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The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field.

Aims & Scope

The scope of the journal is broad. It covers many disciplines and spans molecules (e.g., molecular neuroscience, biochemistry) through systems (e.g., neurophysiology, systems neuroscience) to behavior (e.g. cognitive neuroscience) and clinical aspects (e.g. psychopharmacology). The journal covers all aspects of neuroscience with an emphasis on translational psychiatry and psychology, as long as the goal is to delineate the neural mechanisms underlying normal or pathological behavior.

Preclinical and clinical studies are equally considered for publication. We also invite manuscripts on the methods of computational modeling of psychiatric and neurological disorders, and treatment outcome.

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EDITORIAL

Değerli okuyucu,

Sizlerle buluşturduğumuz Nörodavranış Bilimleri Dergisi'nin ikinci yılının üçüncü sayısında da, yurtiçinde ve yurtdışında çalışmalar yürüten bir çok araştırmacının dergimize sunduğu katkılarıyla, hedefimize doğru ilerlemeye devam ediyoruz.

Dergimizin bu sayısında ilk olarak okuyucuya, Hızlı Sayar ve Tarhan'ın, üniversitemizin alanında uzman bilim insanlarını bir araya getirdiği 2. G20 Dünya Beyin Haritalama ve Tedavileri Zirvesi'ni değerlendirdikleri makalesini sunuyoruz. Sonrasında Ansari ve Raghunath'ın üzerinde çalıştıkları Hintli yetişkinlerdeki Hindu konuşma uyaranına karşı işitsel beyin sapı elektrofizyolojik ölçümünün sonuçlarına değindikleri makaleleri, Tijani ve çalışma arkadaşlarının Boru Çiçeği ektresinin farelerde nöro-toksik bazı etkiler meydana getirdiği sonucuna ulaştığı araştırması yer almaktadır. Bunların yanı sıra dergimizin bu sayısında Yılmaz ve arkadaşlarının bağımlılık tedavisi amacıyla hastaneye başvuran hastalarda, başvuru şeklinin ve bu şeklin tedavi sonuçlarına olan etkisinin tartışıldığı çalışmaya, Bulut ve meslektaşının Trikotilomanide N-asetilsistein kullanımı ile ilgili değerlendirmesine ve Antikacıoğlu'nun öğrenme ve performansın, beyin bölgelerinin katılımı oranında arttığını ileri sürdüğü makalesine ve ayrıca yukarıdaki derleme ve araştırma yazılarının yanında ilgi ile okuyacağınızı düşündüğümüz Evrensel, Cömert ve Şalçini'nin olgu sunumlarına ulaşabilirsiniz.

Saygılarımla,

Yrd. Doç. Dr. Cumhur TAŞ
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BRAIN MAPPING
BEYİN HARİTALAMASI

Gökben Hızlı Sayar*[1], Nevzat Tarhan[1]

Associating the mental illness with underlying neural mechanisms is an aim of modern psychiatry. Various brain imaging techniques have the potential to identify the neural correlates of mental illnesses. Electrophysiological techniques have an important place to identify the biological mechanisms of psychiatric diseases.

Quantitative electroencephalography (QEEG), is a relevant electrophysiological method used in clinical psychiatry and researches. Up to 80% of subjects with mental health problems present different QEEG abnormalities (Coburn et al. 2006). However, QEEG is yet not used sufficiently in the diagnostic evaluation of psychiatric cases. The central reason for the limited clinical use of QEEG is the contradictory results of studies in psychiatry. Due to this discrepancy in research results, utilization of QEEG has to be combined with other diagnostic methods.

QEEG is a numerically processed, digitally recorded EEG. It has the advantage of the versatility of displaying specific waveform components. QEEG systems, generally called, "EEG brain mapping," include topographic displays of voltage, frequency, power and statistical comparisons to normative values.

Previous QEEG studies mostly investigated schizophrenia and mood disorders, and the QEEG findings exhibit a wide range of abnormalities. The most frequently reported QEEG abnormality in schizophrenia is a frontal asymmetry of alpha power (Jetha et al. 2009). Recently study results indicate that the QEEG measures of power spectra can be used as potential biomarkers for the development of schizophrenia in prone subjects (Fugetta et al., 2014).

Quantitative EEG studies in patients with depression found increased slow wave activity decreased slow wave activity and increased alpha and beta activity. Asymmetry in EEG activity over frontal regions in depression was also reported (Allen et al. 2004, Vuga et al. 2006). Combined with other clinical ratings, QEEG parameters may be a useful tool for risk estimation, prevention and treatment response. Decreases in prefrontal cordance; left-right asymmetry of combined theta with alpha power reported to be predictive of therapeutic response in depression (Bares et al. 2007, Iosifescu 2008).

QEEG may be used as a tool for distinguishing discrete diagnostic classes of dementia and etiologies of pseudodementia, such as depression and alcoholism. EEG may be more valuable than neuropsychological tests for recognizing pseudo-dementia since motivational and attentional problems are likely to interfere with testing. Although an abnormal EEG in a depressed patient is not specific for dementia, it does identify the patients at greatest risk for functional decline and, therefore, is a useful part of the evaluation (Holschneider & Leuchter, 1999).

QEEG is an important research and clinical tool, providing information that is useful in differential diagnosis and identifying pathophysiological mechanisms of mental illnesses. Mapping the cerebral function of healthy subjects and psychiatric patients, we can achieve a better understanding of the functional organization of the brain. On the basis of this knowledge, the abnormalities underlying the major mental illnesses can also be mapped (Tricht et al. 2014).

Developing multicenter normative databases would help not only to detect EEG abnormalities across the entire age span, but also to classify the patients seen by clinical psychiatrists into different diagnostic groups. This needs a collaboration of centers to compose a large database and to share knowledge. The G20 World Brain Mapping & Therapeutic Scientific Summit aims to facilitate communication between the G20 nations, getting scientists, engineers, physicians together to rapidly introduce clinical solutions. G20 World Brain Mapping Summit was launched in 2014 on the initiative of The Society for Brain Mapping and Therapeutics. Üsküdar University and The Society for Brain Mapping and Therapeutics are holding the 2. Annual Summit on G20 World Brain Mapping and Therapeutics Initiative in Istanbul, Turkey. Goals of the program are to build collaboration between G20 nations on translational clinical neuroscience, constituting strategic industry-academia-government cooperation for brain discovery; and to facilitate commercialization of innovations in the field of Brain Mapping & Therapeutics worldwide. It is our great pleasure that we invite you to attend the G20 World Brain Mapping and Therapeutics Initiative in Istanbul, Turkey on 13th Nov, 2015.

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ELECTROPHYSIOLOGICAL MEASURES OF AUDITORY BRAINSTEM RESPONSES TO HINDI SPEECH STIMULUS IN INDIAN ADULTS

HİNTLİ YETİŞKİNLERDEKİ HİNDU KONUŞMA UYARANINA KARŞI İŞİTSEL BEYİNSAPI ELEKTROFİZYOLOJİK ÖLÇÜMÜNÜN YANITLARI

Mohammad Shamim Ansari[*1], Rangasayee Raghunath[2]

Abstract

Speech evoked auditory brainstem responses (spABR) assesses brainstem ability to encode speech. However, speech representations at brainstem are affected by acoustic properties of speech, language background and experiences. Hindi has considerable acoustic differences that may evoke dissimilar ABR pattern. Therefore, our objective was to investigate the spABR to Hindi stimulus in normal hearing adults. The 5 formants Hindi stop |dal of 40ms was synthesized to elicit ABRs from 50 normal hearing adults with mean age of 22.7 (SD=2.3) years in the age range 18-25 years. The sub-cortical response latency & amplitude to consonant and vowel portion of the stimulus were recorded. Results: The spABR elicited distinctive peaks for stimulus component. The consonant portion evoked peak V and vowel portion elicited the frequency following response (FFR). The mean, median, standard deviation, minimum, maximum and 95% confidence interval of peak latency & amplitude were measured. ANOVA was studied at 5% significance levels between the current spABR and western data. Conclusions: The obtained brainstem response timing and amplitude values of transient and sustained portion of stimulus are in line with the western reports. However, considering the acoustic differences in Indian languages, culturally & linguistically sensitive stimulus should possibly be developed and norms be established.

Keywords: Speech stimulus, Speech encoding, Speech-evoked auditory brainstem response, Transient response, Frequency following responses.

Özet

İşitsel beyin sapı uyarılmış konuşma yanıtları (spABR) konuşmayı kodlamak için beyin sapı becerilerini belirler. Ancak, beyin sapındaki konuşma simgeleri konuşmanın, dil geçmişinin ve deneyimlerinin akustik özelliklerinden etkilenir. Hindu dili, farklı işitsel beyin sapı yanıtlarını ortaya çıkarabilen hatırı sayılır derecede akustik farklılıklar içerir. Bu yüzden, amacımız normal duyabilen yetişkinlerdeki Hindu uyaranına karşı işitsel beyin sapı uyarılmış konuşma yanıtlarını (spABR) araştırmaktı. 18-25 yaş aralığındaki 22.7 yaş ortalamasındaki(SD=2.3) normal duyabilen 50 yetişkinin işitsel beyin sapını ortaya çıkarmak için 5 tane Hindu biçimlendirici durağı olan |da| sentezlendi. Gecikme süresi ve çokluğunun uyaranların ünsüz ve ünlü kısımlarına karşı korteks altı cevabı kaydedildi. Sonuçlar: İşitsel beyin sapı uyarılmış konuşma yanıtları (spABR) uyaran bileşenleri için farklı hece ortaları ortaya çıkardı. Ünsüz kısmı V hece ortasını ve ünlü kısmı da sıklığı izleyen yanıt(FFR) ortaya çıkardı. Hece ortası gecikme süresi ve çokluğunun ortalama, ortanca, standart sapma, minimum, maksimum ve %95 güven aralığı ölçüldü. Şuanki spABR ve batı dataları arasındaki %5lik önem seviyesinde ANOVA incelendi. Sonuçlar: Uyaranların uzun ve kısa süreli kısımlarının edinilen beyin sapı zamanlama ve çokluk değerleri batı datalarıyla aynı doğrultudadır. Ancak, Hint dillerindeki akustik farklılıklar göz önünde bulundurularak kültürel ve dilbilimsel olarak hassas uyaranlar imkanlar dahilinde geliştirilmeli ve normalar oluşturulmalıdır.

Anahtar Kelimeler: *Konuşma uyaranı, konuşma kodlaması, işitsel beyin sapı uyarılmış konuşma yanıtları, kısa süreli yanıt, sıklığı izleyen yanıtlar(FFR).*

1. Introduction

Auditory brain stem responses (ABRs) to clicks or tones are routinely employed as a metric for determining auditory thresholds in children and difficult to test population (Sininger; 1993 Hood 1998; Hall 2007) to envisage the auditory accessibility to acquire speech and language skills and to estimate the difficulty in perceiving speech. However, auditory system's ability to process speech may not be predictable from transient click or tones because they have poor approximation to behaviorally relevant complex sounds like speech (Skoe & Kraus 2010). Hence, use of speech for ABR measurement has evolved as a reliable method for underpinning the processes involved in speech perception.

Since the last decade, brainstem encoding of speech sound |da| has been investigated extensively to explore the sub cortical functioning to the acoustic- characteristics of speech stimulus with remarkable precision in normal and clinical population (Chandrasekaran & Kraus, 2009; Johnson et al, 2005, 2008; Russo et al, 2004). The poor

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speech encoding have been reported in children with language, literacy, reading, and learning deficits (Banai et al., 2009; Johnson, Nicol, Zecker, & Kraus, 2007; King, Warrier, Hayes, & Kraus, 2002). Children with known language-based learning problems reported to have delayed latencies (Johnson, Nicol, Zecker, & Kraus, 2007; King, Warrier, Hayes, & Kraus, 2002) compared to normal learning peers. Children with poor reading abilities found to have prolonged latencies, poorer waveform morphology and weaker spectral encoding compared to children with better reading abilities (Banai et al., 2009; Hornickel, Anderson, Skoe, Yi, & Kraus, 2012).

These studies have demonstrated a trend that difficulty in language, literacy, reading and effects of training on learning affects the sub cortical representation of speech. Therefore, it has been suggested that the spABR to syllable |da| can be used for clinical assessment of auditory function universally. The Bio MARK (biological marker of auditory processing) procedure has been developed as an objective tool for the assessment of speech sound processing of brainstem for the diagnosis of auditory processing disorders and learning problems.

However, Werker and Tees (1984) reported that 10 to 12 month old infants can discriminate the sounds that are linguistically relevant in their native language, suggesting that psychoacoustic discrimination of consonants are affected by language input. Moreover, the recent studies have shown that experience with language have effects in sub cortical encoding of specific elements of speech sounds (Krishnan et al, 2005, 2009). They reported that mandarin speakers encode more robust pitch patterns of mandarin sound in auditory brain stem measures that convey linguistic meaning in Mandarin than English speakers, but not in English. Furthermore, long-term music experiences selectively enhance specific stimulus features in brainstem activity (Wong et al., 2007).

Additionally, naturally produced sounds have an acoustic – phonetic difference in languages such as voice onset time (VOT) apart from temporal & spectral variations. The stop consonants such as |da| in English are produced by the vibration of the vocal folds that starts at a short lag after the release of the consonant by the articulators. In contrast, in Hindi sound |da|, voicing starts prior to the release of the consonants (for example, Hindi sound |da| has VOT of -140 to -60 ms (Lisker and Abramson 1964). These acoustic parameters delineate the distinctive features for language and speaker identification.

These observations set the theoretical foundation that the acoustic parameters of the culturally sensitive stimulus may uncover the processes involved in specific language user. We assume that the long term experience of the Hindi syllable in Hindi speakers may elicit dissimilar pattern of evoked potentials at brainstem. This may be crucial in diagnostic work up of clinical population. Therefore, the present study proposes to record ABRs with Hindi speech sound |da| in normal hearing Hindi speaking individuals and to compare with literature data.

1.1. Objective of the Study

The purpose of the study was to determine the ABRs to Hindi stimulus in normal hearing Hindi speaker adults.

2. Subjects and Methods

2.1. Research design

This prospective survey was conducted at Electrophysiological Lab of Department of Audiology. The study was accorded necessary ethical clearance from Institutional ethical board. Informed consent was obtained from all subjects.

2.2. Participants

Total 50 subjects of both the sexes in the age range 18–25 years (mean = 21.3 years, SD = 3.2 years) were recruited for the study. The subjects were right-handed native Hindi speaker with no known history of neurological, otological disease or trauma and psychiatric problem. All subjects had pure-tone thresholds ≤25 dBHL at octave frequencies from 250 Hz to 8000 Hz, speech identification score >90% at 40dBSL in both ears and normal middle ear function on Immittance evaluation (A-type tympanogram with acoustic reflexes at normal sensation levels). Subjects also required to exhibit wave V latency to 100µs click at the rate of 21.1 per sec in rarefaction polarity to the right ear within the range of normative values (mean± 1.5 standard deviations, 5.41–5.96ms at 45dBnHL).

2.3. Stimulus and recording parameters

The Hindi stop voiced phoneme of consonant-vowel (CV) combination |da| of 40 ms duration consisting of 5-formants was synthesized (Ansari & Rangasayee 2015) to elicit ABRs. The speech sound consisted of an initial burst of 10ms and a formant transition of 30ms between the consonant and the vowel. The F0 and the first three formants (F1, F2, F3) change linearly over the duration of the stimulus: F0 from 113 to 147, F1 from 240 to 770, F2 from 1670 to 1350, and F3 from 2680 to 2550 Hz. F4 & F5 remain constant at 3700 & 4600 Hz respectively.

The spABR were acquired from the subjects sited comfortably on the reclining chair through Ag-AgCl electrodes with surface contact impedance of < 5 kΩ, positioned centrally on the scalp, at Cz, behind the right mastoid (reference) and on the forehead (ground). The syllable |da| were presented into the right ear at a rate of 11.1 per sec at comfortable listening level of 65 dBSL relative to the threshold at 1000 Hz through ER-3 insert earphones. The sampling rate was 20000 Hz and responses were online band passed filtered from 100 to 3000 Hz at 12 dB/octave. Trials with eye-blinks or other motion artifacts greater than ±35 µV were rejected online. Two traces of 2000 sweeps were collected at alternating polarity. The recording window was 50 ms starting 10 ms prior to stimulus onset. Waveforms were averaged online in Intelligent Hearing Systems (IHS) Smart EP software (version 2.39).

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2.4. Analysis

The obtained waveforms were subjected for peak identification by two experienced observers who had experience in spABR recording and analysis. The stimulus used for recording sub-cortical responses was blinded to observers. The two observers who independently agreed on individuals peaks were analyzed and peak at which disagreement occurred was discarded from data pool.

The identified peaks were labeled as V, A, C, D, E, F, & O. Their absolute latencies & amplitude were analyzed. Waves V and A reflected the onset of the response, wave C the transition region, waves D, E, and F the sustained region (i.e., the frequency following response), and wave O the offset of the response. V-A complex was analyzed for latency, amplitude and slope (VA amplitude/VA duration).

The peak values were descriptively analyzed. The mean, median, standard deviation, minimum, maximum and confidence interval values of individual peak were calculated. One way ANOVA was studied at significance levels of 5% ($P < 0.05$) to compare the mean latency & amplitude values of individual peak between the present study and studies reported in literature.

3. Results

The study used Hindi stop voiced phoneme of consonant-vowel (CV) combination |da| to obtain neurophysiologic responses of brainstem in Hindi speaking adults. All 50 participants exhibited spABR. Figure 1 showing speech evoked auditory brainstem responses with Hindi stimulus |da| in one of the subject.

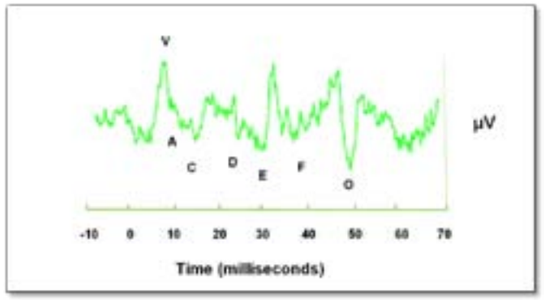

Figure 1. Waveform of speech evoked auditory brainstem responses with Hindi stimulus ldal in one of the subject.

Table 1: Showing mean, standard deviation (in parenthesis), median, minimum and maximum and 95% confidence values of sub cortical responses peaks latencies and amplitudes in Indian adults.

Hindi Speech Stimulus - Evoked ABRs									
	Peaks	N	% of peak detection	Minimum (ms)	Maximum (ms)	Median (ms)	Mean (SD) (ms)	95% Confidence Level Minimum	Maximum
L	V	50	100	5. 77	10. 96	7. 03	6.78 (0.24)	6. 18	7. 73
A	A	50	100	6. 79	12 .09	7.55	8. 04 (0.35)	7.24	8 .19
T	C	50	100	14.01	20.23	17.01	18.81 (0.97)	16.01	19.21
E	D	45	93	19.67	24.26	21.11	22.78 (0.85)	20.10	22.16
N	E	45	94	26.37	33.81	30.06	31.82 (0.20)	29.16	32.21
C	F	50	98	34.3	41.73	37.34	39.48 (0.51)	36.35	40.02
Y	O	47	99	43.1	49.23	47.31	49.03 (0.68)	45.27	49.01
(ms)	V-A	50	100	1.01	1.98	1.23	1.46 (0.19)	1.31	1.69
Slope	V/A	50	100	0.87	1.34	0.91	1.21 (0.37)	0.87	1.27
A	V	50	100	0.16	0.63	0.28	0.29 (0.15)	0.21	0.48
M	A	50	100	-0.93	-0.13	-0.47	-0.37 (0.31)	-0.93	-0.13
p	C	50	100	-0.36	-0.21	-0.36	-0.37 (0.26)	-0.36	-0.21
L	D	45	93	-0.89	-0.16	-0.50	-0.31 (0.17)	-0.60	-0.39
I	E	45	94	-1.06	-0.01	-0.37	-0.34 (0.23)	=0.48	-0.24
T	F	50	98	-0.39	-0.07	-0.31	-0.30 (0.23)	-0.39	-0.07
U	O	47	99	-1.06	-0.01	-0.31	-0.33 (0.18)	-0.01	-0.47
D	V-A	50	99	0.50	1.38	0.51	0.38 (0.25)	0.80	1.06
E	VA	50	100	0.28	1.18	0.43	0.71 (0.26)	0.59	0.83
(µV)									
Area									

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The results indicated that the onset (wave V and A) and the transition (peak C) were observed in all the participants (100%). The FFR (peak D, E and F) were present in 93.3% and the offset response (peak O) was detected in 99% of participants. The latencies and amplitudes of discrete peaks (see Table 1) and sustained components (see Table 2) of the brainstem response to speech stimulus were measured.

3.1. Discrete Peak Measures of the Hindi Speech stimulus-evoked ABRs

The latencies and amplitudes of spABR discrete peaks V, A, C, D, E, F and O as well as the latency, amplitude, area, and slope between waves V and A (known as the V/A complex) were calculated. Table 1 showing mean, standard deviation (in parenthesis), median, minimum, maximum and 95% confidence values of sub cortical responses of individual peak latencies and amplitudes in adults.

Table 2: Showing Mean, standard deviation of (A) Stimulus-to-response correlations (B) spectral amplitude measures of Hindi stimulus in native Hindi speaker

	Number	Mean	Standard Deviation
A) Stimulus–response correlations			
SR corr (r)	50	0.28	0.06
SR lag (ms)	50	7.98	3.42
B) Spectral amplitudes (μV)			
RMS amp	50	2.32	0.02
F0 amp	49	16.13	7.12
F1 amp	45	6.46	4.35
HF amp	44	0.36	0.12

3.2. Sustained Portion of the Hindi Speech stimulus-evoked ABRs measures

The response between waves C and O comprises the sustained portion or FFR (peaks D, E and F), occurs approximately between 10 and 40 ms after the onset in response to the vowel portion of the syllable. Responses to formant transitions of stimuli were analyzed using, Stimulus-Response Correlation, Frequency Fourier Transform (FFT) and Root Mean Squares (RMS) measures (depicted in Table-2). These measures provide information about the overall magnitude of sustained neural activity and phase-locking capabilities of the neural population in auditory system (Krishnan 2002; Russo et al. 2004; Johnson et al. 2005).

The stimulus-to-response correlation (SR corr) and the amount of stimulus-to-response delay or shift (SR lag) were calculated to determine timing (latency) of the FFR. FFT analysis was performed to calculate the magnitude of the neural response over the entire period of the stimulus (RMS amp) as well as the magnitude of spectral components in narrow frequency regions surrounding the stimulus fundamental frequency (F0 amp: 113 to 147 Hz), the first formant (F1 amp: 475 to 740 Hz), and a higher frequency region (HF amp: 760 to 1375 Hz). Timing of the FFR is indicated by S–R correlation and the magnitude of the response was evaluated with RMS, F0, F1 and HF amplitudes. The greatest amount of energy is present in the F0 region (see Figure 2).

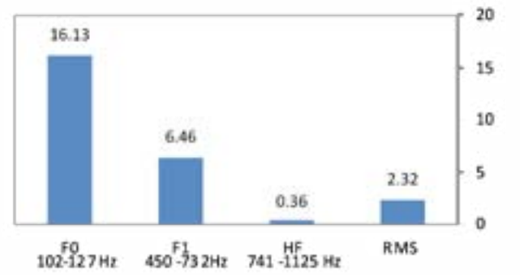

Figure 2: Showing greatest amount of energy is concentrated around F0 area

4. Discussion

The study used Hindi syllable to trace brainstem neurophysiologic responses in Hindi speaking adults. The 96% of subjects evidenced responses by the peak observers. It is reported that the response structures at brainstem level are organized to encode the stimulus with extreme accuracy (Musiek, 1991). The two measures i.e. transient and sustained component of spABR are used to describe the neural activity for temporally & spectrally distributed Hindi syllable.

The transient portion of spABR, exhibited presence of an initial wave V at a mean latency of 6.78 ms analogous to the wave V elicited by a click stimulus. However, this is more than the documented mean latency between 5 and 6 ms of peak V for click stimulus (Jacobson T, 1985). The latencies of the later peaks were calculated with reference to wave V. Peak A appeared at negative trough immediately after wave V at a mean latency of 7.55 ms, wave C emerged at a mean latency of 18.81 ms, wave D occurred at a mean latency of 22.78 ms, wave E crop up at a mean latency of 31.82 ms, wave F was visible at a mean latency of 39.48ms and wave O was visible at a mean latency of 49.03ms. These latencies are similar to the earlier findings (Johnson et al, 2005; Russo et al, 2004).

Fast Fourier analysis was applied between 10 ms and 40 ms of response to analyze the amplitude of F0 and F1. The F0 had larger amplitude as compare to the F1. This may be due to the acoustic characteristics of |da| stimulus which has greater energy at the F0 region compared to its harmonics, and greater energy stimulus components are represented better at the neuronal level. Also, the F0 has a lower frequency compared to its harmonics and it is reported that lower frequency produces better phase locked neuronal responses (Russo et al, 2004). These findings are in the line of previous reports and imply that the rapid timing changes of consonant and vowel portion of the Hindi stimulus |da| are faithfully represented and preserved in normal auditory system (Karawani & Banai, 2010; Johnson et al, 2005; Russo et al, 2004).

4.1. Comparison of Hindi stimulus evoked ABRs values with Western data

Another goal of the study was to compare the obtained spABR to Hindi stimulus |da| with the values reported in literature. The major finding of comparisons between the Hindi sample and previous literature values are on timing measures. Table 3 showing mean (SD) along with minimum and maximum bounds at 95% confidence interval (CI) of the test sample in the left column, Israeli and US norms in middle column and right-most column respectively. The overlap among Hindi, Israeli and US CIs (Table-3) is equivalent to an insignificant result of a t-test with p value at 0.05.

Table 3: Comparisons of mean latency values obtained in the present study with the study by Russo et al. (2004) and Karwani & Banai (2010).

Peaks	PRESENT INDIAN STUDY data at 95% CI		US (RUSSO 2004) data at 95% CI	Israeli (Karawani, 2010) data at 95% CI	p-value at 0.05
	Mean (SD)	Min Max	Min Max	Min Max	
V	6.78	6. 38	6.63	6.50	0.141
	(0.24)	6. 88	6.74	6.66	
A	7.55	7.24	7.51	7.43	0.071
	(0.35)	7 .69	7.68	7.69	
C	18.81	18.31	18.35	18.35	0.415
	(0.97)	19.01	18.67	18.52	
D	22.78	20.10	22.62	22.37	0.621
	(0.85)	22.16	23.00	22.88	
E	31.82	29.16	30.90	30.88	0.354
	(0.20)	32.21	31.15	31.13	
F	39.48	36.35	39.45	39.36	0.153
	(0.51)	40.02	39.69	39.50	
O	49.03	47.27	48.14	48.06	0.519
	(0.68)	51.01	48.36	48.35	
VA slope (μV/ms)	0.77	-0.83	-0.43	- 0.42	0.452
	(0.36)	-0.57	- 0.36	-0.31	

The obtained electrophysiological results do not support our assumption that culturally & linguistically sensitive stimulus may exhibit dissimilar ABR pattern in Hindi speakers. The comparable findings can be argued on two fronts. Firstly, the sub cortical structures may not be able to represent subtle acoustic differences existed in the languages and the system may be responsive to gross durational aspects of the stimulus. Secondly, though the subjects in the current study were native Hindi speaker but were also exposed and had equivalent basic reading and writing skills in other languages including the English.

Further, the Indian basic educational program has compulsory three to four language exposure & learning and it is likely that their auditory systems may have maturational tuning to represent gross/ common features of acoustic stimulus of variants of stimulus |da|. The linguistic and psychoacoustic aspects of these differences may be operated by the higher order auditory function in listeners. However, a systematic investigation is required to address this point.

5. Conclusions

The study provides neural encoding of acoustic aspects of Hindi stimulus in term of latency and amplitude. The latency measures of response provide information about the precision with which the brainstem nuclei synchronously respond to acoustic stimulus while amplitude measures furnish information about robustness of the response of the brainstem nuclei for the acoustic stimulus. The major characteristics of ABR to Hindi sound |da| in adults are in similar lines to non tonal language speakers reported in literature.

The comparable latency values of spABR entails that the ABR also reflects various acoustic properties of Hindi syllable in normally perceiving auditory system suggesting that similar results are expected in the population and languages where this stimulus will be present. Therefore, alterations in peak latency measures may indicate a difference in conduction speed along the dendrites and axon projections, or a difference in kinetic channels of neurons, or even differences in the synchronization of the response generators in clinical population. Hence, it can be suggested that Hindi stimulus can also be used for recording ABR in speakers of Indian languages.

However, the growing body of literature reveals that brainstem encoding of specific elements of speech sounds in Mandarin speakers encode pitch patterns more robustly than English speakers that convey linguistic meaning in Mandarin, but not in English (Krishnan et al, 2005, 2009). Therefore, we would like to emphasize a point here that India is multicultural and multilingual society also have tonal language speakers. Therefore, the acoustic-phonetics variations among the various languages in India may play a crucial role in diagnostic work-up of clinical population. Hence, unlike any other language based speech test, appropriate speech stimulus and norms may be more meaningful in assessment and categorization of clinical population.

6. Acknowledgement

We would like to express our thanks and gratitude to our participants for their help in this research.

7. Declaration of conflict of interest

The corresponding author is doing Ph D under the guidence of second author on same topic.

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NEURO-TOXICOLOGICAL IMPACTS OF DATURA METEL LINN. (FAMILY: SOLANACEAE) LEAVES EXTRACT IN MICE

FAMİLYASI PATLICANGİLLER OLAN BORU ÇİÇEĞİ(DATURA METEL LINN.)'NİN EKSTRESİ FARELERDE NÖRO-TOKSİK ETKİLER BIRAKIR

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Abstract

Datura metel leaves and seeds are widely used in ethno-therapeutic management of Rheumatic pain, asthma and insomnia. Its use has been associated with adverse alteration in behavior which has triggered interest in its safety on the central nervous system. This study was therefore designed to evaluate acute neuro-toxicological effects of aqueous –methanol extracts of Datura metel in mice. Oral Acute toxicity studies of the leaf extract was carried out in mice. The effects of the extract (25-100 mg/kg body weight orally) on total locomotive activity, motor coordination and spatial memory in Y-maze were evaluated in mice. The effect of Datura metel extract (25-100 mg/kg) in the presence of either atropine (0.3 mg/kg b.w.) or naloxone (0.5 mg/kg b.w., i.p.) on total locomotive activity in an open field apparatus was carried out with the view of predicting its mechanism of action. The oral median lethal dose (LD50) was greater than 2000 mg/kg b.w. The extract produced significant decrease ($p<0.05$) in total locomotive activity of the treated mice in the open field apparatus. The extract significantly ($p<0.05$) shortened the time spent on the rota-rod by mice treated with the extract and reduced spontaneous alternation behavior. Datural metel leaves extract produced in mice neuro-toxicological effects characterized by sedation and hypokinesia, motor coordination impairment and disruption of short term memory.

Keywords: Datural metel, extract, mice, neurotoxicity, amnesia.

Özet

Boru çiçeği yaprak ve tohumları romatizma ağrısı, astım ve uykusuzluğun etno-terapötik uygulamasında yaygın biçimde kullanılmaktadır. Kullanımı, davranışlardaki olumsuz değişimlerle alakalı olması ve merkezi sinir sistemi üzerindeki güvenirliliği bu çalışmayı tetikledi. Bu çalışma Boru Çiçeğinin sulu metanol ekstresinin farelerdeki akut nöro-toksik etkilerini değerlendirmek için tasarlandı. Yaprak ekstresinin oral akut toksisite çalışması fareler üzerinde gerçekleştirildi. Ekstrenin Y-labirentteki toplam lokomotif aktivite, motor koordinasyon ve uzamsal hafıza üzerindeki etkileri (ağız yoluyla 25mg-100 kg vücut ağırlığı) farelerde değerlendirildi. Boru Çiçeği ekstresinin (25-100 mg/kg) açık alan aparatındaki toplam lokomotif aktivite üzerindeki etkisi nalokson (0.5 mg/kg b.w., i.p.) ya da atropine (0.3 mg/kg vücut ağırlığı)' varlığında gerçekleştirilip hareket mekanizmasının tahmini maksadıyla gözlemlendi. Oral medyan letal dozu (LD50) 2000 mg/kg vücut ağırlığından daha fazlaydı. Ekstre, açık alan aparatında muamele edilen farelerin toplam lokomotif aktivitesinde önemli bir azalış ($p<0.05$) meydana getirdi. Bu ekstre, işleme alınan farelerin rota-rod üzerinde harcadıkları zamanı önemli derecede ($p<0.05$) kısalttı ve eşzamanlı değişim gösteren davranışları da azalttı. Boru Çiçeği yaprak ekstresi, farelerde sakinlik, uyuşukluk, motor koordinasyon bozukluğu ve kısa süreli hafıza bozulmasıyla nitelenen nöro-toksik etkiler meydana getirmiştir.

Anahtar Kelimeler: *Boru Çiçeği, ekstre, fareler, nörotoksisite, amnezi*

1. Introduction

The medicinal plant Datura metel (DM) (Fam. Solanaceae) has been used in ethno-therapeutic management of asthma, insomnia and rheumatic pain. The smoke from the burning leaf is inhaled for the relief of asthma and bronchitis. The fruit juice is applied to the scalp for the treatment of falling hair and dandruff. Seeds and leaves of D. metel were reportedly used to sedate hysterical and psychotic patients (Gary et al., 2005). The decoction of D. metel leaf has been reported to be effective in management of madness, epilepsy and depression. It has been used as a narcotic and local anesthetic drug in many societies (Das et al., 2012). The bitter narcotic plant relieves pain and encourages the healing process. The seeds of the plant are medicinally the most active. Externally, the plant is used as a poultice in treating fistulas, abscesses wounds and severe neuralgia (Shagal et al., 2012).

Phytochemical studies of the plant revealed the presence of Scopolamine in the plant, which makes it a potent cholinergic-blocking hallucinogen that has been used to calm schizoid patients. Its leaves, containing hyoscyamine

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and atropine, can be used as an immensely powerful mind-altering drug (Strahil et al., 2006). There are reports of intoxication produced by the plant in teenagers who used the plants leaves for non-medical purposes (Ertekin et al., 2005). Hallucinogenic plants have been use as mind altering agents since the beginning of the recorded history. Apart from the therapeutic potential inherent in this plant, it enjoys patronage from criminals who seeks for mood alteration effects (sensory experience of something that does not exits out -side mind).

There are unsubstantiated claims of its leaves being used as hallucinogen by teenagers in parts of Nigeria. This study was therefore designed to study the effects of Datura metel leaves extract on spontaneous motor activity, spatial memory, motor co-ordination and cholinesterase activity in mice with the view to provide scientific evidence for its acclaimed neurotoxicological effects.

2. Materials and methods

2.1. Drugs and reagents

Methanol (Sigma- Aldrich, UK), Atropine (Sigma Aldrich, UK), Naloxone (Sigma Aldrich, UK) were used for the study.

2.2. Plant material

Fresh leaves of Datura metel was collected from Jiwa, Abuja, Nigeria. It was identified by Mallam Ibrahim Muazzaman ethnobotanist and authenticated by Mrs. Ugbabe Grace a taxonomist with the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja. Herbarium specimen (NIPRD/H/6455) was prepared and deposited for future references.

2.3. Preparation of plant extract

The leaves were cleaned, air-dried and crushed into fine powder using a pestle and mortar. Fifty grams of the powdered leaves was cold macerated with 0.5 L of 70% v/v methanol in water for 72 h at ambient temperature (28 – 30 oC). The resultant mixture was filtered using Whatman filter paper (No.1) and the filtrate concentrated to dryness in vacuo at 40 oC using Rotary Evaporator to give 9 g (18 % w/w) of a dark green hygroscopic powder The dried extract was stored in a dessicator. .

2.4. High Performance Liquid Chromatography Analysis

High performance liquid chromatography analysis was performed on the methanol extract of using (Bienvenu et al., 2002) method with some modifications. The chromatographic system includes Shimadzu HPLC system consisting of Ultra-Fast LC-20AB equipped with SIL-20AC auto-sampler; DGU-20A3 degasser; SPD-M20A UV-diode array detector; column oven CTO-20AC, system controller CBM-20Alite and Windows LC solution software (Shimadzu Corporation, Kyoto Japan); column, VP-ODS 5µm and dimensions (150 x 4.6 mm). The chromatographic conditions included mobile phase: solvent A: 0.2% v/v formic acid; solvent B: acetonitrile; mode: isocratic; flow rate 0.6 ml/min; injection volume 10 µl of 250 mg/ml solution of extract in methanol; detection UV 254 nm. The HPLC operating conditions were programmed to give mobile phase comprising solvent B 15% and solvent A 85 %. Column oven temperature was 40 0C. Atropine and scopolamine reference standards were analysed under the same HPLC conditions to establish their retention times. The total run time was 15 minutes.

2.5. Animals

Adult male Swiss albino mice (22–25 g) obtained from Animal Facility Centre (AFC) of National Institute for Pharmaceutical Research and Development (NIPRD) were used for this study. The mice were housed in transparent plastic cages padded with wood shavings, under standard conditions of temperature, relative humidity and light/dark cycles (12/12 h). They were fed with standard rodent chow and water ad libitum. Mice were handled and used for study accordance with the revised 1996 National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80 23).

2.6. Drugs and dosages

The following drugs and dosages were used for pharmacological screening: Normal saline (10 ml/kg body weight) for control group, Naloxone (0.5 mg/kg body weight) dissolved in normal saline; aqueous methanol extract of Datura metel leaves (25, 50 and 100 mg/kg body weight. The extract and normal saline were given by gavage while naloxone was injected intraperitoneally.

2.7. Acute toxicity study

Acute toxicity study was carried out according to the Organization for Economic Co-Operation and Development (OECD) Guidelines No. 423. Three animals were used for each step. The starting dose was selected from one of four fixed levels, i.e., 5, 50, 300, and 2000 mg/kg (b.w. p.o.) In accordance to the OECD recommendations, the starting dose level should be that which is most likely to produce mortality in some of the dosed animals; and when there is no information available on a substance to be tested in this regard; for animal welfare reasons, recommended starting dose is 300 mg/kg body weight. Thus 300 mg/kg body weight was used as the starting dose. The animals were observed for signs of toxicity and pattern of mortality for the first 4 h, then at 24 h and thereafter daily for 14 days.

2.8. Effect on Total locomotive activity

One hour after the administration, mice (N= 6) were transferred to the apparatus which consist of a clear glass box (45 cm×45 cm). The floor was divided by lines drawn into 9 equally sized squares (15 cm x 15 cm). Each mouse was placed individually in the centre of the apparatus and observed for 5 min to record the locomotor (number of squares crossed with four paws) (Santosh et al., 2011). After each test, the floor and walls of the apparatus were thoroughly cleaned with 70% ethanol to eliminate possible bias due to odour clue left by previous subject (Lindholm et al., 2012).

2.9. Study design

Group I: Normal saline (10 ml/kg body weight)

Group II: Datura metel methanol leaves extract 25 mg/kg body weight

Group III: Datura metel methanol leaves extract 50 mg/kg body weight

Group IV: Datura metel methanol leaves extract 100 mg/kg body weight

Group V: Datura metel methanol leaves extract 25 mg/kg body weight + Naloxone (0.5 mg/kg body weight)

Group VI: Datura metel methanol leaves extract 100 mg/kg body weight + Naloxone (0.5 mg/kg body weight)

Group VII: Datura metel methanol leaves extract 25 mg/kg body weight + atropine (0.3 mg/kg body weight)

Group VII: Datura metel methanol leaves extract 100 mg/kg body weight + atropine (0.3 mg/kg body weight)

2.10. Effect on Motor function

After administration of extract or normal saline motor performance of mice (n=6) was assessed using rota-rod apparatus which consists of a bar with a diameter of 3.0 cm, subdivided into five compartments by a disk of 24 cm in diameter. The bar rotated at a constant speed of 16 revolutions per min. A preliminary trial was carried out to select mice for the study on the day of experiment, with exclusion criteria being inability to remain on the rota-rod bar for three consecutive periods of 60 s each prior to treatment. The motor coordination function was assessed on the basis of the number of falls from the rota-rod in 180 s.

2.11. Effect on Spatial memory in Y-maze

One hour after administration of normal saline or extract each mouse (n=6) was placed in the Y-maze. The Y-maze is a three-arm horizontal maze (40 cm long and 5 cm wide with walls 10 cm high) in which the three arms are symmetrically separated at 1200. Each mouse was initially placed within one arm (A), and the arm entry sequence (e.g., ABC, CAB, where letters indicate arm codes) and the number of arm entries were recorded manually for 6-minutes. Alternation was determined from successive entries into the three arms on overlapping triplet sets in which three different arms were entered. The percentage alternation for each mouse was calculated as the ratio of actual to possible alternations (defined as the total number of arm entries minus 2), multiplied by 100 as shown by the following equation:

%Alternation = [(Number of alternations) /(Total arm entries-2)] × 100 (Kim et al., 2006; Heo et al., 2009)

2.12. Statistical analysis

Data were analyzed by analysis of variance test followed by Dunnett's test. All the results were expressed as mean ± SEM. $P < 0.05$ was considered significant.

3. Results

3.1. HPLC analysis

HPLC chromatogram of the standardized extract of Datura metel leaf. Seven peaks were detected with retention times of 3.570, 3.976, 4.346, 4.718, 5.226, 6.234 and 6.773 minutes in the HPLC spectrum of Datura metel leaf extract. Scopolamine appeared at retention time of 4.346 minutes and atropine appeared at 6.234 minutes (Fig. 1).

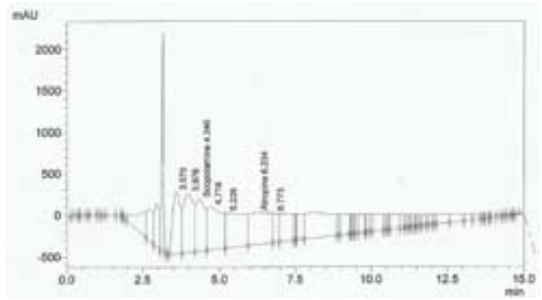

Fig. 1: HPLC chromatogram of the methanol leaf extract of Datura metel in the presence of standard reference atropine and scopolamine.

3.2. Acute toxicity study

Datura metel leaves extract (300 mg /kg body weight p.o.) produced biphasic effect in treated mice. In the first phase it produced restlessness, excitation, and hyper-locomotion while in the second phase mice were observed to be calm, non-responsive to touch, sedated and laboured breathing. Mice treated with the extract at 2000 mg/kg body weight exhibited sedation, laboured breathing and convulsion.

3.3. Effect on Total locomotive activity

The extract (50, 100 and 200 mg/kg body weight p.o.) produced significant ($p<0.05$) decrease in total locomotive activity of the treated mice. The reduced locomotive activity produced by the extract alone was however reversed in the presence of Naloxone (0.5 mg/kg body weight i.p.) as shown. The decrease in speed of mice on open field produced by Datura metel extract was reversed by naloxone (Table 1).

Table 1: Effect of Datura metel methanol leaves extract on total locomotive activity

Treatment	Total locomotive activity
Normal saline	
10 ml/kg	12.50 ± 0.25
Extract	
25 mg/kg	8.36 ± 0.18*
50 mg/kg	6.85 ± 0.37*
100 mg/kg	4.65 ± 0.48*
Extract (25 mg/kg)+ Naloxone (0.5 mg/kg)	11.75± 0.15
Extract (50 mg/kg)+ Naloxone (0.5 mg/kg)	9.48 ± 0.25
Extract (100 mg/kg)+ Naloxone (0.5 mg/kg)	7.76± 0.25

*Significantly different from the control at $p<0.05$

3.4. Effect on motor function

The extract significantly ($p<0.05$) shortened the time spent by treated mice on the rotating rod of the apparatus when compared to the control (Table 2).

Table 2: Effect of Datura metel methanol leaves extract on motor coordination of mice

Treatment	Mean fall off Time from rotarod (Sec)
Normal saline	
10 ml/kg	180.00 ±0.00
Extract	
25 mg/kg	125.52 ± 12.65*
50 mg/kg	56.45 ± 10.49*
100 mg/kg	24.65 ± 0.48*

*Significantly different from the control at $p<0.05$

3.5. Effect on Spatial memory in Y-maze

The extract (25-100 mg/kg body weight p.o.) produced significant ($p<0.05$) decrease in the spontaneous alternation behaviour of treated mice in Y-maze task (Table 3).

Table 3: Effect on Spatial memory in Y-maze

Treatment	Mean± SEM Total arm entry	Mean± SEM % Alternation Behaviour
Normal saline		
10 ml/kg	16.56 ±1.65	53.00 ±0.40
Extract		
25 mg/kg	12.32 ± 0.83*	47.00 ±0.56
50 mg/kg	7.32 ± 0.24*	24. 00 ± 0. 15
100 mg/kg	6.36 ± 0.35	18.50 ± 0.75

*Significantly different from the control at $p<0.05$

4. Discussion

The appearance of Scopolamine at retention time of 4.346 minutes and atropine at 6.234 minutes of the HPLC spectrum of Datura metel leaf extract indicates the presence of these compounds in the extract. This is a useful parameter for identification and classification of substances that may be contaminated or purposely adulterated with Datural metel leaves. It is therefore a potential resource for forensic determination of exposure to Datural metel.

An important step in evaluating CNS drug action is to observe its effect on locomotor activity of the animal. The activity is a measure of the level of excitability of the CNS, and decreased activity results from CNS depression [Ozturk et al., 2002; Tijani et al., 2012). The Datura metel leaves extract significantly decreased the locomotor activity as observed in the results of the open field test. The movement of the treated mice on the open fields was in a disorderly manner when compared to the saline treated group. The ability of naloxone to reverse the depression produced by the extract strongly suggest involvement of opioidergic - receptor in the observed neuro-depression characterized by low activity, freezing on the open field apparatus which accounts for the decreased locomotive activity observed only in the treated animals.

The depressant effect of Datura metel on the Central Nervous System was further supported by the outcome of the rota rod test, which has clearly demonstrated the CNS depressant activity evidenced by decreased fall off time. Rota-rod test is a valid test for predicting motor dysfunction produced by centrally acting drugs to determine possible alterations in the motor coordination ability of the animal, often caused by the use of sedative and antipsychotic drugs. In this test, the difference in the fall off time from the rotating rod between the vehicle and extract treated groups is taken as an index of muscle relaxation. In this study the short fall off time in the extract treated group showed that the extract possesses muscle relaxant effect. This may explain the incoordination in movement observed in all the treated animals on the open field.

The effect of the extract on memory was investigated in the Y-maze apparatus in order to confirm its effect on spatial short term memory. The choice of Y-maze for the study was based on the work of (Kim et al., 2006) which showed that spontaneous alternation behaviour is an indicator of spatial memory. Any agent that increased the spontaneous alternation behavior enhances memory while agents that reduce this parameter produces memory deficit. The extract produced memory deficit as evidenced in the reduced spontaneous alternation behavior.

5. Conclusion

The Datura metel leaves extract distrupted motor dysfunction, reduced total locomotive activity and produced memory deficit in treated mice. These effects were reversed by naloxone suggesting involvement of opiodergic transmission system.

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7. Conflict of interest statement

The authors declare no conflict of interest.

8. Authors contribution

TA- carried out animal study and manuscript writing; UG: Carried out the extraction of the plant extract and manuscript revision; IJ: Revised the manuscript; SO- Carried out HPLC finger printing of the plant extract.

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CLASSIFICATION OF SCHIZOPHRENIA PATIENTS BY USING GENOMIC DATA: A DATA MINING APPROACH

ŞİZOFRENİ HASTALARININ GENOMİK VERİ KULLANARAK KLASİFİYE EDİLMESİ; VERİ MADENCİĞİ YAKLAŞIMI

Kaan Yilancioglu*[1] , Muhsin Konuk[2]

Abstract

Genomic information obtained from robust analysis methods such as microarray and next generation sequencing reveals underlying disease mediating factors and potential diagnostic biomarkers. Data mining methods have been widely chosen for classification and regression studies of health sciences as well as other disciplines since the beginning. In the present study, public Gene Expression Omnibus (GEO) genome wide expression dataset (ID: GSE12679) consisting of mRNA transcripts of post-mortem brain tissues in schizophrenic and normal patients were analyzed by using Multilayer Perceptron Neural Network (MLP NN) algorithm. A set of most differentially expressed genetic features (p<0.001) were used for creating the classifier which can predict disease states in test set with ~82% accuracy. Differentially expressed genes used as classifying biomarkers gain utmost importance for revealing hidden underlying genetic factors associated with important psychiatric diseases. We could also suggest that such data mining tools might be applicable for developing genome-based diagnostic tools.

Keywords: Data Mining, Schizophrenia, Neural Network

Özet

Yeni nesil sekanslama ve mikrodizilim/çip analizlerinden elde edilen genomik veriler, çeşitli hastalıkların altında yatan moleküler sebepleri açığa çıkarmakta ve potansiyel tanı biyomarkörlerinin tanımlanmasını olanaklı kılmaktadır. Ortaya çıktığından buyana klasifikasyon ve regresyon analizlerini temel alan veri madenciliği metotları çeşitli çalışmalarda sıklıkla kullanılmaktadır. Bu çalışmada, NCBI GEO veri bankasından elde edilen, post-mortem beyin dokularından elde edilmiş beyin dokularının mRNA transcript analiz verileri MLP nöral ağ algoritması kullanılarak incelenmiştir. Çalışmada, dokular arasında ki transkripsiyon düzeyleri farkları analiz edilmiştir. Transkripsiyon düzeyleri farkı kullanılarak oluşturulan klasifikatör, şizofrenik ve normal hasta gruplarını %82 kesinlikle tahmin etmiştir. Psikiyatrik hastalıkların altında yatan etmenlerin aydınlatılmasında genetik biyomarkörlerin rolü günden güne önem kazanmaktadır. Ayrıca bu çalışmada kullanılan yöntemlere benzer yöntemlerin, genom temelli tanı yöntemlerinin bulunmasında katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: *Veri Madenciliği, Şizofreni, Nöral Ağ*

1. Introduction

Schizophrenia is a chronic brain disease that impairs normal behavior, speech and thinking processes. Diagnosis of the disease mostly relies on clinical examinations. The disease has many subcategories with various complex symptoms reflecting its biologically heterogeneous characteristics as a mental disease.

There has been an increasing effort for utilization of brain visualization and genetic variation analysis to find potential biomarkers for better understanding of underlying pathologies of brain diseases such as schizophrenia disorder. These kind of classifying perspectives in using disease related biomarkers including genomic information has gained utmost importance. Since the strong genetic association was demonstrated, more research activities have been held by using genomics combined with upgraded statistical methods (Orrù, Pettersson-Yeo, Marquand, Sartori & Mechelli, 2012). In this decade, use of machine learning algorithms, analyzing genomic data obtained from different platforms such as Microarray and Next Generation Sequencing (NGS) has gained importance. Machine learning algorithms have been suggested to be successfully utilized in training classifiers to decode genetic profiles of interest from genomic data (Lu & Han, 2003). Presently, limited work has been carried out using genotypic information to classify patients with brain disorders from normal subjects. One example demonstrated that SVMs can classify both bipolar and schizophrenia from normal subjects with high accuracy by using gene expression data (Struyf, Dobrin & Page, 2008). It is believed in that the schizophrenia may develop as a result of reciprocal action of genetic predisposition and environmental factors. Patients who were diagnosed with schizophrenia have immediate relatives with a history which clearly reflect the importance of genetic factors in development of the disease. However, even monozygotic twins have only about 42% concordance for the disease (Johnson, 2000). High-throughput methods such as microarray and recently next generation sequencing have generated vast information on numerous disease states. Advanced computational power in parallel with the advances on data mining tools enabled us to analyze these huge datasets. Recent genomic data obtained from microarray analysis on schizophrenia might help finding new genomic biomarkers and more importantly classify disease states for better diagnosis by the use of data mining approaches. In this study we present a supervised machine learning method to classify schizophrenic individuals that incorporates publicly available microarray gene expression data.

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2. Data and Analysis Methods

2.1. Data

Publicly available microarray expression data set (ID: GSE12679) was obtained from the GEO database (Harris et al., 2008). The data set was divided into two groups as endothelial and neuronal cell section groups. The samples belong to 7 schizophrenia and 9 non-schizophrenic normal patients for training and 5 schizophrenia and 6 control patients for testing respectively. For each subject, demographic and clinical information were described in the original paper (Harris et al., 2008). The expression data was obtained using Affymetrix Human Genome U133A GeneChip plus 2.0 oligonucleotide arrays containing 54,676 probe sets (Affymetrix, Santa Clara, CA). Probe level data was summarized using the robust multi-array average (RMA) method (Wu & Irizarry, 2005). The data set includes the RMA value of each probe set as a numerical feature. All computational analyses were done by using R (v3.1.2) (R-project.org, 2015). For microarray data preparation "LIMMA" package (Ritchie et al., 2015) was used.

2.2. Multilayer Perceptron Neural Network (MLP NN)

MLP neural networks are typically trained with back propagation (BP) algorithm. BP is an application of the gradient method or other numerical optimization methods to feed-forward ANN (Artificial Neural Network) so as to minimize the network errors. It is the most popular method for performing supervised learning in ANN research community. This dataset was given as an input to the most popular data mining tool WEKA 3.6 for analyzing the correct accuracy prediction of various MLP ANN algorithm (Cs.waikato.ac.nz, 2015).

2.3. Evaluation of Classifier

Performance of the classification technique was evaluated by means of Receiver Operating Characteristic (ROC) curves. ROC analysis allows to simultaneously compare classifier for different misclassification costs and class distributions. It is based on the notions of "true positive rate" (TP, also known as sensitivity or recall) and "false positive rate" (FP, also known as 1.0 – specificity). Area under the curve (AUC) value was calculated for the MLP NN classifier in order to evaluate the power of discriminative power of the method. For evaluation a discrete endothelial cell derived microarray gene expression data (top 500 DE genes with p value < 0.05) was used for training and neuronal cell derived microarray gene expression data was used for the test set.

3. Results and Discussion

3.1. Expression Analysis

2403 differentially expressed probes demonstrating p-value<0.05 (without multiple testing correction) were extracted among 54,676. First 50 most differentially expressed probes (Figure 1) were selected and pathway analysis was applied by using a free, open-source, curated and peer reviewed pathway database, Reactome (Reactome.org, 2015). Accordingly, genes namely PDK1 (226452_at) and GRIK1 (214611_at) were found to be directly related to neuronal system and they were further investigated. It was previously demonstrated that PDK1 CC genotype results to enhanced prevalence of schizophrenia. Moreover, decreased parietal P300 amplitude, which is a well-studied schizophrenic endophenotype and glutamate and glutamine concentrations are increased in the frontal lobe of PDK1 dysmorphic mice and human PDK1 CC individuals (Lang et al., 2015).

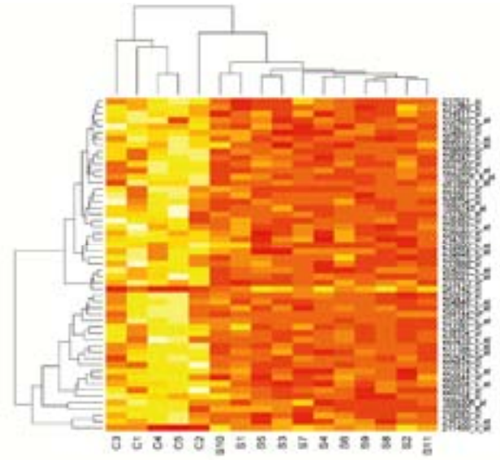

Figure 1: Heatmap of top 50 differentially expressed probes used for pathway analysis.

Recent studies have showed that a reduced abundance of Akt1 which is a crucial component of PDK1-Akt signaling in the brain was found to be significantly associated with

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schizophrenia, and Akt1 deficiency results to greater sensitivity of the disruption of sensorimotor gating mediated by amphetamine (Emamian, Hall, Birnbaum, Karayiorgou & Gogos, 2004). Another important finding is that the deficiency of GABAergic neurons in the prefrontal cortex is shown to be associated with schizophrenia. Loss of neocortical GABAergic neurons related to the absence of PDK1-Akt signaling was suggested to be linked with the pathogenesis of schizophrenia (Gonzalez-Burgos & Lewis, 2012). Glutamatergic function is one of the major hypotheses for schizophrenia. Within the glutamate system, the glutamate receptor ionotropic kainate-1 (GRIK1) gene is suggested to be particularly involved in schizophrenia. In this manner, the reduction of GRIK1 in the dorsolateral prefrontal cortex of schizophrenia patients was previously reported (Hirata et al., 2012).

3.2. MLP NN Classification and Classifier Performance

Microarray gene expression data (NCBI-GEO ID: GSE12679) consisting of both human endothelial and neuronal cells isolated from postmortem dorsolateral prefrontal cortex were used to generate the MLP NN classifier. A set of 500 top DE ($p < 0.05$ without multiple testing correction) genes between control (n=5) and schizophrenia (n=11) endothelial cells were used to train the classifier. Testing data used the same 500 DE gene set derived from neuronal cells as classifying attributes among 6 control and 5 schizophrenia samples. MLP NN model classifies schizophrenic and control patients at very high accuracy on testing data as ~82%. AUC was found to be 0.7. Other accuracy indicators were shown in Table 1.

The biggest limitation of the study was the shortage of sample size. Hence, the study should be considered as pilot study and sample size should be increased in further studies.

Table 1: Detailed accuracy measures of test set using MLP NN classifier. C represents control whereas S represents schizophrenia groups. On the left confusion matrix of the classifier on testing data is shown.

S	C		TP Rate	FP Rate	Precision	Recall	F-Measure	ROC Area	Class
5	0	S	0.667	0	1	0.667	0.8	0.7	C
2	4	C	1	0.333	0.714	1	0.833	0.7	S
Confusion Matrix			0.818	0.152	0.87	0.818	0.815	0.7	Weighted Avg.

4. Conclusions

Differentially expressed genetic markers used as classifying features in this MLP prediction analysis might be used for revealing important genes and gene families associated with schizophrenia disease and more importantly the classifier method might be applicable to developing effective Microarray-based diagnostic tests for this important psychiatric disease.

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WHEN IS THE APPROPRIATE TIME FOR FAMILIES TO BE INVOLVED IN ADDICTION TREATMENT; FROM THE BEGINNING? A RETROSPECTIVE EVALUATION OF INPATIENTS IN A PRIVATE HOSPITAL

BAĞIMLILIK TEDAVİSİNE AİLENİN NE ZAMAN DAHİL EDİLMESİ UYGUNDUR; BAŞLANGIÇTAN İTİBAREN Mİ? ÖZEL BİR HASTANEDE YATARAK TEDAVİ GÖREN HASTALARIN GERİYE DÖNÜK DEĞERLENDİRİLMESİ

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Abstract

Aim of the study is to investigate the referral type of dependent patients and its effect on treatment outcomes. This retrospectively designed study was conducted at a private hospital. The sample included 323 patients, and all patients' records were evaluated according to their referral type, sociodemographic features, criminal history, relapse rates and accompanying axis II disorders. Patients were reassessed six months after their discharge by semi-structured face-to-face or phone interviews with the patient or a family member. There were significant differences in some of sociodemographic characteristics, presence of criminal records, substance use patterns and relapse rates between voluntary inpatients and coerced inpatients. These results indicate a benefit in family participation at the very early stages of dependency treatment. Prospective studies are needed to evaluate whether family participation at the beginning of dependency treatment contributes to prognosis and patient's motivation.

Keywords: Addiction treatment, Family involvement, Treatment outcomes

Özet

Bu çalışmanın amacı bağımlılık tedavisi amacıyla hastaneye başvuran hastalarda, başvuru şeklinin ve bu şeklin tedavi sonuçlarına olan etkisinin araştırılmasıdır. Özel bir hastanede retrospektif olarak gerçekleştirilen bu çalışmaya, verilerine ulaşılabilen ve çalışmaya katılmayı kabul eden 323 hasta dahil edilmiştir. Hastaların başvuru şekli, sosyodemografik özellikleri, kriminal kaydı, relaps oranları ve eşlik eden eksen II psikiyatrik tanılar arasındaki ilişkiler araştırılmıştır. Taburcu edildikten altı ay sonra, yarı yapılandırılmış görüşme formu ile hastaların kendisi ya da bir aile üyesi ile yüz yüze ya da telefonla görüşme sağlanmıştır. Kendi isteği ile hastaneye başvuran hastalar ile bir başkası tarafından yönlendirilen hastalar arasında, sosyodemografik özellikler, criminal kayıt varlığı, uyuşturucu madde kullanım paternleri ve relaps oranları açısından istatistiksel olarak anlamlı fark saptanmıştır. Bu çalışmanın sonuçları, bağımlılık tedavisinin daha erken basamaklarında ailenin de tedaviye katılımının yararlı olduğuna işaret etmektedir. Bağımlılık tedavisinin başlangıcında, ailenin tedaviye katılımının prognoza ve hastanın tedavi motivasyonuna hangi ölçüde katkı sağladığına dair ilerleyen dönemde gerçekleştirilecek çalışmalara gereksinim duyulmaktadır.

Anahtar Kelimeler: *Bağımlılık tedavisi, Aile katılımı, Tedavi sonuçları*

1. Introduction

ASubstance and alcohol dependence is an important health problem which causes serious biological, social and economic costs, both for the patients and their families. Therefore, reducing the consequences of dependence is of great importance for public health. There have been studies investigating the effectiveness and outcomes of the treatments in dependent patients. But the first consideration of engaging the patient in the treatment programme is itself associated with many internal and external factors. Cognitive impairment caused by substances or alcohol may impact upon an individual's motivation to change, their ability to delay gratification and appreciation of adverse consequences (Goldstein, 2002; Brevers, 2014) and patients might refuse treatment owing to a negative attitude towards treatment or feelings of

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hopelesness (Opsal, 2013). There is conflincting evidence about the effectiveness of treatment referral with some studies indicating patients who enter treatment under legal pressure show better treatment responses (Brecht 2005; Knight, 2000; Kelly 2005; Collins 1983), some showed that readiness to change at the admission was not correlated to treatment outcomes (Burke, 2007), and some pointed out that length of stay, risk of voluntary or involuntary readmission were at least equal or greater to the involuntarily admitted patients (Kallert, 2008).

Substance users consist of a heterogenous group of individuals that differ in some dimensions, such as age, substance type, length and severity of their substance use, the extent and type of their criminal involvement, their social functioning and treatment motivation. Because motivation is a dynamic condition, mental health professionals and social service workers have looked for alternative management approaches for every individual, focusing on increasing the patients' awareness and upgrading their ability to actively participate and engage in treatment. Nevertheless, limited research about treatment referral has been conducted so far, and to the best of our knowledge only Bilici and colleagues have investigated the effects of personal volunteering and treatment motivation in substance users in Turkey (Bilici, 2014).

The aim of this study is to investigate possible differences in treatment outcomes and prognosis between dependent patients who were voluntarily admitted to an inpatient addiction clinic and those who were persuaded to take up treatment by their family.

2. Method

The study was conducted in a private psychiatric hospital, between February 2012 and August 2014. This center comprises 49 inpatient beds and accepts patients from all over Turkey and some Middle Eastern countries. This retrospectively designed study was approved by the Ethical committee of Uskudar University.

This study included the medical records of 323 inpatients who met DSM-IV TR diagnostic criteria for Alcohol and Substance dependence. The excluding criteria for this study were any neurological comorbid disorder, dual diagnosed patients and mental retardation. After a detoxification period, all patients were evaluated by clinical examination and Turkish version of Structured Clinical Interview for DSM-IV (SCID-I) (First, 1997; Corapcioglu 1999) was used as a screening test. Sociodemographic variables of patients, presence of criminal record and presence of psychiatric comorbidity were also assessed. Referral type was determined by a single question; "Have you attended this treatment on your own will or has your family motivated you to seek treatment?" All patients were reassessed six months after their discharge by semi-structured face-to-face or phone interviews directly with the patient or with a family member.

2.1. Statistical Analysis

Statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL, USA) for Windows. Categorical variables in the study were compared by means of chi-square statistics. One-way Anova was used to compare continuous variables. Values were stated as median with 25%- 75% values and mean ± standard deviation (SD). Descriptive statistics were also calculated as frequency or percentage. The univariate analyses to identify variables associated with "referral type" was investigated using Chi-square, Fisher exact, Student's t-test and Mann-Whitney U test where appropriate. For the multivariate analysis, possible factors identified with univariate analyses were later entered into the logistic regression analysis to determine independent predictors of patients outcome. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type-I error level was used to infer statistical significance. For all analyses, $p < 0.05$ was regarded as statistically significant.

3. Results

In our study, the medical records of 323 patients (288 men, 35 women; M age=32.5) were scanned retrospectively. Among these patients, 59% were single, 30% were married or cohabiting. Patients had completed 11.5 years of education, on average (SD=±2.4). Approximately 14% of the patients reported having a regular job and more than half of the patients (53.6%) reported being unemployed. (Table 1) Some 199 (61.6%) patients had no history of criminal records and 59 (18.3%) had experienced substance-related conviction. Among all of the patients, 8 (2.5%) had a comorbid Cluster A personality disorder, 203 (62.8%) met the criteria for Cluster B personality disorder and 27 (8.4%) had comorbid Cluster C personality disorder (Table 2). Some 124 (38.4) patients had received psychiatric treatment prior to referral, 78 (24.1%) of them had a history of hospitalisation due to substance use, 91 (28.2%) had been hospitalized more than once and 99 (30.7%) reported alcohol as their primary substance of abuse, 74 (22.9%) reported cannabinoid and its derivatives, 16 (5%) reported heroin, 7 (2.2%) reported cocaine, 3 (0.9%) reported volatile substances, and 81 (25.1%) reported mixed drug abuse(Table 3).

Table 1: Sociodemographic characteristics of the inpatients

	voluntary (n:115)	persuaded (n:208)	t/χ2	p
Age (mean±SD)	33.80 (10.70)	31.70 (10.61)	1.70	0.550
Sex n (%) Female Male	 14 (12.2) 101 (87.8)	 21 (10.1) 187 (89.9)	 0.331	 0.565
Duration of education (mean ± SD)	11.62 (3.01)	11.45 (2.64)	0.506	**0.044**
Marital Status n (%) Single-widow(er) Married Separated	 59 (51.3) 40 (34.8) 16 (13.9)	 131 (63) 58 (27.9) 19 (9.1)	4.438	0.109
Employment Status n (%) Unemployed Employed (temporarily/ part time) Employed (permanently/ full time)	 50 (43.5) 27 (23.5) 38 (33)	 123 (59.1) 67 (32.2) 18 (8.7)	15.087	**0,001**

Table 2: Sociodemographic features of the inpatients

	voluntary	persuaded	t/χ2	p
Duration of substance use (year)(mean±SD)	10.39 (8.32)	10.32 (8.72)	0.074	0.892
Age at first substance use (mean±SD)	18.38 (3.95)	18.09 (4.17)	0.622	0.386
Number of hospitalisations (mean±SD)	1.64 (1.21)	2.11 (2.46)	-1.913	**0.047**
Presence of criminal records n (%) No records Probation Simple offense Major crime	 84 (73) 17 (14.8) 10 (8.7) 4 (3.5)	 115 (55.3) 42 (20.2) 41 (19.7) 10 (4.8)	10.97	**0.012**
Use of SCs n (%) Yes No	 41 (35.7) 74 (64.3)	 98 (47.1) 110 (52.9)	3.97	**0.046**
Slip n (%) Yes No	 70 (63.6) 40 (36.4)	 143 (72.6) 54 (27.4)	2.663	0.103
Relaps n (%) Yes No	 59(53.6) 51 (46.4)	 134 (68) 63 (32)	6.256	**0.012**
Drop n (%) No Yes	 68 (59.1) 47 (40.9)	 123 (59.1) 85 (40.9)	0.000	0.99
Time to slip* (days) (n: 213) median (25%- 75% values)	 40 (23.75-90)	 30 (15-90)	-0.638	**0.042**
Time to relapse** (days) (n:193) median (25%- 75% values)***	 50 (30-120)	 47 (20-100)	0.022	0.348

* Time to slip was assessed among the patients who reported slip
** Time to relapse was assessed among the patients who reported relapse.
*** Median values are given due to skewed distributions of time to slip and time to relapse

Table 3: Substance use profiles in patient groups

	voluntary (n:115)	persuaded (n:208)	χ2	p
Alcohol dependency n (%)	42 (36.5)	57 (24.4)		
Cannabis and its derivatives n (%)	19 (16.5)	55 (26.4)		
Heroin dependency n (%)	10 (8.7)	6 (2.9)	10.745	0.057
Cocaine dependency n (%)	2 (1.7)	5 (2.4)		
Polysubstance dependency n (%)	41 (35.7)	83 (39.9)		
Inhalant dependency n (%)	1 (0.9)	2 (1.0)		

Of the total 323 patients, 115 (35%) joined the treatment under their own motivation and 208 (65%) were referred to the hospital under pressure from family members or friends. The mean hospitalisation time was 21±20, 5 days for all of the patients.

The voluntarily admitted group had a greater duration of education and higher occupation rates. Voluntary inpatients had lower recorded number of hospitalisations and fewer criminal records. It was also determined that inpatients persuaded by their family tended to use synthetic cannabis (SC) (35.7% in voluntarily admitted group and 47.1% in persuaded group) and relapse rates were significantly higher in this group (p=0.012).

Time to relapse was longer in the voluntarily admitted group and voluntary inpatients were less likely to have an accompanying Axis II disorder (Table 4). Inpatients from the persuaded group had higher rates of psychotic symptoms (Table 5). These symptoms were observed by the doctors and noted, none of these patients met the criteria for any psychotic disorder. There was no difference in age, sex, drop rates, and time to relapse between the voluntarily admitted group and persuaded group. On the other hand, there was a relationship between treatment referral type and personality disorder comorbidity, presence of criminal record and relapse rates (Table 6).

Table 4: Comparison of presence of axis II disorders in patient groups

	voluntary (n:115)	persuaded (n:208)	χ2	p
Axis II diagnosis n (%)				
No diagnosis	35 (30.4)	50 (24.0)		
Cluster A	2 (1.7)	6 (2.9)		
Cluster B	61 (53)	142 (68.3)		
Cluster C	17 (14.8)	10 (4.8)	13,09	0.004

Table 5: Distribution of psychotic symptoms

	voluntary (n:115)	persuaded (n:208)	χ2	p
Psychotic symptoms n (%)	12 (10.4)	58 (27.9)	29.686	**p<0.01**

Table 6: Distribution of referral type in binary logistic regression when employment status, presence of criminal records, use of SCs, relapse, Axis II comorbidity, accompanying psychiatric symptoms were independent variables

Risk Factor*	RR (%95 GA)**	p
Employment status	0.760 (0.578 – 0.999)	0.049
Presence of criminal record	1.583 (1.164 – 2.153)	0.003
Use of SCs	0.810 (0.487 – 1.346)	0.415
Relapse	0.526 (0.319 – 0.866)	0.012
Axis II diagnosis	0.983 (0.768 – 1.258)	0.891
Accompanying psychotic symptoms	1.123 (0.927 – 1.361)	0.236

*variables entered: Employment status, Presence of criminal record, Use of SCs, relapse, Axis II diagnosis, Accompanying psychotic symptoms
**RR: odds ratio and %95 confidence interval

4. Discussion

The aim of this study is to provide some additional information about the impact of treatment referral on treatment outcomes in dependent patients. Different from previous studies, our sample included inpatients using synthetic cannabinoids.

All forms of voluntary treatment carry the potential to have some component of pressure and persuasion. Sometimes, pressure from family and friends might be favourable to initiate or continue therapeutic process. The persuasion might vary from verbal encouragement to

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threat of social consequences like divorce, separation or loss of financial support (Stevens, 2006). In this study none of the 323 patients were coerced (mandated) for addiction treatment.

The significantly lower duration of education, and higher numbers of hospitalizations, higher rates of presence of criminal records, relapses, and comorbidity axis II diagnosis in the persuaded group in this study was not surprising. Together with frequently observed Cluster B personality characteristics including impulsivity, low frustration tolerance, and an inability to delay gratification, most of the substance users' motivation for treatment is argued to be poor, unstable, and inconsistent (Maddux, 1998). In the literature, the association between substance use and crime is well-documented, and frequency and severity of criminal behavior has been thought to rise and fall with the level and kind of substance use (Chaiken, 1990; Anglin, 1989). Therefore, one of the reasons that patients are directed to treatment by their families may be because of functional and social impairments and distress emanating from their dependency.

In addition to sociodemographic features affecting treatment referral, we have investigated the presence of synthetic cannabis (SC) use in this patient group and we determined that SC use was significantly higher in the persuaded patient group. When compared to cannabis, SCs are associated with severe intoxication symptoms, more intense withdrawal and craving symptoms, more functional impairments and negative impacts on both education and employment (Papanti, 2013), and because of this families might develop higher treatment seeking tendencies than other patients. In a recent study conducted by Nurmedov et al, (2015) lower levels of education, lower employment levels, and greater numbers of criminal records were more likely to be associated with SC use, when compared to cannabis.

Significant differences in employment status might be associated with the source of financial support. Families might be persuading the patient to seek treatment due to financial burden caused by the dependency. Marlowe and colleagues defined financial reasons as an important treatment entry pressure (Marlowe, 2001). Higher levels of hospitalisation in the persuaded group might be asssociated with the treatment motivation. In their recent study, Bilici and colleagues pointed out that higher motivation is related with voluntarily treatment admission, desire for help and treatment readiness (Bilici, 2014). A limitation of this study is that the motivation levels of the patients were not determined, but accepting family persuasion as an external motivation might help mental health professionals to discover or design new treatment approaches.

Higher relapse rates in the persuaded group are similar to the previous studies (Loneck, 1996). Psychotic symptoms were significantly higher in the persuaded group and this might be related to the effects of the substances they used, the severity of their dependence and impairments in decision-making. This might also be associated with higher synthetic cannabis use in persuaded group (William, 2014)

As stated before, several personality disorders are associated with addiction (Douzenis, 2012). In our study, Cluster B peronality traits were associated with persuaded treatment referral. The distribution of referral type in binary logistic regression when employment status, presence of criminal records, use of SCs, relapse, Axis II comorbidity, accompanying psychotic symptoms were independent variables showed that employment status, presence of any criminal record and relapse can predict results of persuaded treatment. Previous studies also emphasized the association between antisocial personality characteristics, criminal behaviour and substance use (Klag, 2005).

To the best of our knowledge, this is the first study evaluating the referral type in dependent patients, including synthetic cannabinoid users. The widespread collectivistic familial and societic culture type in Turkey, perception of drug or alcohol use as immoral and self-destruction and disability of a family member due to dependence does affect the other family members. Besides financial and health problems in the short time, being exposed to psyhopathological role models and negative identities about dependence force families to act at once. These cultural motives might play an important role in persuading patients in Turkey.

Several limitations of this study should be mentioned. The treatment motivation wasn't measured, the study was retrospectively designed and other factors affecting the prognosis or results of this treatment were not examined. Prospectively designed future work using motivation scales with longer follow up intervals would contribute valuable information to the literature.

The results of this study indicate that substance users are subjected to a broad range of pressures that contribute to their entry into treatment, suggesting that prediction of treatment retention and treatment outcomes might be improved by considering and assessing the full range of treatment entry pressures including their individual and interactive influence on their social environment.

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N-ACETYLCYSTEINE IN TREATMENT OF TRICHOTILLOMANIA

TRİKOTİLOMANİDE N-ASETİLSİSTEİN KULLANIMI

Hüseyin Bulut[1], Gökben Hızlı Sayar[*2]

Abstract

Trichotillomania is a chronic mental disorder characterized by recurrent hair-pulling. Hoarding, excoriation and trichotillomania are classified as obsessive-compulsive related disorders in DSM-5, which share similar clinical presentations, characterized by inappropriate and excessive repetitive behaviors and dysregulation of inhibitory control processes. Research evidence suggests that abnormalities in the cortico-striato-thalamic-cortical circuits are one of the key factors underlying the pathophysiology of obsessive-compulsive related disorders, including trichotillomania. Glutamate is the primary neurotransmitter within the cortico-striato-thalamic-cortical circuits. Therefore, the use of glutamate-modulating agents is subject to interest for obsessive-compulsive related disorders. N-acetylcysteine, a derivate of the amino acid L-cysteine, has been explored as potential therapy for obsessive-compulsive related disorders, including trichotillomania. Pharmacotherapies that target the prefrontal glutamatergic system, such as N-acetylcysteine, may correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. Even a limited number of studies are suggesting that N-acetylcysteine is a promising treatment option, these studies did not assess treatment effects exceeding 3-4 months treatment period. Longer term effects of N-acetylcysteine therapy in trichotillomania require further evaluation.

Keywords: N-acetylcysteine, obsessive compulsive related disorders, treatment, trichotillomania.

Özet

Trikotilomani tekrarlayan saç çekme ile karakterize kronik bir ruhsal bozukluktur. DSM-5'te istifleme, ekskoriasyon ve trikotilomani, uygunsuz ve aşırı tekrarlayıcı davranışlar ve inhibitör kontrol süreçlerinin bozulması ile karakterize benzer klinik sunumlar paylaşan bozukluklar olarak "obsesif-kompulsif ilişkili bozukluklar" olarak sınıflandırılır. Araştırma bulgularına göre kortiko-striato-talamik-kortikal devrelerde anormallikler, trikotilomaninin de dahil olduğu obsesif kompulsif ilişkili bozuklukların patofizyolojisinde yer alan en önemli faktörlerden birisidir. Glutamat kortiko-striato-talamik-kortikal devrelerde birincil nöroiletkendir. Bu nedenle, glutamat modüle edici ajanların kullanımı, obsesif kompulsif ilişkili bozukluklar için ilgi çekicidir. N-asetilsistein, amino asit olan L-sisteinin bir türevidir ve trikotilomani de dahil olmak üzere, obsesif kompulsif ilişkili bozukluklarda potansiyel tedavi olarak incelenmiştir. N-asetilsistein gibi prefrontal glutamaterjik sistemi hedefleyen farmakoterapiler, trikotilomani belirtileri ve altta yatan patofizyolojik bozukluklarda etkili olabilir. Sınırlı sayıda çalışmada N-asetilsistein umut verici bir tedavi seçeneği olarak izlenmiş olsa da bu çalışmalar 3-4 ay tedavi süresini aşan etkinliği değerlendirmemiştir. Trikotilomaninin N-asetilsistein ile tedavisinin uzun dönemli etkileri incelenmelidir.

Anahtar Kelimeler: *N-asetilsistein, obsesif kompulsif ilişkili bozukluklar, tedavi, trikotilomani*

1. Introduction

Trichotillomania is chronic mental disorder characterized by recurrent hair-pulling. In Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of trichotillomania requires that recurrent hair-pulling must result in hair loss; an indication of an attempt to decrease or stop hair-pulling must also be necessary. Furthermore, the diagnosis of trichotillomania requires hair-pulling not to be better accounted for by another disorder or being a result of a general medical condition. Finally, for a diagnosis of trichotillomania, recurrent hair-pulling must cause significant distress or impairment in functioning. Hoarding, excoriation and trichotillomania are now categorized as obsessive-compulsive related disorders (OCRD) in DSM-5. OCRD and OCD share similar clinical presentations, characterized by inappropriate and excessive repetitive behaviors and dysregulation of inhibitory control processes, suggesting similar pathophysiology (Chamberlain et al., 2006).

Evidence suggests that abnormalities in the cortico-striato-thalamic-cortical circuits are one of the key factors underlying the pathophysiology of OCDR, including trichotillomania. Particularly, orbitofrontal cortex, anterior cingulate and ventromedial striatum hypermetabolism has been linked to OCD (Ahmari et al., 2013). Glutamate is the primary neurotransmitter within the cortico-striato-thalamic-cortical circuits and evidence suggests that abnormal glutamate metabolism is manifested in subjects with OCRD (Chakrabarty et al., 2005). Also, high levels of glutamate result in excitotoxicity and oxidative stress

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(Burdo et al., 2006). Oxidative stress markers, lipid peroxidation, have been detected in serum samples of patients with OCDR (Ozdemir et al., 2009). Also, higher levels of oxidative stress found to be correlated with symptom severity (Chakraborty et al., 2009).

Glutamate's role in the cortico-striato-thalamic-cortical pathway and its pro-oxidant properties supports its suggested role in the pathophysiology of trichotillomania and other OCRD. The efficacy of glutamate modulating agents on regulating impulse control is becoming increasingly evident (Grant et al., 2009). Thus, the application of glutamate-modulating agents is of growing interest for OCRD. More recently, N-acetylcysteine (NAC), a derivate of the amino acid L-cysteine, is promising as a potential therapy for OCRD, including trichotillomania.

1.1. Nac

NAC is the acetylated precursor of the L-cysteine. NAC is a well-known mucolytic agent. NAC has demonstrated neurochemical, antioxidant, anti-inflammatory, mucolytic and hepatoprotective activity (Berk et al., 2013). It has been used in clinical practice for the treatment of numerous disorders. Treatment of acetaminophen intoxication, acute respiratory distress syndrome, bronchitis, chemotherapy-induced toxicity, HIV/AIDS, chemical induced nephropathy are some of the numerous treatment indications for NAC (Zafarullah et al., 2003; Atkuri et al., 2007;, Millea, 2009; Radomska et al., 2012).

NAC is available in intravenous, oral and inhale forms. It has been associated with mild side effects (Atkuri et al., 2007). It has a half-life of 5.6 h after a single intravenous administration, and renal excretion clears 30% of it. NAC has a low bioavailability (almost %5). The redox exchange reactions between NAC, cysteine and cysteine proteins occur in the plasma, leading the synthesis of glutathione (Radtke et al., 2012). Glutathione is an important antioxidant involved in neurotransmitter signaling (Sies, 1999).

There is growing evidence that NAC has an effect on the glutamatergic system (in the nucleus accumbens) which may target symptoms of compulsive behaviors (Kalivas, 2005). Therefore, NAC may correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. NAC increases glutathione and cysteine levels in glial cells (Mayer, 1994); therefore it may be protective to glial cell functioning during hyperglutamatergic states (Hart et al., 2004). Glial cells are capable of the clearance of glutamate from the synapse; that may be essential for the glutamate-modulating effects of NAC.

1.2. Nac and Psychiatric Disorders

NAC is a promising agent for the treatment of neuropsychiatric disorders due to the multi-factorial etiology that involves inflammatory pathways, oxidative stress, glutathione metabolism, glutamatergic transmission and mitochondrial function (Berk et al., 2013). In recent years, several controlled randomized clinical trials have demonstrated the efficiency of NAC as an adjunctive treatment option for methamphetamine, nicotine, cannabis and cocaine addiction (Van et al., 2002; LaRowe et al., 2007; Grant et al., 2010; Gray et al., 2012), pathological gambling (Grant et al., 2007), obsessive–compulsive disorder (Lafleur et al., 2006), trichotillomania and skin picking (Grant et al., 2009), schizophrenia (Lavoie et al., 2008), bipolar disorder (Berk et al., 2008) and autism (Hardan et al., 2012).

NAC was also used to modulate inflammatory pathways in central nervous system, reducing the levels of pro-inflammatory cytokines in traumatic brain injury (Beloosesky et al., 2012). NAC can modulate the levels of extracellular glutamate, which is important in excitotoxic damage models of schizophrenia and addiction (Baker et al., 2003). NAC modulates intracellular calcium, which is relevant to the dysregulation of receptor-mediated calcium release, reported in psychosis (Berk et al., 2000). It has been also demonstrated that NAC blocked amphetamine-triggered dopaminergic response in vivo and prevented the down-regulation of dopamine transporter that is highly associated with neuropsychiatric disorders (Hashimoto et al., 2004).

1.3. Nac in Treatment of Trichotillomania

Although trichotillomania has been well described, data regarding treatment options is limited. A recent meta-analytic study of randomized treatment trials in adults demonstrated that habit reversal therapy, have the greatest efficacy in the treatment of trichotillomania. Selective serotonin reuptake inhibitors are widely used in the treatment of trichotillomania, despite evidence that their efficacy is no greater than placebo (Bloch et al., 2013). A recent randomized trial has also suggested that olanzapine was more effective than placebo in adults with trichotillomania (Van Amerringen et al., 2010). Pharmacotherapies that target the prefrontal glutamatergic system, such as NAC, are promising options for correcting the underlying pathophysiologic abnormalities and symptoms of trichotillomania.

In a 12 week, double-blind, placebo-controlled trial, Grant et al. tried to determine the efficacy and tolerability of NAC in adults with trichotillomania. Their study group was composed of 50 individuals with trichotillomania (45 women and five men; with a mean age of 34.3) were administered either NAC (dosing range, 1200-2400 mg/d) or placebo for 12 weeks. Patients assigned to receive NAC had significantly greater reductions in trichotillomania symptoms. Fifty-six percent of patients "much or very much improved" with NAC use compared with 16% taking the placebo. No adverse events occurred in the NAC group, and NAC was well tolerated (Grant et al., 2009).

In another double-blind placebo-controlled trial (N=39), no significant differences in improvement between NAC and placebo groups were reported in children and adolescents with trichotillomania, both groups significantly improved (Bloch et al., 2013). In the NAC group, 25% of subjects were responded to treatment, compared to 21% in the placebo group. The authors suggest that their study results may differ from previous studies reporting a positive response to trichotillomania, due to a younger

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aged sample or more severe trichotillomania symptoms among the placebo group in their study. Although research on the developmental course of trichotillomania is sparse, there is some evidence to suggest that children and adults experiencing hair pulling are fundamentally different. The authors reported that among children with trichotillomania, urge and severity of hair pulling increases with age. It has been hypothesized that NAC may work in hairpullers by reducing the frequency and intensity of the urge to pull. This hypothesis arises from the substance abuse literature, in which NAC has been demonstrated to modulate glutamate in the nucleus accumbens and reduce drug-associated cravings. If it is true that NAC acts by reducing pulling associated urges, it may be that NAC has decreased efficacy in children compared to adults.

Promising results were obtained from the case report of Rodrigues-Barata et al. (Rodrigues-Barata et al., 2012) involving two females diagnosed as trichotillomania. Both cases were non-responsive to previous psychotherapy and SSRIs. Both patients demonstrated complete regrowth of their hair within three months when supplemented with 1,200 mg/day of NAC. In another case of a 40-year-old female with trichotillomania, improvement reported with a treatment of NAC 1200 mg twice daily within three weeks (Odlaug et al., 2007). Another case of a 28-year-old male with nail biting and trichotillomania, significant improvement observed with 1,800 mg/day NAC within two weeks. Symptoms were relapsed when the failed to use the NAC for two weeks (Odlaug et al., 2007106).

Similarly, NAC was also used in another OCRD, namely, skin picking. An open-label prospective case-series (N=35) of individuals with Prader–Willi syndrome demonstrated a significant improvement in skin-picking symptoms and skin lesions in the majority of persons with 12 week NAC treatment (Miller & Angulo, 2014). Several adult case series have also reported a decrease in the frequency of skin picking behavior with NAC treatment (Grant et al., 2012; Silva-Netto et al., 2014). All the studies showed positive effect, so NAC seems like a promising treatment option for skin picking, but further controlled studies are needed.

2. Conclusion

NAC could be an effective and well tolerated treatment option for people with trichotillomania. But trichotillomania is a chronic disease which may require long term therapy. The case series in adults reported improved hair growth with NAC. The results however are mixed as one out of two controlled trials was negative for improvement. Larger clinical trials are needed to confirm the effectiveness of NAC in trichotillomania. Even several studies are suggesting that NAC is a promising treatment option; these studies did not assess treatment effects beyond 3-4 months treatment period. Longer term effects of NAC therapy require further evaluation.

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THE MORE BRAIN PARTS ARE INVOLVED THE BETTER IS LEARNED AND PERFORMED

ÖĞRENME VE PERFORMANS, DEĞİŞİK BEYİN BÖLÜMLERİNİN KATILIMI ORANINDA ARTAR

Levón Antikacioglu*[1]

Abstract

In this article, has been discussed the characteristics that make knowledge unforgettable. The attention has been attracted to the role of the involvement of multiple brain layers, locations and connections, in learning and performing process. It is sustained that "learning and performing are systemic issues" and proposed that "a successful learning and performance is directly proportional to the sum of created appropriate personal ties – created personal functional connectomes - in the entirety of the central nervous system" and the "strength or weakness of a learned material is directly proportional to the quantity, quality and intensity of the ties made within the entire Central Nervous System Network". In other terms; the more brain parts are involved the better is learned and performed. And, it has been outlined that "the same fact is the explanation of why in different subjects, the memory storages are relatively in different localities, and in vague concentrations."

Keywords: Learning and performing, functional connectomes, attitudes-habits, dissonance, phobias, biases and prejudice.

Özet

Bu makalede, bilgiyi unutulmaz kılan karakteristikler tartışılmıştır. Bu amaçla dikkatler, çoklu beyin katmanlarının, lokasyonlarının ve bağlantılarının, öğrenme ve performansa katılımlarının rolüne çekilmiştir. Sonuçta, "öğrenme ve performansın sistemik bir konu olduğu" ve "başarılı bir öğrenme ve performansın, Merkez Sinir Sisteminin bütünü içinde, kurulmuş olan uygun kişisel bağlantıların (yaratılmış kişisel fonksiyonel konnektomların) toplamı ile doğru orantılı olduğu" ve "öğrenilmiş materyalin zayıf ya da güçlü oluşunun, Merkez Sinir Sistemi Ağının bütünü içindeki bağlantılarının kalite, kantite ve yoğunluğu ile doğru orantılı olduğu" teklif edilmiştir. Başka bir deyişle, "öğrenme ve performansın, beyin bölgelerinin katılımı oranında arttığı" ileri sürülmüştür. Bu olgunun da, "farklı bireylerde hafıza depolamasının neden, nisbi olarak farklı yerlerde ve düşük yoğunluklarda oluştuğunu", açıkladığı belirtilmiştir.

Anahtar Kelimeler: *Öğrenme ve performans, fonksiyonel konnektom, tutum-adet, dissonans, fobi, önyargılar*

1. Introduction

Everybody is familiar to the fact that some learned materials are easily forgettable. Some others by some effort are recoverable. But some others instead are never forgotten.

It looks that the crucial point stands in the ability of connecting, tying, associating the learning materials through multiple receptors, to multiple brain structures.

In fact; there is no need of scientific reference to proof that swimming, driving, cycling, once learned are never forgotten. For any mature adult know perfectly this fact by his/her daily life. If they are not performed for some years, it's true that they can fade out, but are never erased; these skills after some training effort can easily be recovered.

We do not forget the cultural milieu where we lived our babyhood, childhood and youth: The accents, smells, tastes, sounds, views, weaved and embedded in each other's context, which in turn form what we call in general manner, ritual, tradition etc., once printed in mind, are never forgotten. Even after being away for years from our homeland, just by a single clue, we can be precipitated by our lovely memories in details.

Experts in any profession can more easily memorize novelties concerning the area of their expertise than laymen or novices. The cognitive load plays a substantial role in facilitating performance (Sweller 1988).

Mnemonics generally develop strategies to memorize, by giving meaningless items a meaningful context (Purves, D. at al. 2001). For this purpose, they use visual imagery (Lewinsohn, P. M., Danaher, B. G., & Kikel, S. 1977) make associations (Purves, D. at al. 2001) and exercise (Ericsson, K. A. 2003). In these ways they facilitate their learning and remembering.

The positive effects on learning and performance of motivation (Leeper, R. 1935; Pintrich, P. R. and Schunk, D. H. 2002), will power or self-regulatory strategies (Zusho, A. at al., 2003), attitudes (Gardner, R. C. 1985), interests (Krapp, A. 1999), contextualization, personalization, and choice (Cordova, D. I. and Lepper, M. R. 1996), are all well documented facts.

During military services, trainings are done in groups interactively. Along with their verbal orders, they count loudly their steps and they act or perform or sing songs, marches etc. All these are, effective factors facilitating the learning and performance.

The underlying assumption of polygraphs is that, any question/word/phrase which we pose to the participant, if for him is of emotionally critical value, will evoke autonomic reactions (Bashore, T. R. and Rapp, P. E. (1993). It can be true that a lie cannot produce any "specific" psychophysiological reaction. It can be true that "especially trained" participants can cheat the polygraph. But those are facets that do not interest our argument. What interests instead, is, that there are findings by fMRIs, suggesting the involvement of frontal cortical regions during lying and that, "the neural substrates responsible for cognitive control of behavior may also be engaged during deception" (Phan, K.L. et al. 2005). Other studies also suggest that measures of the brain electrical activity, can be used to infer the possession of information in persons attempting to conceal it (Bashore, T. R. and Rapp, P. E. (1993). Thus, in any case we can conclude that critical information and their processes have multidirectional implications. Almost nothing is limited to specific locations only.

The purpose of the inpatient, substance abuse treatment-rehabilitation centers, which are generally in isolated locations, are primarily based on the principle of loosening and cutting the ties which are triggering the abusers' habits. Because it is well known that if the abuser, undergoes an outpatient treatment, as long as he/she conducts his/her daily life in his/her usual environment, will eventually be facing the risk of being attracted by some of those countless clues, leading him/her to his/her old habits. So their treatment is based on the acceptance that abusing is strongly associated to a myriad of stimuli and, at any time, any of them, can be able to recall the habit.

As in the above mentioned examples, there are many other cases which are confirming that learned materials are never isolated and independent, but strongly interweaved.

Aside those examples, important information undoubtedly is that since 1920, thanks to the series of ingenious experimental researches conducted by Karl Spencer Lashley, we understood that in our brain, our specific memories do not reside in specific locations.

It is clear that visual memories are related to occipital or sensory memories to sensory cortex, but they are only loosely concentrated. We do not have in our brain, specific locations, confined with marked borders, to store specific memories or abilites, as phrenologists in the past thought. It looks that *"the memory storage is deployed in many locations and recalled in a holistic way."*

On the other hand, there are experiments done by neuroimaging techniques and/or EEG, trying to localize positive and negative emotions. Accordingly it is observed "relative left-hemispheric activation for positive emotions, and, relative right-hemispheric activation for negative emotions (Ahern, G. L. and Schwartz, G. E., 1985)". Similar researches have been done also under hypnosis, and have been found that stronger activity for anxiety, was located, more right then relaxation, and, relaxation located more left then anxiety (Isotani,T, 2001). On the other hand, even if we locate those sub-cortical emotional modulators, we are not able to exactly identify, how those emotional centers are associated in different individuals. For they are always differently associated; take the example of the phobic reaction evoked in one person by a dog, in another one, by a spider. Thus, it is obvious that although both are using a common emotional center, their functional connectomes are different.

Finally, whatever is the material we are learning and associating, in neurophysiological terms we are dealing with an electrical-chemical-electrical conductivity between our neurons. And neurophysiological conductivity works by well-known and defined principles.

2. Discussion

Therefore it looks that we have good reasons to think that;

Probably cycling, driving, swimming all need the involvement of most of the proprioceptive, interoceptive and extereoceptive receptors and their reciprocal interaction, either during learning or performance. All the extremities as well, (in short the entire body), even the "apparently unrelated" (like any sensation perceived during the activity) parts, are all participating-contributing to their learning and performance.

Probably living for a long time in homeland, especially during our developmental ages, gives us the possibility of tying almost any type of experiences, through our extereoceptive, proprioceptive and interoceptive receptors and their reciprocal interactions, to our surrounding cultural environment.

Probably expert professionals have had the possibility and time of associating and connecting almost every possible situation in which they live, to their job. In this way their professional activity, as is highly associated to their interoceptive, proprioceptive and extereoceptive experiences, they have acquired the ability of remembering and performing their profession at the presence of any of them. Thus, any new knowledge concerning their profession, can inevitably and easily find a connection and meaning, among the accumulated old ones. And the newly arrived knowledge also, quickly goes tied to the old repertoires. And, as a natural consequence, facilitates its acceptance. (A novice instead doesn't even know to which hook he/she can hang the completely new knowledge; and gets confused, hesitates and becomes unfruitful.)

Eventually mnemonics, while learning even totally

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meaningless materials, by giving them meanings or, associating them to visual imageries, are tying the new material to previously well-known ones.

Motivation, will power, self-regulation, attitudes, contextualization, interest, personalization, vigilance are all, in close relation with our previously learned deeper materials and/or sub-cortical areas. Eventually the arousal of the deep-old materials, are actively contributing to the participation and intervention of tying and gluing the new ones, to the old ones.

Everything aside, "operant and classical conditioning themselves, are almost purely associative procedures."

In military training, learning and performance, is enjoying all the facilitating effects of learning in groups. As already documented since years, in class one psychology undergrad lessons, learning in groups is a facilitating agent.

Independently from discussions on polygraphs, whether they can be used or not as a lie detector, nobody is refusing the fact that critical learning and performance have multiple ligaments between mesencephalon and cortical areas.

Attempting to treat substance abusers far from their daily life, is mainly to prevent the remembrance of the substance by the multitude of eventual clues, that neither the patient nor the therapist, are aware of.

It is beyond doubt that every researcher is accepting the complex multidirectional relation of the newly learned materials, with the previously learned ones. In fact *"Different regions of the brain must communicate with each other to provide the basis for the integration of sensory information, sensory-motor coordination and many other functions that are critical for learning, memory, information processing, perception and the behavior of organisms"* (Miltner, W. H. et al., 1999).

By combining the above discussed facts, with the findings of Lashley, it seems to be clear that even the simplest learning and performing behaviors, have associations with the *entire Central Nervous System Network.* Thus it seems to be obvious that learning and performing are absolutely a *"systemic issue".* But these ties hypothetically, will be varying in *"quality, quantity and intensity"*, and, will be vaguely localized, because "in learning and performing, we are not dealing with neuroanatomical but with *functional connectomes."*

The functional connectomes while in action, reveal themselves in form of electrical activities, they can perfectly be detected by EEG/qEEG or by more sophisticated neuroimaging technics.

The problem stands simply in formulating the above assumption in an adequately measurable way.

3. Conclusion

As a natural consequence, "the above mentioned statements explain perfectly why the old habits are difficult to forget or change; because any habit or old belief or knowledge or phobia or bias or attitudes, are all deeply embedded and deployed into every aspect of our daily life, experience and repetitively strengthened by reinforcements, almost every instant. Thus, any attempt to make forget or change them, encounters a serious resistance, because discords and dissonates with the rest of the *entire* CNS Network".

Therefore, it is time to deduct that probably *"in learning and performing processes, the more brain parts the person involves, either through exteroceptors, proprioceptors and interceptors, the better the material is learned and performed." In other words, "success in learning and performing is directly proportional to the quantity, quality and intensity of the ties made with the entire CNS Network ". And the strength or weakness of a learned material will reveal itself in form of functional connectomes detectable through qEEGs and/or newly developed neuroimaging techniques.*

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EARLY ONSET PROGRESSIVE NONFLUENT APHASIA
ERKEN BAŞLANGIÇLI PROGRESİF TUTUK AFAZİ

Alper Evrensel*[1], Gökçe Cömert[1], Celal Şalçini[1]

Abstract

Progressive nonfluent aphasia is a slowly progressive degenerative disease characterized by atrophy in left hemisphere particularly frontotemporal. It is one of three subtypes of frontotemporal lobar degeneration (frontotemporal dementia). Unlike Alzheimer's disease it begins between 45-65 years of age and occurs equally in both sexes usually. The reported youngest case was 21 years old. Atrophy is seen in the left hemisphere more in temporal lobe on magnetic resonance imaging. Approximately half of the cases have family history. In early it might confuse with depression and therefore diagnosis may be delayed. Brain magnetic resonance imaging is important for verification of diagnosis. In this paper, a case who early onset progressive nonfluent aphasia was mentioned.

Keywords: Frontotemporal dementia, Progressive nonfluent aphasia, depression

Özet

Progresif tutuk afazi, sinsi başlangıçlı, yavaş ilerleyen, sol hemisferde (özellikle frontotemporal) atrofi ile seyreden dejeneratif bir hastalıktır. Frontotemporal lobar dejenerasyonun (frontotemporal demans) üç alt tipinden biridir. Alzheimer hastalığının aksine genelde 45-65 yaş arasında başlar ve her iki cinsiyette eşit oranda görülür. Bildirilmiş en genç olgu 21 yaşındadır. MRI'da sol hemisferde daha çok temporal lobda atrofi görülür. Olguların yaklaşık yarısında aile öyküsü vardır. Erken dönemlerde depresyon ile karıştırılabilir. Bu nedenle tanıda gecikilebilir. Beyin MRI tanıyı doğrulamada önemlidir. Bu makalede erken başlangıçlı bir progresif tutuk afazi olgusu sunulmuştur.

Anahtar Kelimeler: *Frontotemporal demans, progresif tutuk afazi, depresyon*

1. Introduction

Frontotemporal dementia (FTD) is the most common group of clinical syndromes associated with circumscribed degeneration of the anterior temporal and prefrontal lobes (Neary et al., 2005). It has been called frontotemporal lobar degeneration (FTLD) same time and non-Alzheimer disease type pathology. Behavioural changes are the presenting feature. It is dominate the clinical picture throughout the disease course. Cognitive impairments in executive function and qualitative changes in language occur. The absence of early neurological signs and findings of focal abnormalities in the frontotemporal lobes on neuroimaging contribute to diagnosis (Neary et al.,1998).

Progressive nonfluent aphasia (PNFA) may be speech production is effortful and halting, with speech sound (phoneme) errors, and simplified or "agrammatic" productions. Word and simple sentence comprehension, as well as recog¬nition of nouns are preserved. Although usually with some loss of comprehension for complicated syntactic constructions. Patients with PNFA rarely have underlying Alzheimer disease. Most have a tauopathy. This is especially true of patients who manifest both apraxia of speech and agrammatism. Language variant may appear relatively non-fluent, but they do not have the more specific features of agrammatism and apraxia of speech in the some patients (Rohrer et al., 2010).

2. Case

A 33-year-old male patient was admitted to the clinic with depressive symptoms. He divorced for years ago. He was treated with antidepressants for 2 years. It had been an increase in his depressive symptoms for the last one year. He also complained about forgetfulness, difficulty understanding, unwillingness, sadness and suicidal thoughts. His speech was hypophonic, slow and includes phonemic paraphasias. He occasionally stammered. He was apathic. In the neurological examination, could not be found a problem. His Hamilton Depression Rating Scale point was 18. His mother was diagnosed with dementia when she was 55 years old. Left hemispheric cortical atrophy and lateral ventricular asymmetry were detected in his cranial magnetic resonance imaging (MRI) (Figure 1, Figure 2, and Figure 3). Increase in theta-delta and alpha frequency was detected in his quantitative electroencephalography (QEEG) without any paroxysmal activity (Figure 4). Neuropsychological tests demonstrated impairment in cognitive functions. He was diagnosed with progressive non fluent aphasia.

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Figure 1: MRI shows left temporal atrophy

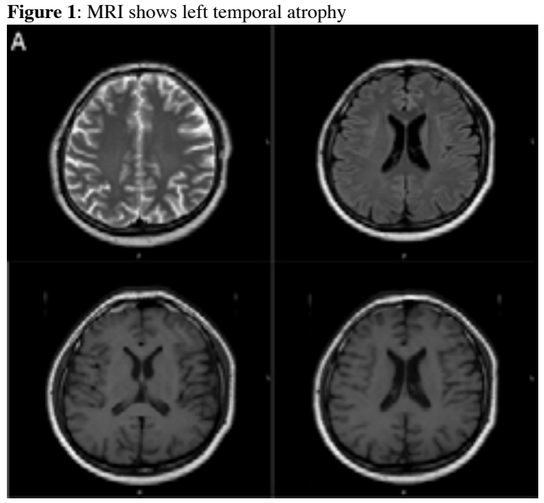


Figure 2: MRI shows left temporal atrophy

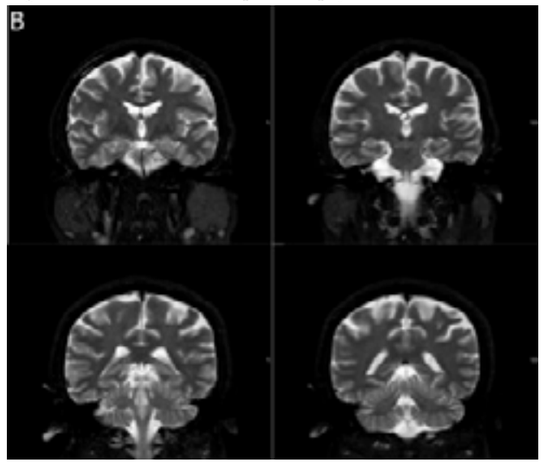


Figure 3: MRI shows left temporal atrophy

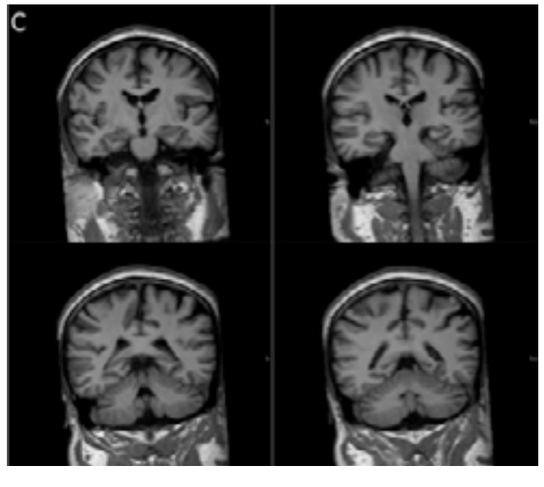
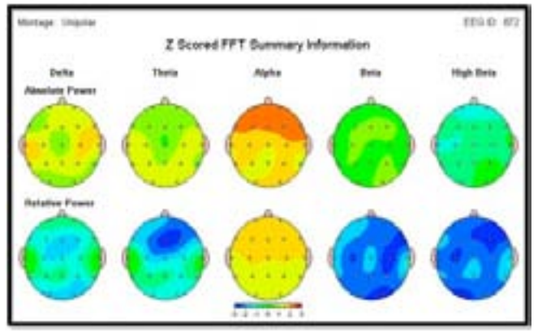


Figure 4: QEEG shows increase in theta-delta and alpha frequency



3. Discussion

For the first time in 1982, primary progressive aphasia (PPA) has been reported as a distinct clinical syndrome by Mesulam. In 6 cases, Mesulam has reported slow progressive aphasia symptom without comorbid dementia findings (Mesulam 1982). In subsequent years, clinical, imaging and postmortem properties of the syndrome have been defined. PPA is a neurodegenerative syndrome with progressive and isolated deterioration in language functions (Mesulam et al 1997). While mental functions such as attention, memory, visuospatial abilities, abstraction, judgment and behavior are maintained, an isolated and progressive deterioration in using and understanding words is seen at least two years long (Mesulam 2001). To date, a small number of PPA cases have been reported in the literature. Weak neurological findings in the right half of the body, asymmetric slowdown in electroencephalography, cortical atrophy, hypometabolism in the left hemisphere (especially in the frontotemporal and perisylvian regions) was found in most of these cases (Mesulam et al 1997). Two subtypes of PPA have been identified as non-fluent (PNFA) and fluent (Turner et al 1996). These have many common features with Pick disease and nonspecific lobar atrophies that cause focal degeneration in frontal and/or temporal lobes. In the light of this, it is believed that PPA and frontal lobe dementia can be addressed as a single clinical appearance (Mesulam 2001). PPA neuropathologically shows similar findings as nonspecific cortical degeneration with and without Alzheimer disease, Parkinson disease, Creutzfeldt-Jakob disease and spongiform changes (Karbe et al 1993, Mandell et al 1989).

PNFA is a slowly progressive degenerative disease characterized by atrophy in left hemisphere (particularly frontotemporal). It is one of three subtypes of frontotemporal lobar degeneration (frontotemporal dementia) (Neary et al., 2005). Unlike Alzheimer's disease it begins between 45-65 years of age and occurs equally in both sexes usually (Neary et al., 1998).

The youngest reported case was 21 years old (Snowden et al., 2004). Atrophy is seen in the left hemisphere more in temporal lobe on MRI. Approximately half of the cases have family history (Neary et al., 1998). In early it might confuse with depression and therefore diagnosis may be delayed. Brain MRI is important for verification of diagnosis.

Herein, we demostrated a case who early onset progressive nonfluent aphasia in this paper.

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LETTER TO THE EDITOR

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THE EFFECTS OF TV WATCHING ON THE AUTISM LIKE SYMPTOMS: AN OPINION ABOUT THE PATHOPHYSIOLOGY

TV İZLEMENİN OTİZM BENZERİ SEMPTOMLARA ETKİSİ: PATOFİZYOLOJİ İLE İLGİLİ BİR DÜŞÜNCE

Zeynep Çubukçuoğlu Taş*[1]

Autism is a neurodevelopmental disorder that effects one in every 250 children (Baird et al. 2006) and characterized by significant impairments before the age of three in verbal and non-verbal communication, social interaction and a general loss of interest (APA, 1994). Notably, despite the ongoing efforts the underlying pathophysiology of autism is not well-understood. Currently, stress diathesis model argues that a genetic vulnerability may later trigger autism by environmental stressors. Although the environmental triggers are not entirely revealed some potential ones were identified. For instance, substantial number of studies has shown that children with autism display an increased affinity for excessive TV and video viewing, and an increased viewing of screen media may trigger autistic symptoms. Chonchaiya et al. (2008) has shown that autistic children spends more hours in front of TV as compared with the same age children with delayed language development. Nevertheless, whether or not tv viewing predispose autism is a presumption that needs to be investigated in longitudinal trials. In 2006, Waldman et al., performed a thought provoking study in which they conducted a nationwide survey in USA and found an increased viewing time for TV in countries where autism prevalence were higher than the others. Interestingly, they demonstrated that county autism rates were positively related with the rate for subscribing cable TV. Moreover, in 2005 Zwaigenbaum et al. demonstrated an in increased predilection for TV viewing in children who are at-risk for autism.

An indirect interpretation of this relationship came from Canell (2008). He hypothesized that in the presence of increased hours spent in front of TV, children may develop D-vitamin deficiency that can disturb normal brain development. Here, I believe a more direct hypothesis may be developed, using the famous Bandura's social learning theory. Real-life social interaction that includes not only information exchange but also reinforce social imitation and learning processes could enhance social development of the children. In the lack of such interaction, merely interaction with the characters in the TV may imitate rewarding features of human-human interaction which may decrease the children's motivation to engage real-life social activities. Therefore, a vicious cycle that increases social isolation may occur. Taken as a whole despite the benefits of technology on the development of children, without careful parental control, these technologies may be harmful for our children. Patients who experience such autistic like symptoms may be aware of the problems that are triggered my media over consumption. Besides, clinicians should question the amount of time spend in front of TV and video, while evaluating the mental problems of their patients. Serious cases should immediately refer to child and adolescent psychiatrists to get further counseling and treatment.

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