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Review Article

Brain and Behavior: Evidences of Neuroimaging and Neuropsychological Testing in Alzheimer's Disease Pathology

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ABSTRACT

The impairment in cognitive functions is an important indicator in neurodegenerative disease. Both in-vitro and in vivo studies indicates that various neurochemical activities in the brain seems to play an important role in the disease etiology. Along with neuroimaging, neuropsychological tests are done to identify the nature of cognitive deficits. These are performance-based measures of individual's cognitive capacities. Studying brain region-specific alteration of these neurochemicals along with specific neuropsychological tests in can provide an insight towards diagnosis, progression pattern, response towards treatment functional potential and prognosis. This article aims to highlight the importance ofneuropsychological testing in neurodegeneration as strong diagnostic indicator collaborating the literaturebased findingswith different neuroimaging techniques.

Keywords:*Neuropsychology, Neuroimaging, Neurodegeneration, Cognitive impairment, Alzheimer'sDisease*

HIGHLIGHTS

- Neuroimaging techniques can quantify changes in neurometabolites in brain diseases.
- Neuropsychological tests provide cognitive profile to understand brain deficits.
- Brain Autopsy and In vivo studies of neurodegenerative diseases are discussed.
- Correlation indicated an early predictive model of cognitive decline in AD.
- These changes are also seen in different psychiatric disorders.

INTRODUCTION

In the modern era of technological advancements human life expectancy has significantly increased due to several factors like education, income, advanced healthcare facilities(Mathers et al., 2015). Old age-related problems are increasing in number with all these advances. Dementia as one of the geriatric diseases affecting millions of people bringing negative consequences to patients as well as family members as caregiver's burden, affecting emotional wellbeing and quality of life worldwide making it a pressing issue that needs to be addressed(Mohamed et al., 2010).

The numbers of cases of Alzheimer's disease (AD) are increasing exponentially as more than half cases of dementia are diagnosed as AD(Garre-Olmo, 2018), characterized by cerebral atrophy caused by microscopic changes as amyloid plaques and neurofibrillary tangles(Terry et al., 1964).Researches are going on find the diagnostic markers for these neurodegenerative diseases(Liu et al., 2022; Mandal et al., 2022a, 2022b).Alongside various advanced brain mapping techniques, neuropsychological assessments have proved toplay an important part in the early identification ofsigns &symptoms and ensuring the timely diagnosis so that it could lead to better outcome for patients with neurodegenerative conditions(Pasquier, 1999).

Various structural and chemical changes occur in the neurodegenerative disease. These changes might lead to change in brain functionality which is represented by impairment in many aspects of behavior. Brain mapping and imaging techniques can be highly beneficial tools for predicting changes in specific brain areas in neurodegenerative conditions. However, due to limited accessibility to these techniques and the high cost of administration, neuropsychological tests can provide a useful alternative for initial screening and detailed analysis of brain functioning. While brain mapping and imaging techniques remain an important diagnostic tool, neuropsychological tests can play a critical role in the comprehensive assessment and management of neurodegenerative conditions. Structural aspects of brain are studied widely however efficacy of neuropsychological testes in relation to a deeper level i.e., relating to brain neurochemistry has not been explored in detail. This article provides insight that how neuropsychological tests are of importance by takingliterature evidencesand correlating the findings with neurochemical functioning in neurodegeneration, especially in AD,which ultimately can be used for neuro-rehabilitation.

Brain Neurochemistry in various psychiatric disorders:

Inter neuronal communication primarily occurs by electrical and chemical transmission. The two differs in the mode of transmission. In electrical transmission the current flows through gap junctions whereas in chemical transmission major role is played by several neurotransmitters which binds to receptors and facilitate

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the communication process (Pereda, 2014). Each neurotransmitter directly or indirectly is linked with regulation of human behavior as they act on specific sites of brain which are responsible for their respective behaviors. Different neurological and psychiatric disorders are linked with altered functioning of neurochemicals in various brain regions (Table 1). This alteration in neurochemicals can lead to significant contribution towards pathology. It is important to look for such changes that helps in the identification of various biomarkers in various neuropsychiatric illnesses.

Table 1: Various neurochemicals involved in various psychiatric and neurological disorders

Disorders	***Major Brain Regions involved***	***Neurochemicals and neurotransmitters***
Alzheimer's Disease	• Medial temporal lobe (MTL) • Hippocampus • Parahippocampalgyrus (Kesslak et al., 1991)	• Acetylcholine • Glutamate • γ-Aminobutyric acid (GABA) • N-Acetylaspartate (NAA) • Serotonin(Kristensen, 1990)
Parkinson's Disease	• Substantia nigra • Basal ganglia (Lees et al., 2009)	• Lack of dopamine • The alterations in cholinergic, adrenergic, serotoninergic and peptidergic systems (Pascual & Misiego, 1997).
Schizophrenia	• Prefrontal lobe • MTL (Karlsgodt et al., 2010)	• Dopamine (Guillin et al., 2007) • Serotonin excess as a cause of both positive and negative symptoms in schizophrenia (Woolley & Shaw, 1954) • A selective neuronal degeneration within the norepinephrine reward neural system has been hypothesized for the occurrence of anhedonia (Wise, 2008). • GABA-ergic dysfunction (de Jonge et al., 2017). • Acetylcholine (ACh) and Nicotine (Martin & Freedman, 2007)
Mood Disorders	• Medial and caudolateral orbital cortex • Amygdala • Hippocampus, • Ventromedial parts of the basal ganglia,	• The activity of catecholamines (norepinephrine and dopamine) is too high or low. Elevated levels are associated with mania and diminished levels with depression (Lambert et al., 2000). • Norepinephrine: Down regulation or decreased sensitivity of β-adrenergic receptors (Pandey et al., 1985). • Dopamine: Mesolimbic dopamine pathway are dysfunctional in depression (Nestler & Carlezon, 2006). • CSF is the major metabolite of Dopamine, homovalllinic acid is elevated in mania (Swann et al., 1983). • Deficiency in serotonin activity in both mania and depression (Moncrieff et al., 2022). • Reductions in GABA levels (Petty, 1995). • Adrenergic cholinergic disbalance (Fritze, 1993).
Panic Disorder	• Brainstem • Limbic system • Prefrontal cortex. (Sobanski & Wagner, 2017)	• Low levels of GABA (Goddard et al., 2001). • Cardiovascular symptoms of panic can be triggered by Noradrenergic activity within various brain areas (Gorman & Sloan, 2000).
OCD	• Prefrontal cortex • Basal ganglia, • Thalamus (Huey et al., 2008)	• Dysregulation of serotonin (Pigott, 1996). • Involvement of norepinephrine (Dell'Osso et al., 2006).
ASD	• Cerebellum • Frontal cortex • Amygdala (Donovan & Basson, 2017)	• Elevated platelet serotonin (5- HT), and mTOR (Veenstra-VanderWeele & Blakely, 2012).
ADHD	• Prefrontal cortex • Basal ganglia • Cerebellum (Curatolo et al., 2010)	• Involvement of dopaminergic and adrenergic systems (Levy, 1991).

Neuropsychology and Neuroimaging in neurodegeneration:

Neuropsychology is a specialized branch of psychology which deals with brain–behavior relationships. Introduction of scientific methods in psychology led towards the origin of psychological testing William James hypothesized for more empirical based research for mental processes in his functionalistic viewpoints. This effort led towards development of more scientific methods to study psychology (Stebbins, 2007). Lashley, Halstead and Luria further contributed towards the basis for neuropsychology as a specialized function to assess brain lateralization and localization functions (Stebbins, 2007). These tests or batteries are used for evaluation of cognitive functions to target any pathology or insult to the brain and impairment related to severe mental illnesses. This functional assessment helped in identifying abnormal behavior related to brain changes in different disorders through paper pencil based tests. These tests are performance-based tests specialized in assessing different cognitive domains like memory, executive functioning, decision making etc.

Various neuropsychological tests provide information about diagnosis, areas and level of cognitive impairment, pattern of disease progression, response towards treatment, functional potential and prognosis.Detailed neuropsychological assessments provide a panoramic view for the cognitive deficits. Also these can prove valuable in initial stages of disease which is important for early identification of various diseases such as of AD. Studies have highlighted the efficacy of Tests like Mini mental status examination (MMSE) (Folstein et al., 1975), Clock Drawing test (CDT)(Wolf-Klein et al., 1989), Trail making tests (TMTs) (Ashendorf et al., 2008). These tests assesses the possibility of any cognitive deficits and thus has the ability to be used as screening tools.

Structural and functional brain impairment are important indicators in various disorders. There are many changes that occur in different psychiatric, neurological, neurodevelopmental another medical conditions. With detailed information about cognitive capacity and brain functioning of an individual, these tests are helpful in eliciting pathognomonic signs. For disorders like depression, anxiety, personality disorders, alcohol and substance abuse, developmental disorders etc. with behavioral symptoms clinical interview and psychological assessments act as key diagnostic indicator. However, in specific neurological disorders like AD, it become important to do understand various neuroimaging technique and their specific functionality towards diagnosis. Neuroimaging methods can be of invasive and noninvasive in nature. Invasive approaches involve stimulating the targeted brain area by inserting some chemical compound in the body. In contrast noninvasive methods do not use any external agentto enter in the body to stimulate are of interest. These techniques study brain regions majorly in three different aspects i.e. structural, functional and neurochemical. Structural aspects represent anatomical study of brain which gives details about location of various brain regions and changes. For e.g. cerebral atrophy which a major change in AD can be seen through volumetric magnetic resonance Imaging (MRI)(Scahill et al., 2002). Functional techniques try to assess the brain regions which are involved in different body functioning. Electroencephalogram (EEG) can map brain electrical signals, functional MRI (fMRI) which identifies functional changes through blood flow and metabolic activity in brain region (Glover, 2011). Newer research tool is magnetic resonance spectroscopy (MRS) which identifies neurochemistry and detects presences of neurochemicals in various brain region in healthy and disease conditions. For e.g., changes NAA concentration in hippocampus is detected in AD(Schuff et al., 2006). Figure 1 represents a detailed flowchart of several neuroimaging techniques along with list of major cognitive areas that are measured by neuropsychological tests.

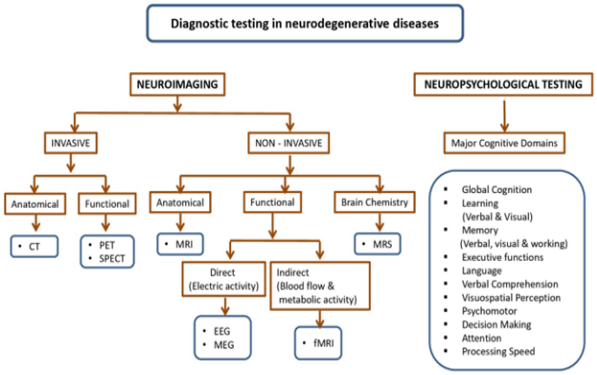

Figure 1. Details of various techniques of neuroimaging and neuropsychological testing used for diagnosis making in different types of neurodegenerative diseases.

CT=Computerized Tomography; PET=Positron Emission Tomography; SPECT= Single-Photon Emission Computerized Tomography; EEG=Electroencephalogram; MEG = Magnetoencephalography, fMRI = functional MRI, MRS = Magnetic resonance spectroscopy

Diseases where neuropsychological testing has advantage over other methods including neuroimaging as clinical features have significant behavioral symptoms. These tests help in identifying underlying disease much before the actual functional impairment so that an early diagnosis can be made. In psychiatric disorders testing provides important information as for disorders like depression, personality,developmental disorders where no set imaging biomarkers are available. In neurological disorders like Dementia, Parkinson's disease (PD), traumatic brain injuries (TBI)

and in case of tumors where neuroimaging markers are quite sensitive, psychological testing helps in determining brain changes as it gives confidence in making early diagnosis and further rehabilitation strategies can be applied.

Evidence from literature:

Neuroimaging is widely used in diagnosing neurodegenerative diseases like AD and PD. Neurobiological boundaries remain unclear in psychiatric disease like schizophrenia,schizoaffective and bipolar disorders(Kloppel et al., 2012). Braun et al. (2011) highlighted importance of assessments in neurological,neurodevelopmental, medical and psychiatric disorder. Various studies have also proved that there is much need of research in field of neuroimaging to set and validate biomarkers in different mental illnesses. However most of these studies provide evidence about utility of neuropsychological tests.

Table 1: Relationship of various neuroimaging modalities and neuropsychological tests in AD.

S.No.		Sample	Imaging Method	Area of study	Imaging and Neuropsychological tests correlation results
1.	(Waragai et al., 2017)	289 subjects	MRI and ^{1}H MRS	PCC	▪ Significant positive correlation of MMSE scores with the NAA/MI ratio. ▪ MMSE scores showed negative correlation with the MI/Cr ratio ▪ No correlation with the NAA/Cr ratio.
2.	(Duff et al., 2018)	17 MCI 8 HC	MRI	Hippocampal volumes	▪ Hippocampal volume was positively correlated with Brief Visuospatial Memory Test – Revised (BVMT-R) and Hopkins Verbal Learning Test – Revised (HVLT-R) (Total &Delayed Recall). ▪ Hippocampal volume was negatively correlated with Trail Making Test- B.
3.	(Riese et al., 2015)	21 HC and 15 aMCI	MRS	PCC	▪ GABA, Glx, and NAA levels were found to be correlated to positively to CERAD word learning scores.
4.	(Zhu et al., 2015)	28 aMCI and 24 V-MCI 34 HC	^{1}H-MRS	left frontal lobe, left basal ganglia and left hippocampus.	▪ Positive correlation betweenCAMCOG-C (in recent memory domain in and NAA/Cr ratio measured in the brain region of left hippocampus in A-MCI group. ▪ NAA/Cr ratio and frontal lobe were also found to be positively correlated with CAMCOG- Cin various domains like praxis, orientation, language, language comprehension in V-MCI group.
5.	(Watanabe et al., 2012)	54 HC, 42 aMCI and 67 AD.	MRI,^{1}H-MRS	Bilateral hippocampi and PCG	▪ Apositive correlation was found between NAA concentration in left hippocampus cognitive domains of verbal, visual and general memory, attention and concentration, delayed recall, logical memory 1, verbal paired memory 1, visual paired memory 2, and verbal paired memory ▪ NAA conc. in right hippocampus was also positively related with verbal and general memory. ▪ However the MI concentration in left hippocampus were significantly negatively correlated with verbal, logical and general memory, delayed recall, verbal paired memory , visual paired memory and visual reproduction. ▪ Right hippocampal MI concentration was also negatively correlated with verbal, logical memory 1, visual reproduction 1, digit span, and visual reproduction in WMS - R.
6.	(Oeltzschner et al., 2019)	13HC and 13 MCI	MRS, Beta amyloid PET,		▪ mI/tCr in ACC and PCC was negatively correlated with MMSE test. ▪ D-KEFS scores had a positive correlation with GSH/tCr in the PCC ▪ Glu/tCr and NAA/tCr were having positive correlation with CVLT scores and these scores were negatively correlated with mI/tCr.
7.	(Jessen et al., 2001)	13 AD	MRS	MTL	▪ A decrease in MMSE scores was corelated with decline in NAA/Cr ratios in MTL. ▪ NAA/Cr negatively correlated with cognitive part of AD Assessment scale (ADAS – Cog)
8.	(Kantarci et al., 2002)	67 HC, 18 MCI and 33 AD	^{1}H MRS	Posterior cingulate gyri	▪ Positive correlation between Dementia Rating Scale Total and NAA/Cr. ▪ Auditory Verbal learning test was not associated

S.No.		Sample	Imaging Method	Area of study	Imaging and Neuropsychological tests correlation results
					with any of the ^{1}HMRS metabolite ratios.
9.	(Lee et al., 2007)	29 AD & 15 HC	^{1}H MRS	PCC	▪ Naa/Cr ratio had a positive correlation with MMSE scores ▪ mI/Naa ration was negatively correlated with MMSE scores. ▪ The mI/Cr ratio showed no correlation with scores of MMSE.
10.	(Zhang et al., 2009)	13 AD, 9 MCI and 13 HC	^{1}H MRS, apparent diffusion coefficient (ADC)	The hippocampus and the temporoparietal region	▪ Decrease of NAA/Cr and phosphocreatine (NAA/Cr) was correlated with decrease in MMSEscore. ▪ Myoinositol/Cr (mI/ Cr) and the MMSE score were found to be negatively correlated.
11.	(Zimny et al., 2011)	30 AD, 23 aMCI and 15 HC	MRI, H-MRS, PWI,DTI	Posterior cingulate region	▪ NAA/Cr ratio was positively correlated with MMSE scores. ▪ NAA/Cr was negatively correlated with scores on CDR. ▪ mI/NAA was negatively correlated with MMSE and significantly positively correlated with CDR score. ▪ mI/Cho was negatively correlated with MMSE scores. ▪ mean FA was significantly positively correlated with MMSE and negatively correlated with CDR.
12.	(Lim et al., 2012)	23 HC, 36 AD and 19aMCI	MRS	Anterior and posterior cingulate gyri	▪ Negative correlation was seen between mI/Cr of the posterior cingulate gyrus with the scores of MMSE. ▪ The mI/Cr of the anterior cingulate gyrus found to be positively correlated with the scores on neuropsychological inventory.
13.	(Chiang et al., 2017)	Cognitively normal subjects (N= 15)	^{1}H MRS and PET	PCC and precuneus	▪ Lower GSH levels were found to be associated with greater brain amyloidosis in the temporal and the parietal region. ▪ No significant associations between GSH and Repeatable Battery for Neuropsychological Status (RBANS).
14.	(de Rover et al., 2011)	16 control and 15 MCI	f-MRI	Hippocampus	▪ Percentage of correct response on PAL task was significantly lower in the MCI group compared to the control group. ▪ MCI patients activating significantly more than controls at low loads and significantly less at higher loads
15.	(Grossman et al., 2013)	18 HC, 15 PAD, 18 aMCI	fMRI	Temporal–occipital cortex (TOC), prefrontal cortex (PFC)	▪ Significant positive correlation between overall judgment accuracy on fMRI task and performance on the Pyramid and Palm Tree. (Semantic memory)
16.	(Binnewijzend et al., 2012)	Total 105 AD (N= 39), MCI (N= 23) & HC (43).	fMRI	Regional functional connectivity (FC)	▪ Lower regional functional FC is associated with lower scores on MMSE. ▪ Lower regional FC and worse test performance were found for Digit Span (backward), Stroop test, TMT (A and B), VAT, RAVLT (immediate and delayed), Category Fluency, and Rey Figure Copy test. ▪ A strong correlation was found between DMN FC values and RCFT outcomes in AD.

AD = Alzheimer's Disease; CAMCOG,= Cambridge Cognitive Examination; CDR = Clinical Dementia Rating Scale; CSF = cerebrospinal fluid ;cerebral blood flow ; CERAD = Consortium to Establish a Registry for Alzheimer's disease; Cr = creatine compounds; CVLT = California Verbal learning test; DLB = Dementia with Lewy bodies ; DMS= Delayed matching to sample; DTI = Diffusion tensor imaging; DVR = delayed verbal recall test, FA = Fractional anisotropy; FAS = letter fluency for words beginning F, A, S; FCSRT = Free and Cued Selective Reminding Test ; fMRI = Functional MRI;GABA = Gamma-Aminobutyric acid; Glx= Glutamine/glutamate , GSH = glutathione ; HC = Healthy Controls; MD = mean diffusivity ; MCI = Mild cognitive impairment; MRI = Magnetic resonance imaging; MMSE = Mini-Mental State Examination ; MRS = Magnetic resonance spectroscopy; MTL= medial temporal lobe; MI = Myo-inositol; NAA= N-Acetylaspartic acid; PAL = Paired Associate Learning; PCC = Posterior cingulate cortex;

PCG = posterior cingulate gyrus; PET = Positron Emission Tomography ;^{1}H-MRS = Proton magnetic resonance spectroscopy; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey–Osterrieth Complex Figure Test TMT = Trail Making Test; WMS = Weschler Memory Scale.

Various advanced neuroimaging techniques like positron emission topography (PET), diffusion tensor imaging (DTI), MRI, fMRI, MRS can help in diagnostic clarification of these clinical conditions but these are majorly restricted up to diagnosis of neurological and organic brain diseases. Above discussion indicated a high correlation with various neurochemical level changes in diseased condition with different neuropsychological test. MMSE being the most widely used test in AD relates with the neurochemicals, which proves its efficacy. Along with this other neuropsychological test relating to cognitive domains also measure functions in various brain regions. Figure 2 show conclusive findings of various biomarkers in AD measured through various neuroimaging techniques.

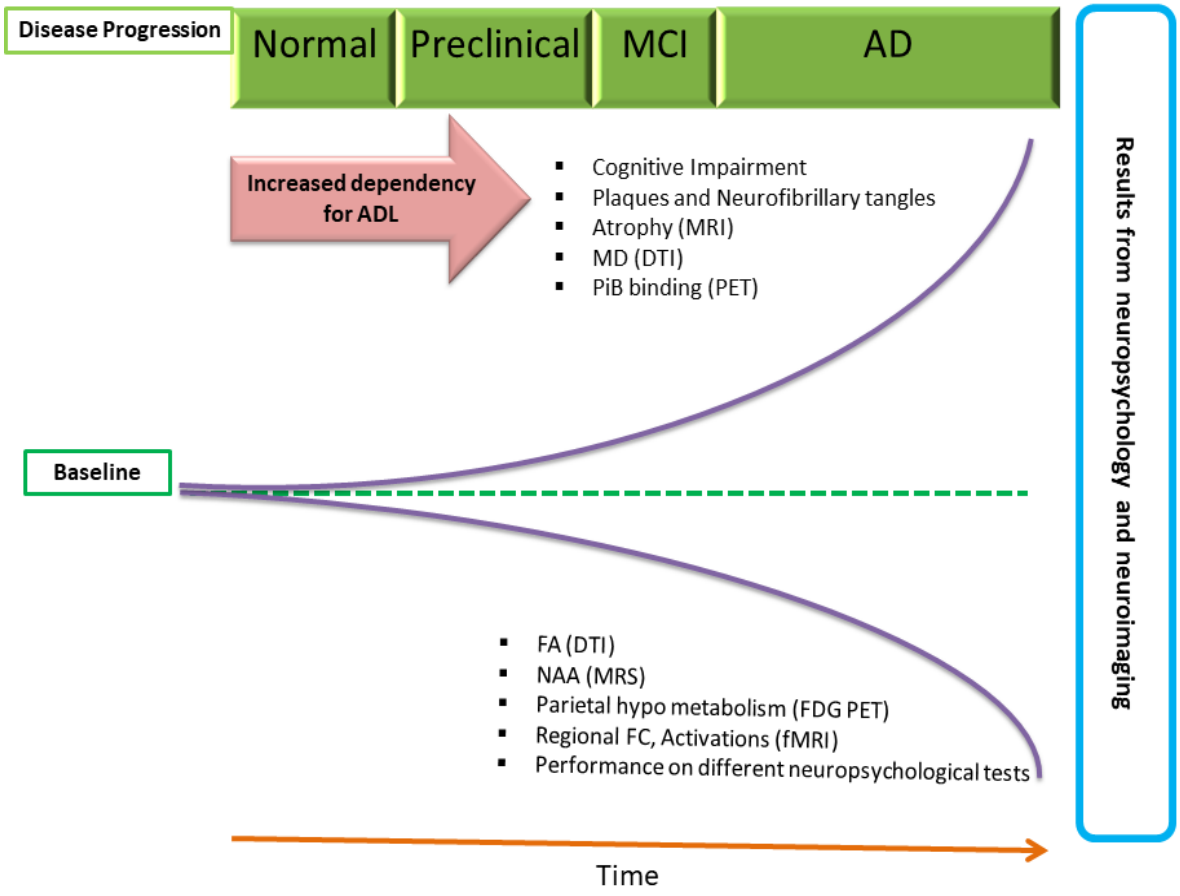

Figure 2 Changes in different domains in from normal toMCI and AD. There is increase in cognitive impairment, number of plaques and neurofibrillary tangles, cerebral atrophy, Mean Diffusivity and PiB Binding. Also there is decline in performance on various neuropsychological tests, amount of certain neurochemicals like NAA, Fractional anisotropy, regional Functional connectivity & activation level measured by different techniques with progression in time, age and diseases severity.

Combined perspective:

Different imaging techniques are also able to monitor brain's structure and functioning as these techniques are more closely able to detect changes in neurochemicals and neurotransmitters that are linked to behavioral changes that can be detected by neuropsychologicaltests. There is much scope present in the field of neuropsychology for early screening and diagnosis of suchdisorders. Early diagnosis allows for the prompt initiation of treatment, which can significantly improve outcomes and slow down the progression of the disease. As, Neurodegenerative disease pathology of brain is linked with dysregulation

in various neurochemicals like Choline (Cho), total Creatine (tCr), lactate, inositol, dopamine, serotonin etc. Hypothalamus, a region primarily affected in AD, shows alteration in various neuro chemicals and neurotransmitters. These changes results in significant impairments in behavior so, a systematic analysis of neuropsychological, neuroimaging, and neurochemical data can provide a comprehensive understanding of the underlying mechanisms of neurological and psychiatric conditions, leading to more accurate diagnosis and personalized treatment plans. Some widely used test like MMSE, MoCA, TMTs can provide quick screen to a large population whereas presently, neuroimaging at a greater scale cannot be a feasible solution. Tests like Stroop test, digit span, verbal tests, memory tests etc. point out to region specific, cognitive impairment in patients and help in diagnosis of various neuropsychiatric diseases. Hence, specialized training in neuropsychology is the need of the hour for possible early screening, treatment and management of these diseases.

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