on all physical existence in the entire universe without being selective.

After pointing out that living organisms have goals and purposes while atoms and molecules just blindly follow physical laws, physicist and astrobiologist Davies[10] also attracts attention to life acting as an agent: "*Life's ability to construct an internal representation of the world and itself to act as an agent, manipulate its environment and harness energy — reflects its foundation in the rules of logic. It*

is also the logic of life that permits biology to explore a boundless universe of novelty."

A *physical phenomenon* is recognized as the *effect* under the action of an *influence* exerted on physical existence made of matter and energy, such as water flowing downwards under the influence of gravity. An observed *influence* indicates the existence of an *influencer*. The discovery of dark matter and dark energy is simply the inferred result of the observed new influences. Observed regularity of effects under the action of influences as evidenced by repeatability and predictability are indicators of the presence of underlying laws which includes the rules and principles. As such, the laws of physics are expressions of the regularity of the effects that manifest in the physical realm under the action of influences in a repeatable and predictable manner. The formulations of the laws are simply the cause-and-effect relations between the *causative influences* and the *manifested effects*.

The universal laws and forces of physics qualify as an *agency* with causal power since, collectively, they govern the behavior of all physical existence in the entire universe. Alfred Montapert has expressed this eloquently as "*Nature's laws are the invisible government of the earth*." Einstein put it as "*Everyone who is seriously involved in the pursuit of science becomes convinced that a spirit is manifest in the laws of the Universe – a spirit vastly superior to that of man, and one in the face of which we with our modest powers must feel humble.*"[11] The notion of existing beyond the visible universe and fully governing the entire physical existence is a peculiar characterization of the laws of physics which have no mass or energy.

The Brain versus the Neuromorphic Computer (Artificial Brain)

The brain is often likened to a microprocessor or a computer. But the human brain is obviously much more than a super-powerful computer or a central signal-processing unit: It seems to be home to subjective mental faculties like imagination, intelligence, thought, and consciousness as well as sensations. The web of interrelations between the physical brain and the nonphysical faculties associated with it further complicates the mind–brain problem.

The intense electric signal activity in the brain is no different from the intense electric signal activity in microprocessors, and the brain waves generated are no different from the electromagnetic waves encountered in broadcasting, telecommunications, microwave ovens, and even ordinary light. However, neither microprocessors' intense electric signal activity, produced by billions of transistors, nor the constant barrage of electromagnetic waves, produced by the sun and many common devices and appliances, has ever produced anything like a subjective quality. The intense electric and chemical signal activity throughout the rest of the human body, with about 30 trillion interconnected cells (like the electrical signals transmitted from the eye to the brain), does not produce any such subjective qualities, either.

The new generation intelligent computers that learn by trial and error and modify their software are still lifeless dummies, with no awareness of what they are doing and no ability to initiate things. All their actions are governed by the objectives set by their conscious programmers with purpose and free will, and the algorithms devised by the same programmers. That is, the impressive acts of computers and robots that mimic the learning of a child while acquiring motor skills simply reflect the will of the programmers. There is an army of code writers behind those so-called self-learning and evolving intelligent computers and robots that write their own codes. If the software is removed, those marvelous machines with their state-of-the-art microprocessors will turn into a pile of metal and plastic parts. If a different software is loaded, same machines would be doing something else.

The nearly 100 billion neuron cells of the brain stand out from the nearly 100 trillion cells in an average human body by the electrical activity through about 100 trillion synapses triggered by the motion of the ions. The information processing in the brain via electrical signal transmission resembles the information processing in a modern computer via electrical signal transmission. This resemblance gave rise to the idea to label the brain as a very advanced computer. With this notion, *mental processes* are reduced to *computational processes*.

To model and simulate the brain, which is orders of magnitude more energy efficient than a computer since it combines processing and memory, IBM and other technology companies have been working on neuromorphic computing since early 2000s. In 2008, DARPA announced the SyNAPSe program with the aim to develop a *neuromorphic computer* using cognitive computing architecture with 10 billion neurons and 100 trillion synapses, which is basically a *brain simulation*. Neuromorphic computing involves the production and use of *neural networks*, and it deals with *mimicking* the way the brain performs its functions like producing information from data and deducing fact.

As part of this project, IBM announced in 2012 that it has managed to build a neuromorphic computer with 530 billion neurons and 100 trillion synapses, using the world's second fastest supercomputer with over 1.5 million processor cores. The result was a new generation of faster and more energy-efficient computer, but again with *no trace* of subjective qualities such as consciousness, thoughts, free will and emotions.[12]

The engineering of neuromorphic computers involves the development of components whose functions are analogous to their organic counterparts in the brain. Therefore,

neuromorphic computers differ from the digital computers, which are deterministic given a specific set of inputs, they always produce the same set of outputs. Despite the claims by hard determinists that the brain activity is absolutely determined by the laws of nature, the observations of neuron firings, which are displays of peak electrical charges, point to a probabilistic nature instead. The same inputs to the neurons sometimes produce different electrical outputs. Furthermore, some inputs produce excitation in the neuron, while other inputs inhibit it.

The activity of individual neurons occurs in *milliseconds* compared to clocked speeds of *nanoseconds* for modern microprocessors. That is, the electric signal activity in the brain is millions of times slower than that of microprocessors. Therefore, neuron activity is much easier to trace and fully understand. However, obviously this understanding is no help in unearthing how neuron activity connects with subjective qualities like consciousness, emotions, intent, and free will. Some neuromorphic engineers and neurologists question the accuracy and adequacy of truly simulating the real brain activity. Gerard Marx of MX Biotech, for example, points out the missing of an *active agent* in the brain's recall process in current simulations.[13]

At base level, computers consist of 0's and 1's, corresponding to switches being on or off. Deep down, everything we see on the screen is the result of manipulations of these 0's and 1's and the resulting electrical activity. The drivers or programs onboard or on the cloud, which reflect the *will of the programmers*, control and direct the computation and information flow.

Despite their impressive computational power, computers have value and meaning only in the hands of *external users*. Without an operator, a computer with all its powerful circuitry and sophisticated software is just a marvelous thing sitting idle on a table. That is, it is the conscious and intelligent users that give computers functionality and meaning, and makes sense out of its output. If all people were suddenly to disappear from the world, for example, all the computers in the world, including those which learn by trial-and-error modify their software, would suddenly be meaningless and functionless.

Even a sophisticated computer with billions of transistors is a dummy since, despite the intense electrical activity in its brain, it is not aware of anything and it cannot initiate anything. The human brain with billions of neurons with sporadic intense electrical activity is not any different. A computer has meaning and utility only in the hands of an external conscious and intelligent user. If all the people were to vanish today, all those state-of-the-art computers, including the smart ones with artificial intelligence, would just sit there and wait for instructions. The same can be said about the brain, which is often viewed as a computer. It also needs an *external agent* with consciousness and intelligence to perform purposeful acts. Otherwise, all the sporadic electrical activity goes astray.

If a computer produces meaningful outputs, this is an indication that there is knowledgeable user with purpose behind it. Similarly, if the brain produces meaningful and purposive outputs, it is only logical that there is an invisible operator with purpose behind the scenes. This is because outcomes of computations have no meaning unless they are interpreted by a conscious, external agent. The patterns that both a computer and a brain produce by processing signals have no causal power, and neither is equipped with an intrinsic agency.

Intuition is a credible source of information, and any person can intuitively feel that it is the innate willpower extrinsic to the brain that dictates the behavior of a person. Otherwise, we would act like a preprogrammed robot or a zombie. When someone steps on our toe, we feel the pain in the toe and not in the brain. This shows that the body is fused with a subjective sentient avatar, which is an extension of the mind. Mental qualities such as intention, initiation, and goal orientation which are extrinsic to the brain do not originate from the brain, they govern the brain. These traits cannot be explained by the chaotic, disjointed, nonpurposive neurophysiological processes of the brain.

Also, there is no indication that the brain has an *internal software*. But even if it did, this does not alleviate the need for an *external operator* which determines the algorithms to be executed and implemented. A *software* or a *computer program* is merely a set of instructions to perform certain tasks, and it has no ability to initiate things– just like a cookbook being a set of cooking instructions with no ability to cook. There needs to be an *external programmer* in the first case, and a chef in the second. Without an operator to assign tasks and make sense of the results, a computer is a maze of electric signals. Similarly, a brain is like a maze of spark plugs or fireworks firing aimlessly unless there is an external agent with purpose.

Does the Brain Qualify as an Experiencing Agency?

When existence is limited to matter and energy, the sentient and conscious subjective entity with knowledge and skill is necessarily imbedded into the brain. This chunk of opaque matter is portrayed as a marvelous gadget with traits such as (1) being aware of everything; (2) having a mastery of all the intricate physiological processes in the entire body; (3) instantly converting millions of electric signals that correctly to images, sounds, tastes, and smells; and (4) giving orders to other parts of the body that are made of the same material as itself, etc. How tenable is it to think that all these wondrous acts are done by a cluster of atoms and molecules made of electrons, protons and neutrons?

All the marvelous acts listed above are associated with a subjective agency. Considering that *acts* are indicators of the traits and capabilities of the *actor*, which is the mind in this case, we infer that the mind is an *agent* that comes with the traits of unity, organization, control, knowledge, skill, and power.

The perceived physical reality is something that the mind renders out of the sensory signals received from the physical world.[14] The things that we see are nonphysical depictions of the mind [Figure 1]. As it turns out, we live in a mentally constructed subjective virtual reality world. As Glattfelder[15] puts it: "*Recall that neuroscientists are quite clear: Our perception of reality is a hallucination tethered by a bit of sensory input. What I experience through sober waking consciousness is an elaborate virtual reality rendering in my brain. The nature of this hallucination can be modulated by the chemical composition of the brain*."

The electric signals that arrive at the brain are decoded and woven into what we perceive by an agency which resembles a veiled skillful *virtual mechanism*. As Metzinger[16] puts it: "*The global model of reality constructed by our brain is updated at such great speed and with such reliability that we generally do not experience it as a model. For us, phenomenal reality is not a simulational space constructed by our brains; in a direct and experientially untranscendable manner, it is the world we live in*." Of course, a capable mysterious invisible agent must be doing the depicting of visual images, not the material brain itself, since 'matter' is inherently incapable of constructing images and perceiving them.

The notion of the random firings of the inept neurons in the brain constantly constructing the virtual vivid world that we live in and experience day and night, complete with sights and sounds, is as implausible as the claim that the shows we watch on TV are the constructs of the random flickering of the pixels of the LCD screen alone, with no controlling agent with purpose, knowledge and power behind the scenes. Yes, we cannot watch a TV show unless

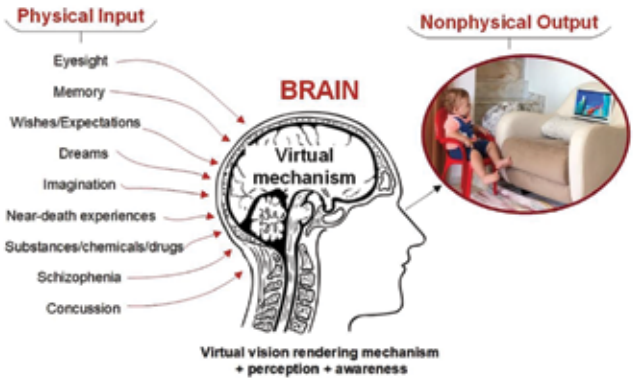

Figure 1: The mechanism of the construction of the life-like subjective 3D visual images out of electric signals triggered by various phenomena by a sentient conscious agent associated with the brain[14]

the millions of pixels on the screen flicker in a cohesive pattern. But the reasoning '*there is no TV show when there is no flickering pixels; therefore, pixel flickering is the maker of the TV shows*' is obviously unacceptable. Not knowing the nature of the mind is no valid reason to deny its necessary existence. It takes an active agent with intent, consciousness, knowledge, skill, and power to make a TV show, and the pixels on an LCD screen are anything but such an agent [Figure 2].

The Pilot Cabin with Flickering Signals and the Pilot

The cockpit of an airplane is equipped with the most sophisticated microprocessors and flashing displays that show the intense signal activity occurring in the processors. Yet, the controls equipment in the cockpit is far from having the necessary consciousness and free will to fly an airplane. If there is an airplane flying in the sky, surely there is a live pilot with emotions, consciousness, and free will who flies the airplane through the controls in the cockpit. If there is no physical pilot present in the cockpit, then we know that there is a distant pilot controlling the airplane remotely. In the case of an autonomous airplane, again we know that essential information such as the time of departure and the city of destination is keyed in by an authorized person.

The one-to-one correspondence between the patterns of the lit display signals and the action of the airplane is no proof that it is the cockpit with the flickering lights which determined what the airplane will do [Figure 3]. The inability of the airplane to fly when the cockpit malfunctions again does not show that the cockpit is the active agent with the ability to control and fly the airplane as it wishes. This is because the signal activity in the microprocessors and the control rooms, no matter how intense, is inherently incapable of generating subjective qualities such as consciousness, intent, and free will.

Similarly, to the contrary of what neuroscientist Harris[17] asserts, the one-to-one correspondence between a certain pattern of brain electrical activity and a certain act performed does not show that the involuntary electrical brain activity is the active agent behind the acts of a person. Therefore, his conclusion that there is no free will is flawed. We intuitively confirm the existence of an innate sense of freedom of action, and his contention that free will is a delusion is obviously disregarded by the courts of law as they hold people accountable for their willful acts. If there were no accountability, some people would act very differently with the same underlying physiology of the brain. We innately reject the notion of denying responsibility for our choices and actions and putting the blame on the neural activity of the brain which we have no control over.

Also, there is deterministic one-to-one correspondence between a bullet leaving a gun toward a target and a pulled

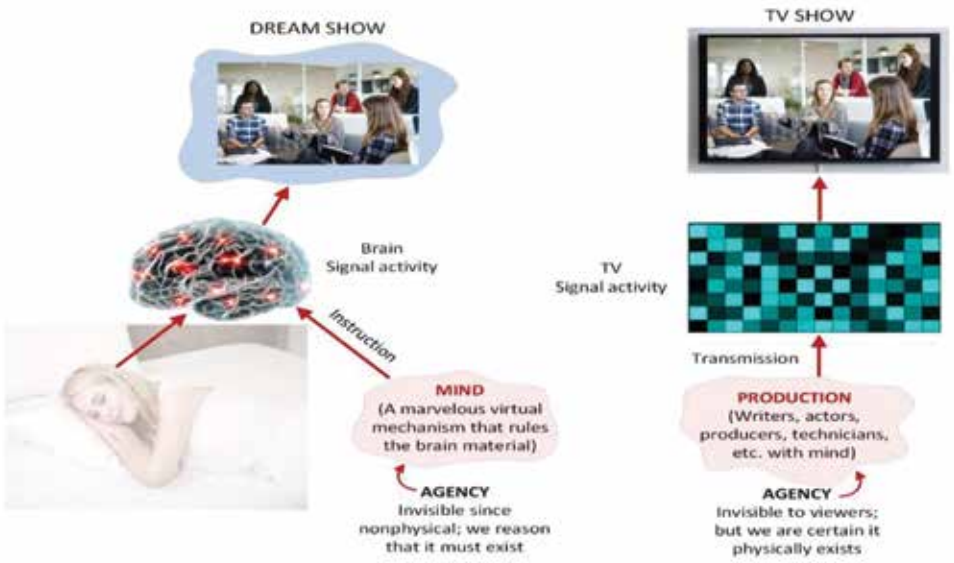

Figure 2: The virtual agency (invisible mind) involved in constructing a cohesive dream is no less sophisticated than an actual agency (visible TV production team) involved in making a TV show[14]

Figure 3: The one-to-one correspondence between the patterns of the lit display signals in the cockpit and the behavior of the airplane does not mean that the electric signal activity is what flies and controls the airplane. Same is true for the electric signal activity in the brain

trigger. By observing the direction the gun points to when the trigger is pulled, we can accurately predict the intended target before the bullet leaves the barrel of the gun. But this does not mean that the gun is responsible for shooting the targeted person—after all, the gun is just a dummy item, and it does what its user wills. A gun cannot intend anything, and it cannot choose a particular person to go after. It cannot do anything by its own volition. If there is a firing gun and a person killed by its shots, we know that there is killer out there as the active agent, whether we see that person or not. This is because a physical thing made of inanimate matter cannot develop any subjective qualities like consciousness, intent and vengeance. It is against their character, and there is no theoretical or observational evidence that suggests otherwise. Also, there is no such thing as animate raw material from which to build animate beings.

Despite the intense electrical activity in the cockpit, we contend that if there is an airplane flying, there must be a pilot in the cockpit of the airplane, regardless of how many billions of operations per second are being performed in the cockpit's microprocessors and the patterns of the flashing lights on its display screens. This is also the case even if there is no visible pilot in the cockpit, but the plane is being piloted from a distance using remote-control technology. There can be no doubt that the airplane is controlled *through* the cockpit, not by the cockpit.

For an airplane to be functional, all its essential parts—including its cockpit and the pilot—must be properly functioning. But for the airplane to fail, the failure of just one essential part is sufficient. Obviously, the observation-based argument, "When this part fails, the entire airplane fails; therefore, it is this part that makes the airplane fly," is invalid. Such simplistic and short-sighted linear thinking is responsible for a lot of misunderstandings and misjudgments.

In the case of human beings, the brain is made up of the same atoms (with the same electrons, protons, and neutrons) that the cockpit is made of, and neurons fire the same electric signals that the cockpit processors do. Both the brain and the cockpit are mere assemblies of matter, like other bodily organs and the body of the airplane. And as inept material beings, they cannot possibly have, or give rise to, subjective qualities such as consciousness, perceptions, emotions, and free will. All claims to the contrary are not evidence based. Therefore, commonly expressed thoughts like, "The human brain can compose symphonies, or create beautiful works of art" and "It allows us to navigate our world, to probe the universe, and to invent technology that can do amazing things,"[18] consist of baseless characterizations and unjustified glorifications of a lump of meat. Similarly, a microprocessor which can

perform billions of calculations per second is, at the end, an inept piece of silicon.

The electromagnetic *brain waves* measured by EEG devices are no different than the waves transmitted to and from the airplane cockpit, except for their wavelength or frequency. The material of the brain as well as the signals it generates are as inept as the matter and signals encountered everywhere else. Therefore, like the pilot in the cockpit, there must be a subjective agent called the mind equipped with a compatible set of subjective traits like consciousness, emotions, life, and free will that operates as the active agent through the brain. Otherwise, we will continue to be amazed and amused by what we think the brain is doing, as we talk about its mind-blowing mysteries. We will have to continue giving the brain supernatural powers, like telling other bodily parts what to do and how to do it, although it is a bodily part itself, made of the same atoms and molecules as the rest of the body.

By following the same line of argument, if we deny the existence of the enigmatic agency of life, we will also have to keep describing life as chemical reactions, knowing well that no chemical reaction has ever produced life, and that there is no indication on the horizon that it ever will. Sciences are based on impartial observations with no prejudice and is open to confirmation and refutation. To preserve this objectivity, we should abstain from mixing sciences with opinions or ideology. The notion of limiting existence to physical realm is a plain ideology or worldview since no experiment can be conducted to confirm or refute it. Nonphysical things obviously cannot be studied by science because the sciences are based on observations of the physical realm.

An Advertisement Billboard with an LCD Screen

To appreciate the scale of the qualities we attribute to the brain without devoting much thought or critical scrutiny, consider a large advertisement billboard with thousands of pixels (or small light bulbs) on its surface. The billboard works by powering the pixels selectively so that they form intelligible phrases like ‘Joe’s Coffee’ with rendered pictures of coffee, as shown in Figure 4. We don’t think much of the billboard ads since we know that there is a person with intelligence, knowledge, and intent behind them. The sequence of the pixels turning on and off and the patterns formed by them are determined by that operator, who is the active agent behind the scenes. The billboard with all its flickering lights is simply a dummy interface equipped with the necessary switches to turn the right pixels on and off at the command of an external agent. This way, the operator dictates and fully controls the intelligible patterns formed on the billboard by the lit pixels on the LCD screen.

Now, if we try to make sense of the intelligible ads exhibited by the light activity on the billboards without including the human operator in the scenario, and we certainly will understand why the brain is such a deep mystery. The lamps or the pixels come alive, so to speak, when they are lit, and fascinate us with their flickering meaningful messages. But the pixels and their switches are lifeless inept beings with no knowledge, intelligence, or intent. The pixels are not even aware of their own existence, let alone the existence of the neighboring pixels and the coffee shops in the neighborhood. And they have no idea about what happens when electric current passes through them. A switch cannot simply *decide* to allow electric current to pass to the lamp it is connected to, and to cut it off after a while. A switch cannot align its activity with the activities of other switches, and the switches cannot decide collectively to turn on and off selectively so that the phrase ‘Joe’s Coffee’ together with related pictures is depicted by the lit lamps or pixels. Yes, there is a one-to-one correspondence between the patterns of on switches and the intelligible message that appears on the billboard. But this does not mean that the switches are the author of those messages.

Figure 4: The one-to-one correspondence between the patterns of lit pixels and the intelligible message that appears on an LCD billboard does not mean that the pixels are the intelligent author of the message

If we disregard the human operator and associate the relevant attributes of the operator—intelligence, consciousness, knowledge, sight, and intent with the billboard, it is no wonder that we will have to describe that extraordinary billboard as mysterious, mind-boggling, and perplexing. Whether we realize it or not, we end up including in our mental picture of the billboard the mysterious human operator that we have disregarded since he or she is nowhere in sight. But this presumption did not solve the mystery of the billboard; it simply locked the mystery inside it.

Therefore, it should come as no surprise that attempts to build such an extraordinary billboard that makes its own decisions about which ads to compose and how long to display them will end up in plain failure. This is because there are no physical components with subjective or nonphysical qualities like consciousness, will, or intent.

Such subjective qualities appear on matter, but don't originate from matter. And thus, they cannot be reduced to matter, as all attempts to do otherwise have shown.

Both the billboard and the brain are composed of the same atoms, and both operate by the same electric current triggered by an electric potential. Neither electric signals nor atoms or subatomic particles possess subjective qualities like consciousness, intelligence, will, intent, purpose, or knowledge. Laws of nature, such as the law of gravity, are not equipped with these qualities, either. Therefore, we cannot solve the puzzle of the physical brain by rejecting outright the possible existence of an external invisible operator with those qualities, just as we cannot develop a factual understanding of the operation of a billboard by rejecting the existence of an unseen external human operator. After all, the whole being more than the sum of its parts is a commonly encountered natural phenomenon.[19]

The Causal Chain of Existence

The occurrence of something is contingent upon the presence of all contributing factors that together constitute a complete *causal mechanism* or the *causal chain*. The absence of one of those factors is sufficient cause for the nonoccurrence of that thing. That is, for something to occur, the entire set of the necessary factors must be present concurrently and make their contributions. That thing will not occur if one of the necessary factors is disabled or is absent.

Failure to make this subtle distinction is a common cause of blunt misjudgments, especially when all the contributing factors in the causal chain other than one are always present. This paints a false picture of one-to-one correspondence between the 'occurrence or non-occurrence' of something, and the 'factor being present or absent.' As a consequence, that factors is mistakenly viewed as a powerful causal agent. This delusion is based on the false logic that if something disappears when one of its constituents disappears, then that constituent must have served as the 'causal agent' of that thing.

The lighting of a lamp in a room, for example, is dependent on the presence of a light bulb in the lamp, the light switch being turned on, the electric wiring through the grid being intact, and the power plant generating electricity. That is, for the lamp to give light, all the necessary components that constitute the causal mechanism must be in place. Removing or disabling one of those components, such as turning the light switch off, is sufficient to halt the entire mechanism and cause the lamp to go out. In this simple case, we all know that the light switch is simply one of many passive links in the chain of causal mechanism, and we do not identify the light switch as an agency with causal power. Besides, a light switch is never observed to produce electricity or light and it is inherently incapable of doing so.

Likewise, a TV show can appear on the screen only if all the elements of the entire causal chain– the performers, cameras, broadcasters, TV set, and electric power, etc.,– are actively involved and are properly linked to one another. The removal of just one of the links in the chain – like cutting off electricity to the LCD screen – is sufficient to make the show disappear. However, this does not mean that the TV show is the making of the electrical activity within the millions of pixels of the LCD screen [Figure 5].

Furthermore, a slew of contributing factors such as sunlight, water, nutrients, temperature, etc., must be in place for a tomato plant to grow and bear tomato fruits. Watering is a necessary condition for the plant to eventually bear tomatoes, and failing to water the plant for several days may cause the plant to die. But this does not mean that watering alone is the sufficient condition for the making of tomatoes, and that it is the water which deserves all the credit for the formation of the tomatoes. Furthermore, a person cannot live more than a few minutes if his or her lungs stop functioning. However, all the vital organs need to be working properly for the person to continue living. The absence of functioning lungs is a sufficient cause for the absence of life, but the presence of functioning lungs is one of many necessary conditions for the presence of life.

When some of the links in the causality chain as well as the outcomes are nonphysical, such as the mind, consciousness, free will, the sense of sight, and the emotions, we do just that without questioning– like ascribing supernatural causal powers to the brain which is a lump of inept fatty meat. Superficial explanations such as 'vision was lost when a certain part of the brain was damaged, and the sense of vision was restored when that part was repaired; and this shows that that part of the brain is responsible for the

Figure 5: A TV show can appear on the screen only if all the elements of the entire causal chain of the performers, cameras, broadcasters, TV set, and electric power, etc., actively participate

creation of vision' abound. But this is no different than saying "the light of the lamp was gone when the light switch was damaged, and lighting was restored when the switch was repaired; and this shows that the light switch is responsible for the generation of light.' Of course, both statements remain equally as pure speculations, not scientific facts, until a light switch which generates light, and an artificial brain which generates vision, mind, consciousness, etc., are built.

A damaged or turned-off switch is sufficient to cause the absence of light, but a complete causal mechanism with all constituents being in place is necessary to cause the presence of light. It is a deep delusion to put the presence and absence on equal footing. The notion that a constituent factor is a causal agent on the basis of the observation of something disappearing when the factor is absent and reappearing when the factor is present is a blunt deception.

This delusion of crediting one of the links of the causal chain for the outcoming effect is so deeply entrenched in our minds that we view the link as the source of the effect. For example, we ordinarily think that the source of the pleasure of eating an apple is the apple itself, since, when there is no apple, there is no pleasure of eating an apple. But this is a delusion, and dreams are sufficient to burst this bubble of deep-rooted notion. The virtual apple that we eat in our dreams with our eyes and mouth closed is as pleasurable as the physical one.

We are so conditioned to concurrently having perceptions and experiences of the material world that we have developed this deeply entrenched notion that the physical realm is the source of everything we experience – such as the taste being embedded throughout the food as virtual miniscule particles. In reality, the sense of taste emerges out of nowhere when certain chemicals in the food that we eat react with the thousands of taste receptor cells in the mouth and on the tongue. This phenomenon is a common delusion called *habituation*, which describes the mental blindness and conditioning that occur after countless experiences of two things always occurring simultaneously.

A casual observer will easily deduce based on observations that corporeal things which consist of tangible material bodies are characteristically passive, recessive, submissive, affected, subjugated, controlled, and governed by external influencers. In contrast, the active, dominant, forceful, effective, subjugating, controlling, and governing things are intangible and nonphysical, and they are not made of matter. All material things such as air, water, soil, stones, bricks, tools, etc., do not initiate anything of their own; but rather, they are fully controlled by the immaterial laws and forces of physics which qualify as an agency.

Therefore, it is no surprise that all entities that qualify as active agents with causal power are of nonphysical nature, with no limitations of space and time, ruling over the bodies of physical entities made of matter-energy. This is also the logical basis for the postulation of the immaterial agency of life which governs the corporeal bodies of living beings built of atoms and molecules. Physical but immaterial ethereal things such as light, radio waves, and other electromagnetic signals appear to be sharing some aspects of nonphysical things, such as not occupying any space and being almost timeless.

Closure

In this article, the plausibility of the materialistic worldview that reduces all subjective qualities of the human mind to the brain which is a lump of material tissue is challenged on the basis of reason, logical consistency, and conformity with observations. It is demonstrated that the existence of a distinct nonphysical mind which qualifies as an agent is the most plausible representation of observed reality. The mysterious and miraculous mind appears to be an attribute of conscious animate beings like the humans. The nonmaterial mind reigns supreme over the material body, and it is irreducible to matter or energy. As such, it is in the same category of existence as consciousness, free will, beauty, knowledge, and meaning, except that the mind qualifies as an agency with causal power. The mind seems to be equipped with subjective qualities such as consciousness, free will, knowledge, and skill.

All ambitious investigations in recent decades to create artificial life and artificial consciousness from inanimate matter have amassed considerable evidence that life and consciousness cannot be reduced to matter, and life and consciousness cannot be generated from lifeless matter. This line of reasoning is constantly underscored by the scientists and philosophers who advocate emergence theories. These findings again point to the necessary existence of an invisible nonphysical active agent equipped with subjective qualities such as life, consciousness, will, and emotions that distinguish live humans from the lifeless bodies. Similarly, the view that the physical brain creating the nonphysical mind should be treated as a hypothesis only rather than a scientific fact until a brain which produces a sentient mind is built. Until then, mind should be treated as a subjective agency that transcends matter.

It is recognized that we do not fully understand the natures of emergent qualities and agencies, and it is difficult to make the physical and nonphysical realms work together cohesively. But not knowing the nature of a thing is not a valid reason for rejecting the existence of that thing. Having no idea about the natures of dark matter and dark energy did not keep physicists from recognizing their existence on the basis of the observed influence on known physical realm. As it turns out, the mysterious dark matter and dark energy together constitute 95% of the physical existence.

Science and philosophy exist to unearth the mysteries of such apparently insurmountable challenges using

observations and logic-based inductive reasoning. In the end, our picture of reality must conform to the observed external world. Besides, the test of falsifiability is always in our weaponry to discard any fallacies that may slip in. After all, in physical sciences, it takes only a single contradiction of observed phenomenon to falsify a proposition.

When we hear the sporadic firing sounds of hundreds of fireworks followed by meaningless mix of captivating bright colors, we just enjoy the show. However, if the bright colors organize to form intelligible letters that spells "Juliet, will you marry me?" we know that there is a Romeo with life, consciousness, and intent somewhere out there.

Patient informed consent

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Original Article

Quantitative Structured Reporting in Dementia Studies with Magnetic Resonance Imaging: Application to Neuroinformatics

Abstract

Introduction: Nowadays, radiology is playing a very essential role in quantitative imaging from medical images to quantitative biomarkers. Integration of this numerical information into structured reports can make it more practical tool for an accurate diagnosis of dementia. **Materials and Methods:** This research developed a structured radiological report template for dementia as an automated integration of quantitative imaging biomarkers of magnetic resonance images into neurological structured reporting as a new achievement in the Management of Radiology Report Templates in a more organized style. **Results:** A significant accuracy rather than free conventional style for dementia patients. **Conclusion:** Final aim of this study is making this feature available to make the best decision on patients with some dementia signs.

Keywords: *Dementia, imaging biomarkers, magnetic resonance imaging, quantitative measurements*

Mojtaba Barzegar[1,2,3,4], Joan Carreras[5]

[1]Intelligent quantitative biomedical imaging (iqbmi), Tehran, Iran, [2]Medical School (Medical Physics and Medical Engineering Department), Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran, [4]Society for Brain Mapping and Therapeutics (SBMT), Los Angeles, CA, [5]Radiology and Biomedical Imaging Research Group (GIBI230), La Fe University and Polytechnic Hospital and Spain La Fe Health Research Institute, Valencia, Spain

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Orcid
Mojtaba Barzegar: {ORCID: 0000-0002-3467-9109}
Joan Carreras: {ORCID: 0000-0003-2667-2019}
Luis Marti-Bonmati: {ORCID: 0000-0002-8234-010X}

Address for correspondence:
Mr. Mojtaba Barzegar, Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, 71348-14336, Iran University/Organization: Intelligent quantitative biomedical imaging (iqbmi), Tehran, 1955748171, Iran.
E-mail: mojtaba.barzegar@brainmappingfoundation.org

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Introduction

Alzheimer's disease, dementia's most common subtype, is predicted to grow from 50 million to 130 million people by 2050 due to fast increases in aging worldwide.[1] Screening people with computed tomography or magnetic resonance imaging at least once is highly recommended as a diagnostic workup of patients with cognitive problems to prevent exacerbation of dementia.[1]

Currently, radiology plays an essential role in the extraction of quantitative imaging biomarkers (QIBs) from medical images.[2] A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or a response to a therapeutic intervention."[2,3] Developing an analysis pipeline for measuring QIBs and integrating it into the clinical reporting workflow is an important step in neurological procedures.[2] Owing to the many advantages of structured reporting over freestyle reporting, integrating the healthcare enterprise (IHE) is an organization that has developed the Management of Radiology Report Templates (MRRT) profile to specify a standardized approach for imaging reporting.[4,5] On the other hand, the Radiological Society of North America (RSNA) and the European Society of Radiology have developed libraries for radiologists to find exemplary best-practice templates.[4] Hence, combining QIBs with structured reports (SRs) has many advantages to foster radiologists' knowledge. However, there are some challenges to practicing this method in a routine approach, in particular, methods for automating brain volume quantification in a clinical setting.[2,6] This combination includes SRs that seem to be necessary for more accurate diagnoses.[7] Diagnostic procedures mainly include magnetic resonance imaging as an integral part of the diagnosis, treatment allocation, and follow-up.[8,9] Furthermore, artificial intelligent (AI) and quantitative methods for enhancing the role of biomarkers are developing fast.[10] However, these developments might have some challenges from data acquisition to managing the data which make them impractical for radiologists and referring physicians.[11]

The final aim of this study, prepared by the Radiology and Biomedical Imaging

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Ethics committee approval: There is no need for ethics committee approval.

Research Group (GIBI230) with the collaboration of QIBs in Medicine (QUIBIM S.L.), is to develop a novel system to change the radiology report template to a more organized style with some important quantitative measurements for dementia as the most common type of neurological disorders in the world,[12] which is included in a well-designed radiological workflow.

Materials and Methods

Ethics committee approval: There is no need for ethics committee approval.

Four major aspects have to be addressed a dedicated procedure for making it practical in clinic:(1) preparing the SRs template; (2) QIBs integration; (3) installation of quantitative structured reporting (QSRs) on hospital platform; and (4) clinical validation.

Neurological quantitative structured reporting framework

According to our design, we created an accurate, fast, and reliable QSRs framework to help radiologists. This will be used as a valid tool in diagnostic neurological procedures.

It is necessary to develop a classified, structured, and dynamic dataset for the diagnosis of dementia. The RSNA suggests a vender natural standard for this purpose, such as a specific XML structure, which was later replaced by HTML5-based format and has used as a trial implementation by IHE under the MRRT profile.[4] The report template file basically describes an HTML form and allows for text areas, input field, and selection boxes as described below.

Clinical information

This part includes four information sections: ID number, age, gender, and exam date. These sections directly come from the header of Digital Imaging and Communications in Medicine (DICOM).

Technical information

Other technical data were considered, such as study type, study region, sequences features, contrast agent condition, scanner's features, and comparative conditions. This data comes from the Picture Archiving and Communication System that we developed in Figure 1.

Findings

This section communicates our findings that we specified toward dementia patients. This section includes both anatomical and numerical data, which are able to report information about pathological disorders. According to the previous studies about dementia, evaluation of the disease should be divided into independent subsections as formatted below.

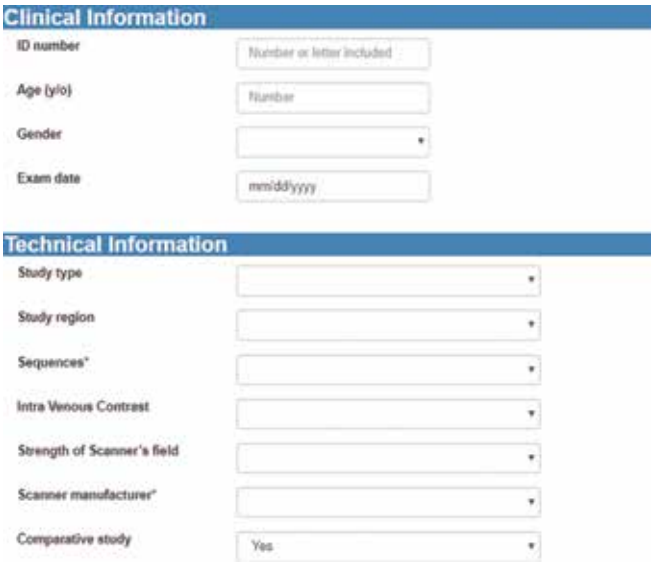


Figure 1: Clinical and technical information

The subsections are as follows: evaluation of global cortical atrophy (GCA) and the medial temporal lobe atrophy (MTA) score, white matter (WM) hyperintensities on T2-weighted sequences mainly for Fazekas scale, infarcts (lacunar and nonlacunar), micro bleedings (lobar or deep), hydrocephalus pressure, and iron evaluations in thalamus, putamen, globus pallidus, caudate nucleus, and amygdala. In addition, there is free blank box for adding any other findings for radiologists. In the case of comparing data with a previous study, a comparative subsection can be added dynamically [Figure 2].

GCA scale is the mean score for cortical atrophy throughout the complete cerebrum from 0, for normal aging, to 3, for severe (end-stage) atrophy; cortical atrophy is best scored on fluid-attenuated inversion recovery (FLAIR) images. In some neurodegenerative disorders, the atrophy is asymmetric and occurs in specific regions, thus a radiological report should mention any regional atrophy or asymmetry.

MTA score should be rated on coronal T1-weighted images with a consistent slice position. The score is based on a numerical rating from 0, for normal aging, to 4, for severe volume loss of hippocampus.

The Fazekas scale is a scale for WM lesions which provides an overall impression of the presence of WM hyperintensities (WMHs) in the entire brain ranging from a 0 score, for non or single-punctate WMH lesions, to 3, for large confluent lesions. It is best quantified with transverse FLAIR or T2-weighted images for the evaluation of small vessel disease as well.

This section will be translated into natural language processing (NLP) in the last section titled "Summary."

Impression

A conclusion box, suggestion box, and a free blanked box were designed for the impression section of

our report. All possible diagnoses were predicted. Furthermore, if a study were to be a comparative study, then this part would add another subsection for new findings.

Summary

NLP aims to translate all the above information into a classified brief or abstract for referring physicians in an understandable overview of a patient's condition. Furthermore, this section would be able to be in any local language [Figure 3].

Information extraction of imaging biomarkers from magnetic resonance images (Radiomics)

The role of artificial intelligence in data management

For the last few decades, various models and methods have been proposed for the extraction of imaging biomarkers from different parts of the body, with applications in diffuse diseases such as Alzheimer's, steatosis, cancer, etc.[10] AI helps the field of imaging biomarkers in both segmentation and data mining steps. However, dealing with AI is a challenging task because of the computing infrastructure and the processing algorithms that require very dedicated profiles in different fields such as computer science, statistics, mathematics, image processing, and Machine Learning (ML) (which is designed to learn patterns from data with various techniques).[4,10] Using AI for radiomics demands two major steps in during development: training and testing.[10] [Figure 4].

Magnetic resonance protocol for dementia patients

For the evaluation of dementia according to standard protocols, there are many multiplanar series including: t2_tse_tra, t1_MPRAGE_3D, SWI_tra_2D, t2_FLAIR_dark fluid_3D, epi_diff_tra_32 dir_2D, epi_bold_tra_resting state, and t2*_tra_multi echo.

Information Extraction with designated modules

There are various designed modules based on AI (as a short-term and long-term measurement tool) and ML on QUIBIM precision platform for the extraction of numerical data and for algorithm training.

Designed modules for extracting biomarkers are R2* relaxometry for iron depositions, WM lesions for lesion number, total lesion volume calculation, brain volumetry with parcellation, Frontotemporal atrophy, voxel-based morphometry for automatic determination of the structural alterations present in the gray matter with respect to control group, and brain atrophy screening for the calculation of brain parenchyma fraction [Figure 5].

Implantation on enterprise imaging repository platform

This reporting template was designed according to standard guidelines (e.g., PI-RADS v2.1) and consensus of key opinion leaders (e.g., RSNA TLAP) to ensure that relevant information was collected.

The report template files describe an HTML form, text areas for radiologists' comments, input fields, quantitative information, and selective boxes. These QSRs are transferred as plain text into NLP for clinicians by some Java software codes. These techniques can be used for categorizing and extracting semantic information from QSRs.

The platform is organized to support all different imaging modalities or formats and also services such as worklist provider, auditing, image exchange, media import, etc. Standard interfaces include DICOM, DICOM web, XDS-I. b, and QSRs templates for different diseases, which can support many imaging

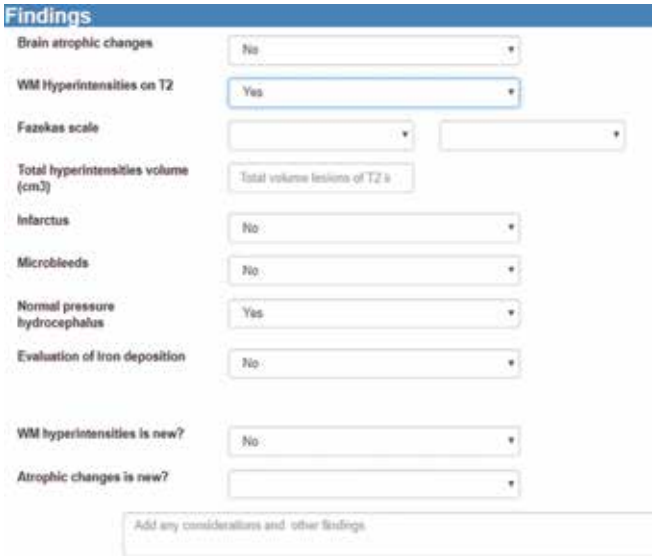


Figure 2: Findings

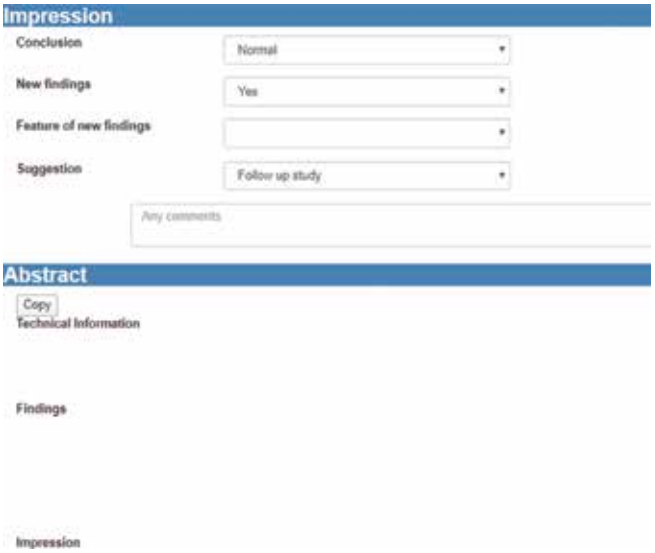


Figure 3: Impression and automated abstract maker

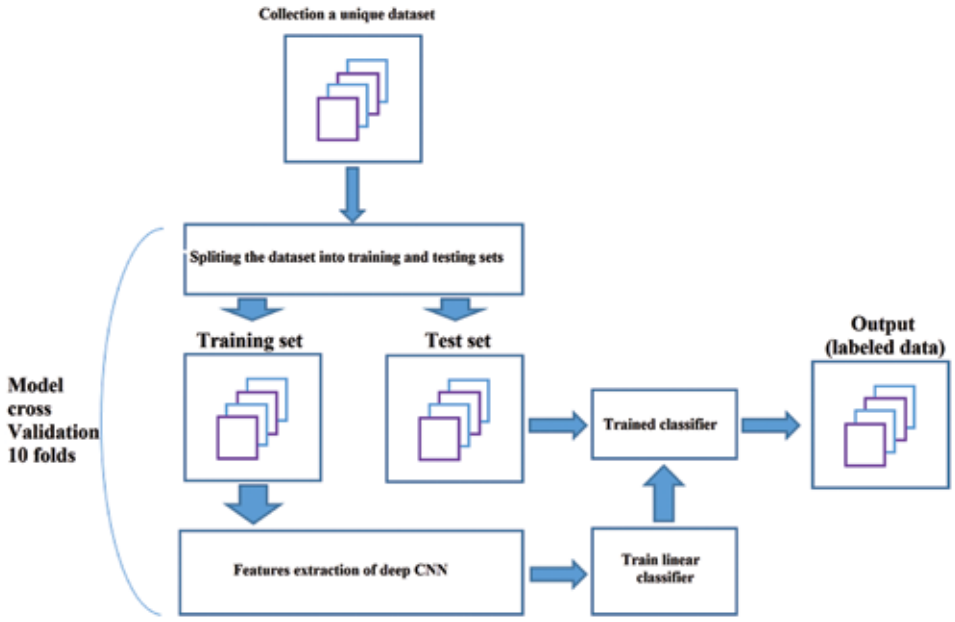
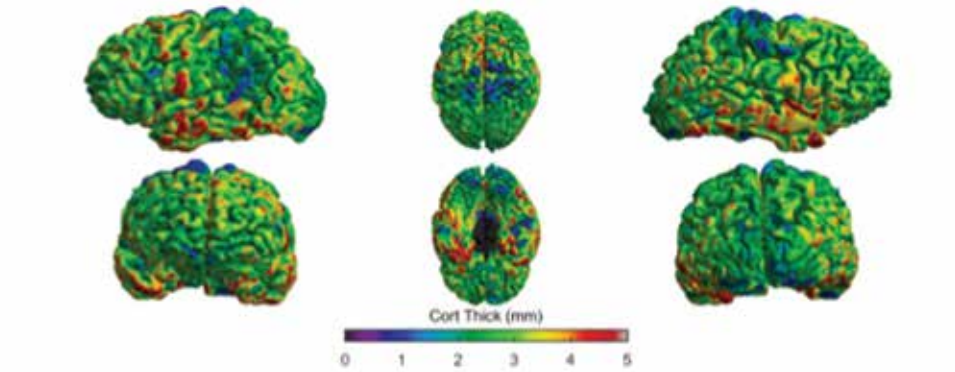
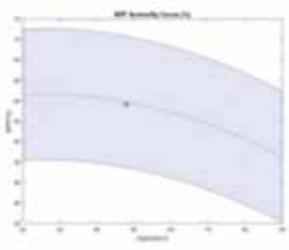


Figure 4: Flowchart for data labeling



	Volume		Brain Parenchyma Fraction (%)
	Absolute (mL)	Relative (%)	
Gray Matter	552.66	38.81	63.66
White Matter	353.96	24.85	
CSF	517.37	36.33	

	Volume (mL)		Healthy Volume (mL)	
	Right	Left	Right	Left
Hippocampus	4.05	3.67	3.66 ± 0.36	3.43 ± 0.33
Temporal	47.15	41.77	44.00 ± 3.50	42.00 ± 4.00
Enthorinal	0.92	1.01	1.40 ± 0.10	1.41 ± 0.12



Data from this quantification report should be considered as the results of research with an evidence level 2 (Centre for Evidence-based Medicine) in phase of clinical approval. QUIBIM S.L. - Quantitative Imaging Biomarkers in Medicine. EDIFICIO EUROPA - Avenida Aragon 30, 12th Floor, Office I, Valencia (SPAIN). Phone: +34 961243225

Figure 5: Quantitative measurements

sources across an enterprise. Management of scanned documents in electronic health record environments, for example, forms, consents, and external reports are often handled through an enterprise content management system.

Prepared HTML5 templates for dementia were uploaded on the designed platform of La Fe hospital and all sections were reviewed several times for proper function to be implemented as a trial service to patients.

In this environment, the quantitative parts of QSRs are being filled in automatically from QUIBIM services and other parts of this template would be completed by neurologists. After approving the reports, they would be saved and sent to the storage for the next recall.

Clinical validation

According to a research by Goodkin *et al*. in 2019,[2] four stages are suggested for validation: creditability, accuracy, patient management, and socioeconomic impact which have been expanded below.

Results

In this study, tried to validate data according to the above standard on 150 real cases on La Fe and re-evaluate all results with radiologists, neurologists, and related engineering staff. Five reports needed more information to be significant by this method.

Conclusion

To our knowledge, there have been no previous studies that investigated the quantitative measurements integrated with structured reporting. QSRs might be introduced as a powerful tool that potentially enables to improve the precision, speed, and accuracy, although some limitations can be considered to have a spotless report. More investigations are suggested to increase the accuracy.

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Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

- Mojtaba Barzegar (70%): contributed in in proposing the research idea, providing the research funding, and writing the manuscript, designing and carrying out the research, supervising the data processing, modeling.
- Joan Carreras (30%): contributed in clinical application and classification of lesions. All authors contributed to the article and approved the submitted version.

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Original Article

Investigation of the Effect of Anxiety Disorder on Time Perception with Zimbardo Time Perspective Inventory

Abstract

Background: Linguists first coined the term anxiety in the 1600s to define a state of severe restlessness and worry. When we look at the Turkish dictionaries and printed sources, we see that the definition of anxiety is made simply as anxiety, fear, and worry. Anxiety; which we can describe as a mental and physical reaction, a defense strategy, against an event or fear. It will threaten the survival of the life; it is seen in two ways as situational anxiety and trait anxiety. Situational anxiety, as the name suggests, arises when faced with a threat or stress factor, while trait anxiety is an anxiety that occurs internally, independent of the event or situation. **Aims and Objectives:** For the continuity of one's cognitive and behavioral abilities, not only anxiety but also the perception of time has a great place in the continuity of life. The findings that help us understand one's time perspective are internal clock models and related mechanisms. This study aims to investigate the effect of anxiety on time perspective. **Materials and Methods:** To this end, the Beck Anxiety Scale, the Zimbardo Time Perspective Inventory, and the demographic information form were used to collect data. Data were collected from a total of 168 participants, 44 females and 124 males. **Results and Conclusion:** When the findings are evaluated in general terms, there was a moderately negative relationship between anxiety and past positive perspective and a moderately positive relationship between past negative perspective. Based on this result, anxiety prevents a positive perception of the past; on the contrary, it can be said that it causes a negative perception of the past.

Keywords: *Anxiety, Beck Anxiety Inventory, time perception, Zimbardo Time Perspective Inventory*

Huseyin Oguzhan San[1], Sultan Tarlaci[2], Korkut Ulucan[3], Tolga Polat[4], Ozlem Ozge Yilmaz[4], Beste Tacal Aslan[4]

Departments of [1]Neuroscience and [2]Neurology, Institute of Health Sciences, Üsküdar University, [3]Department of Dentistry, Faculty of Dentistry, Marmara University, [4]Department of Molecular Biology and Genetics, Marmara University, Istanbul, Turkey

Introduction

Anxiety was used by linguists for the first time in the 1600s in the sense of severe restlessness and anxiety.[1] When we look at the Turkish dictionaries and printed sources, we see that the definition of anxiety is made simply as anxiety, fear, and worry.

Contrary to popular belief, anxiety is not an entirely negative trait. An individual must live their life despite threats from the outside world.[2,3] Anxiety prepares us for internal and external dangers we will encounter and saves our lives; it may also allow us to get good grades for an examination. Although they do not look the same, these two emotions, which show similar characteristics, contain a high level of arousal and a low level of satisfaction.[2,4-7]

Anxiety; which we can describe as a mental and physical reaction, a defense strategy, against an event or fear. It will threaten the survival of the life; it is seen in two ways as situational anxiety and trait anxiety.[8-10] Situational anxiety, as the name suggests, arises when faced with a threat or stress factor, while trait anxiety is an anxiety that occurs internally, independent of the event or situation. In situational anxiety, the severity of anxiety is directly proportional to the closeness of the event or condition to the person; such a relationship cannot be mentioned in trait anxiety. Studies show that people who experience high levels of trait anxiety experience situational anxiety more severely.[5,9]

An anxiety disorder can occur even if the person develops anxiety without encountering any threat or objective fear, as if one has experienced such a situation. Although this is a psychopathological phenomenon, its severity or course varies greatly depending on the individual and requires pharmacological and/or psychological support.[11-14]

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Orcid
Huseyin Oguzhan San {ORCID: 0000-0001-7302-7771}
Sultan Tarlaci {ORCID: 0000-0001-7634-1467}
Korkut Ulucan {ORCID: 0000-0002-1304-9386}
Tolga Polat {ORCID: 0000-0002-2064-6613}
Ozlem Ozge Yilmaz {ORCID: 0000-0002-4085-6159}
Beste Tacal Aslan {ORCID: 0000-0001-5271-7917}

Address for correspondence:
Mr. Huseyin Oguzhan San, Institute of Health Sciences, Üsküdar University, Istanbul, Turkey.
E-mail: h.oguzhansan@gmail.com

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In psychology, there are different definitions of anxiety and fear that have been made over time. For example, the cognitive approach argues that fear is a cognitive response and anxiety is an emotional response. In other words, while fear is resorting to the ways the mind leads, anxiety is thinking about these ways and making an evaluation. Anxiety is not caused by an event but simply by erroneous perception and distorted interpretation.[15,16] According to social learning, anxiety is a conditioned response acquired through social learning. Individuals react according to how they perceive the place and situation. According to the psychodynamic approach, anxiety appears as a result of unconscious contradictions and ego imbalance.[17]

On the other hand, the existential approach focuses on the fear and anxiety that will be experienced if life becomes meaningless. In other words, unless a person enjoys life and is satisfied with his life, he cannot make sense of it and makes anxiety feel much more.[15] In other words, the person defines life through anxiety and tries to drown the reaction of his emptiness and meaninglessness in this way.[18-20]

The cognitive and emotional symptoms of anxiety observed in humans are as follows: perceiving the surroundings differently than normal, hyperarousal, excessive self-focus, memory problems, hanging around and diving far, distractibility, obsessive thoughts, difficulty concentrating, flight of ideas, the thought of being constantly harmed, fear of being poorly judged by people, despair, uneasiness, approval request, intolerance, horror, irritability, constant fear and irritability most of the day, fear of losing mind, and obsessive fearful thoughts.[17,21-24]

The physiological and behavioral symptoms of anxiety in humans can be listed as follows: compulsive behaviors, avoidance of anxiety, locking, speech disorder, restlessness in the limbs, pupillary enlargement, goose bump condition, thirst, pain and pain in the abdomen, pressure, nausea, difficulty defecating or diarrhea, dry mouth, blood pressure, irregular heartbeat, shortness of breath or frequent and shallow breathing, itching, sleep disturbance, early fatigue, inability to rest, sleeping disorders, muscle twitches, premature ejaculation, decrease in sexual desire, frequent toilet visits, tiredness, weakness muscle, and back pain is observed.[21,22,3,5]

Most studies on time in psychology focus on the concept of time perspective, which was first observed by Levine and was formulated over time and brought to the world of science.[25,26] This concept emphasizes that individuals' perceptions of time develop oriented to the past, future, or present. Studies on the effect of the focal point of one's daily routine on the rest of life reveal a series of outcomes such as learning and self-regulation of one's perception of time.[30,26,24]

The most well-known and most influential time perception study conducted in this field is the Zimbardo Time Perspective Scale study, developed by Zimbardo and Boyd, based on Lewin's studies.[27] According to this study, perspectives in the scale were shown to be negatively related to the psychopathic tendencies of the individual and the general anxiety level.[27-30]

For example, it is widely accepted that having a future perspective in the scale or giving this perspective more weight than others is related to positive results (Zimbardo and Boyd 1999). Future time perspective is defined as making plans for the future, setting goals, and focusing on the possible future effects of issues. The future perspective considered within the scope of this definition is associated with lower psychopathy tendencies; it has also been shown that future perspective is negatively related to general anxiety level.[29,30]

Today, although many mental health experts and neuroscientists reveal that anxiety and time perception are related in different ways, this relationship still exists as a subject discussed on various platforms by the scientific world. Our research aims to contribute to the emergence of the relationship between anxiety and time perception by embodying the participants' attitudes, behaviors, and cognitive processes with the help of a self-reported scale.

Materials and Method

Ethics committee approval: The ethics committee approval has been obtained from Uskudar University Committee on Animal Use and Care (61351342/2020-302).

Sample

The research sample consists of 168 randomly selected participants who want to participate in the study and meet the appropriate conditions. The age ranges are between 16 and 52. During this study, we observed variables such as socioeconomic factors, the use of drugs that are thought to affect the study, alcohol use, smoking and substance use history, hunger and satiety, and sleep and hormone states (such as menstruation). These variables did not affect the research data. It was assumed that the participants answered the inventories and tests used in the research honestly and sincerely. The data of some people thought to have a negative impact on the study were excluded from the evaluation. Forty-four of the participants were women and 124 of them were men. Only 10.8% of the participants were in the age range of 16–20, 50.4% were 21–25, 24% were in the 26–30 age range, 9% were 31–39, and 4.6% were in the other age range. Only 10.7% of all samples are high school graduates, 65.5% university graduates, 22.6% graduate graduates, and 1.2% doctorate graduates.

Demographic information form

The purpose of using the demographic information form is to obtain detailed information about the individuals who contributed to the study and determine the effects on the hypothesis. In this regard, some questions were formed

to complement the data obtained during the experiment. Information such as age, gender, education, and so on was recorded via Google Forms.

Beck Anxiety Scale

This scale consists of 21 questions. Each question is evaluated between 0 (never) and 3 (severe), and high scores indicate increased anxiety complaints. Thus, the total score that can be obtained from this scale varies between 0 and 63. The high total score indicates the severity of the anxiety experienced by the individual. The Turkish adaptation of the scale was carried out by Ulusoy.[31,32] It is an easy-to-apply scale that individuals can answer on their own. It is stated that the Cronbach's alpha internal consistency coefficient of the scale is 0.93, the item-total test correlation coefficients vary between 0.45 and 0.72, and the test–retest reliability coefficients are $r = 57$.[31] Within the scope of the current study, the Cronbach's alpha value of the scale was calculated as 0.90.

Zimbardo Time Perspective Inventory

Zimbardo Time Perspective Inventory consists of a Likert-type 5-point scale and 56 items. As a result of the factor analysis performed by Zimbardo *et al*., five different factors, namely five different time perspectives, were determined.[30] (Positive evaluation of the past, negative evaluation of the past, fateful in the present, hedonistic in the present, and future tense perspective). According to the findings from 361 participants, factors explained 36% of the total variance. In the analysis, the reliability coefficients of the subscales were found to be satisfactory. The Cronbach's alpha value of the "past negative" factor, which was 0.1 in 10 items, was found to be 0.82, and this value explained 12% of the variance of the Time Perspective Inventory. The Cronbach's alpha value of the "present hedonistic" factor, which was. 1 in 15 items, was calculated as 0.79, and this value explained 9% of the inventory variance. Cronbach's alpha value of the "future" factor, of which 0.1 was performed in 13 items, was calculated as 0.77, and this value explained 6% of the variance of the inventory. The Cronbach's alpha value of the "past positive" factor, of which 0.1 was performed in 9 items, was found to be 0.80, and this value explained 5% of the variance of the inventory. Finally, the Cronbach's alpha value of the "present fatalistic" factor, of which 1.1 was calculated in 9 items, was calculated as 0.74, and this value explained 4% of the variance of the inventory.[30]

Process

The scales were given to the individuals participating in the study, accompanied by standard instructions. They were randomly selected and asked whether they would like to participate in the research. The volunteers were read the informed consent form requested by the ethics committee, and their approval was obtained (61351342/2020-302). The study was carried out online due to the COVID-19 global epidemic.

Results

Before the research analysis, the accuracy of the data entry and the compatibility of the distributions of the variables with the assumptions of multivariate statistical analysis were tested. In the test phase, to obtain more reliable data from the sample group, variables that were thought to affect the results of the study adversely were detected in 44 of 212 participants, so they were excluded from the evaluation, and the study was continued with the data of 168 participants. With the tests performed, it was observed that the population variances were equal, and it was decided that the two groups were comparable.

As shown in Table 1, there is a significant difference according to the results of the independent *t*-test applied to find out whether there is a substantial difference between the anxiety scale scores of the sample group and the gender variable. In addition, there is no significant difference between the variables of age, marital status and education level, and anxiety scale results.

As shown in Table 2, the independent *t*-test applied to find the significant difference in the scores of the sample group according to the Zimbardo Time Perspective Inventory according to the anxiety variable is given in the table.

According to the independent *t*-test applied to find the significant difference between the scores they received according to the past positive subscale, according to the anxiety variable, there is a substantial difference as the option "No signs of anxiety" in the past positive subscale gets more points.

According to the independent *t*-test applied to find the significant difference between the scores they received according to the past negative subscale, according to the anxiety variable, there is a significant difference since the anxiety symptom scores are higher in the past negative subscale.

According to the results of the independent *t*-test applied to find the significant difference, according to the anxiety variable, there is no significant difference in the scores of the present hedonistic, present fatalistic, and future subscales.

Relationships between variables

Correlation analysis was performed to determine the relationship between anxiety symptoms and Zimbardo Time Perspective Inventory.

Between the Beck Anxiety Inventory and the Zimbardo Time Perspective Inventory, past positive subscale score was moderate and negative; there is a moderate and positive correlation between the past negative subscale score.

Table 1: Independent *t*-test analysis result table for the difference between age, marital status, and education level variables according to the gender variable of the sample

	Beck Anxiety Scale	*n*	$\bar{X}$	SS	*t*	SD	*P*
Gender	There are signs of anxiety	117	1.79	0.406	2.38	166	0.02
	No signs of anxiety	51	1.61	0.493			
Age	There are signs of anxiety	117	26	6.382	−0.743	166	0.459
	No signs of anxiety	51	26.84	7.351			
Marital status	There are signs of anxiety	117	1.31	0.725	−1.404	166	0.162
	No signs of anxiety	51	1.49	0.880			
Level of education	There are signs of anxiety	117	2.16	0.587	0.636	166	0.526
	No signs of anxiety	51	2.10	0.640			

$P<0.05$. *n*: Population size, $\bar{X}$: Mean, SS: The sum of squares, SD: Standard deviation

Table 2: Results table of independent *t*-test analysis applied for the difference between Zimbardo Time Perspective Inventory scores according to the anxiety variable of the sample

	Beck Anxiety Scale	*n*	$\bar{X}$	SS	*t*	SD	*P*
Past positive	There are signs of anxiety	117	3.3371	0.62666	−2.755	166	0.007
	No signs of anxiety	51	3.6144	0.53211			
Past negative	There are signs of anxiety	117	3.4598	0.77371	4.751	166	0.000
	No signs of anxiety	51	2.8725	0.64252			
Present hedonistic	There are signs of anxiety	117	3.5624	0.53228	−0.422	166	0.674
	No signs of anxiety.	51	3.5987	0.46562			
Present fatalistic	There are signs of anxiety	117	2.8490	0.53615	0.938	166	0.350
	No signs of anxiety.	51	2.7691	0.43538			
Future	There are signs of anxiety	117	3.6003	0.45656	−1.733	166	0.085
	No signs of anxiety	51	3.4646	0.48941			

$P<0.05$. *n*: Population size, $\bar{X}$: Mean, SS: The sum of squares, SD: Standard deviation

There is a moderate and negative correlation between the past positive subscale and past negative subscale scores of the Zimbardo Time Perception Inventory. In addition, there is a moderate and positive relationship between past positive subscale and present hedonistic subscale scores, and there is a moderate and positive correlation between past negative subscale and now fatalistic subscale scores.

There is a weak and positive correlation between now hedonist subscale and now fatalistic subscale scores. There is a weak and negative correlation between the hedonist now subscale and the future subscale scores. There is a moderate and negative relationship between the fatalistic now subscale and the future subscale scores.

Conclusion

Perception of time is one of our most important skills, which enables us to subjectively predict, perceive and understand the duration of experiences, feelings, and achievements, which is necessary for us to maintain our daily practices and make long-term plans.[32-35]

The deterioration observed in the perception of time in people with psychiatric disorders has inspired many studies both in the past and in the future. Different results were obtained in these studies, which were mainly carried out on attention deficit and hyperactivity disorder, parkinsonism, depression, and schizophrenia, and these studies also aroused great repercussions.[5,9]

Anxiety is a condition that varies according to the event and situation, although there is no pathology. Therefore, it is very difficult to examine the relationship between the perception of time and the anxiety experienced within the limits of normality. Currently, it is also thought that the physical symptoms of anxiety affect cognitive processes.[28,36] Anxiety, is observed both alone and in combination with many disorders. It has also been claimed that there may be a relationship between the perception of time and some findings related to the subject. Some of these findings show us that people with anxiety disorder have an accelerated perception of time and a shorter perception estimation. More significant differences were found in studies with adolescents.[7,28,37,38]

When the findings are evaluated in general, there was a moderately negative relationship between anxiety and past positive perspective and a moderately positive relationship between past negative perspective. According to this result, anxiety prevents positive perception of the past; on the contrary, it can be said that it causes a negative perception of the past as shown in Table 3.[39,40]

On the other hand, the scores of the past positive subscale and the now hedonist subscale are moderately positive, the past negative Subscale and the now fatalist subscale are moderately positive, and the now hedonic subscale and the

Table 3: Correlation chart between Beck Anxiety Scale and Zimbardo Time Perspective Inventory

	Beck Anxiety Scale	Past positive	Past negative	Present hedonistic	Present fatalistic	Future
Beck Anxiety Scale						
R	1					
P						
N	168					
Past positive						
R	−0.345**	1				
P	0.000					
N	168	168				
Past negative						
R	0.436**	−0.307**	1			
P	0.000	0.000				
N	168	168	168			
Present hedonistic						
R	−0.087	0.357**	−0.058	1		
P	0.260	0.000	0.459			
N	168	168	168	168		
Present fatalistic						
R	0.078	0.064	0.436**	0.207**	1	
P	0.315	0.408	0.000	0.007		
N	168	168	168	168	168	
Future						
R	0.114	0.002	0.069	−0.225**	−0.300**	1
P	0.142	0.983	0.372	0.003	0.000	
N	168	168	168	168	168	168

$P<0.01$/$P<0.05$. *n*: Population Size, $\bar{X}$: Mean, SS: The sum of squares, SD: Standard deviation

present fatalistic subscale are weak and positive. There is a weak and negative relationship between the now hedonist subscale and the future subscale scores and a moderate and negative relationship between the now fatalistic Subscale and the future subscale scores. According to these results, people with a positive perspective on the past avoid perceiving the past negatively and enjoy the present; those who remember the past negatively have a more fatalistic attitude in the present. It can be argued that hedonistic people have a more negative perspective on the future in the present and fatalistic people have a negative perspective on the future in the present.[41-43]

Patient informed consent

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Huseyin Oğuzhan ŞAN (55%): Design the research, data collection and analyses and wrote the whole manuscript.

Sultan TARLACI (15%): Organized the research and supervised the article write-up.

Korkut ULUCAN (15%): Contributed with comments on research design and slides interpretation.

Tolga POLAT (5%): Data collection and analyses.

Ozlem Ozge YILMAZ (5%): Data collection and analyses.

Beste Tacal ASLAN (5%): Data collection and analyses.

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Management of Psychosis Accompanying Tourette Syndrome with Quetiapine

Onur Toktamış[1], Cansu Çakır Şen[1], Nesrin Buket Tomruk[1]

[1]*Department of Psychiatry, Bakırköy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey*

Abstract

Gilles de la Tourette (or briefly Tourette) syndrome (TS) is a neurobehavioral disorder that often begins in childhood and is characterized by motor and vocal tics. Many psychiatric disorders may accompany TS, attention-deficit hyperactivity disorder, and obsessive–compulsive disorder being the most frequent. However, literature regarding the association between TS and psychosis is controversial. We present a patient who has comorbid TS and psychosis and is treated successfully with quetiapine.

Keywords: *Brief psychotic disorder, first-episode psychosis, psychosis, quetiapine, Tourette syndrome*

Introduction

Gilles de la Tourette (or briefly Tourette) syndrome (TS) is a neurobehavioral disorder, characterized by motor and vocal tics with a waxing-and-waning nature, which typically commences in childhood and may accompany many psychiatric conditions.[1-3] The lifelong prevalence of TS in population is 0.3%–0.8%,[3,4] and men are three to five times more likely to be affected than women.[5-7] With attention-deficit and hyperactivity disorder (ADHD) being the most frequently seen comorbidity in TS,[3,5] obsessive–compulsive disorder (OCD), anxiety disorders, and poor impulse control are the psychiatric conditions that may occur in the course of TS.[3,5-7] Along with papers stating that intelligence is not affected and the prevalence of psychosis is not increased in TS,[5,8] there are also papers that describe psychotic comorbidities in the literature.[9-11] In a study conducted by Müller *et al*., the prevalence of schizophrenia among patients with TS is said to be high,[12] and Kerbeshian *et al*. found that the prevalence of schizophrenia is 2.5% among 399 patients with TS.[13] As seen, medical literature regarding the comorbidity of TS and psychosis is yet controversial and inadequate.

Pharmacotherapeutic intervention of TS mainly consists of alpha-2 (α_2) adrenergic receptor agonists and antipsychotics.[6,7] Antipsychotics are more effective than alpha-2 agonists;[3] however, since the side effect profiles of alpha-2 agonists (clonidine and guanfacine) are more favorable, they are recommended as the first-line agents.[6,14] Amid the antipsychotic drug choices, pimozide and haloperidol are the most supported agents.[3,6,14] Other antipsychotics that are used for the management of TS are risperidone,[3,7,14] aripiprazole,[7,14] olanzapine,[7,14] sulpiride,[14] ziprasidone,[14] and quetiapine.[3]

Case Report

The patient presented hereby was female aged 22 years. She attended our hospital's psychiatric emergency department with complaints of "hearing voices," "seeing things," and suicidal thoughts. Via a psychiatric interview, the psychiatric history of the patient was ascertained. During her primary school years, she had been attended our hospital's child and adolescent psychiatry department with motor and vocal tics and diagnosed with TS. The pharmacological management was initiated with haloperidol; however, as a result of an oculogyric crisis, haloperidol was replaced with aripiprazole and she was followed with this agent until the age of 16. Vocal tics completely disappeared and motor tics

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Orcid
Onur Toktamış {ORCID: 0000-0001-6745-2843}
Cansu Çakır Şen {ORCID: 0000-0001-8086-6012}
Nesrin Buket Tomruk {ORCID: 0000-0002-1889-7608}

Address for correspondence:
Dr. Onur Toktamış, Department of Psychiatry, Bakırköy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey. E-mail: toktamisonur@gmail.com

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diminished in intensity nearly closing to inexistence. At the time she attended our hospital, she stated that because her motor tics hardly affected her daily life, she was not using her medicine for nearly 6 years. Three weeks before her attendance, she was settled to a women's shelter due to family issues and her complaints began 1 week afterward. Two weeks after the onset of her complaints, suicidal thoughts emerged.

After the assessment in the emergency department, she was hospitalized because of the risk of suicide. On hospitalization, physical and neurological examinations, complete blood count, analysis of blood chemistry, urinalysis, and urine toxicology screening were performed to rule out any psychiatric condition due to general health problems or substance use. Electrocardiogram (ECG) was also carried out. No abnormalities were detected in physical examination and ECG. Blood ferritin and folate levels were detected low, and during hospitalization, oral iron and folate replacement was done. In neurological examination, there were no abnormal findings apart from motor tics of upper extremities with low intensity.

In the mental status examination, she was conscious and cooperative. She was oriented to person, place, and time. She was willing for the psychiatric interview and establishing eye contact. Her self-care was slightly decreased. Her speech was spontaneous and in the normal range in terms of amount and speed. Her mood was dysphoric, and her affect was anxious and congruent with mood. She was crying, especially when talking about her suicidal thoughts. Throughout the psychiatric interview, her thought process was linear, organized, and goal-directed. In thought content, no delusions, obsessions, and overvalued ideas were detected, but there were suicidal thoughts. No compulsions were encountered. From time to time, she had abnormal perceptions such as auditory hallucinations experienced as "whisperings" or "voices that order me not to tell anyone that I hear them," visual hallucinations experienced as "indistinguishable but somehow horrifying faces," auditory illusions experienced as hearing people's voices hoarse, and finally visual illusions as seeing people's faces twisted. There were no perceptional abnormalities in other modalities and no dissociative symptoms. Her reasoning and abstraction were normal. Her attention, concentration, and memory were normal. Her linguistic capacity and calculation were not impaired. She had a nearly full insight.

In light of her psychiatric history and examination, she was diagnosed with tic disorder (Tourette's disorder) and brief psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. At the time of attendance at our hospital, she was experiencing the fore-mentioned psychotic symptoms and psychotic anxiety. As she had an oculogyric crisis history with haloperidol, primarily, aripiprazole was thought to be given as an agent that is beneficial both for TS and psychotic symptoms; however, since she was also experiencing overwhelming anxiety symptoms, treatment was initiated with 300 mg/day quetiapine instant release (IR formulation) in three divided doses. Because this was the first psychotic episode, to rule out any neurological disorder, cranial magnetic resonance imaging and electroencephalography were carried out, and neurology consultation was requested. No neuropathologies were found. She was followed with this treatment, and after the 10th day of her hospitalization, no psychotic symptoms remained. She was prescribed 300 mg/day quetiapine IR in three divided doses and discharged from the hospital.

Discussion

In the presence of TS, psychosis is not the first comorbidity that comes to mind; however, especially with comorbid OCD that may present with overvalued ideas, psychotic disorders might go unnoticed particularly in the absence of hallucinations. Being aware of psychotic disorders in the course of TS is of great importance in terms of prognosis. Accordingly, Takeuchi *et al*. state that TS and psychotic disorders have common clinical and biochemical properties and similar pathophysiology; thus, they might be seen together.[13,15]

Since antipsychotics are used extensively in the management of TS, after cessation of these agents rebound, psychosis may be seen.[11,16,17] Furthermore, there are studies in the literature that express usage of these agents might even mask possible underlying psychotic symptoms.[13] Both rebound psychosis and the comorbid psychotic disorders supervene on tics.[12,15]

It is well demonstrated that second-generation antipsychotics are the most beneficial drugs in the treatment of TS.[3] Evidence also supports quetiapine use, although relatively less robustly.[3] The case we present herewith suggests that quetiapine is a suitable choice as it ameliorates both the anxiety symptoms in the acute period and the psychotic symptoms in the course of TS, but further research in this area is needed.

Conclusion

In the literature, it is stated that psychotic symptoms are seen in patients with TS more prevalently than in the general population. Keeping this in mind, patients with TS should be examined for possible psychotic symptoms as these symptoms both necessitate the usage of antipsychotics instead of alpha-2 agonists, which are the first-line agents in the treatment of TS, and complicate the clinical picture. Tics in TS may generate anxiety and psychosis that may further aggravate the symptoms. Quetiapine should be considered in the treatment, particularly in this condition.

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Author contribution subject and rate

- Onur Toktamış (%40): Contributed with literature research, writing of manuscript and treatment of patient
- Cansu Çakır Şen (%30): Contributed with comments on manuscript and treatment of patient
- Nesrin Buket Tomruk (%30): Contributed with comments on manuscript and treatment of patient.

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Research Article

The Effect of Child-Centered Play Therapy on Children with Anger Control Problems is true

Afra Ahbab[1], Büşra Özdoğan[1], Gökben Hızlı Sayar[1]

[1]Department of Clinical Psychology, Institute of Social Sciences, Üsküdar University, Istanbul, Turkey

Abstract

Background: Children's anger and aggressive behaviors become a problem for teachers and parents at home, in the classroom, or the playground. Pharmacological and psychotherapeutic approaches are recommended for children who cannot control their anger. Child-centered play therapy is one of these approaches. **Aim:** This study aimed to reveal the effect of child-centered play therapy on children with anger issues. **Materials and Methods:** The study group consists of 25 volunteer child clients with anger symptoms, and the control group consists of 25 volunteer child clients without anger symptoms. Each participant was given child-centered play therapy with 45-min sessions twice a week for 3 weeks during the research process. The Trait Anger-Anger Style Scale was administered to the participants before and after the therapy. **Results:** As a result of the study, it was shown that children with anger issues experienced a significant change and improved after child-centered play therapy. Children have become able to control their anger. At the same time, improvement was observed in the verbal and behavioral expression of anger. **Conclusion:** The results of this study indicate that child-centered play therapy can be an effective treatment option for children with anger issues and aggressive behaviors.

Keywords: *Anger, anger control, anger style scale, child-centered play therapy*

Introduction

Anger is an emotional response that individuals give when frustrated, disappointed, or unmet needs or wants. However, when anger cannot be controlled, it causes many negative consequences for both the individual and society.[1] Children's anger and aggressive behaviors become a problem for teachers and parents at home, in the classroom, or the playground.[2] Pharmacological and psychotherapeutic approaches are recommended for children who cannot control their anger.[3] One of the psychotherapeutic approaches is child-centered play therapy. Child-centered play therapy aims to help children with emotional and behavioral problems. The therapist accepts the child and the child's play unconditionally and empathizes with the child while following the principles of safety and structure.[4] This therapy does not aim to change or control the child. In this approach, the aim is to make the child become aware of his own behavior and to allow himself to be managed. The therapist relies on the child and his or her resources for change in therapy. The child uses this relationship between the therapist and the client to grow and develop.[5] In the literature, there are studies investigating the effect of Child-Centered Play Therapy on behavioral and psychological problems in children. In Teber's study, Child-centered Play Therapy has been identified as anxiety, depression, social introversion, somatic complaints, breaking the rules, aggressive behaviors, social problems, thought problems, attention problems, heavy cognitive tempo, posttraumatic stress problems, obsessive-compulsive problems. It has been found to be effective in areas that are described as psychological problems.[6] There are other studies showing that child-centered play therapy reduces anxiety/depression scores.[7,8]

In the literature, research has been done on the effects of child-centered play therapy on anxious children, its comparison with other types of play therapy, its application

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Orcid
Afra Ahbab: {ORCID: 0000-0002-6003-5745}
Büşra Özdoğan {ORCID: 0000-0002-2449-9147}
Gökben Hızlı Sayar {ORCID: 0000-0002-2514-5682}

Address for correspondence:
Dr. Gökben Hızlı Sayar, Üsküdar University- Altunizade Üsküdar, İstanbul, Turkey.
E-mail: gokben.hizlisayar@uskudar.edu.tr

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in developmental disorders. However, the effect of child-centered play therapy on children with anger issues has not been investigated. This study aims to reveal the effect of child-centered play therapy on children with anger issues.

Materials and Methods

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (61351342-/2019-353).

The sample of this quasi-study and retrospective study, which examines the effectiveness of child-centered play therapy in children with anger issues, consists of 50 child clients aged 5–12 years who applied to the Aura Psychology and Counseling Center in Istanbul. The study group consists of 25 volunteer child clients with anger symptoms, and the control group consists of 25 volunteer child clients without anger symptoms. The criteria for inclusion in the study in the study group were not to have any neurological or physical disorders, have an anger problem, and be between the ages of 5–12. The criteria for inclusion in the study in the control group were not to have any neurological or physical disorders, not to have anger issues, and to be 5–12-year-old.

Each participant was given child-centered play therapy with 45-min sessions twice a week for 3 weeks during the research process. During the research, supervision support was received regarding therapeutic functioning. The Trait Anger-Anger Style Scale was administered to the participants before and after the therapy. The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (61351342-/2019-353).

Data collection tools

Sociodemographic Data Form: In this form, parents are first asked questions about their children's name, age, and gender, and then parents are asked to obtain sociodemographic information.

Trait anger-anger expression style scale

The scale was adapted to Turkish, and its reliability and validity studies were conducted.[9] The scale consists of three subscales and is evaluated with a four-point Likert type, consisting of 34 items. In this scale, the expressions suitable for the person himself/herself, "How much does it describe you?" In order to answer the question, they are asked to tick one of the options "Not at all," "Somewhat," "Quite much," and "Totally." "Does not describe at all" receives 1 point, "Describes somewhat" receives 2 points, "Quite describes" receives 3 points, and "Describes completely" receives 4 points. Anger control subscale scores are obtained by summing the scores of items 11, 14, 18, 21, 25, 28, 30, and 34; The anger in subscale score is calculated by adding the scores of items 13, 15, 16, 20, 23, 26, 27 and 31. The anger out subscale score is calculated by adding the scores of items 12, 17, 19, 22, 24, 29, 32, and 33. Obtained by collecting.[10]

Table 1: Statistical comparison of the children's scores in the study group before and after child-centered play therapy

Children with anger ıssues (study group)					
	Mean	*n*	SD	Standard error	*P*
Trait anger scale					
Before therapy	33.56	25	2.844	0.569	0.0001
After therapy	13.40	25	2.160	0.432	
Anger control subscale					
Before therapy	12.08	25	2.397	0.479	0.0001
After therapy	22.08	25	3.628	0.726	
Anger control subscale score					
Before therapy	12.00	25	2.363	0.473	0.0001
After therapy	21.68	25	3.544	0.709	
Anger out subscale score					
Before therapy	25.72	25	3.781	0.756	0.0001
After therapy	13.08	25	2.676	0.535	

Values with $P<0.05$ were considered statistically significant.
SD: Standard deviation, SE: Standard error

Table 2: Statistical comparison of the scores of the children in the control group before and after child-centered play therapy

Control group					
	Mean	*n*	SD	SE	*P*
Trait anger scale					
Before therapy	11.64	25	1.777	0.355	0.001
After therapy	10.52	25	0.823	0.165	
Anger control subscale					
Before therapy	28.40	25	1.633	0.327	0.0001
After therapy	30.80	25	1.291	0.258	
Anger control subscale score					
Before therapy	28.16	25	1.519	0.304	0.0001
After therapy	30.16	25	1.405	0.281	
Anger out subscale score					
Before therapy	9.24	25	1.332	0.266	0.007
After therapy	8.60	25	0.913	0.183	

Values with $P<0.05$ were considered statistically significant.
SD: Standard deviation, SE: Standard error

Statistical analysis

IBM SPSS Statistics 17.0 (IBM Corp. Released. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). The *t*-test was used in the analysis of normally distributed measurement data. A dependent-Paired Sample *t*-test was applied in the comparison before and after therapy within the same group. While comparing the parameters of both groups, matches were made, and Independent Samples (Student's) *t*-test was applied. $P < 0.05$ was accepted as a statistical significance level.

Table 3: Comparison of trait anger scale (first 10 items) scores between control and study groups

	Trait anger scale (10 items)				
	Mean	***n***	**SD**	**SE**	***P***
Before therapy					
Control group	11.64	25	1.777	0.355	0.006
Study group	33.56	25	2.844	0.569	
After therapy					
Control group	10.52	25	0.823	0.165	0.002
Study group	13.40	25	2.160	0.432	

Values with P<0.05 were considered statistically significant.
SD: Standard deviation, SE: Standard error

Results

A total of 50 people, 8 girls and 17 boys (n = 25) in the study group (children with anger issues) and 15 girls and 10 boys (n = 25) in the control group, participated in the research. The age range of the study and control groups was 5–12; the mean age was 8.44 ± 1.08 for the study group and 8.12 ± 1.12 for the control group. When the marital status of the parents (married/divorced) was examined, it was seen that they were in the study group (married n = 19, divorced n = 6) and in the control group (married n = 25). When it was asked whether there were individuals with anger issues in their families, it was observed that the study group (present n = 24, no n = 1) and the control group (present n = 3, no n = 22). Statistical comparison of the children's scores in the study group and the control group before and after child-centered play therapy are given in Table 1, 2 and 3.

Discussion

In this study, the effect of child-centered play therapy on the anger problem of children aged 5–12 was investigated. The Trait Anger-Anger Style Scale was applied to the children before and after the therapy, and the effectiveness of the therapy was investigated.

In this study, when the parents' marital status (married/divorced) was examined, it was determined that the scores of the children whose parents were divorced and who had anger issues from the Trait Anger-Anger Style Scale were statistically significant significantly different from the control group. The most common emotions in children going through a family divorce process are anger, fear, anxiety, and guilt.[11,12] In this study, it was seen that the anger issue is severe in children of divorced parents. In this study, it is seen that the family anger issues are severe in the families of the children in the group with anger issues. It can be said that this situation causes constant anger issues in children. It has been stated that children express their anger when their emotions are triggered by internal or external events under certain conditions.[13] Studies have observed that parental attitudes and emotions strongly cause children's anger issues.[14] In the literature, child-centered play therapy has proven to be an effective intervention to support the recovery of children who have been exposed to domestic violence, and it is an appropriate approach to treatment.[15-19]

This study determined a statistically significant decrease in the scores of the children with anger issues in the study group from the Trait Anger-Anger Style Scale before and after child-centered play therapy. Child-centered play therapy is a developmentally appropriate method that allows children to express a wide variety of emotional expressions, including anger, that can be used effectively to regain their sense of control and empowerment in their lives.[17,20] The fact that a significant change was observed in angry children after child-centered play therapy in our study reveals the effectiveness of this therapy. This study also observed that child-centered play therapy improved the way children with anger issues reflected their emotions and behaviors. When the anger control subscale results were examined, a statistically significant increase was observed in the values of children with anger issues before and after child-centered play therapy. This finding shows that children can control their anger after therapy. In their study, Perryman and Bowers examined the effectiveness of child-centered play therapy on four different types of behavior (task distribution, behavior control, assertiveness, and social ability).[21] As a result, it was observed that child-centered play therapy effectively affected children's emotions and social behaviors. In this study, when the Anger-Out Sub-Scale was examined, the decrease in children's values with anger issues after child-centered play therapy indicates an improvement in children's verbal and behavioral expression of anger. In the study of Ray *et al*., it was observed that child-centered play therapy caused improvement in children with aggressive behavior.[22]

In this study, it was determined that there was a statistically significant decrease in the scores of the children in the control group from the Trait Anger Style Scale before and after child-centered play therapy. This finding shows that child-centered play therapy has a curative effect even in children without anger issues. According to the anger control subscale comparison results, a statistically significant increase was observed in the children's values in the control group before and after child-centered play therapy. This finding shows that the children in the control group were able to control their emotions better. In the comparison results of the anger inside subscale, an increase was observed in the pre- and post-therapy values of the children in the control group, and a significant decrease was observed in the anger-out subscale. Studies in the literature have shown that child-centered play therapy is an effective tool for treating internalization and externalization problems.[23,24] In the literature, there are also studies in which children who experience emotional difficulties after child-centered play therapy show improvement, but the curative effect is not seen in the control group.[25]

However, in a study examining the effect of child-centered play therapy on primary school children with and without aggressive behavior, it was found that there was an improvement in aggressive behavior in both groups.[22]

When the Trait Anger Scale, Anger Control Sub-Scale, Anger Inside Sub-Scale, and Anger-Out Sub-Scale data were compared in the control and study groups, there was a statistically significant difference in the values of the control group and children with anger issues before the therapy. At the same time, this scale was found in children with anger issues after therapy. Values were found to be close to control values. However, the difference between the control group and children with anger issues is still statistically significant. It has been stated that child-centered play therapy is a developmentally appropriate intervention method that focuses on the relationship between play therapists and children and supports children's ability to solve problems using their innate potential for self-direction and growth.[23,26] Studies in the literature have shown that play therapy has beneficial effects in the short and long term.[27] This study showed that children with anger issues experienced a significant change and improved after child-centered play therapy.

Conclusion

In this study, the effect of child-centered play therapy on the anger problem of children in the 5–12 age group was examined. The Trait Anger-Anger Style Scale was applied to the children before and after the therapy, and the effectiveness of the therapy was investigated. As a result of the study, it was shown that children with anger issues experienced a significant change and improved. Improvement was observed in the verbal and behavioral expression of anger and the ability to control anger.

This research has some limitations. This study needs to be repeated with a larger sample group. Thus, it can be shown that child-centered play therapy is a proven intervention for children with anger issues and aggressive behaviors. In future research, studies can be conducted in which different types of play therapy are compared within themselves. In this way, it can be revealed which types of play therapy are more effective in child psychopathology.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (61351342-/2019-353).

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There are no conflicts of interest.

Author contribution subject and rate

- Afra Ahbab (50%): Design the research, data collection, and analyses and contributed with comments on research design and manuscript.
- Büşra Özdoğan (30%): Design the research, data collection, analyses, and wrote the whole manuscript, contributed with comments on research design and manuscript.
- Gökben Hızlı Sayar (20%): Supervised the research, contributed with comments on research design and manuscript.

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Women with Epilepsy in Reproductive Age Years and Requisite Psychosocial Management Strategies

Dear Editor,

Epilepsy is the second-most prevalent neurological illness, and it places a significant strain on those who suffer from it, their families, and health-care systems.[1] According to the World Health Organization, epilepsy affects over 50 million people worldwide, with 80%of those living in low-and middle-income nations suffering from it.[2] Epilepsy was found to be present in 0.4% of people aged 30–39 years in India.[3] The neurologists preferred the mode of intervention for the treatment of epilepsy is typically pharmaceutical. Women with epilepsy (WwE) face additional and unique obstacles compared to men, including sexual development, sexuality, menstruation, fertility, pregnancy, breastfeeding, mother–baby interactions, and menopause.[4] As a result, compared to other chronic illnesses, WwE in reproductive age years would require additional care and psychosocial (PS) management. In this context, there is a scarcity of health-care experts such as medical social workers, clinical psychologists, and counselors who can assess PS concerns and provide tailored PS management is critical. Health-care professionals play an important role in providing PS interventions to patients and their families to improve their quality of life by changing their knowledge, attitude, and practice regarding the illness and its treatment.[5]

Given the particular nature of PS issues among WwE in reproductive years, there is a need to look beyond symptomatology and illness while providing care. Poor knowledge about the illness, concerns about marriage, sexuality, pregnancy, pregnancy outcomes, breastfeeding, childbearing practices, taking and continuing antiepileptic drugs (AEDs), side effects of AEDs, AEDs management, polytherapy, stigma, myths and misconceptions about the illness, delivery-related concerns, offspring health condition, and family pressure to stop AEDs, are the most commonly encountered PS issues among WwE in reproductive years. The tailored PS interventions would address the aforementioned PS issues to improve WwE's quality of life. Individuals (WwE), families (caregivers, spouses, family of origin, and family of procreation), and communities should all be targeted for PS interventions. Female counselors (if needed), maintaining privacy and secrecy, interview room circumstances, and WwE language are just a few of the variables to consider for a successful conclusion.

Counselors should be available at all primary health-care clinics, district hospitals, and private hospitals for discussions about the PS concerns that affect women during their reproductive years. Sensitizing health-care professionals involved in the management of epilepsy (neurologists, gynecologists, medical social workers, and counselors) about the various PS issues and the impact of providing PS interventions timely on quality of life among WwE in reproductive years will also need to be considered. The importance of PS variables on WwE illness, treatment, recovery, and outcomes is particularly

Table 1: Psychosocial interventions for women with epilepsy in reproductive age years

Individual level	Family level	Community level
Psychoeducation about the epilepsy, management to promote the knowledge, attitude, and practice	Psychoeducation about the epilepsy to promote the knowledge, attitude, and practice	Conducting the awareness camps, workshops to promote the knowledge, and management of epilepsy
Supportive psychotherapy to ventilate the WwE psychosocial issues	Importance of drug adherence, treatment adherence	Conducting webinars with neurologists and other health-care professionals to understand the unique psychosocial issues of WwE
Providing counseling to address their myths and misconceptions	Supportive psychotherapy to ventilate the WwE psychosocial issues	Referrals to the gynecologist or other required medical care professionals
Disclosing about the illness before the marriage	Providing counseling to address their myths and misconceptions	Conducting programs at district hospitals to the health-care teams
Explaining the importance of continuation of AEDs and not taking own decision	Disclosing about the illness before the marriage	Developing and distributing the information booklets leaflets to the WwE and their caregivers, other paramedical professionals
Pre and postconceptual counseling	Importance of spouse, in-laws support, especially during pregnancy and understanding of the WwE	Initiating the peer support groups
Teaching healthy coping skills		
Marital counseling		
Importance of timely and open communications about their concerns with the neurologists or counselors or social workers		

AEDs: Antiepileptic drugs, WwE: Women with epilepsy

Ethics committee approval: There is no need for ethics committee approval.

important for neurologists. A social worker who focuses on the biopsychosocial factors which are contributing toward the maintaining of the illness behavior and consequences of it. To identify interrelated factors associated with the issues of WwE and make a tailor-made intervention to address the concerns related to it for the management of illness and their well-being. Early identification of the PS issues and addressing their issues by providing timely tailor-made interventions would benefit WwE and enhance their quality of life. The list of required PS interventions has mentioned in Table 1.

Patient informed consent

There is no need for patient informed consent.

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- Srikanth Pallerla (25%): Contributed to writing a manuscript draft, literature search
- Vranda Mysore Narasimha (25%): Contributed to writing a manuscript draft, review of the manuscript
- Priya Treesa Thomas (25%): Contributed to writing a manuscript draft, review of the manuscript
- Raghvendra Kenchaiah (25%): Contributed to the review and content of the manuscript.

Pallerla Srikanth[1], Mysore Narasimha Vranda[2], Priya Treesa Thomas[3], Kenchaiah Raghvendra[4]

[1]PhD Scholar, [2]Additional Professor, [3]Associate Professor, Department of Psychiatric Social Work, [4]Assistant Professor, Department of Neurology, NIMHANS, Bengaluru, India

Address for correspondence:
Dr. Mysore Narasimha Vranda, Department of Psychiatric Social Work, National Institute of Mental Health And Neuro Sciences, Institute of National Importance, Bengaluru - 560 029, Karnataka, India.
E-mail: vrandamn@nimhans.ac.in

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Orcid
Srikanth Pallerla
{ORCID: 0000-0001-7513-8264},
Vranda Mysore Narasimha
{ORCID: 0000-0002-8456-5468}
Priya Treesa Thomas
{ORCID: 0000-0003-2421-7303}
Raghvendra Kenchaiah
{ORCID: 0000-0002-3984-0379}

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