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EDITORIAL

Değerli okuyucu,

Nörodavranış Bilimleri Dergisi'nin 2. yılının ilk sayısını sizlere sunmaktan büyük mutluluk duymaktayız. Söze bu sayıya destek veren tüm araştırmacılara teşekkür ederek başlamak isterim. Nörodavranış Bilimleri Dergisi, ülkemizde ve dünyada gelişen sinirbilim eğilimine paralel olarak kurulan ve geçen yıldan bu yana hem yurt içinde hem de yurt dışında çalışmalarını sürdürmekte olan akademisyenlerin yazıları ile güzel bir ivme kazanmıştır. Henüz arzu edilen yerden uzak olmak ile birlikte, uluslararası saygınlığa sahip, yüksek okunma oranlarına sahip bir bilimsel yayın oluşturmak en büyük gayemizdir. Bu sayıda öncelikle Taş ve arkadaşlarının Sema Meditasyonu konusunda ülkemiz literatürüne yaptıkları önemli katkıyı bulabilirsiniz. Bilindiği gibi meditasyon bireylerin fiziksel ve ruhsal gelişimlerine katkı sağlayan, yurtdışında oldukça yaygın olarak kullanılan bir egzersiz biçimidir. Birçok kültür ve dinde meditasyonun spiritüel formlarına da rastlamak mümkündür. İslam dini içerisinde bir felsefe olarak kendisine geniş yer bulmuş sufizm ve beraberinde bir meditasyon olarak görülen sema ayini ne yazık ki günümüze değin nörobilim bakışı ile incelenmemişti. Taş ve arkadaşlarının yayınladığı fonksiyonel manyetik rezonans çalışmasında sema meditasyonun nörolojik temelleri ile ilgili ilk verileri bulabilirsiniz. Ayrıca bu sayıda Metin ve arkadaşlarının hazırladığı epilepsi cerrahisinde temporal lobektomi öncesi yapılan fMRI çalışmalarının sistematik bir gözden geçirmesi bulunmaktadır. Bu çalışmaların yanında dikkatin uyarılmış potansiyeller ile ilişkisini inceleyen Krzan ve günümüzde git gide artan bir alanda ilgi çeken nöropsikiyatrik hastalıklarda saptanan olfaktör disfonksiyon ile ilgili güzel bir derleme okuyucuların dikkatine sunulmuştur. Nörodavranış Bilimleri Dergisi'nin son sayısında yukarıdaki derleme ve araştırma yazılarının yanında özgün olgu sunumları yine okuyucuların ilgili ile okuyacaklarını düşündüğümüz diğer makaleleri oluşturmaktadır.

Saygılarımla,

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FUNCTIONAL BRAIN CHANGES DURING SEMA MEDITATION: NEURONAL CORRELATES AND THEIR ASSOCIATIONS WITH AFFECTIVE STATES

SEMA MEDİTASYONU SIRASINDAKİ İŞLEVSEL BEYİN AKTİVİTESİNDEKİ DEĞİŞİKLİKLER: NÖRAL AKTİVİTELER VE DUGULANIM İLE İLİŞKİSİ

Cumhur Taş[*1, 2], Rukiye Karaköse[1], Barış Metin[1], N. GülçinYıldız[1], Şehadet Ekmen[1], Elliot C.Brown[2, 3], K. Nevzat Tarhan[1]

Abstract

Sufi meditation is a spiritual form of physically active meditation in which performers (Semazens) whirl without losing conscious awareness and while internally focusing on reaching an ecstatic state, thus requiring substantial motor and cognitive control and monitoring. Studies have argued that the experience of the meditator may affect the strength of the brain activations because more experienced meditators may need less cognitive effort to reach the ecstatic state. Despite this, our knowledge about the associations between emotional states of the meditators and activated brain areas during meditation remains unknown. With this in mind, fourteen male Semazens were recruited for this study. All Semazens performed Sema meditation under the scanner using imagined whirling techniques. An active control condition was used to explore brain areas specific to Sema meditation. Measures of affective states and psychiatric symptoms were also collected. Statistical parametric maps were created to compare the meditation vs. control conditions. Accordingly, Sema meditation specifically evoked activations in left anterior cingulate cortex (ACC) and left orbitofrontal areas. Activations in ACC were negatively correlated with the positive affect of the Semazens suggesting that less cognitive effort required to reach the meditative state in Semazens was associated with more positive affect. Despite previous studies highlighting the experience of the meditators as a predictor of brain activation, we found that affective state may also be an important factor that may facilitate emotion regulation and cognitive monitoring in the brain. Our findings may also be applicable to the effects of meditation on psychological and emotional wellbeing.

Keywords: Sufism, Meditation, fMRI, anterior cingulate cortex

Özet

Sufi meditasyonu, uygulayanların (semazenlerin) bilişsel farkındalıklarını kaybetmeden kendi etrafında döndükleri ve bundan dolayı önemli bir motor, kognitif kontrol ve gözlem gerektiren fiziksel hareketli bir manevi meditasyon biçimidir. Bir çok çalışma, meditasyon yapan kişinin deneyiminin, beyin aktivasyonlarındaki kuvvet üzerinde etkili olacağını ileri sürmüştür. Çünkü meditasyon yapan kişinin tecrübesi arttıkça, kiki esrik duruma ulaşmak için daha az kognitif çaba harcamaktadır. Buna karşın, meditasyon yapan kişilerin duygusal durumu ve bunun meditasyon sırasında aktive olmuş beyin alanları arasındaki ilişkisi konusundaki bilgi yeterli değildir. Tüm bu bilgiler ışığında, bizim çalışmamız 14 erkek semazen ile yapılmıştır. Tüm semazenler, MRI cihazı içerisinde, sema dönüşünü zihinlerinde canlandırarak meditasyon yapmışlardır. Bu duruma karşıt olarak, Sema meditasyonunda spesifik olan beyin alanlarını bulmak için aktif kontrol durumu uygulanmıştır. Katılımcılardan duygulanım durumu ve psikiyatrik semptom ölçümleri toplanmış, ve fMRI analizleri, istatiksel parametrik harita, meditasyon ve kontrol durumlarını karşılaştırmak amacıyla oluşturulmuştur. Sonuç olarak, sema meditasyonu sırasında özellikle sol anterior cingulate kortex ve sol orbitofrontal alanda aktivasyon gözlemlenmiştir. Önceki çalışmalarda meditasyon yapan kişinin tecrübesi beyin aktivasyonu için öngörücü olmasına rağmen, bu çalışmada duygulanım durumunun beyinde meditasyon esnasında, duyguları düzenlemeyi kolaylaştırmada ve kognitif gözlemleme süreçlerinde önemli bir etken olduğunu bulunmuştur. Bu bulgular, meditasyonun psikolojik ve duygusal iyilik haline olumlu etkileri perspektifinden de açıklanabilir.

Anahtar Kelimeler: *sufizm, meditasyon, fMRI, ön singulat korteks*

1. Introduction

The term Meditation refers to a broad variety of spiritual practices, including techniques, which instantly promote relaxation and aims to improve well-being and composure as a long-term goal (Davidson et al., 2008). Sufi Whirling as a central practice of Sema Meditation is a form of physically active meditation performed for spiritual purposes by Semazens of the Mevlevi order (Geoffroy,

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2010; Tarhan, 2015). Different from any other meditative practice, Sufi Meditation requires excessive cognitive and motor control as the performers (Semazens) are expected to turn around him/herself while constantly repeating words, experiencing a high spiritual state, without losing their motor and conscious awareness (Geoffroy, 2010; Tarhan, 2015). Today, increasing number of studies are investigating the effects of meditative exercise in the brain using functional neuroimaging techniques (i.e., Cahn and Polich; Baron Short et al., 2010; Holzel et al., 2011; Guleria et al., 2013). Studying the effects of meditation in the brain is important because reaching a "meditative" mental state involves diffuse brain activations. Studying such activations are crucial in understanding more fundamental issues related to the regulation of cognitive and emotional states. This issue may be more challenging when it is expected to take place during Sufi meditation (Nizamie, et al., 2013).

In general, fMRI studies found increased activations in the areas involved in reward processing and emotion regulation, including the orbitofrontal cortex (OFC), cingulate cortex and thalamus during meditation (Fox et al., 2014; Newberg, et al., 2010; Baerentsen et al., 2001). Furthermore, depending on the type of the meditation, activated patterns in the brain have differed in various ways. For instance, a recent fMRI study found that focus-based meditation elicits activity in a wider network of brain regions when compared to breath-based meditations, particularly in frontal regions, the limbic system and anterior cingulate cortex (Wang et al., 2011). Another fMRI study on Soham Meditation, a meditation type that includes verbal rehearsal synchronized with the breathing of the practitioner, found activations in the left middle prefrontal cortex, left inferior frontal gyrus, left supplementary motor area and left precuneus (Guleria et al. 2013). Bilateral hippocampal activations were activated, together with the middle cingulate cortex (MCC) and prefrontal cortex (PFC) during another traditional meditative practice that involves silent repetition of specific words (Engström et al., 2010). It is not only the techniques used in the meditation but also the experience of the meditator which impacts on activation patterns in the brain. Baron-Short et al., (2010) found dorsolateral prefrontal cortex (DLPFC) and an anterior cingulate (ACC) activation that was modulated by the experience of the meditator. The activations in ACC and DLPFC were specifically explained by the fact that meditation requires self-focused attention, which may be achieved by ignoring distracting stimuli, actively monitoring one's own mental and cognitive processes and engaging attentional control (Baron-Short et al., 2010). Based on this explanation, one might conclude that the activity changes in these brain regions could interfere with the quality of meditation, which may also impact on the affective and behavioral benefits of the meditation.

However, the associations between affective and behavioral traits of meditators and their brain activations during meditation are still unbeknown. Investigating this issue is crucial in revealing the neuronal basis of the positive and soothing moods of meditators. Nonetheless, the relationship between the meditative practice and an individual's psychological status has been investigated in a few studies (i.e. Kemeny et al., 2012; Hoffman et al., 2012; Innes (2012) demonstrated the meditation's effect on Alzheimer's patients revealing its positive influences on stress, sleep disturbances and memory functioning. Moreover, it has been demonstrated that meditation can diminish an unbounded anger behavior (Kemeny et al., 2012; Hogffman et al., 2010). In another study, individuals practicing mindfulness were less likely to be aggressive compared with non-practitioners (Singh et al., 2007). A feasible conclusion from the above studies would suggest a strong relationship between meditation and the psychological affective state of the meditators.

Some traditional focus-based meditations rooted in Eastern culture have their unique philosophy that ultimately affects the practitioner's daily functioning in life, and Sufi Meditation may be considered to be one of these. Sufism dominates the individual's ego (i.e., self-nefs), balancing the mental and physical experiences and creating inner harmony (Geoffroy, 2010).

The ceremony of Semazens in Sufi Meditation focuses on the recollection and remembrance of the Divine, which ends in the effacement of the creature and attainment of the limitless state of self being. Sometimes this "state of being" or "ecstasy" already exists at the beginning of the dance, and this dance then becomes the exterior manifestation of an interior state (Michon & Gaetani, 2006). Sometimes the dance appears like an "effort of seeking" which, according to the predisposition of the dancer, may or may not lead to a veritable ecstatic experience (Geoffroy, 2010). Sufism contributes to the regulation of people's mental ego stage and transforms their behavior in a more positive way, while soothing their mood. To date, there are no studies that have investigated the neuronal correlates of Sema Meditation and the relationship between neuronal activations and psychological traits of the practitioners.

The ultimate goal of this study was to explore the regional brain activations during Sufi Meditation in the MRI scanner. Furthermore, we intended to address whether or not activated brain areas were related to affective states of the Sema practitioners. Based on our goals, this study had the following two-fold hypothesis: First, in line with previous studies, we predicted that Sema Meditation could exert significant brain activations that were related to self-focused attention such as ACC and DLPFC. Second, the strength of these activations could be associated with the affective schedule of the practitioners in such a way that those who find the meditation more effortful would benefit less from it in terms of positive affect.

2. Methods

2.1. Participants

Fourteen male Semazens (mean age: 30.43± 5.94 years, mean education: 17.07± 2.5, all right handed) were recruited for this study. Semazens were enrolled from a Meditation Centre in Istanbul, where traditional Sema meditation is taught together with its philosophy. Participants' mean duration of meditation practice was 6.70±3.42 years and the meditators in their first year

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of practice were not included. All Semazens underwent a structural clinical interview for psychiatric disorders (SCID-I), and none received a diagnosis. Any participants with previous neurological disorders, current or previous use of psychotropic medication or previous history of head trauma were excluded. The study received approval by the Institutional Human Research Ethics Committee and all study participants gave written consent before the scanning was initiated

2.2. Task and protocol

Participants were asked to perform Sema Meditation with their eyes open in the scanner. Sema meditation, which usually involves the traditional whirling dance of the Semazen, with their arms stretched and one hand turned towards the soil and the other to sky. Due to the practical limitations of fMRI scanning, we asked the practitioners to perform Sema Meditation by only imagining whirling in the scanner. In general, Sema ceremonies start with a preparatory session in which the Semazen listen to traditional melodies of Sufism. This step is believed to facilitate the recollection and remembrance of Divine (Michon and Gaetani, 2006). In the preparation phase of the current study, all of the Semazens where left in a room for 30 mins while they listened to the recordings of an original traditional preparation ceremony. Following this, we asked to them to perform Sema Meditation as well as a control task under the scanner. Lastly, the session ended after all Semazens completed a likert scale with four questions to evaluate the quality of their ecstatic state during meditation. Each question included evaluations between 1 to 10 and the questions read as follows: 1) "I successfully followed the rituals during meditation", 2) "I successfully concentrated on the meaning of Sema during meditation", 3) "The recollection and remembrance of Divine was successful during meditation" and 4) "I was successful in avoiding to think about daily routines during meditation". This Sema meditation quality scale was prepared by the head of Semazen community in Istanbul for the current study (Fatih Çıtlak).

During the control period, subjects viewed a series of geometric images every four seconds and were asked to determine whether they were blue or yellow and select the appropriate button on a fMRI compatible pad. As a note, a very similar design has been used in several other fMRI studies in meditation (Baron Short et al., 2010; Guleria et al., 2013). An active control task was selected instead of a resting control task as to avoid meditation in the control condition. Each run consisted of two 12 minute meditations and two 6 minute control blocks, which were counterbalanced across participants. Following the scanning session, Semazens completed the Sema meditation quality scale.

2.3. Behavioral assessments

The severity of psychiatric symptoms of Semazens was assessed by using the Symptom Checklist 90 (SCL–90, Derogatis,, 1994). The SCL-90 provides a widely used 90–item measure of general psychiatric distress comprised of nine subscales (somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, anger–hostility, phobic anxiety, paranoid ideation, and psychoticism).

The affective states of the Semazens were evaluated by the Positive and Negative Affect Schedule (PANAS) which includes the two original 10-item adjective checklist subscales (Watson et al., 1988) of positive affect (PA) and negative affect (NA). Using the "moment" instruction (i.e., "right now, that is, at the present moment", Watson et al., 1988), where participants were asked to rate the intensity of each symptom on a scale of 1 (not at all or very slightly) to 5 (extremely).

2.3. Functional MRI data acquisition

Data was collected on a 1.5 Tesla Philips Achieva scanner at the Istanbul Neuropsychiatry Hospital. We used foam padding to minimize head movement within the coil. T1 weighted MPRAGE type structural images were collected (TR/TE = 8.6/4.0 s, flip angle=8°, FOV = 240 mm, matrix=192×192, 1 mm isotropic voxels, sagittal sections, scan duration = 4.30 min per volume). T2 weighted functional images were acquired using a gradient-echo EPI sequence (TR=4000 ms, TE=30 ms, flip angle=90°, FOV=208 mm, matrix=64×64, 30 slices with thickness of 3 mm, 3 mm × 3 mm in-plane spatial resolution, and FOV 230 mm, in total 541 dynamic scan, scan duration = 36.16 min).

2.4. Statistical analysis

The preprocessing and analyses of functional MRI images were conducted using Statistical Parametric Mapping software (SPM 8, Wellcome Department of Cognitive Neurology, London, UK,using Matlab version 2013a). Anatomical images were spatially normalized using the SPM segmentation procedure for parameter estimation and re-sliced to a voxel size of 1×1×1mm. The single subject preprocessing of fMRI images consisted of the following steps: slice time correction, realignment of all EPIs to the first volume, normalization based on the T1 segmentation parameters, re-slicing to a final voxel size of 3x3x3 and lastly smoothing with a Gaussian kernel of 8 mm full width half maximum (FWHM). The first level of analysis was performed using a fixed effect model to construct the General Linear Model using a canonical hemodynamic response function (HRF) (Friston et al., 1999). In the resulting GLM, motion parameters created during the realign process were used as six user-specified regressors to account for any activity related to head movement. A high pass filter of double the length of the longest trial (720 s) was used to remove low-frequency noise without sacrificing the signal of interest. In the statistical model, individual t-maps were created using two contrasts of interest: meditation>control task and control>meditation. These individual t-maps were taken into the second level of group analyses. For the second level of group analyses, we employed one-sample t-test to identify the brain regions significantly activated during meditation using multiple comparison with a cluster level threshold of $p < 0.05$, with voxel-level threshold of $p < 0.01$ and a minimum cluster size (k) of 58 voxels,

using the AlphaSim software (http://www.restfmri.net/forum/REST_V1.4), which applied Monte Carlo simulation (parameters: individual voxel p = 0.01; rmm = 5; 5.000 simulations).

Lastly, we extracted the beta values for the significant brain regions in the meditation condition using the MarsBaR toolbox together with AAL templates. Pearson correlation analyses were performed to identify the association between beta values and the behavioral measures. Correlations between the behavioral scales were also performed in this step.

3. Results

3.1. Meditation vs. Control task

Compared with the active control condition, stronger activations were found in the left anterior cingulate including the dorsal regions and left inferior orbitofrontal cortex during mediation. All local maxima in the activated cluster, t and z values together with the MNI coordinates are summarized in table 1. These results are based on the anatomical location of the peak voxel in the activated cluster.

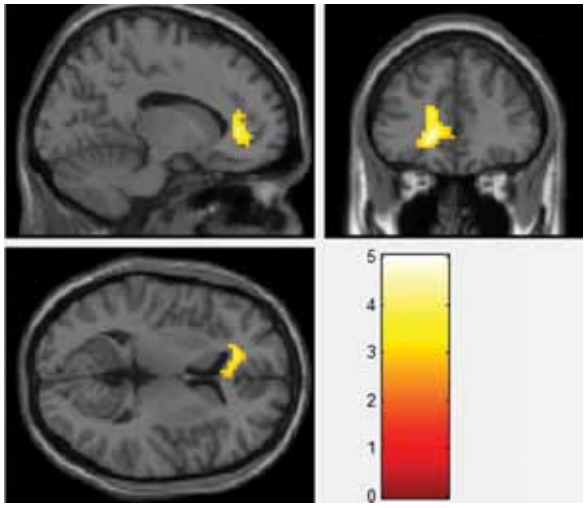

Figure 1: SPM t-map of significant activations in the meditation > control contrast in (alphasim corrected with a cluster level threshold of $p < 0.05$, with voxel-level threshold of $p < 0.01$ and a minimum cluster size (k) of 58 voxels)

Table 1: Brain regions activated by the Sema meditation

Brain areas	Peak voxel coordinates (MNI)			T value	Z value
	x	y	z		
Left anterior cingulate cortex	-18	41	-2	5.03	3.68
Left anterior cingulate cortex / BA 32	-15	38	13	3.94	3.14
Left inferior orbitofrontal	-21	32	-11	4.55	3.46

Notes for Table 1: MNI; Montreal Neurological Institute. Results were alphasim corrected at voxel level 0.001 (cluster level =<.05 FWE; Extent threshold = 58 voxels; df = 1,45)

3.2. Control task vs. Meditation

Compared with meditation, stronger activations were found in the left postcentral gyrus, left inferior parietal cortex, left post central gyrus, right precuneus, left cuneus and left inferior parietal cortex in the active control condition. All local maxima in the activated cluster, t and z values together with the MNI coordinates are summarized in table 2. These results are based on the anatomical location of the peak voxel in the activated cluster.

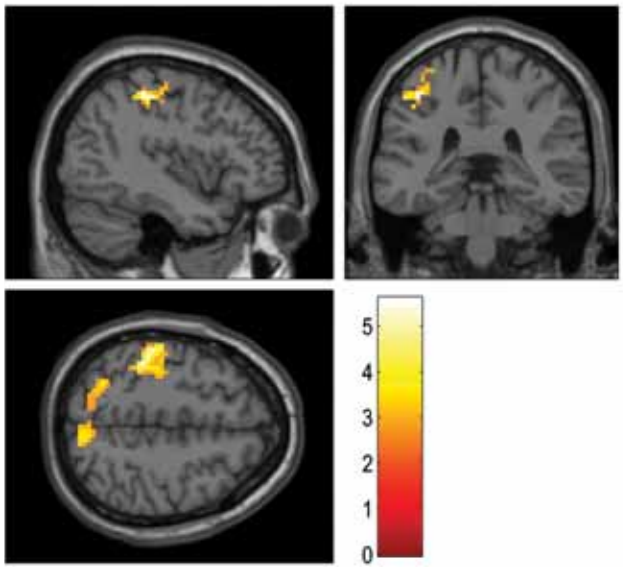

Figure 2: SPM t-map of significant activations in the meditation < control contrast in (alphasim corrected with a cluster level threshold of $p < 0.05$, with voxel-level threshold of $p < 0.01$ and a minimum cluster size (k) of 58 voxels)

Table 2: Brain regions activated by the control condition

Brain areas	Peak voxel coordinates (MNI)			T value	Z value
	x	y	z		
Left postcentral gyrus	-42	34	52	5.60	3.93
Left inferior parietal cortex	-51	-31	49	5.58	3.92
Left postcentral gyrus	-48	-22	43	4.33	3.35
Right precunes	9	-76	49	3.94	3.14
Left cuneus	1	-82	40	3.86	3.10
Left inferior parietal cortex	-30	-61	49	3.84	3.08

Notes for Table 2: MNI; Montreal Neurological Institute. Results were alphasim corrected at voxel level 0.001 (cluster level =<.05 FWE; Extent threshold = 58 voxels; df = 1,45)

3.3. Correlational analyses

According to the correlational analyses; beta values in the left anterior cingulate cortex were negatively correlated with the Positive Affect (PA) subscale of PANAS ($r=.723$; $p<.01$; see figure 3 for the scatterplot). Such correlations were not present with inferior orbital cortex

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and PANAS. No correlations were found between SCL-90 subscales and the activity in the brain regions for Sema condition. Regarding correlations between behavioral scales, significant associations were observed between Negative Affect (NA) subscale of PANAS and the anger-hostility subscale of SCL-90-R ($r=.80$; $p<.01$), but not for the PA subscale ($p>.05$). No associations were found between the quality of ecstatic state under the scanner and all behavioral and neuroimaging findings (all p values >.05). Lastly, the experience of meditation practice was not correlated with the outcome variables (all p values >.05).

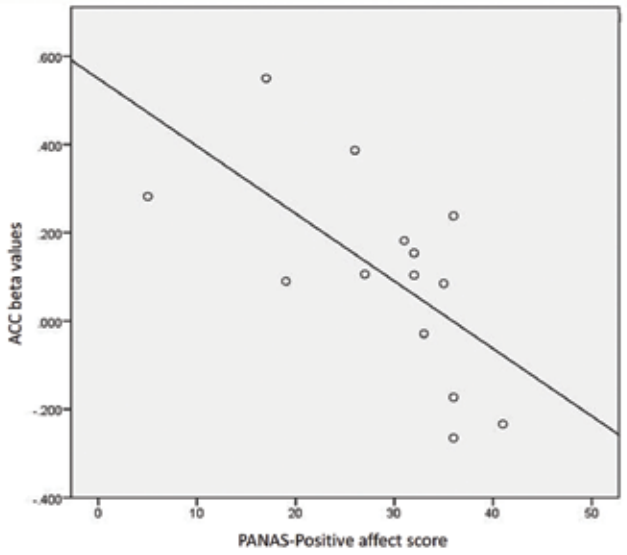

Figure 3: Scatterplot showing the associations between the ACC activity and PA subscale of the PANAS.

4. Discussion

According to the results, our hypotheses were partially confirmed. Here, we found significant activations in the ACC during meditation as compared to the control condition. Moreover we demonstrated an association between the neuronal efforts during meditation and psychological state of the Semazens. Specifically, participants with greater ACC activation exerted less positive affect in this study.

ACC is a part of frontal cortex that is primarily involved in conflict monitoring and emotion regulation (Mathalon,, et al., 2003; van Veen, 2001). Studies have confirmed that it is mainly activated during tasks evoking significant response conflict and tasks requiring mental effort (Croxson et al., 2009). In addition, the activity in ACC decreases as the subjective value of the effortful option increases. Thus, ACC evaluates whether or not it is worth producing a given effort for the reward at stake. (Prévost et al., 2010). Taken together, a plausible interpretation of our results could be that those Semazens who were in a positive and soothing state before the session took place may have experienced less cognitive conflict when getting into the meditative state and thus, spending less effort in the scanner. Alternatively, Sema practitioners who perceived the meditation more effortful, as reflected in greater ACC activation, would also have shown less affective benefit from the meditation. Therefore, meditators who were engaged in the meditation, and with less ACC activity, were more likely to show affective benefit. Similarly, Baron-Short et al. (2010) argues that the experience of the meditators may affect the ACC and DLPFC activity. They showed that experienced meditators didn't need as much error-monitoring as the inexperienced meditators, and could focus their attention more easily. Here, we did not find any correlation between the duration of practice and other study measures. As a note, the Baron-Short study did not evaluate the affective state of the meditators in addition to the duration of practice which ultimately effected the ACC activations in this study.

In addition to ACC, OFC was significantly activated during meditation. OFC is primarily related to reward expectancy and decision making (Kringelbach, 2005). In fMRI studies, it has been shown that OFC activation correlates with values of both social and monetary rewards (Lin et al. 2012). OFC activations were reported in previous neuroimaging studies on meditation and this finding might suggest that meditation is perceived as a self-stimulating reward condition (Hölzel et al., 2008; Kang et al., 2013). In this study, we did not find a significant correlation between PANAS scores and OFC activation. Besides, the quality of ecstatic state during meditation was not correlated with OFC activations. Here, we have some explanations for the lack of correlations. Firstly, the quality of ecstatic state scale for Sufi Meditation may not have been suitable to identify the rewarding features of Sufi Meditation (Geoffroy, 2010). Alternatively, the affective schedule of the Semazens may directly relate to conflict monitoring processes, whereby the internal rewarding features of meditation may not reach conscious awareness. This is also because; the philosophy of Sufism is based on neither social nor monetary reinforcements. It has been referred as the journey to the understanding of Divine, a spiritual contemplation with internal rewarding features (Michon and Gaetani, 2006).

This study had certain limitations. First only 14 individuals participated and recruiting more participants would have increased the power of the study. Second, we only could evaluate the affective traits that were associated with the Sufi Meditation. However, in the literature several other behavioral benefits of meditation were investigated, including increased quality of life and reduced anxiety and depressive symptoms (i.e. Kemeny et al., 2012). Third, using an active control task may have masked more subtle activation patterns in the meditation condition. Notably, the active control condition in our study resulted in several areas that had greater activation than the meditation condition. The activation of the inferior parietal cortex were also demonstrated in another study using a very similar control condition (Baron-Short et al. 2010). In addition, activations in the postcentral areas are mostly related to the expected motor response and have also been shown in other previous studies (i.e. Tomczak et al., 2000). Lastly, we asked the Semazens to imagine whirling during meditation, which may have also lead to activation of motor areas. However, the active control condition in this study, which includes a motor response, may have masked the activations related to the

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imagination of whirling.

In conclusion, this is the first study investigating the brain correlates of Sema Meditation. In addition to the activations in ACC and OFC, we also found that the activations in ACC may moderate the daily positive affect of the Semazens. To further investigate the behavioral effects of meditation, longitudinal studies are required to reach confident conclusions. This is also important in understanding the role of ACC and related network activity in the course of Sufi Meditation practices such as the whirling dance of Semazens.

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REVIEW ARTICLE

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CLINICAL ASSESSMENT AND IMPLICATION OF OLFACTORY DYSFUNCTION IN NEUROPSYCHIATRIC DISORDERS OF CHILDHOOD AND ADULTHOOD: A REVIEW OF LITERATURE

ÇOCUKLUK ÇAĞI VE ERİŞKİN NÖROPSİKİYATRİK HASTALIKLARDA KOKU BOZUKLUĞUNUN KLİNİK DEĞERLENDİRİLMESİ VE ÖNEMİ: BİR LİTERATÜR DERLEMESİ

Yasin Yılmaz*[1], Ezgi İnce[2], Halim Uğurlu[3], Alper Baş[2], Burak Tatlı[4], İbrahim Balcıoğlu[2]

Abstract

Olfactory function comes into prominence in the neuroscience study area after revealing that olfactory dysfunction is considered as an early diagnostic pre-motor biomarker of Parkinson's disease. Researchers have also examined the sense of smell in detail in patients with other neuropsychiatric disorders. Here, we present data from a systematic literature review in olfactory function in child and adult neuropsychiatric disorders. We have researched autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive-compulsive disorder (OCD). Due to smell test techniques and heterogeneity of studies, the total number of studies was limited. The disorders were grouped according to smell test techniques. The most commonly-used tests were Sniffin Sticks Test (SST) and the University of Pennsylvania Smell Identification Test (UPSIT). Although some researcher did not find any significant impairment in olfaction, most studies indicated that olfactory dysfunction was very striking, especially in disorders involving in the dopaminergic pathway (e.g., ADHD, autism, and schizophrenia). In this review, possible future diagnostic or prognostic markers of olfactory dysfunction in neuropsychiatric disorders have been discussed. More studies that combine imaging methods, the electrophysiologic system, and genetic research are needed to clarify the relationship between olfaction and neuropsychiatric disorders.

Keywords: Olfactory Dysfunction, Olfactory Assessment, Neuropsychiatric Disorders, University of Pennsylvania Smell Identification Test (UPSIT), Sniffin Sticks Test (SST)

Özet

Parkinson hastalığında koku bozukluğunun erken tanısal pre-motor belirteç olarak gösterilmesinden sonra, koku fonksiyonunun sinirbilim çalışma alanında önemi artmıştır. Araştırmacılar, koku duyusunu diğer nöropsikiyatrik hastalıklarda da detaylı olarak araştırmıştır. Bu çalışmamızda, çocukluk çağı ve erişkin nöropsikiyatrik hastalıklarda koku fonksiyonu üzerine sistematik bir derleme sunmaya çalıştık. Otizm spektrum bozuklukları (OSB), epilepsi, dikkat eksikliği/hiperaktivite bozukluğu (DEHB), şizofreni, bipolar bozukluk, yeme bozukluğu ve obsesif kompulsif bozukluk (OKB) araştırılmıştır. Koku testi teknikleri ve çalışmaların heterojen dağılımından dolayı, toplam çalışma sayısı kısıtlı kalmıştır. Çalışmalar koku testi tekniklerine göre ayrıldı. En sık kullanılan koku testleri Sniffin Sticks Testi (SST) ve Pensilvanya Üniversitesi Koku Tanımlama Testi (UPSIT) idi. Bazı araştırmacılar koku fonksiyonunda anlamlı bir bozulma bulmasalar da, çalışmaların çoğunda özellikle dopaminerjik yolağı ilgilendiren hastalıklarda (ör. DEHB, otizm ve şizofreni) koku bozukluğu dikkati çekmiştir. Bu derlemede, nöropsikiyatrik hastalıklarda koku bozukluğunun olası tanısal ve prognostik belirteç özelliği tartışılmıştır. Görüntüleme yöntemleri, elektrofizyolojik sistem ve genetik çalışmalarla entegre araştırmalar, koku ve nöropsikiyatrik hastalıklar arasındaki ilişkiyi aydınlatmak açısından önem taşıyacaktır.

Anahtar Kelimeler: *Koku bozukluğu, koku alma değerlendirmesi, nöropsikiyatrik hastalıklar, Pensilvanya Üniversitesi Koku Tanımlama Testi (UPSIT), Sniffin Sticks Testi (SST)*

1. Introduction

"Smell is the orphaned sense; it has been forgotten by medicine" (Birnbaum, 2011)

The sense of smell is currently arousing a great deal of interest in the neuroscience area. This distinct sense has some unusual features: that it is the only sensory system

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not to use the thalamus as a central relay station and that it maintains plasticity and exhibits neurodevelopment throughout life by regenerating approximately every 2–3 months (Turetsky et al., 2009) render the olfaction unique. Turetsky et al., (2009) postulated that the olfactory system offers an unparalleled opportunity to observe the developmental processes of neurogenesis and synapse formation that are no longer evident in other adult brain areas.

As the neuroanatomy of olfaction was revealed, the relation to some neuropsychiatric disorders was demonstrated. The complex association of the olfactory pathway with other brain areas such as the thalamus, amygdala, and hypothalamus, inferior frontal, lateral and medial temporal areas is necessary for olfactory identification, discrimination, and sensitivity (Kareken et al., 2003).

The important proximity of olfactory pathway to some certain neuropsychiatric disorders like schizophrenia has underlined the association of olfaction with these diseases. Schecklmann et al., (2013) indicated that specific alterations in olfactory function were found especially in disorders with dopaminergic pathology (e.g., ADHD, autism, and schizophrenia). Olfaction is mediated by neurotransmitters such as dopamine, and dopaminergic interneurons modulate odor detection and discrimination via D2 receptors (Hsia et al., 1999).

Within the sensory system, olfactory system is most closely associated with temporolimbic and frontal lobe regions (Fig. 1). These domains are related to affective and mnemonic functions, which are mainly impaired in schizophrenia (Turetsky et al., 1995). It has even been postulated that olfaction can be used to assess disease-related cognitive and emotional disturbances (Pause et al., 2008; Schneider et al., 2007).

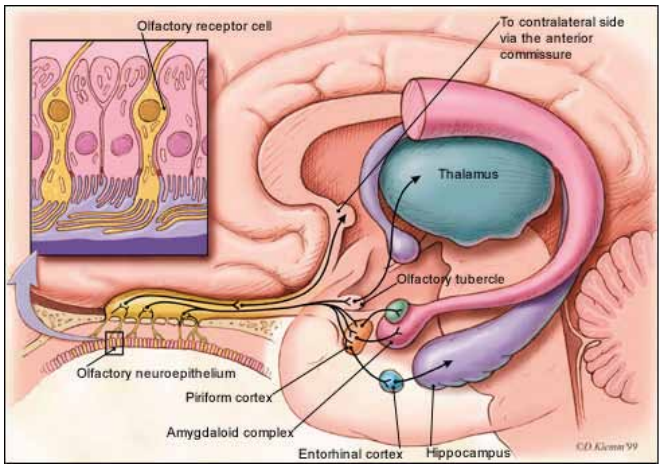

Figure 1: The simplified illustration of olfactory processing in the brain. From Bromley SM. (2000). Am Fam Physician, 61(2), 427-436. Copyright ©David Klemm (2000).

In some neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), general olfactory deficit (odor sensitivity, discrimination, and identification) has been detected. Furthermore, this olfactory deficit was considered as early diagnostic pre-motor biomarker of PD (Doty, 2007; Kranick and Duda, 2008). Along with valuable feature of olfactory testing in the differential diagnosis of idiopathic PD from a number of other neurodegenerative diseases (e.g., essential tremor, vascular Parkinsonism) (Katzenschlager et al., 2004), the disease predicting characteristics of olfactory loss in PD patients relatives (Ponsen et al., 2004) makes olfaction as a diagnostic tool in neurodegenerative disorders. Moreover, some researchers implied that olfactory dysfunction can be related to disease progression (Tissingh et al., 2001).

When olfactory dysfunction was shown in neurodegenerative disease, the field of neuropsychiatric disorders became a study area in terms of olfaction. The important dopaminergic pathway along with strategically anatomic proximity is maybe a key for studying olfaction in neuropsychiatric disorders.

The aim of this work was to provide a systematic review on olfactory function in neuropsychiatric disorders of childhood and adulthood. Due to smell test techniques and heterogeneity of studies, we focused on available literature about autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive-compulsive disorder (OCD). We tried to give some basic information to aid the discussion about potential diagnostic and clinical bio-markers of the olfactory system in neuropsychiatric disorders.

2. Materials and Methods

2.1. Assessment of Olfactory System

The assessment of olfactory system is mainly based on psychophysic and electrophysiologic tests. The applicability of these tests on children has been performed and shown that between age of 3 and 5 years the psychophysical tests were unreliable. After the age of 6 years, these tests can be applied for routine olfactory assessment. On the other hand, studies provided that it is possible to obtain an objective measurement of olfactory function in children from the age of 3.5 years using electrophysiologic tests (olfactory ERP recordings) (Hummel et al., 2007).

There are two common modalities in screening olfactory system; how the stimulus is given and how the stimulus is recorded.

Stimulus induction is mainly achieved with standardized odorants, which are given through the nasal aperture. Different odorants can be used like phenyl-ethyl alcohol for positive valence or isobutyraldehyde for negative valence. There are few differences in odor perception among study groups, but adaptation is the most frequently-used method. The technique of odorant stimuli is split into two ways. The first way uses olfactometers (Knecht and Hummel, 2004). By using an olfactometer device, odors are applied intranasally by means of a cannula that typically has an inner diameter of 2 to 3 mm. This cannula is inserted approximately 1 cm into the nostril to make it possible to stimulate directly olfactory mucosa. The device has two tubes into which air or odorant samples flow. Odorant samples can be diluted by mixing

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with air. Mixture percentages are important to identify the threshold levels in participants. The second way for odor stimuli uses psychophysical tests (Hummel and Welge-Luessen, 2006). This method use odors that are produced with a settled mixture of air-odor samples. This is different from the olfactometer because the odorant sample has to be inspired by the participant and the inter stimulus intervals (ISI) cannot be managed as strictly as in the olfactometer. The constant air flow is directed into the subject's nose mask for humidification (80% relative humidity) and thermostabilization (36°C) because dry, cool air produces nasal congestion, mucus discharge, and pain, which interferes with olfaction in many ways (Henkin et al., 2013). However, psychophysical tests are more widely used because of their simplicity and accessibility.

Recording data that comes from the olfactory system is the other important part of these studies. Psychophysical tests contain questions; participants are asked whether they can smell the odor sample (anosmia or threshold level), and to name the odor. Regional epigenetic confounding factors like being familiar or not with some odors were overcame by modifying the smell tests. (Tourbier and Doty, 2007).

Another way of collecting data about olfaction is through event-related potentials (ERPs). Olfactory-ERPs (OERPs) are electroencephalograph (EEG)-derived polyphasic signals. They originate from the activation of cortical neurons that generate electromagnetic fields (Rombaux et al., 2006). With OERPs, sequences of stimuli with different quality, intensity, duration, or inter stimulus interval can be analyzed. OERPs are direct correlates of neuronal activation and have a high temporal resolution in the range of microseconds. These characteristics allow the sequential processing of olfactory information to be screened and can be obtained independently of the subject's response bias, i.e., they allow the investigation of subjects who have difficulties in responding properly (e.g., children, aphasic patients, malingering) (Hummel and Welge-Luessen, 2006).

The most commonly-used tests for assessing the olfactory system are psychophysical tests. Some of these tests include the Barcelona Smell Test-24 (Cardesin et al., 2006), Sniff Magnitude Test (Frank et al., 2003), Connecticut Chemosensory Clinical Research Center (CCCRC) Test (Cain et al., 1988), Sniffin Sticks Test (SST) (Hummel et al., 1997) and University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984). The last two tests, SST and UPSIT, are the most commonly used and the best-validated olfactory tests in clinical study.

The Sniffin Sticks Test is performed using pen-like odor-dispensing devices (Fig. 2). As Hummel et al. explained in detail in their article, it comprises three tests of olfactory function, namely tests for odor threshold (n-butanol, testing by means of a single staircase), odor discrimination (16 pairs of odorants, triple forced choice) and odor identification (16 common odorants, multiple forced choice from four verbal items per test odorant) (Hummel et al., 1997). Odorants were presented in commercially available (unfilled) felt-tip pens. The tampon was filled with liquid odorants or odorants dissolved in propylene glycol. For odor presentation, the cap was removed by the experimenter and the pen's tip was placed circa 2 cm in front of both nostrils. For odor identification, 16 odorants were chosen. Criteria for the selection of odorants were as follows: First, subjects should be familiar with all odors used in the test; second, odorants included in the test should be similar with regard to both intensity and hedonic tone; and third, the successful identification of individual odorants from a list of four descriptors should be greater than 75% in healthy subjects. The identification test consists of 16 choices and requires the identification of the smelled odor from a choice of four verbally presented odors. For odor discrimination, triplets of 16 odorants were used. Subjects had to decide 16 times which stick out of three had a smell distinct from the other two. To prevent visual detection of the target sticks, subjects were blindfolded with a sleeping mask. For odor threshold, n-butanol or 2-phenylethanol was used as the odorant. A triplet of sticks was presented with one stick that contained a defined concentration of 2-phenylethanol / n-butanol and two odorless samples. The subject had to decide which of three sticks smelled "like a rose" (scent of 2-phenylethanol) or n-butanol. Using a staircase method, the concentration of odorant is varied and the individual sensitivity threshold can be obtained by averaging the last four reversal points. The sum of the three scores gives a definitive TDI score between 0 and 48, which determines whether the patient has normosmia (TDI > 30), hyposmia (TDI > 15 = 30) or anosmia (TDI ≤ 15) (Kobal et al., 2000).

Figure 2: Sniffin' Sticks. Phenyl ethyl alcohol or n-butanol odorants presented by felt-tip markers. Photo courtesy of Burghart Messtechnick GmbH, Wedel Germany.

The University of Pennsylvania Smell Identification Test (UPSIT) is another best-validated test used in neuropsychiatric disorders (Fig. 3). As Doty et al. described in their paper, it was just used for assessment of olfactory identification (Doty et al., 1984). As a highly standardized (from age 5–85 years) and validated scratch-and-sniff format test, the UPSIT consists of four booklets that contain 40 test items. Each page holds a microencapsulated strip onto which a suprathreshold odorant has been embedded and this can be released by scratching the surface with a pencil. Four possible responses appear on each page. The

examiner scratches the label with a pencil and holds it under the participant's nose. The participant is instructed to smell the label and the experimenter pointed at and named each of the four picture responses on the picture card, such as ''chocolate, pizza, peanut, or banana?'' The answer was then recorded on the response sheet. Scores on UPSIT test range between 0 and 40, with each correct identification scoring 1 point. Normosmia is defined by a score > 34 for females and 33 for males. Mild microsmia is defined by a score of 31–34 for females and 30–33 for males. Moderate microsmia is defined by a score of 26–30 for females and 26–29 for males. Severe microsmia is defined by a score of 19–25 for females and males. Total anosmia is defined by a score of 6–18 (Cumming et al., 2011). The UPSIT contains also scores for children's smell identification abilities (from the age of 5 years).

Figure 3: The 40-item University of Pennsylvania Smell Identification Test (UPSIT). Photograph courtesy of Sensonics International, Haddon Heights, New Jersey USA. Copyright©2013, Sensonics International.

Although it has not been definitely proved, it is strongly believed that the threshold parameter usually reflects the peripheral aspect of olfactory function (i.e mediated by lower-order neural pathways) while identification and discrimination parameters reflect central aspect of olfactory function (higher cortical function) (Hummel and Welge-Luessen, 2006). In accordance with these assumptions, patients with sinunasal disease showed a low threshold with normal olfactory identification and discrimination, whereas patients with diseases that involved the central nervous system demonstrated selective impairment of olfactory identification and discrimination with a normal threshold (Klimek et al., 1998; Koss et al., 1988). However, there are also controversial studies and arguments; it has been proposed that olfactory thresholds correlate highly with odor identification scores in controls and patients and the reliability of threshold determination is lower than that for other measures (Doty et al., 1994; Mesholam et al., 1998).

There are some other ways for assessing the olfactory system such as Olfactory ERP, Electroolfactrogram (EOG) and functional magnetic resonance imaging methods. As the focus of this paper is on psychophysical test, we tried to give some basic information about psychophysical assessment of olfactory function.

2.2. Literature Research / Study Selection

A computerized literature search for studies on olfaction (threshold, identification, and discrimination) in neuropsychiatric disorders performed in childhood and adulthood (autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive–compulsive disorder (OCD)).

We searched the PubMed database for English language studies between the date of June 2014 and November 2014. Keywords for olfactory system were ''olfaction'', ''smell'', ''odor'', "olfactory dysfunction" and "olfactory assessment". For neuropsychiatric disorders we used "autism spectrum disorder", "epilepsy", ''attention deficit hyperactivity disorder'', ''schizophrenia'', "bipolar disorder", ''eating disorder'', ''obsessive compulsive disorder''.

The papers were selected based on the titles and abstracts. In addition, manual searches were done by examining article references elicited through the database. We focused on certain neuropsychiatric disorders because the number of olfaction studies in children and adolescents is low. We limited our paper to certain trials that had been performed a few times and therefore a general idea could be concluded.

The first results were very heterogeneous even within the respective categories. Reasons for these heterogenic findings may be due to methodological design, especially the use of different olfactory testing procedures, and phenotypical heterogeneity of the samples. As the SST and UPSIT tests were the best-validated and most commonly-used psychophysical tests, only studies with SST and UPSIT were ultimately included. Studies with electrophysiologic and imaging techniques were excluded.

Table 1 shows an overview of study results. The alterations in the olfactory system were termed as "impaired" or "improved". The second bar contains the tests, SST or UPSIT, and the third bar contains the domains. Normally, SST tests include an olfactory threshold, olfactory identification, and discrimination tasks, whereas UPSIT test includes only olfactory identification task. However, some studies included olfactory threshold tests in addition to UPSIT.

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Table 1: Olfactory assessment and neuropsychiatric disorders according to smell test techniques

Disorder	Test	Domain	Results	Age Group	References
Autism SD	SST	OT OI OP* *(pleasantness)	No significance No significance No significance	Childhood	Dudova et al.2013
	UPSIT	OI	Significantly impaired	Childhood	May et al.2011
	SST	OT OI	Significantly impaired No significance	Childhood	Dudova et al.2011
	SST	OI	Significantly impaired	Childhood	Bennetto et al.2007
	UPSIT	OI	No significance	Childhood	Brewer et al.2008
Epilepsy	SST	OT OI	Significantly impaired Significantly impaired	Adulthood	Hummel et al.2013
	UPSIT	OT OI	No significance Significantly impaired* (*only right TLE, but not left TLE)	Adulthood	Kohler et al.2001
	SST	OT OD OI	No significance No significance* Significantly impaired** *(Significance after lobectomy) **(Significance both before and after lobectomy)	Adulthood	Haehner et al.2012
ADHD	SST	OT OD OI	Significantly improved No significance No significance	Childhood	Romanos et al.2008
	UPSIT	OI	Significantly impaired	Childhood	Karsz et al.2008
	SST	OT OI OD	No significance No significance Significantly impaired* *(improved by cessation of medication)	Childhood	Schecklmann et al.2011a
	SST	OT OD OI	No significance No significance No significance	Adulthood	Schecklmann et al.2011b

Disorder	Test	Domain	Results	Age Group	References
OCD	UPSIT	OI	Significantly impaired	Adulthood	Goldberg et al.1991
	UPSIT	OI	Significantly impaired	Adulthood	Barnett et al.1999
	SST	OT OD OI	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Segalas et al.2011
	SST	OT OD OI	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Segalas et al.2014
Eating Disorder *Anorexia Nervosa & Bulimia Nervosa*	UPSIT PEA	OI OT	No significance* No significance* (*Significance only in very-low-weight anorexics)	Adolescent/ Adulthood	Fedoroff et al. 1995
Anorexia Nervosa	SST	OT OD OI Overall	No significance No significance Significantly impaired No significance	Adulthood	Rapps et al. 2010
Anorexia Nervosa	UPSIT	OI	No significance	Adolescent/ Adulthood	Kopala et al.1995
Anorexia Nervosa	SST	OT OD OI	Significantly impaired Significantly impaired No significance	Adolescent	Roessner et al. 2005
Anorexia Nervosa & Bulimia Nervosa	SST	OT OD OI Overall	Significantly impaired* Significantly impaired No significance Significantly impaired *(only in BN)	Adolescent/ Adulthood	Dazzi et al.2013
Anorexia Nervosa & Bulimia Nervosa	SST	OT OD OI Overall	No significance Significantly impaired* No significance Significantly impaired* (*only in AN)	Adulthood	Aschenbrenner et al. 2009
Anorexia Nervosa	SST	OT OD OI	No significance No significance No significance* (*significantly improved in “pure anorexia nervosa group)	Adolescent	Schecklmann et al.2012
Anorexia Nervosa	SST	OT OD OI Overall	No significance* Significantly impaired Significantly impaired Significantly impaired *(significance only in hunger state)	Adulthood	Schreder et al.2008

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Disorder	Test	Domain	Results	Age Group	References
Bipolar Disorder	UPSIT	OI	Significantly impaired	Adulthood	Lahera et al.2013
	UPSIT	OI	Significantly impaired	Adulthood	Cumming et al.2011
	UPSIT	OI	No significance	Adulthood	Hardy et al.2012
	SST	OT OI OP* *(pleasantness)	No significance No significance No significance	Adulthood	Swiecicki et al.2009
	SST	OT OD OI	No significance* No significance No significance *(event related impairment)	Adulthood	Krüger et al.2006
Schizophrenia	UPSIT	OI	Significantly impaired* *in male subjects	Adulthood	Kopala et al.1992
	UPSIT	OI	Significantly impaired	Adulthood	Houlihan et al.1994
	UPSIT	OI	Significant impairment* *in ultra-high-risk group who later developed schizophrenia spectrum disorder	Adulthood	Brewer et al.2003
	SST	OI OD OT	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Clepce et al.2013
	UPSIT	OI	Significantly impaired* *in family members	Adulthood	Kopala et al.2001
	SST	OD OI	Significantly impaired* *in patients and youth at clinical risk Significantly impaired** *in paitents, at-risk youth and relatives	Adulthood	Kamath et al.2014
	UPSIT	OI	Significantly impaired* *Significantly worse scores in deficit syndrome patients than non-deficit patients	Adulthood	Malaspina et al.2002
	UPSIT	OI	Significantly impaired* *in early onset psychosis patients	Adolescent	Corcoran et al.2005
	UPSIT	OI	Significantly impaired* *Significantly lower baseline in patients with non-remission of negative and cognitive symptoms compared to patients with remission	Adulthood	Good et al.2006
	UPSIT	OI	Significantly impaired* *in pleasant odors	Adulthood	Crespo-Facorro et al.2001

2.3. Olfactory dysfunction in specific neuropsychiatric disorders

We presented the findings and interpreted them within subheadings respectively. In every category, some specific information about each disorder was given and then trials were discussed.

2.3.1. Autism Spectrum Disorders and Olfactory Dysfunction

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by deficits in socialization, verbal and nonverbal communication, stereotyped patterns of behavior, and a range of interests (DSM-5).

The response to sensory stimuli or sensory perception in children with autism is often impaired. These sensory problems in ASD were reported by studies using sensory questionnaires including Short Sensory Profile (Kientz and Dunn, 1997; Lane et al., 2010; Schoen et al., 2009; Tomchek and Dunn, 2007), and interview methods including Diagnostic Interview for Social and Communication Disorders (DISCO) (Leekam et al., 2007). The mutual results of these types of studies showed significant sensory perceptional differences (especially sensory hypersensitivity) and clinical symptoms in children with autism. The main interest field of this paper, smell sensitivity, was also impaired in children with autism (Schoen et al. 2009; Lane et al. 2010) and the olfactory symptoms were more outstanding in ASD (Leekam et al., 2007).

Bennetto et al., (2007) investigated odor identification using SST in children with autism and showed significantly worse olfactory identification in ASD. Brewer et al., (2008) researched odor identification using UPSIT in children with high functioning autism (HFA) and showed no significant difference. However, smell identification ability was negatively associated with age in HFA. Dudova et al., (2011) reported significantly impaired odor detection thresholds using SST in children with Asperger's syndrome and high functioning autism but failed to show differences in odor identification. In that study, autistic participants were significantly better in identifying the odor of an orange and significantly worse at identifying the odor of cloves. The same team, Dudova et al., (2013) investigated olfactory dysfunction using SST among high-functioning patients (children) with ASD and showed no significant correlations between autism severity (as expressed by total CARS score) and odor-detection thresholds, odor identification or odor pleasantness. They argued that most of their patients had Asperger's syndrome (AS) (27 of 35 patients), which was atypical, and it did not represent the most common diagnosis in the ASD group. May et al., (2011) investigated the olfactory identification in a longitudinal study using UPSIT between children with high functioning autism (HFA) and Asperger's syndrome. There was a slight difference in olfactory identification between HFA and AS. The authors considered that the orbitofrontal cortex (OFC) was involved in the behavioral deficits of autism and AS. The psychophysical olfactory tests like SST and UPSIT are believed to be alternative ways to assess OFC function and development. Olfactory detection is mediated by lower-order neural pathways, whereas olfactory identification (OI), which requires recognition, is based on the OFC (Martzke et al., 1997; Qureshy et al., 2000). There are also OI deficits when the OFC is damaged in patients with cerebrovascular accidents (Savage et al., 2002). There are left-hemisphere deficits of orbitofrontal fascicules in HFA versus right-hemisphere deficits in AS (McAlonan et al., 2009); these differences might indicate the distinct neurologic development and different orbitofrontal functioning in AS and HFA.

2.3.2. Epilepsy and Olfactory Dysfunction

Epilepsy is one of the most common chronic neurologic disorders, which is characterized by recurrent and unpredictable seizure (Fisher et al., 2005). The International League against Epilepsy has classified seizures into two major types; generalized seizures and partial (focal) seizures. Temporal lobe epilepsy (TLE) is the most common type of partial epilepsy (Engel, 1996).

Sensation and perception are clearly involved in epilepsy and there is a perceivable correlation between sensation and epilepsy syndrome (Grant, 2005). For example, olfaction is commonly affected in temporal lobe epilepsy, whereas the processing of visual information is disturbed in occipital lobe epilepsy. Although many studies have shown impaired perceptual ability in epilepsy, heightened sensitivity has also been reported (Carroll et al., 1993; Grant, 2005; West and Doty, 1995).

Kohler et al., (2001) evaluated odor threshold (using the phenyl ethyl alcohol (PEA) test) and odor identification using UPSIT in patients (adults) with right- and left temporal lobe epilepsy and found significant impairment in odor identification in patients with right TLE but not in left TLE. The detection threshold sensitivity was normal in all groups. Haehner et al., (2012) researched odor threshold, odor identification, and odor discrimination using SST in patients (adults) with and without temporal lobe resection. Overall, there was no difference between groups in terms of odor threshold, but after temporal lobe resection, patients presented with significantly impaired bilateral discrimination and identification abilities compared with the healthy controls. The odor identification test results of patients with epileptic focus were lower than the results of the healthy controls. The authors concluded that olfactory function was only partially impaired preoperatively and would deteriorate further after partial resection of the epileptic focus. Hummel et al., (2013) reported significantly impaired olfactory function using SST in patients with TLE compared with healthy controls, both at threshold level and odor identification. They also showed smaller olfactory bulb volume by neuroimaging methods.

The reason why temporal lobe epilepsy was chosen for olfactory dysfunction study can be explained by close anatomic associations between the olfactory and limbic systems (Grant, 2005). Olfactory processing is performed in two ways. Primary processing occurs in the priform and entorhinal cortex, whereas secondary processing occurs in the orbitofrontal, mesial temporal, thalamic, and hypothalamic regions (Kohler et al., 2001; West and

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Doty, 1995). As temporal lobe epilepsy is a dysfunction of the temporo-limbic neural circuit (Kohler et al., 2001), olfaction is commonly affected and is a necessary topic of study. In such studies, the main olfactory tasks were identified as olfactory threshold, identification, and discrimination. Overall, studies showed that the odor detection threshold is not totally impaired in patients with epilepsy. The preservation of primary olfactory processing in epilepsy might mean that the odor threshold is more closely related with peripheral function (Hedner et al., 2010; Lötsch et al., 2008). However, the impairment of odor identification and discrimination in epilepsy could be explained by the involvement of secondary olfactory processing because odor identification and discrimination exhibit a significant relationship with higher cognitive proficiency (Hedner et al., 2010). The disruption of association of orbitofrontal cortex may be involved in odor discrimination as a higher cortical function in epilepsy. Through some studies, the expression of olfactory dysfunction in the right rather than the left TLE (Kohler et al., 2001) might be based upon olfactory processing asymmetry in the brain.

2.3.3. Attention Deficit Hyperactivity Disorders and Olfactory Function

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset behavioral disorder characterized by clinical core symptoms such as inattention, impulsiveness, and hyperactivity (Tannock, 1998). The subtypes of ADHD can be classified as predominantly inattentive, predominantly hyperactive – impulsive, and combined group (DSM-5).

In the pathophysiology of ADHD, an inhibitory dopaminergic effect at striatal/prefrontal level is supported by neuroimaging, genetic, and stimulant medication studies (Levy and Swanson, 2001). Structural and functional changes in the prefrontal and striatal regions have also been implicated (Schneider et al., 2006). The orbitofrontal cortex, through its connections with other zones of the prefrontal cortex (PFC), plays a crucial role in controlling impulsivity (Davidson et al., 2000) and damage to this area has been associated with the symptoms of impulsive and inappropriate behavior (Berlin et al., 2004).

Olfaction is mediated by the olfactory nerve, which courses through the prefrontal cortex to the entorhinal cortex (Murphy et al., 2001). Damage to the prefrontal cortex can result in a decrease in olfactory sensitivity or identification (Varney and Menefee, 1993). The lesser activity of PFC in ADHD can imply the olfactory dysfunction in ADHD (Murphy et al., 2001). Romanos et al., (2008) interestingly revealed improved odor sensitivity (lower threshold) using SST in children with ADHD. However, patients given medication normalized their olfaction. These correlations may imply the close interaction between dopaminergic striatal system and olfaction. Karsz et al., (2008) reported significantly poorer olfactory identification using UPSIT in patients with ADHD. They emphasized that the decreased ability was consistent with prefrontal impairment in ADHD. Schecklmann et al., (2011) demonstrated using the SST test the normalization (increase) of olfactory discrimination after cessation of methylphenidate (MPH) in children. However, they found no medication effect on sensitivity in contrast to Romanos et al., (2008). The authors concluded that increased sensitivity in non-medicated patients and its normalization with MPH treatment as well as increased discrimination induced by cessation of MPH treatment in patients with chronic medication may be related to modulation of dopaminergic neurotransmission and to alterations in striatal dopaminergic function. Both the change in olfactory sensitivity (threshold) as a primary olfactory processing (peripheral function) and in olfactory discrimination as a secondary olfactory processing (higher cortical function) in patients with ADHD might indicate that there could be an important alteration / modulation extending from the olfactory bulb to orbitofrontal cortex in term of dopaminergic tone.

2.3.4. Obsessive-Compulsive Disorder (OCD) and Olfactory Dysfunction

Obsessive-compulsive disorder (OCD) is a psychiatric condition described as the presence of recurrent and persistent thoughts, urges or images (i.e. obsessions), and repetitive behaviors or mental acts in response to these (i.e. compulsions) (DSM-5). Various functional and structural changes have been observed in the gray and white matter areas, particularly in the cortical-striatal-thalamic-cortical (CSTC) circuits and orbitofrontal cortex (OFC) (Menzies et al., 2008; Peng et al., 2012; Piras et al., 2013; Rotge et al., 2010). Several neurocognitive domains have been investigated together with olfactory function in OCD because they are in close proximity (Shin et al., 2014).

The first study that assessed olfaction was by Goldberg et al., (1991) who used UPSIT for olfactory acuity. Although the number of subjects was limited, they found differences between the obsessional group (adults) and the otherwise healthy group.

Barnett et al., (1999) investigated olfactory identification in patients with OCD (adults) using UPSIT and they found that olfactory identification ability was significantly impaired in the patient group compared with the healthy controls. They added that most of the patients with OCD had moderate to mild degree microsmia but none of them were anosmic. However, there was no association between OCD severity and degree of dysfunction in olfactory abilities.

Segalàs et al., (2011) evaluated odor identification, threshold and discrimination with Sniffin Sticks Test (SST), along with nonverbal memory, anxiety levels, depression levels, and Axis I diagnosis. There were statistically significant olfactory impairments in the patient group (adults) for all three olfactory domains. However, after excluding patients with Axis I comorbidities, no significant differences were observed between the OCD patients and healthy controls. Scores for olfactory identification were negatively correlated with depression and anxiety levels in patients with OCD and it did not change after discarding the patients who had Axis I comorbid disorders. A significant

negative correlation was also present between olfactory identification dysfunction and disease intensity in patients without comorbid psychiatric diagnoses. There were no significant association between nonverbal memory and olfactory dysfunction. The authors concluded arguing that symptoms of obsession, compulsion, and depression might alter olfaction, particularly olfactory identification in patients.

The same research group examined the association between regional gray matter volume, as assessed by analysis of magnetic resonance images (MRI), and olfactory function using SST in adult patients with OCD (Segalàs et al., 2014). They found significantly impaired olfactory function (threshold, identification and discrimination) and association with volumetric changes in brain areas (left anterior cingulate cortex and left medial orbital gyrus) in patients with OCD. Olfactory dysfunction in patients with OCD can indicate that frontal and temporal lobe circuits are related to both disease activity and olfaction owing to their close strategic proximity.

2.3.5. Eating Disorder and Olfactory Dysfunction

Eating disorders are chronic conditions defined as disturbances of eating or eating-related behavior, which result in impairment of physical health and psychosocial function (Treasure et al., 2010). The complexity associated with these disorders derives from its high morbidity (up to 20%) and comorbidity rates (Hoek, 2006; Treasure et al., 2010). Pica, rumination disorder, avoidant/restrictive food intake disorder, anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder are categorized as eating disorders in the new edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Disturbances of sensation and perception towards internal and external stimuli are believed to play an important role in the development and progress of eating disorders (Connan et al., 2003). Distorted perception of body size, physical properties of food (Berry et al., 1995), hunger and satiety (Halmi and Sunday, 1991; Rolls et al., 1992) as well as diminished hedonic capacity to respond to olfactory, gustatory and visual food related stimuli were previously reported.

A variety of psychophysical tests are used to show olfactory disturbances in people with eating disorders. However, the results are controversial. The very first studies that investigated olfactory dysfunction in eating disorders, Koppala et al., (1995) used UPSIT and found no differences in olfactory identification ability between patients with anorexia nervosa and the healthy control. On the other hand, Fedoroff et al., (1995) recruited patients who had food-restricting type anorexia, anorexia with bulimic features, and bulimia nervosa and found olfactory detection and identification impairment only in the very-low-weight anorexic group using UPSIT and the phenyl ethyl alcohol (PEA) test.

In more recent years, Roessner et al., (2005) used the SST test to examine olfactory dysfunction in patients with anorexia and stated that significantly higher scores were detected in odor threshold and impairment was found in odor discrimination, but not in odor identification. They argued that these findings indicated that patients with anorexia showed a reduction of peripheral olfactory perceptual ability.

Supporting findings were obtained from a study conducted by Dazzi et al., (2013) who found poorer outcomes in olfactory discrimination in patients with AN and olfactory threshold and discrimination in patients with BN. When comparing overall function (TDI scores in SST), patients with both AN and BN fell on the hyposmic range, which was significantly higher than the control group.

In a longitudinal study, Aschenbrenner et al., (2008) compared AN patients with BN patients and a healthy control group. They reported that patients with AN had a small but significant decrease in odor discrimination and overall olfactory function compared with healthy controls and patients with BN. In the same study, an improvement in olfactory function was observed after effective treatment in patients with AN.

Conversely, Schecklmann et al., (2012) argued that the conflicting results of previous studies might be derived from selection criteria and designed a study with adolescent girls who had never smoked and a well-matched healthy control group. They defined a subgroup of patients who had received no medication and had no psychiatric comorbidity, this subgroup was called "pure anorexia nervosa". Using SST, there were no difference between patients and healthy controls in any olfactory domain. Higher olfactory identification was observed in the "pure anorexia nervosa group", which could be attributed to increased attentional processing towards food-related stimuli.

Schreder et al., (2008) investigated olfactory dysfunction of patients with anorexia nervosa in hunger and satiety conditions using SST. They performed threshold tests in a hungry and satiated state, but odor discrimination and odor identification only when satiated. The olfactory discrimination and identification abilities of patients with AN were significantly lower. The olfactory threshold sensitivity for isoamyl acetate (food-related odor) was only significantly lower in hunger. Hence, hunger and satiety state may be considered to be other determinant factors of sensation and perception disturbances.

2.3.6. Bipolar Disorder and Olfactory Dysfunction

Bipolar disorder is a psychiatric disorder that causes shifts in a person's mood, energy, and ability to function (DSM-5). It is characterized with episodes of mania and depression, and accompanied by impaired executive function and emotional dysregulation (Hardy et al., 2012).

The etiology of bipolar disorder is unknown, but functional and anatomic differences have been found in imaging studies in patients with bipolar disorder, especially in the amygdala, anterior cingulate, striatum, ventromedial prefrontal cortex, and orbitofrontal cortex (Agarwal et al., 2010; Keener and Phillips, 2007). In the last two studies, it was demonstrated that euthymic patients with bipolar disorder have a decreased regional cerebral blood flow in the orbitofrontal cortex at rest and a stronger decrease after provocation with a sad mood–

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induction paradigm compared with healthy volunteers using positron emission tomography (PET). These regions have also been shown to play important roles in olfactory processing, particularly the amygdala, hippocampus, and orbitofrontal cortex receive projections from the piriform cortex and are key secondary olfactory areas (Kivity et al., 2009). It has been postulated that olfactory dysfunction might be accompanied by bipolar disorder on the basis of the anatomic and functional relationships (Hardy et al., 2012).

In two recent studies, patients (adults) with bipolar disorder showed significant impairment in olfactory identification compared with healthy controls (Cumming et al., 2011). Krüger et al., (2006) showed a close relation between olfactory function and mood regulation. In that study, a heightened olfactory acuity in patients with bipolar disorder whose mood episodes were triggered by emotional events was demonstrated. It has been reported that depressive symptoms were related to increased sensitivity (the ability to detect odors at a lower concentration) and mania symptoms were related to decreased sensitivity for odor detection (Hardy et al., 2012). On the other hand, comparatively intact olfactory function in bipolar disorders have also been shown (Swiecicki et al., 2009).

2.3.7. Schizophrenia and Olfactory Dysfunction

Schizophrenia is a neuropsychiatric disorder characterized by disruptions in thought processes, perceptions, and emotions. In the pathophysiology of schizophrenia, there are abnormalities in the temporolimbic and frontal lobe regions (Seidman et al., 1995). These areas, namely the temporolimbic and orbitofrontal cortex, have been shown to be responsible for olfactory information process in animal studies (Tanabe et al., 1975). The alteration in these areas might be associated with olfactory dysfunction because these regions serve for the affective and mnemonic functions, and these functions are most intimately related to olfaction among sensory processing (Turetsky et al., 2009).

The impairment of sensation in schizophrenia can be explained by olfactory dysfunction due to strategic anatomic proximity. The assessment of olfactory dysfunction among patients with schizophrenia has also been broadly done by various methods including psychophysical tests such as UPSIT (Houlihan et al., 1994; Kopala et al., 1993) and SST (Clepce et al., 2013; Kamath et al., 2013).

The decreased threshold sensitivity in schizophrenia has been shown by some studies (Rupp et al., 2005; Serby et al., 1990). Olfactory identification deficits in patients with schizophrenia have been reported by numerous studies to be independent of sex, neuroleptic use, and smoking status (Moberg et al., 1999). However, identification deficits significantly correlate with duration of illness (Moberg et al., 1997). In addition, olfactory memory is proven to be impaired (Wu et al., 1993) and this finding was supported by more recent studies (Moberg et al., 2014).

Many studies have also explored olfaction in association with positive and negative symptoms in schizophrenia. In these studies, there is a greater correlation of olfactory dysfunction with the degree of negative symptoms (Corcoran et al., 2005; Good et al., 2006; Malaspina et al., 2002). Patients with schizophrenia also have deficient response to emotional stimuli and decreased hedonic capacity to odorant stimuli, especially to pleasant ones but not unpleasant odors (Crespo-Facorro et al., 2001; Kamath et al., 2011; Moberg et al., 2003; Strauss et al., 2009).

Olfactory dysfunction has been investigated in patients with schizophrenia and also in high-risk individuals, healthy first-degree family members, and people with schizotypal personality features (Kopala et al., 2001; Brewer et al., 2003; Kamath et al., 2014;). Although the findings were controversial for individuals with schizotypal personality features (Compton and Chien, 2008), there were positive associations between olfactory dysfunction and the high-risk population as well as healthy first-degree relatives of schizophrenia patients when compared with the control groups. These findings suggest that impaired olfactory abilities may be considered as a susceptibility marker or an endophenotypic feature for schizophrenia.

3. Discussion and Conclusion

Although olfactory loss often goes unnoticed, data suggest that olfactory dysfunction (loss) might guide us in the way of determining the risk of some certain neurodegenerative and neuropsychiatric diseases. Olfactory dysfunction occurs before any movement or cognitive disorder in Parkinson's disease, Alzheimer's disease (AD) (Hawkes, 2006), and hyposmia; anosmia in particular significantly increased the risk of subsequent cognitive failure in AD (Graves et al., 1999).

Due to strategic anatomic proximity, it has been shown that olfactory loss is coexistent in ADHD, autism, and schizophrenia. The dopaminergic pathway within temporolimbic and frontal lobe regions revealed this association, especially in disorders that involve this pathway (e.g., ADHD, autism, and schizophrenia) showed olfactory dysfunction. Improved olfactory function in ADHD and normalization by dopaminergic medication was also shown. Overall olfactory deficit (threshold, identification and discrimination) is possible in OCD. Olfactory identification may be especially impaired in ASD and epilepsy. Impairment in olfactory discrimination has been reported in anorexia nervosa, and deficits in olfactory identification in schizophrenia might be especially described.

High-risk individuals for neuropsychiatric disorders are targets for determining the biomarker feature of olfaction and several recent studies detected positive associations between olfactory dysfunction and this risk group (Brewer et al., 2003; Kamath et al., 2014). Based upon these trials, olfactory dysfunction might precede the pending diseases as in neurodegenerative disorders. However, risk- group studies have thus far been limited to schizophrenia.

Methodologic design, sample heterogeneity, control groups, inconsistent findings, low number of studies in childhood and adolescence are primary concerns for

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drawing certain conclusions. The putative biomarker features of olfactory dysfunction in neuropsychiatric disorders remain unclear, especially because of the limited number of risk group studies.

More studies with better methodologic design are required for absolute conclusions. Longitudinal studies that start from childhood might provide more important information about the putative prognostic features of olfactory dysfunction. The applicability problem of smell tests in childhood might be overcome with electrophysiologic tests. Along with developmental screening tests, studies in ADHD and ASD and in their risk groups could be valuable for determining the diagnostic role of olfaction in neuropsychiatry. Imaging and genetic techniques may add supplementary information to these purposes.

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ATTENTIONAL GUIDANCE BY THE CONTENTS OF WORKING MEMORY AND THE N2PC COMPONENT

DİKKATİN ÇALIŞAN BELLEK İÇERİĞİ TARAFINDAN TAHSİS EDİLMESİ VE N2PC BİLEŞENİ

Fatma Keskin Krzan*[1]

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Abstract

The Biased Competition Model suggests that stimuli matching the contents of working memory increase the likelihood that memory-matching items will be attended. According to this account, the representations in working memory create an involuntary capture of attention toward memory-matching items in the visual field. This influential assumption proposed by the biased competition model has been explored in a number of studies, showing that the contents of working memory exert an automatic bias in favor of memory matching items. These studies showed that active maintenance of objects in working memory automatically shift attention toward the memory matching-object and produce a negative early lateralized event related potential (ERP), the N2pc, toward the side of visual field where the memorized item appeared. This component, the N2pc is an important tool to investigate the allocation of attention by working memory representations, especially for the activity the activity that is specific to the hemisphere which is contralateral with respect to the hemifield containing e.g. the to-be-remembered items could be measured. This characteristic of the N2pc facilitates measuring the general direction of attention with fine-grained temporal resolution. Therefore, the N2pc could be used as an index to describe the lateralization effect of memorized items on attention related studies.

Keywords: Attention, Working Memory, The N2pc, Lateralization

Özet

Yanlı Rekabet Modeli çalışan bellek içeriği ile eşleşen uyaranların, hafıza ile uyumlu olan uyaranların dikkat olasılığını arttıracağını ileri sürer. Bu açıklamaya göre, çalışan bellek içindeki temsiller, görsel alan içerisindeki temsillerle eşleşen uyaranlara doğru istemdışı bir dikkat oluşturur. Yanlı Rekabet Modeli tarafından önerilen bu etkili varsayım, çalışma belleğinin içeriğinin bellekle eşleşen öğeler lehine otomatik önyargı oluşturduğunu gösteren bir dizi çalışmada araştırılmıştır. Bu çalışmalar, çalışan bellekte sürdürülen nesnelerin, bellekle eşleşen öğelere yönelik otomatik bir dikkat oluşturup, bellek temsilinin oluştuğu görsel alanda erken negatif lateral olaya ilişkin potansiyelini (N2pc) ortaya çıkardığını göstermiştir. Bu bileşen, N2pc, dikkatin çalışan bellekteki temsiller tarafından tahsis edilmesini araştırmak için önemli bir araçtır ve bu bileşenin özellikle hatırlanan nesnelere kontralateral hemisfere özgü aktiviteyi ölçmektedir. N2pc bileşeninin bu özelliği dikkatin genel yönünü detaylı bir şekilde ölçmeyi kolaylaştırmaktadır. Bu nedenle, N2pc bileşeni dikkat ilgili çalışmalarda hafızada korunan öğelerin yanallaşma etkisini açıklamak için bir indeks olarak kullanılabilir.

Anahtar Kelimeler: *Dikkat, Çalışma Belleği, N2pc, Lateralizasyon*

1. Introduction

For our adaptive control of actions, we have to selectively process and store relevant information from among distractor stimuli in the environment. Attention enables observers to focus on a subset of the information present in a complex visual scene (Bundesen, 1990; Desimone & Duncan, 1995; Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Wilson, Woldorff, & Mangun, 2005). Working memory is crucial in guiding attention to form a link between controlled action and perception that provides limited and temporary access to maintain recently encountered information in mind (Desimone & Duncan, 1995). In the course of this complex visual processing, the neural representations of objects in a visual scene compete to gain access to higher level of processing (Desimone, 1996; Soto, Hodsoll, Rotshtein, & Humpreys, 2008). During this competition, working memory guides shifts of attention in favour of the information matching the items recently maintained in working memory (Duncan & Humphreys 1989; Desimone & Duncan 1995; Desimone, 1996; Soto, Heinke, Humphreys, & Blanco, 2005; Olivers, Meijer, & Theeuwes, 2006; for a review, see Soto et al., 2008). As a result, the content of working memory often determines the winner of the competitions, and thus determines which stimulus is attended (Desimone, 1996). For instance, when we search

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for something in a crowded place (e.g., looking for a red shirt in a full of clothes), stimuli stored in our working memory (e.g. the red shirt) can guide the deployment of attention to visually matching item (e.g., a red sweater) in the environment. In this example, the deployment of attention is determined by an active mechanism in which the stronger attentional capture is controlled through the voluntary and goal-oriented guidance of working memory (Desimone & Duncan, 1995; Bundensen, 1990). However, this memory-driven guidance by items stored in working memory can also automatically influence visual selection even when those items are task-irrelevant and while observers' attention is focused on another demanding visual monitoring task (Soto et al., 2005; Downing, 2000; Eimer & Kiss., 2007). For example, driving a car near a forest area requires scanning our visual field for animals that may suddenly leap into the road. Holding a representation of an animal in working memory will automatically guide our attention to any animal-like objects while driving in a forest zone, even without the goal of looking for the animal per se. This example shows how the information stored in working memory (e.g. the animal) guides attention in an involuntary manner, even though it is irrelevant to the current task (e.g. maintaining the presentation of the animal while driving the car).

Recent studies have used a variety of techniques to explore the mechanism involved in memory-driven guidance of visual selection. Behavioral studies (Soto et al., 2005; Downing, 2000), electrophysiological (ERPs) and imagining studies (fMRI) in human (Mazza et al., 2011; Eimer & Kiss., 2010; Kumar et al., 2009; Dell'Acqua et al., 2009; Soto, Humphreys, & Rotshtein, 2007; Lepsien, Griffin, Devlin, & Nobre, 2005) and in monkeys (Chelazzi, Duncan, Miller, & Desimone,1998; Soto, Greene, Chaudhary, & Rotshtein, 2012) have shed light on some aspects of the role of working memory in guiding visual attention. Compared with other techniques, the event related potential technique (ERP) has been widely used in these attention related studies because of its high and precise temporal resolution measures of cognitive processing (Kumar et al., 2009; Awh, Anllo-Vento, & Hillyard, 2000; Kuo et al., 2009; McCollough, Machizawa Maro, Edwar, & Vogel, 2007; Carlisle, Geoffrey. & Woodman, 2011; Mazza et al., 2011).

Specifically, a specific ERP response, called N2pc component, reflecting the orienting of selective attention to targets or relevant locations in the visual field, has been intensively used to measure observers' attention across visual space (Woodman, Arita, & Luck, 2009; McCollough et al., 2007; Mazza et al., 2011). This lateralized ERP component reflects a direct measure of attentional process, acting differentially in the hemisphere contralateral to visual targets/relevant locations compared with the hemisphere ipsilateral to the targets/relevant locations (Luck & Hillyard, 1994; McCollough et al., 2007; Robitaille, & Jolicœur, 2006). Most experiments measured the N2pc component during visual search tasks in which stimuli were presented either to the left or right of a central fixation point (bilateral visual search displays) to produce stimulus-driven responses equally from both left/right visual fields. This bilateral presentation of the search array was thought to provide balanced perceptual stimulation to both hemispheres and allow measuring the activity that is specific to the hemisphere which is contralateral with respect to the hemifield containing e.g. the to-be-remembered items (McCollough et al., 2007; Kuo et al., 2009; Kumar et al., 2009; Mazza et al., 2011; Kiss et al., 2008; Dell'Acqua et al., 2009). The N2pc component can be isolated at posterior electrode sites as the difference in mean amplitude between the contralateral and ipsilateral waveforms with a latency of 180-300 ms post-stimulus interval (Woodman & Luck, 1999). Results showed that active maintenance of an object in working memory automatically shifts attention toward the memory matching-object and produces the N2pc component to the side of visual field where the matching item appeared (Kumar et al., 2009; Mazza et al., 2011; Kuo et al., 2009; Kiss et al., 2008; Dell'Acqua et al., 2009). More recently, the N2pc has been also observed in an ERP study investigation memory-driven attentional capture with no lateralized stimuli presentation. A recent ERP study (Astle et al., 2010) found a lateralized brain activity (e.g. the N2pc) after a single test object presentation at the center of visual field, toward the original location of those test object-matching items in a preceding memory array. Namely, when the test object appeared at the fixation point, participants' attention was automatically allocated to the original (lateralized) location of an item in the preceding memory array that matched the test object (Astle et al., 2010; Kuo et al., 2009; McCollough et al., 2007). This N2pc activity found by Astle et al. (2010) is unusual for the reason that the N2pc component has been typically measured during lateralized visual targets. Therefore, (hypothetically) there should be no N2pc activity, if there are no lateralized stimuli in a visual display. However, despite non-lateralized stimuli presentation, maintaining an item in working memory biased visual selection automatically to its original location whenever a match occurred between the memory item and the central object matching the memory contents (Astle et al., 2010). Astel et al.'s study provides novel evidence that the lateralized spatial bias of memory content is so powerful that it can also occur even with a central item, presented at the fixation point (and even when it is presented subliminally).

Several dominant theories of visual attention propose that the contents of working memory automatically guide attention toward memory-matching objects (Bundesen, 1990; Desimone & Duncan, 1995; Duncan & Humphreys, 1989). This claim was at the basis of one of the most influential models on attention: the "Biased Competition Model". According to this model, stimuli compete with each other in the visual field for processing capacity, and the stronger sensory input becomes the focus of attention (Desimone & Duncan, 1995). This competition can be biased by an attentional template that preserves short-term description of information recently held in memory and is prioritized in the visual cortex (Desimone & Duncan, 1995). If one searches for a particular item (e.g., a yellow car), information matching the internal representation (attentional template) of that item will be pre-activated and therefore gaining a competitive advantage over other sensory inputs (e.g. a red car). This sustained neural

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activity derives from neural circuits mediating working memory, especially in the prefrontal cortex and provides an automatic competitive advantage for matching sensory inputs (Desimone & Duncan, 1995). Within this framework, the deployment of attention is automatically determined by an active mechanism in which the stronger attentional capture is explained through the voluntary and goal-oriented guidance of working memory (Desimone & Duncan, 1995).

2. Review of the Literature:

2.1. Attentional Guidance by the Contents of Working Memory

Several dominant theories of visual attention propose that the contents of working memory automatically guide attention toward memory-matching objects (Bundesen, 1990; Desimone & Duncan, 1995; Duncan & Humphreys, 1989). This claim was at the basis of one of the most influential models on attention: the "Biased Competition Model". According to this model, stimuli compete with each other in the visual field for processing capacity, and the stronger sensory input becomes the focus of attention (Desimone & Duncan, 1995). This competition can be biased by an attentional template that preserves short-term description of information recently held in memory and is prioritized in the visual cortex (Desimone & Duncan, 1995). If one searches for a particular item (e.g., a yellow car), information matching the internal representation (attentional template) of that item will be pre-activated and therefore gaining a competitive advantage over other sensory inputs (e.g. a red car). This sustained neural activity derives from neural circuits mediating working memory, especially in the prefrontal cortex and provides an automatic competitive advantage for matching sensory inputs (Desimone & Duncan, 1995). Within this framework, the deployment of attention is automatically determined by an active mechanism in which the stronger attentional capture is explained through the voluntary and goal-oriented guidance of working memory (Desimone & Duncan, 1995).

2.2. Single Unit Recordings

Chelazzi and colleagues (1998) provided evidence for the Bias Competition Model in a study on monkey neurophysiology during memory-guided visual search task. Chelazzi et al., (1998) examined the role of attention in temporal cortex of monkeys, using single cell recordings. Each trial began with a fixation stimulus. While the monkeys maintained fixation, a target object (e.g. a flower) at the center of the display was presented for 300 ms and they were trained to hold that object in memory (Figure 1). After 1500 ms, a visual search display with two test objects was presented simultaneously for 600 ms. On target-present trials, one of the objects matched the previous object (the other object was novel) and the monkeys were rewarded for responding to the object matching the cue. On target-absent trials, neither of the two objects matched the previous object. In the search display, the monkey's task was to direct its gaze to the memory-matched object.

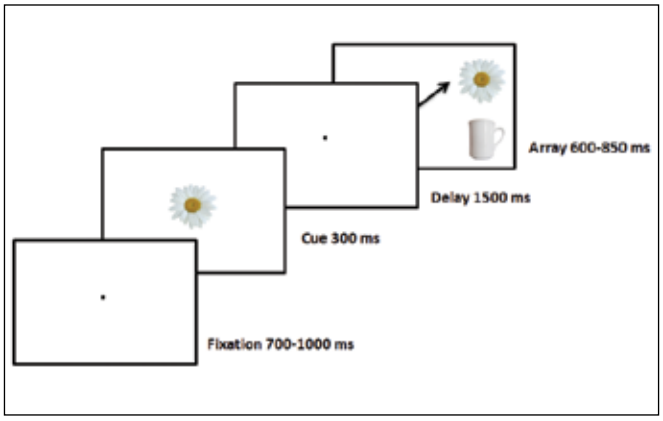

Figure 1: An illustration of a trial sequence. Data were obtained while the monkeys performed a task in which they were briefly presented with a target object at the center of their visual fields and were required to remember it (flower). After a blank, a visual search display with multiple objects was presented, one of which would be the same as the remembered object (flower) and other one was novel (a cup). The task was to make an eye movement to the object matching the memorized object. Adapted from Chelazzi et al. (1998).

Behavioral data showed that, when the search array was presented, object matching the cue appeared to dominate the response (Chelazzi et al., 1998). Namely, the monkeys made significantly greater responses (eye movements) to the object that matched the memorized item (the flower) relative to non-matching stimuli (the cup). Single-cell recording results also showed that cells in the inferior temporal cortex contralateral to the object matching the cue had a higher firing rate relative to non-matching object.

2.3. Behavioral Studies

In line with bias competition model, many studies demonstrated that the activation of object representations in working memory biases associated representations making them automatically more attractive to bias attention (for a review, see Olivers, 2008). More recently, a number of behavioral studies demonstrated that working memory can bias the deployment of attention automatically towards to items that match the contents of working memory even when they are irrelevant for the current task (Olivers, Meijer, & Theeuwes, 2006; Soto et al., 2005; Downing, 2000). For example, Soto et al. (2005) investigated the effect of irrelevant contents of working memory on attention while participants were required to hold an object cue in working memory followed by a search task for a titled line. On some trials the cue could contain either the search target (valid trials) or a distractor (invalid trials) in the following search array. Namely, the target could appear inside a surrounding object that either matched or did not match the memorized item. Behavioral data showed that the participants were faster when the target appeared within the objects that matched the memory item (Soto et al., 2005). Other evidence for irrelevant working memory content on attention has been

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demonstrated by Downing (2000) in a visual memory task, in which observers were asked to memorize a central face. During a delay period, the simultaneous representations of two faces were shown on either side of the fixation point, only one of which matched the one held in working memory. After a delay, the subjects were required to perform an orientation discrimination task on a small bracket oriented left or right that appeared at the location of one of the two faces. When the small bracket appeared at the location of the face that matched the one in working memory, reaction times to the small bracket were faster than when it appeared over the non-matched face (Downing, 2000). A similar paradigm was used to test a group of patients with visual extinction with difficulty detecting the presence of a contralesional stimulus when ipsilesional items appeared simultaneously (Soto, Humphreys, & Heinke, 2006; for a review, see Soto et al., 2008). The patients showed enhanced awareness for contralesional targets when the visual search array contained the item held in working memory. However, no such effect was found when the initial items were merely identified or viewed passively (Soto et al., 2006).

2.4. fMRI Studies

Further evidence that underline the effect of irrelevant working memory content on orienting attention comes from functional brain imagining (fMRI). Recently, Soto et al. (2007) reported fMRI evidence showing that maintenance of an object in working memory is accompanied by increased neural signal in occipital and frontal regions (see also, Woodman & Luck, 2007). Neuronal correlates were measured when subjects were presented with an initial cue and subsequently required to search for a target presented at the center of a surrounding either cued or non-cued object (Figure 2). With the reappearance of the stimulus held in working memory, they found an enhanced activity in a network of areas, including the superior frontal gyrus, parahippocampal gyrus and lingual gyrus. In the working memory condition where subjects had to hold the cue in their working memory, an enhanced neuronal signal in the areas that encode the prior occurrence of stimuli (superior frontal gyrus, midtemporal, and occipital regions) was found to drive attention to locations where the item reappeared (Soto et al., 2007). In contrast, when the cue reappeared in the repetition condition where the subjects were required to identify and compare two cues, reduced neuronal signal was observed in the same areas. These results suggest that there is neuronal dissociation on visual selection between the working memory and priming effects when the search target matched the content of working memory.

Awh and colleagues (Awh, Jonides, Smith, Buxton, Frank, Love, Wong, & Gmeindl, 1999) have also measured fMRI activation to provide sensitive measure of the direction of attention in a spatial working memory task. They asked participants to perform a spatial memory task in which they were required to remember the locations of the memory cues. After presentation of a flickering grid, a memory probe was shown either right or left side of the fixation point and the participants were asked to indicate whether it was in the same location as any of

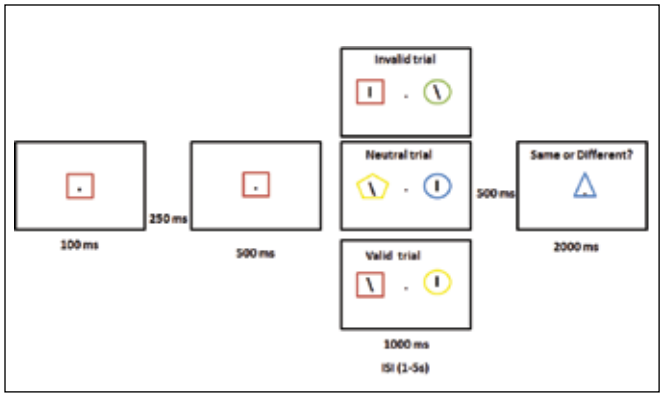

Figure 2: An Illustration of the experimental stimuli used in Soto et al.'s study (2007). Each trial began with a cue and participants were required either hold the cue in working memory or merely identify. Subsequently, they were asked search for a target (tilted line) that could appear surrounded by either a cued (red square, valid trials) or non-cued item (green circle, invalid trials). At the end of the trial, an object was presented and the participants were asked to decide whether it was the same or different with the memorized object shown at the beginning of the trial. Adapted from Soto et al. (2007).

those locations shown in the beginning of the trial. They found enhanced fMRI activation in the early visual areas contralateral to attended locations that are being held in working memory relative to irrelevant locations.

2.5. Event Related Potential (ERP) Studies

More recently, these behavioral and fMRI methods were supported by event-related brain potentials (ERPs) in order to provide information concerning the time-course of neuronal mechanisms underlying the effects of orienting attention to the internal representations held in working memory. Specifically, studies have focused on a specific ERP response, called N2pc component reflecting direction of attention (Woodman & Luck, 1999; McCollough et al., 2007; see also Luck, 2005). For instance, several ERP studies demonstrated that task-irrelevant working memory representations guide attention toward memory-matching items in visual search displays and elicit the N2pc activity at posterior electrode sites over the hemisphere contralateral to the visual field of these memory-matching items (Kumar et al., 2009; Astle et al., 2009; Eimer & Kiss, 2010). Additionally, when a search target was presented in the same side of an item matching the content of working memory (e.g. a task irrelevant distractor) the amplitude of the N2pc component was larger relative to other conditions where the spatial position of the target and the memory-matching item was different (Mazza et al., 2011; Kumar et al., 2009; Kuo et al., 2009).

2.6. Event Related Potential (ERP)

Event-related potentials (ERPs) reflect brain activities associated with the operation of information processing in preparation for or in response to discrete events such as encoding, selecting, and memorizing (Fabiani, Gratton,

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& Federmeier, 2007; Luck & Hillyard, 1994; Luck, 2005; Hillyard & Kutas, 1983). ERPs provide online measures of cognitive processing with fine-grained temporal resolutions and allow for examination of informational processing by means of noninvasive electrical recordings from the intact scalp (Hillyard & Picton 1987; McCollough et al., 2007; Luck, 2005; Hillyard & Kutas, 1983). ERP waveforms are scalp-recorded voltage changes related to a particular psychological or neural process, and consist of a series of positive and negative voltage deflections which are called components (Hillyard & Kutas, 1983).

The N2pc is one of the well-studied ERP components in attention-related studies. This is a negativity typically elicited 180-300 ms following the onset of a search array and can be defined as a difference between the contralateral and ipsilateral sites with respect to the target or relevant locations in the visual field (Luck, Chelazzi, Hillyard, & Desimone 1997; Mazza et al., 2011; Luck, 2005; Luck & Hillyard, 1994). The N denotes a negative polarity, 2 describes its latency in the waveform (i.e. it is second negative deflection, around 200ms), and pc refers "posterior-contralateral" as it appears over posterior (p) electrode sites contralateral (c) to the target side (Luck, 2005; Fabiani et al., 2007; Luck & Hillyard, 1994). This negative deflection can be examined clearly by measuring the difference in amplitude between the activities generated in contralateral and ipsilateral electrode sites relative to the position of the target in a visual search array. Woodman and Luck (1999) demonstrated that when the participants shift their attention from the left visual field to the right visual field, the N2pc component also shifts from the right hemisphere to the left hemisphere, enabling millisecond-by-millisecond measurement of the attentional orienting (See also Luck et al., 2005). As illustrated in Figure 3, two distinctively colored items were presented in one hemifield, making it possible to examine the ERPs elicited by identical stimuli with differing spatial directions of attention (Luck, 2005). When participants attended to the left side of the visual display, the voltage was more negative for right-hemifield (contralateral to the side of the left-hemifield targets) than for the left-hemifield targets (ipsilateral to the side of the left targets) (Luck, 2005).

Traditionally, the N2pc component is regarded as an indicator of the spatially selective attentional processing of target versus distractor items in visual search (Kiss et al., 2008). Dell'Acqua et al., (2009) measured the N2pc activity when observers were searching for a target held in visual short-term memory and when they searched for a target in visually presented displays. Perceptual search consisted of a target (pre-cue) followed by a search array. The task was to decide whether or not the pre-cue was present in the search array. In the visual short-term memory search, a post-cue was preceded by a visual search task, and the task was to decide whether the post-cue was present in the previously displayed search array. They found similar scalp distribution of the lateralized ERP response (the N2pc) in short-term memory and perceptual search trials. More importantly, a lateralized ERP response was elicited by the central post-cue target (e.g., colored square) when observers were searching the

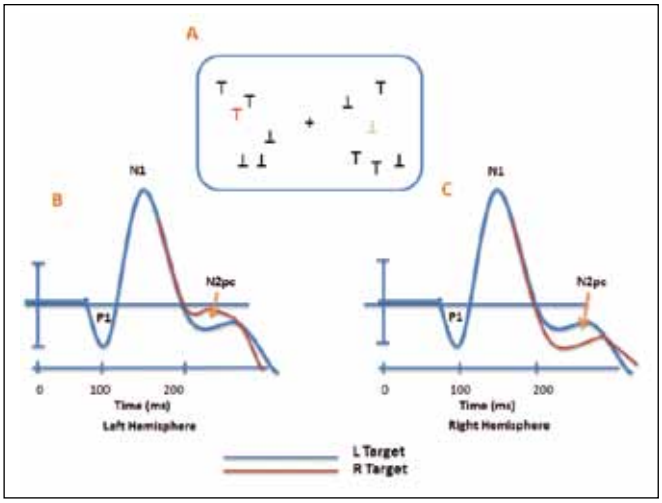

Figure 3: An illustration of a typical paradigm for eliciting an N2pc component. (A) At the beginning of each trial, the participants are required to attend to one color and to indicate the orientation of the item drawn in color (e.g. upright T or inverted T). ERP activity was recorded from electrodes over right and left posterior visual areas (B) The activity at posterior left scalp sites is more negative (grey shaded areas) when the target (colored T) was presented in the right hemifield than when it appeared in the left hemifield. (C) On contrary, the activity is more negative when the target was in the left hemisphere than when the target appeared in the right hemisphere. Adapted from Luck (2005).

array held in visual short-term memory which was similar to the N2pc activity observed in pre-cued trials. Notably, this modulation of the N2pc as a function of location was thought to indicate that some of the intrinsic spatial configuration of the original perceptual array is preserved together with the remembered items (Dell'Acqua et al., 2009; See also Kuo et al., 2009; Gratton, 1998; Jiang, Makovski, & Shim, 2009; Desimone & Duncan, 1995).

The link between the N2pc component and shifts of attention by irrelevant memory content was also explored in a combined working memory - attention task. Kumar et al. (2009) provided ERP evidence that irrelevant contents of working memory can bias visual selection and produce the N2pc component during a visual search task where search target was surrounded by a memory matching-distractor. At the beginning of each trial, participants were presented with a memory prime to perform a match-to-sample task at the end of some trials. Subsequently, they were presented with a search task in which four lines were located at the center of surrounding shapes (square, circle, triangle, and hexagon) appearing at one of eight possible locations in visual search. The task was to report the orientation of a tilted line presented among three other vertical lines (Figure 4). Each of the stimuli surrounding the lines was unique in color and shape, and in some trials, one of these shapes matched the memory item (matching distractor). There were three conditions in which the locations of the matching distractor and the search display varied. In ipsilateral invalid cueing trials, the matching distractor appeared on the same side of the fixation point as the target; in contralateral invalid cueing

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trials, the matching distractor appeared on the side of the fixation point opposite the target. In neutral trials, the matching distractor did not appear in the search display.

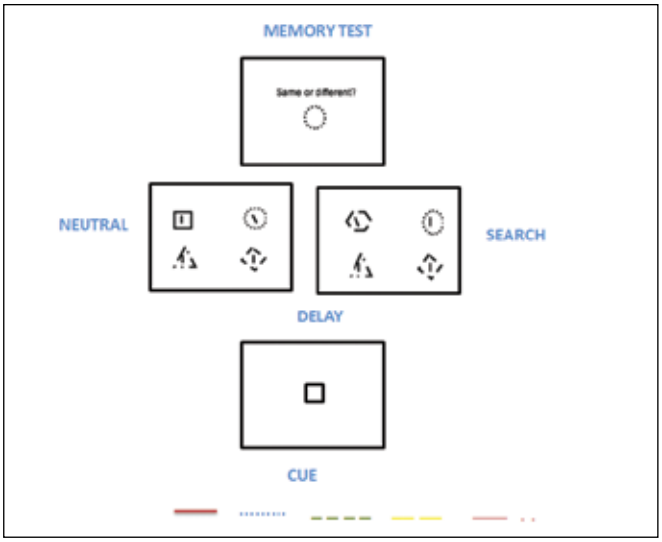

Figure 4: An illustration of the trial sequence used In Kumar et al.'s study. The observers were shown a cue appeared either for 133 ms or for 500 ms in the beginning of each trial. After 800 ms, the subjects were presented a search display containing four lines located in the center of surrounding shapes (square, circle, triangle, and hexagon). In the working memory condition, participants were required to memorize the cue for the memory test shown at the end of the trial. In the priming condition, they were asked to compare the two presentations of cues and refrain from responding to the search display if the second presentation of the cue differed from the first one in either color or shape. Adapted from Kumar et al., 2009.

Behavioral results showed that visual searches were significantly affected by the presence of a distractor matching the one held in memory (matching distractor), but not when the prime was merely identified and not held in memory (Kumar et al., 2009). More importantly, in ipsilateral invalid cueing trials, the N2pc was more pronounced relative to the contralateral invalid cueing and neutral trials. Kumar et al. proposed that involuntary effects of the working memory content can determine the efficiency of target selection (i.e., at early stage) and this effect is reflected in the measures of the N2pc activity (2009).

Astle et al. (2010) found that when an item (test object) matching the content of working memory appeared at the fixation point, participants' attention was automatically allocated to the original (lateralized) location of items in the preceding memory array that matched the test object (Figure 5). Namely, after a single test object presentation appearing at the center of visual field (i.e., there are no lateralized stimuli only a single item at the fixation), they found a lateralized brain activity (e.g. the N2pc) at electrode sites contralateral to the original location of those object-matching items in the preceding visual display.

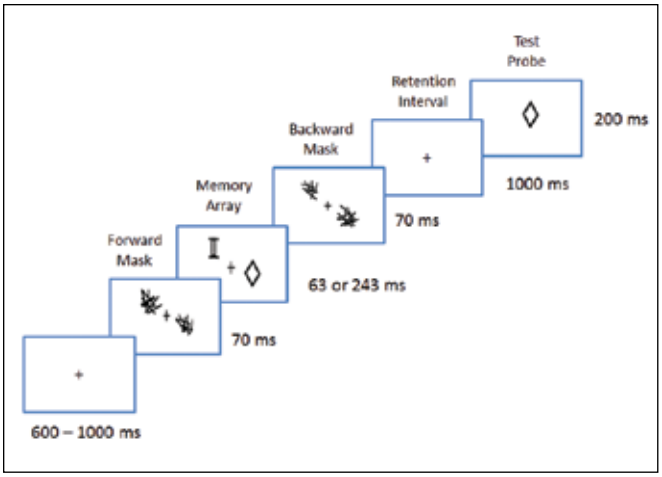

Figure 5: An illustration of the trial sequence used in Astle et al.' study (2010). Each trial started with a fixation cross (duration: 600-1000 ms). A memory array of two items was presented either subliminally for 63 ms or supraliminally for 243 ms before and after two pattern mask comprising a lateralized visual noise. After a further delay of 800-1000 ms, a central test object was presented for 200 ms at fixation point.

In their study, the electrophysiological sessions started and concluded with an explicit memory task: at the beginning of each trial participants were either subliminally (63 ms) or supraliminally (243 ms) presented with a memory array of two items interspersed between two masking displays. The memory array was followed by the presentation of an item (test object) appearing at the fixation point at the end of the trial. The task was to decide whether the test probe had been present in the original memory array and only on half of the trials the test probe appeared in the preceding memory array. During EEG session, the participants were asked to perform a perceptual judgment task: to judge the symmetry along the vertical midline of the centrally presented test probe. This task was unrelated the contents of the memory array and was designed to explore whether maintaining the information of the memory array shape influences the processing of the test object in a spatially specific way (i.e., having seen that item before at a particular location).

In certain trials the test object was the same as the one in the memory array (probe-present trials), and in other trials the memory array did not contain the test object (probe-absent trials). When the participants were presented with the display including a centrally located test object matching the memory array item, they observed an N2pc toward the original location of the probe-matching item in the memory array in both subliminal and supraliminal conditions. They also found a behavioral facilitation (faster reaction times and higher accuracy in congruent relative to incongruent trials) when the shape in the memory array matched the test object. They concluded that information stored in memory leaves a trace that contains the original spatial layout of the items in the memory array (Dell'Acqua et al., 2009; See also Gratton, 1998; Kuo et al., 2009; Jiang, Olson,

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& Chun, 2000; Desimone & Duncan, 1995), and that this trace captures attention automatically whenever a match occurs with currently perceived item (i.e., a match between the items in the preceding memory array and the test object) (Astle et al., 2010).

One of the most significant findings emerging from that study is that although the task was unrelated to the contents of the memory array (e.g. judging the symmetry along the vertical midline of the test object), the spatially specific biasing of mnemonic information held in working memory still survived and captured the participants' attention and to its original location and yet produced the N2pc when there was a match between the memory matching item and the upcoming stimulus (test object) (Figure 5). Interestingly, the results also indicate that although the participants failed to perceive previously presented stimuli in memory array (e.g. in a subliminal condition) and failed to recognize them subsequently, the participants' attention was captured by the lateralized items (in memory array) due to the original spatial layout of the memory array that is preserved in working memory. Namely, the participants were unintentionally storing the items with their spatial configuration although they were irrelevant to the content of working memory and consciously undetectable (Astle et al., 2011; Kuo et al., 2009).

3. Conclusion

Research reviewed here highlights the few characteristics of the N2pc component that appear to play a role in attention and display properties that enable to evaluate the direction of attention. Studies of visual spatial attention showed that active maintenance of objects in working memory automatically shift attention toward the memory matching-object and produce an N2pc toward the side of visual field where the memorized item appeared (Kumar et al., 2009; Mazza et al., 2011; Kuo et al., 2009; Kiss et al., 2008; Dell'Acqua et al., 2009). In these studies, the N2pc component was typically measured under conditions in which the items were presented on each side of the fixation (bilateral visual search displays) (McCollough et al., 2007; Robitaille & Jolicoeur, 2006). Due to bilateral presentation of the search array, which provides balanced perceptual stimulation to both hemispheres and allows for measure of activity specific to the contralateral hemifield containing the to-be-remembered item, this characteristic of the N2pc facilitates measuring the general direction of a person's attention with fine-grained temporal resolution.

Despite further research will need to evaluate and assess this aspect more deeply, recent findings may still provide important insights regarding the nature of automatic capture of attention and spatial bias by the content of working memory. For instance, many previous studies also proposed that visual working memory contains the spatial information of the object (Kuo et al., 2009; Astle et al., 2010; Dell'Acqua et al., 2009; See also Gratton, 1998; Jiang et al., 2000; Desimone & Duncan, 1995; Astle et al., 2009; Lepsien, 2005; Olson & Marshuetz, 2005). Additionally, studies, linking spatial attention and spatial working memory by demonstrating considerable overlap between brain areas that are active during attention task and those active during spatial working memory tasks (Awh & Hillyard, 2000; for a review, see Awh & Jonides, 2001) are convincing reason for a linkage between the spatial information and the working memory. Therefore, exciting directions for future research, providing new insights into the effects of the N2pc on spatial attention by the content of working memory may also intensify our understanding how attention and memory link together. This phenomenon can be also found in everyday life experiences. For instance, when we look for something, we typically start to search at the initial location of the previously seen object. Particularly, reconsidering the first example mentioned in the introduction part (e.g. driving a car near a forest area), if one were to see an animal at particular location while driving to work (e.g. on the left side of the road), then on a way back home, having seen the animal at that particular location would bias the observers' attention automatically to the same location, whenever there is any evocative information related to the presence of an animal in the environment (e.g. a traffic sign containing animal figure). However, further investigation will be required to explore this important issue more intensively.

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FUNCTIONAL MRI AS A PREOPERATIVE PREDICTOR FOR MEMORY PERFORMANCE FOLLOWING TEMPORAL LOBECTOMY: A SYSTEMATIC REVIEW

OPERASYON ÖNCESI FONKSIYONEL MR'IN TEMPORAL LOBEKTOMI SONRASI BELLEK PERFORMANSINI YORDAMADA KULLANIMI: SISTEMATIK BIR DERLEME

Merve Çebi*[1], Barış Metin[1], Çiğdem Özkara[2]

Abstract

Most of the patients with temporal lobe epilepsy suffer from memory decline following anterior temporal lobectomy (ATL). Studies examining memory decline following ATL show that post operative memory decline can be predicted in advance through the pre operative determination of memory lateralisation. Therefore, preoperative memory lateralisation plays a crucial role for epileptic surgery. Recent research suggests that instead of WADA test which is known as an invasive and high-risk operation, functional MRI can be used as a non-invasive and repeatable method to lateralize memory in the brain and to predict post operative memory decline. The aim of this article is to review the utility of fmri in prediction of post operative memory decline and to summarize the results of recent memory lateralisation studies using fmri.

Keywords: epilepsy, fmri, memory decline

Özet

Epilepsi hastalarının çoğu anteriyor temporal lobektomi (ATL) sonrası bellek performansında düşüş yaşamaktadır. ATL sonrası görülen bellek kaybını araştıran çalışmalar, operasyon sonrası bellek bozukluğunun operasyon öncesinde bellek lateralizasyonu ile yordanabileceğini göstermektedir. Buna göre, operasyon öncesi bellek lateralizasyonunun belirlenmesi epilepsi cerrahisinde önemli role sahiptir. Güncel çalışmalar, beyinde belleği lokalize etmek ve böylece operasyon sonrası bellek performansını yordamada noninvasif ve yinelenebilir bir yöntem olarak fonksiyonel MR görüntülemenin (fmr) invasif ve riskli bir operasyon olan WADA testinin yerine kullanılabileceğini göstermektedir. Bu makalenin amacı, bellek lateralizasyonunda fmr kullanan çalışmaların sonuçlarını özetlemek ve operasyon sonrası bellek bozukluğunu yordamada fmr'ın kullanılabilirliğini gözden geçirmektir.

Anahtar Kelimeler: *epilepsi, fmri, bellek kaybı*

As one of the most prevalent neurological disorders, the majority of epilepsy cases still remain untreated despite the common use of antiepileptic drug treatment strategies. In patients with intractable mesial temporal lobe epilepsy (MTLE), anterior temporal lobe resection (anterior temporal lobectomy: ATL) is being used to eliminate the seizures as an alternative method to medical treatments (Richardson et al., 2004). Namely, ATL involves removal of the large part of anterior medial temporal lobe, as well as some parts of the hippocampal and parahippocampal regions. Despite the 60-80 % of success rate, on the other hand, ATL mostly brings about a decline in memory performance due to the well-known involvement of temporal regions in memory localization, especially in memory encoding (Primrose and Ojemann, 1992). In 1982, a more selective surgical method started to take the place of ATL in which only the subcortical mesial structures (amygdala, hippocampus and parahippocampus) are preferred for removal (Wieser and Yasargil, 1982). This new resection method called selective amygdalohippocampectomy (SAH) is thought to end up with relatively better postoperative cognitive functions, because, in contrast to the anterior temporal lobectomy the surrounding structures (temporal lobe) are mostly preserved. Most of the studies have found that SAH is as effective as ATL in eliminating epileptic seizures and can be preferred to temporal lobe resection (Wendling et al., 2013).

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According to the previous literature, most of the right-handed patients who underwent the left-sided temporal lobe resection, experience a significant verbal memory decline (Richardson et al., 2004). There is strong evidence that preoperative memory performance positively correlates with post operative memory decline. In other words, patients who performed better in their memory performance before the surgery experience more serious memory decline after the operation (Helmstaedter and Elger, 1996; Jokeit et al., 1997). The severity of hippocampal sclerosis, on the other hand, inversely correlates with post operative memory decline meaning that patients who have more severe sclerosis in resected hippocampus tend to have less memory decline as compared to patients with a milder hippocampal sclerosis in resected side (Sass et al., 1994). Most of the authors agree on the fact that the latter result provides evidence for the functional reorganization of the brain in patients having severe and early onset MTLE (Powell et al., 2007).

Therefore, preoperative determination of memory lateralisation is crucial to assess the unilateral hemispheric support of memory functioning and in turn, to minimize the possible postoperative memory decline.

The traditional method to determine the language and memory lateralisation is known as the WADA (intracarotid amobarbital test: IAT) in which a rapidly acting barbiturate, sodium amytal, is injected into the one of the internal carotid arteries (left or right) and, in turn, results in a short dysfunction of the ipsilateral hemisphere (Wada and Rasmussen, 1960). Although IAT was firstly developed to localize language; evidence suggests that it may be used to assess the dominant hemisphere for memory as well. This pre-operative procedure provides information about the dominant hemisphere for memory encoding and predicts the possible language and memory decline after the surgery (Loring et al., 1995). However, there are many possible medical complications about IAT application. Studies report that the risk factors include serious complications like stroke, infarction, carotid artery dissections and allergic reactions to sodium amytal (Loring et al., 1992). Especially regarding that children and older patients are at high risk to experience such complications, the WADA method might be even more threatining. Given that it is an invasive method with such risk factors, recent research suggests that IAT can be replaced by functional MRI in preoperative assesment of memory lateralisation as a non-invasive, repeatable and more convenient method (Binder, 2011). By means of detecting increased BOLD signals during certain cognitive processes, fmri has the additional advantage of providing information about the intrahemispheric localization of memory in addition to determining the dominant hemisphere. Recent studies indicate the involvement of the extratemporal regions in memory functioning such as frontal lobe, amygdala and thalamus. Given the widespread neural network of memory functioning and the individual variations in the human brain, fmri might be a more promising tool to determine the exact localisation of memory processes for each patient.

A variety of preoperative paradigms ara available that can selectively localise both verbal and nonverbal memory encoding in the brain. Most of the verbal memory paradigms involve a verbal encoding and a delayed recognition task in which patients are instructed to remember a word list which is visually presented during fmri scanning. For recognition, patients are asked to indicate, by a manual finger response using the dominant hand, whether the word was present in the previous word list or not. Some of the encoding tasks, on the other hand, do not explicitly ask patients to remember the list but still present the recognition task afterwards. Nonverbal memory paradigms mostly involve a visual memory task, in which patients are presented with a list of object pictures or visual scenes in a blocked design. Similarly, a recognition task is administered following the encoding task and patients are asked to indicate whether the visual stimuli is old or new (Binder, 2011, Richardson et al., 2004, Golby et al. 2002, Sperling et al., 2001).

In the past decades, there is an increase in studies assessing memory performance and predicting the lateralisation of memory using fmri. With a few exceptions, most of the fmri paradigms seem to be in concordance with IAT results and be able to predict the memory dominant hemisphere before ATL (Binder, 2011). One of the earliest fmri studies in temporal lobe epilepsy conducted by Detre et al. (1998), for instance, included complex scene-encoding task and demonstrated concordant results with IAT. The study provided evidence for the asymmetric activation of temporal lobe in epilepsy patients while a bilateral posterior temporal activation was observed in the control group. Similarly, Bellgowan et al. (1998) were able to demonstrate decreased left temporal lobe activation in patients with left MTLE during a semantic encoding task, while left temporal lobe activation was predominant in patients with right MTLE. Findings of these studies support the adaptive functional reorganisation of the brain and reveal that medial temporal lobe structures have high rates of plasticity. Accordingly, age at onset of epilepsy, epilepsy duration and seizure frequency have been shown to be effective in the reorganisation of memory structures in the brain (Golby et al., 2002).

However, such a reorganisation does not neccessarily take place in all epilepsy patients and therefore, it becomes essential to predict the post operative memory decline in advance. Literature suggests that the preoperative fmri findings have the ability to predict the postoperative memory decline, as it was mentioned before. Findings of the studies provide strong evidence that preoperative memory encoding asymmetry is a good predictor for post operative memory decline (Richardson et al., 2004) . A common widely used method to document memory asymmetry is lateralisation index (LI). This index is calculated as followes: activated voxels above a certain threshold are basicly counted for each hemisphere and a number is calculated simply by dividing the subtraction and addition of the counted voxels of hemispheres ((L-R). (L+R)). As a result of the calculation, an index number is created between -1 and +1, indicating left hemisphere activation as the number approaches to 1 and right hemisphere activation as the number approaches to -1 (Binder, 2011). As the core areas for memory encoding that are selectively resected

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in the surgery, hippocampal and temporal lobe LIs seem to be a sensitive post operative memory predictor for post operative memory performance in epilepsy. Frings et al. (2008), for instance, conducted an fmri study with 19 epilepsy patients (9 left, 10 right MTLE) before the ATL and studied the relationship between non-verbal memory performance and hippocampal activation. By using a ROI (region of interest) analysis, only hippocampal area was selected for LI computation. The results showed that preoperational memory deterioration was greater in in patients with ipsilesional lateralisation than contralesional lateralisation. This finding was also reproduced by Powell et al. in 2008. Morever in another study conducted by Binder et al. in 2008, pre-operative LI calculated using verbal memory task predicted post-operative memory decline better than WADA test.

Overall, the results of the studies suggest that preoperative memory lateralisation is a good predictor for post operative memory decline and the use of fmri paradigms can be a promising method to determine the dominant hemisphere for memory support. In addition to the advantages as being a non-invasive and repeatable method, fmri provides a more sensitive data of activated regions by using LI and therefore minimize the potential of unexpected memory decline in patients with MTLE. Further investigation is still needed, to develop standardized fMRI paradigms for effective memory lateralization. In addition, most of the previous studies mentioned above used verbal encoding paradigms to create hippocampal activations. Incorporation of non-verbal items to the tasks may produce more predictive lateralization indices for different types of memory. Finally as most of the studies were conducted with small samples, large scale studies with pre and post operative neuropsychological testing are needed to estimate the predictive power of fMRI for post operative memory decline.

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CASE REPORT

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MELODIC INTONATION THERAPY IN AN APHASIC PATIENT

AFAZİK BİR OLGUDA MELODİK ENTONASYON TERAPİSİ

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Abstract

Communication deficits resulting from aphasia can negatively impact stroke survivors' social life. It has been reported that patients with severe non-fluent aphasia are better at singing lyrics than speaking the same words. Based on lesion studies, it is generally proposed that the right hemisphere is dominant especially for melody production.

We present a 28-year-old woman with non-fluent aphasia as the result of a left hemisphere ischemic stroke involving mainly the superior division of the middle cerebral artery, and classified as having Broca's aphasia. She was taken into melodic intonation therapy with speech therapy. Singing is accessible and enjoyable for many people with aphasia and melodic intonation therapies may facilitate recovery in such non-fluent aphasic patients.

Keywords: Aphasia, Melodic Intonation Therapy, Speech

Özet

Afaziye bağlı iletişim sorunları strok hastalarının sosyal yaşamlarını olumsuz yönde etkileyebilir. Akıcı olmayan afazi hastalarının söyleyemedikleri kelimeleri şarkı içinde daha rahat söyleyebildikleri bildirilmiştir. Lezyon çalışmalarına göre melodi üretiminde ağırlıklı olarak sağ hemisfer görev alır.

Bu yazıda orta serebral arterin superior bölümüyle ilişkili strok nedeni ile Broca afazisi olarak sınıflanmış akıcı olmayan afazi gelişmiş 28 yaşında kadın hasta sunulacaktır. Olguya konuşma terapisi ile birlikte melodik entonasyon terapisi uygulanmıştır. Şarkı söyleme birçok kişi için kolay yapılabilir ve eğlenceli bir etkinliktir. Akıcı olmayan afazi hastalarında melodik entonasyon terapisi iyileşme sürecini hızlandırabilir.

Anahtar Kelimeler: *Afazi, Melodik Entonasyon Terapisi, Konuşma*

1. Introduction

Aphasia is a disorder that occurs as a result of damage to the dominant an usually left hemisphere caused by reasons such as cerebrovascular disease, brain trauma or degenerative disorders like left variant of frontotemporal dementia. Accordingly, the patient's speech, spoken word comprehension, naming, repetition, reading and writing skills are also commonly damaged. Aphasia adversely affects the social lives of stroke patients due to the communication difficulties. Chronic aphasia studies revealed the important role of Broca's area in various speech and language function. Moreover, functional neuroimaging studies have identified activation of Broca's area with various speech tasks. However, the results of damage to Broca's area can be surprising. For example, if the damage was caused by slow growing brain tumors, speech ability could be maintained, relatively. This case suggests the shift of the functions of the damaged neurons. (Geranmayeh et al., 2014)

Another surprising clinical condition associated with aphasia can be the preserved ability of singing, despite the loss of speech (Albert et al., 1973). Some non-fluent aphasia patients were reported to use some words fluently in a song although they cannot say them during a speech task (Parker et ., 2013). Processing of music in the brain is rather complex issue. Based on the lesion studies in such aphasic patients who can sing fluently, it has been suggested that the right hemisphere is more dominant on the melody production and singing should promote a transfer of language function from left frontotemporal neural networks to their preserved right-hemisphere homologues (Benjamin et al., 2014).

Melodic intonation therapies (MIT) is a therapeutic process with specific protocoles and different styles of singing that supposed to stimulate activation of homologues part right-hemisphere (Benjamin et al., 2014), or reactivation of left-hemisphere due to neuroplasticity (Roy et al,. 2011). Also MIT can be combined with noninvasive brain stimulation to increase effectiveness of treatment (Roy et al,. 2011).

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2. Case

Twenty-eight-year-old, right-handed female patient had a motor vehicle accident that resulted in a widespread neuronal damage due to ischemia. She was treated for 2 months at neurological intensive care unit and was admitted to the outpatient clinics with sequel hemiparesis and severe non-fluent aphasia with restricted expression of words, disturbed naming and repetition, relatively preserved comprehension. She had non-fluent aphasia and right hemiparesis. On the right, Babinski was determined as positive. Mental status examination was normal. She scored 28 on Mini Mental Status Examination. Her complete blood count, biochemistry, and thyroid function tests were found to be normal. The electrocardiogram was normal. Cranial magnetic resonance imaging showed chronic infarct in the left frontal and temporal areas that are supplied by superior division of middle cerebral artery.

Melodic intonation therapy was added to the speech therapy that was begun for motor aphasia. The speech and language therapist observed that, when the melody of a song known by the patient was played, the patient could continue the melody and the lyrics to incorporate fully and without hesitation, except for mild dysarthria. But she could not repeat the words of the song without melody. It was observed that the patient generally failed to initiate the song spontaneous, with the start of the therapist or upon the piano gives the melody, she could attend to the song. Aphasia rehabilitation, as well as melodic intonation therapy was applied to the patient who did not receive any musical education in the past. At the end of seven months follow-up, non-fluent motor aphasia was improved greatly.

3. Discussion

In this case report, a 28-year-old female patient with non-fluent aphasia related to left hemispheric infarct was described. In aphasia patients, the neuropsychologist gets detailed information about the patient at the beginning of speech therapy. The cause of the aphasia and the detailed examination of language would shape the treatment plan. General mental status of the patient, the type of speech disorder, the localization and the pathophysiology of cerebral lesion are important. Based on these data, the neuropsychologist constitutes a rehabilitative training program together with the speech therapist. A similar treatment planning made also for the presented case.

Motor aphasia was observed in this case which has left frontotemporal cerebral damage. Left inferior frontal gyrus plays a major role in the production of speech by various aspects such as phonology, semantics and syntax (Schön et al., 2010). Damage to the left inferior frontal gyrus causes fluent aphasia, without any difficulty in nomenclature, comprehension and repetition. In this case, it is notable that, despite the fluent aphasia, singing skill was preserved.

Music function is a complex event. Although, it is usually considered that left frontotemporal region is the specialized area for speech and right frontotemporal region is important for musical abilities (Callen et al., 2006; Brown et al., 2006), the neuroimaging data indicates that both functions need wide and similar neural plexus (Schön et al., 2010). In the literature, similar to our case, there are cases in which singing skills are protected despite an infarct in left Broca's area (Polat et al., 2013). In the reported cases, left temporal and frontal regions were found to be activated on speech process and right temporal and frontal regions were found to be activated on music process.

The use of different brain regions during language processing and music processing uncovered the melodic intonation therapy that would increase the treatment success of non-fluent aphasia patients. Language and speech therapy plays major role in aphasia rehabilitation. Starting speech rehabilitation immediately after diagnosing aphasia, would increase the success and accelerate the patient's recovery. Singing is an entertaining and easy access event for many aphasic patients and melodic intonation therapy can accelerate recovery in such cases non-fluent aphasic patients.

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EFFICACY OF EYE MOVEMENT DESENSITIZATION AND REPROCESSING BEYOND COMPLEX POST TRAUMATIC STRESS DISORDER: A CASE STUDY OF EMDR IN PAKISTAN

KOMPLEKS TRAVMA SONRASI STRES BOZUKLUĞU ÖTESİNDE GÖZ HAREKETLERİYLE DUYARSIZLAŞTIRMA VE YENİDEN İŞLEME TEDAVİSİNİN YARARLILIĞI: PAKİSTAN'DAKİ BİR EMDR VAKA ÇALIŞMASI

Muhammad Sami Bilal[*1], Mowadat Hussain Rana[2], Safi Ullah Khan[3], Rashid Qayyum[4]

Abstract

Objective: To demonstrate the efficacy of EMDR in complex multiple psychological trauma after failed drug treatment from selective serotonin reuptake inhibitor (SSRI) in a diagnosed case of post traumatic stress disorder (PTSD).

Material and method: Single participant of this case study, a sitting session judge of judicial governmental scaffold reported to this mental health tertiary care facility at his own accord with features of intense anxiety, depression, maladjustment issues and post-traumatic stress for a duration of several months. As a partial responder to full trial of SSRI he was enrolled for EMDR therapy to address his symptoms of intense anxiety, panic attacks, being overwhelmingly fearful, depressed, low self-esteem, inappropriate feelings of guilt, flashbacks, avoidance, nightmares, hyper-arousal and inability to perform as a judicial head in active war stricken area of northern Pakistan. Complete psychiatric evaluation was carried out and after the discontinuation of SSRIs he was scored on Impact of Event Scale (IES). He fulfilled the diagnostic criteria for PTSD as evaluated by the English version of the PTSD module of the Structured Clinical Interview for DSM-IV administered once before commencement of EMDR. Safe place of the client was established and 8 staged protocol of EMDR was started with him. Multiple EMDR sessions were conducted.

Result: The case presented in this paper had multiple psychological trauma forms and failed drug treatment and yet it was observed that EMDR provided marked improvement in all the domains of his deficits and this was at a prompt speed as compared to cognitive behavioural therapy (CBT) which usually takes longer duration of therapy to achieve similar results.

Conclusion: EMDR provides marked improvement in all domains of complex mental trauma and traumatic memories. Improvement attained was prompt and enduring as compared to other forms of established therapies and drug treatment indicating permanent changes happening at neurobiological levels of brain.

Keywords: EMDR, PTSD, Tf-CBT, man-made disasters, natural disasters, psychological trauma, Pakistan, IES-R, SCID-I, CTRPI, AFIMH and ACTR.

Özet

Amaç: Travma sonrası stres bozukluğu(PTSD) teşhisi konmuş bir vakada selektif serotonin reuptake inhibitörü ile yapılan ilaç tedavisinin başarısız olmasından sonra kompleks çeşitli psikolojik travmada EMDR'nin yararlılığını göstermek.

Materyal ve Metod: Bu çalışmanın tek katılımcısı, pek çok aylık bir sürede aşırı kaygı, depresyon, uyumsuzluk ve travma sonrası stres gibi özelliklerle uyumluluk gösteren, hukuki bir yargılama sehpası düzenindeki bir oturma seansında üçüncü basamak mental sağlık bakımının rapor edildiği bir kişidir. Bütün bir SSRI denemesinin parçasal bir cevaplayıcısı olarak bu kişi; aşırı kaygı, panik ataklar, aşırı derecede korkan, depresif, özgüvensiz, gereksiz suçluluk duygusu, geçmişe dönüşler, kaçınma, kabuslar, aşırı uyarılmışlık ve kuzey Pakistan'ın aktif savaşta harabeye dönmüş bir kesiminde muhakeme gücünü kullanamama gibi semptomları adres gösteren EMDR terapisine alınmıştır. Bütün psikiyatrik değerlendirmeler tamamlanmıştır ve SSRI'ların tamamlanmasından sonra IES (Impact of Event Scale) üzerinde puanlandırılmıştır. EMDR'nin başlangıcından önce bir kez yapılan DSM-IV için Yapılandırılmış Klinik Görüşme PTDS modülünün İngilizce versiyonu ile değerlendirilmiş PTDS tanı kriterlerini yerine getirmiştir. Hastanın güvenli bir yerde olması sağlanmıştır ve EMDR'nin 8 adet protokol safhası hastayla başlamıştır. Çoklu EMDR seansı gerçekleştirilmiştir.

Sonuç: Bu makalede sunulan çalışma çoklu psikolojik travma formları içermiş ve ilaç tedavisi başarısız olmuştur ve yine de EMDR'nin hastanın

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eksikliklerinin olduğu bütün alanlarda göze çarpan ilerlemeler sağladığı ve benzer sonuçları almada genellikle daha uzun süren bir terapi olan kognitif davranışsal terapiyle kıyaslandığında bu terapinin daha hızlı olduğu gözlemlenmiştir.

Varılan sonuç: EMDR mental travma ve travmatik hafızaların bütün alanlarında göze çarpan gelişmeler sağlamıştır. Elde edilen gelişmeler, beynin nörobiyolojik seviyelerinde oluşan kalıcı değişimleri gösteren varolan diğer terapiler ve ilaç tedavilerine nazaran daha hızlı ve devamlıdır.

Anahtar Kelimeler: *EMDR, PTSD, Tf-CBT, insan kaynaklı afetler, doğal afetler, psikolojik travma, Pakistan, IES-R, SCID-I, CTRPI, AFIMH ve ACTR.*

1. Introduction

1.1. Transition from Trauma focused cognitive behavioural therapy (Tf-CBT) to EMDR

Post-traumatic stress disorder (PTSD) is an anxiety disorder that is diagnosed when a person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others and the person's response involved intense fear, helplessness, or horror (DSM-IV-TR-2000). There are numerous forms of psychological trauma sustained by multiple natural and man-made sources. These atrocities include incidences like domestic vehemence, physical abuse, rape, street assault, mugging or battles cause extensive psychological trauma. Similarly natural disasters and calamities produce direct physical injuries as well as widespread mental trauma in individuals. An individual can be the victim of single traumatic experience or suffer from enduring adversities (Michael et al., 2005). After experiencing a traumatic event, a person may display a range of disorders, including acute stress disorder (ASD), post-traumatic stress disorder (PTSD), depression, generalized anxiety disorder, childhood traumatic grief, specific phobias, and separation anxiety (Stallard 2006).

Among the trauma therapies, cognitive behavioral therapy (CBT) is qualified as an established treatment (Saxe et al., 2007). A recent systematic review of effects of interventions for trauma symptoms revealed that individual and group CBT was most effective (Wethington et al., 2008). CBT for trauma is based on the principles of cognitive and learning theories and aims to decrease negative emotions and behaviors, and to transform dysfunctional cognitions and attributions about the traumatic event (Saunders et al., 2004). Trauma-focused CBT (Cohen et al., 2005). Cohen et al., 2004) consists of multiple components, including: trauma narrative, in vivo mastery of trauma reminders, affect modulation, cognitive processing, psycho-education, relaxation, parenting skills and enhancing safety, healthy sexuality, and future development (Cohen et al., 2007). There are multiple exposure based therapies for mental traumas, yet all these therapies may not be fruitful in some individuals and this may considerably hamper treatment outcomes.

1.2. Synopsis of Eye Movements Desensitization and Reprocessing (EMDR)

An American psychologist Francine Shapiro is the originator of the Eye Movement Desensitization and Reprocessing (EMDR) and this therapy first came into lime light in 1989. With eight stages of protocol of EMDR, the traumatic memory is desensitized by short imaginal exposure to this memory and the subsequent offering of bilateral stimuli (Rodenburg et al., 2009). This is repeated until the accompanying level of disturbance has disappeared and the dysfunctional cognitions about the trauma have become functional (Shapiro 2007). Traumatic memories are expected to transform into least stress inducing memories through EMDR. The adaptive information processing (AIP) model shares features with the emotional processing model, which explains the reduction of fear in anxiety disorders (Foa & Kozak 1986). Thus, free association and distancing is allowed by means of the EMDR procedure; within the emotional processing model free association is generally not allowed (Lee 2008). (Rogers & Silver 2002),(Solomon & Shapiro 2008).

With EMDR a three-pronged approach is used, which includes questions regarding the etiology of the traumatic event (past), the triggers of PTSD symptoms (present), and the installation of future templates related to adequately coping with upsetting events (future)(Shapiro 2001). Initial phases of EMDR is collecting of history of the client and planning clients treatment, explanation of the process of EMDR and preparation of client for EMDR. Client is taken through all phases of EMDR in each session. Through the process of EMDR each negative cognition is extracted and substituted with a healthy positive cognition for a traumatic incident. The physical dissonance associated with that traumatic memory are transformed or relieved subsequently. Subjective Units of Disturbance (SUD) is a ten point Likert-scale used to measure the level of subjective disturbance and desensitization is attained until the disturbance is substantially reduced. Therapist carries out sets of bilateral stimuli which basically give access to the traumatic memory and its associated emotional burden in the client. Validity of Cognition Scale (VOC) is a seven point Likert-scale used to measure the strength of the faulty negative cognition. The process of bilateral stimuli is repeated till the individual consigns a positive thought in place of the older negative thought. The last phases of EMDR are accomplished by positive closure and re-evaluation. The number of sessions essentially depends upon the severity of traumatic event and negative memories. Initially, bilateral eye movements were considered as a key element in the EMDR therapy, however, other external bilateral stimuli have also been used in the EMDR treatment, such as taps (tapping the hands of the therapist)(Beer & De Roos 2008) and ear tones (Shapiro 1993) (Shapiro 2007). With EMDR unprocessed memories of traumatic experiences, stored in neural networks, become linked with the adaptively processed memories of positive experiences, which are referred to as reprocessing(Shapiro 2007). Following a review of seven meta-analyses which explored the effectiveness of EMDR, Spates et al, concluded that EMDR was an effective treatment for PTSD, and equally

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effective as exposure based therapies, with large effect sizes, and considered EMDR as robust in its overall effect, recommending it as a Level A treatment intervention for adult PTSD.(Spates et al., 2009) (Farrell et al., 2011).

1.3. Inception of EMDR in Pakistan

EMDR in Pakistan owes its inception to a massive tragedy that occurred in October 2005 in the form of an earthquake. An estimated 80,000 people lost their lives in this natural calamity. There was extensive destruction of assets and property. Yet soon after this disaster steered an age of international help and support. One such support was in the form of Humanitarian Assistance Programme (HAP) of United Kingdom. The main contributors to the project being those from the University of Birmingham, Belfast Health & Social Care NHS Trust, Edge Hill University Liverpool and the Centre for Trauma Research & Psychosocial Interventions (CTRPI), Rawalpindi, Pakistan (Farrell et al., 2011). To date more than 180 Pakistani mental health workers have now been fully trained in EMDR including Armed Forces psychiatrists, civilian psychiatrists, clinical psychologists and registered social workers who were predominantly working with earthquake survivors(Farrell et al., 2011). A pertinent question to ask would be as to how would EMDR, as effective evidence based psychological treatment intervention, adapt to being utilized by mental health clinicians in Pakistan (Farrell et al., 2011)?

This case study aims to investigate the effectiveness of EMDR therapy in myriad of complex psycho-trauma in unique circumstances with an overarching theme contaminated with persistence of terrorism, pressure to perform effectively as a judicial head in a terrorist hit area and failure of response to full trials of SSRIs. The innumerable complex psycho-trauma events included frequent witnessing of brutally tortured headless human torsos, fear of Improvised Explosive Devices (IEDs) enroute to court and his residence, being shot at by the terrorists at his cavalcade multiple times and death of one his close bodyguards. Furthermore distress was caused by constant threatening roar of nearby army artillery guns and helicopters landing in the yard next to his court, pressure from family and friends to quit the job and intention to start afresh in the civil sector all became what was the dilemma that this individual was going through.

2. Materials and Method

2.1. Subject

Single participant of this case study was a sitting session judge of judicial governmental scaffold who reported to this mental health tertiary care facility at his own accord with features of intense anxiety, depression, maladjustment issues and post- traumatic stress for a duration of 3 months. One of his challenges was to keep a 'sane mind' and to give out judicial rulings and judicial orders and by every passing day he felt being compromised at this capacity. The client was initially treated by the one of the authors, a consultant psychiatrist and put on selective serotonin reuptake inhibitor (SSRI) paroxetine with an adequate dose. After undergoing a full trial of SSRI, he remained a partial responder and his symptoms of intense anxiety, terror attacks, being overwhelmingly fearful, depressed mood, low self-esteem and harbouring inappropriate feelings of guilt. Then there were flashbacks of numerous critical incidence coupled with avoidance, nightmares, hyper-arousal and inability to perform as a judicial head in active war stricken area of northern Pakistan. After a trial of SSRIs had failed the patient was offered an alternate in the form of EMDR therapy considering his lukewarm response and plethora of non-relenting psychiatric symptoms. EMDR was offered only as a substitute treatment after discontinuation of paroxetine (SSRI). Prior to start of EMDR he was scored on Impact of Event Scale (IES) and this was noted as pre EMDR IES score. Safe place was established and reinforced with the client. There were more than 25 traumatic events considered as major target and almost all of them were declared as 'severe' in intensity and scored on subjective units of distress (SUDS) as 10+. The patient suffered from multiple psychological traumas of diverse forms and fulfilled diagnostic criteria for PTSD as assessed by the English version of the PTSD module of the Structured Clinical Interview for DSM-IV (First et al., 1997). Symptoms were endorsed and informed consent was obtained. EMDR treatment strictly followed the protocol suggested by Shapiro (Shapiro 1995) and included all eight phases described in her book. Three authors of the study (M.S.Bilal, M.H.Rana and R.Qayyum) – all classified psychiatrists, carried out the treatment at different times. Duration of each EMDR session was one hour more or less.

2.2. Treatment settings

Centre for Trauma Research and Psychosocial Intervention (CTRPI) which is a supplementary mental health unit of Armed Forces Institute for Mental Health (AFIMH) Rawalpindi was the treatment venue. CTRPI in essence is a tertiary care mental health facility and is a drainage point for peripheral mental health facilities. This centre was established in collaboration with the Aberdeen Centre for Trauma Research (ACTR) Scotland, in direct response to providing services for any form of psycho-trauma and its treatment. In topographical connotations however this centre is about 230 km away from the workplace of the client. He would travel twice weekly for the EMDR sessions from northern Pakistan to CTRPI, a journey demanding considerable bravery and risk involved. A total of 17 EMDR sessions were undertaken.

2.3. Instruments

2.3.1. Impact of Event Scale (IES)(Horowitz M et al 1979)

Developed by Horowitz et al this is a widely used 15 item self-report questionnaire evaluating experiences of avoidance and intrusion which attempts to reflect the intensity of posttraumatic stress reactions.(Horowitz M et al 1979).

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2.3.2. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)(First, Michael B., Spitzer, Robert L, Gibbon Miriam, a 1996)

This is a semi-structured interview for making the major DSM-IV Axis I diagnoses(First, Michael B., Spitzer, Robert L, Gibbon Miriam, a 1996). The Clinician Version, SCID-CV, is an abridged version of the SCID-I-RV, adapted specifically to cover diagnoses most commonly seen in clinical settings(Zanarini MC, Frankenburg FR 2001).

2.3.3. Subjective Units of Distress (SUDS)

This is a scale that integrally incorporated in EMDR protocol ranging from 0-10. Subjectively 0 is considered as the least distressful level and scoring of 10 is considered as most distressful level for the client.

3. Result

After 17 sessions of EMDR, there was marked improvement in his anxiety and mood symptoms. He gradually improved in his mental wellbeing with each EMDR session. His mood improved from subjectively being depressed to subclinical depression/ euthymic. His symptoms of flashbacks, nightmares, avoidance of his work place and also fear for the daily route to his court reduced significantly and hyper-arousal diminished considerably. His life in social and occupational domains improved. The individual was scored on the two scales with pre and post EMDR evaluations. These results are tabulated below in a table form (Table 1). IES scores were taken regularly as they indicated a stressful or traumatic event within the subjects past seven days and since the subject was part of an ongoing traumatic scenario IES scores were taken before each session.

Table 1: The pre and post IES and SUDS score of the patient

EMDR Session No	Pre EMDR IES score	Post EMDR IES score	Pre EMDR SUDS score	Post EMDR SUDS score
1	72	15	12	2
2	69	12	10	1
3	67	11	11	2
4	71	13	10	1
5	66	9	9	1
6	68	7	9	1
7	65	9	9	1
8	69	14	8	1
9	64	7	9	2
10	66	8	8	1
11	63	9	7	0
12	58	6	8	0
13	57	7	8	0
14	62	11	7	0
15	52	7	8	0
16	47	6	9	1
17	36	13	7	0

4. Discussion

This case serves to give a preview of the efficacy of EMDR beyond complex PTSD in an individual with multiple complex psychological traumas and suffering with a plethora of anxiety and affective symptoms. His failure to respond to a completed trial of SSRI paroxetine further gave impetus to the debate of pharmacological versus non pharmacological interventions. Where pharmacological means seemed deficient, this synclactic therapy brought marked improvement in an enduring onslaught of mental horrors for this patient. This individual was not occupationally performing adequately as a judge. If his mental condition had persisted for more time the full aspects of his disorder would have had surfaced. This would have complicated the situation even further by bringing doubt to the court orders passed recently by him. So burden of time to get healthier rapidly was also part of the expected resolution. With the continuing sessions of EMDR more and more traumas were un-repressed and targeted with EMDR. The high pre EMDR scores improved tremendously and SUDS for various events/ targets dropped from 11 or 12 (on a scale of 10) to 1 or 2. The total EMDR sessions undertaken were 17. Where drug treatment had failed for this patient, EMDR brought him back to working levels of occupational effectiveness. After several EMDR sessions he managed to continue with the same line of work in the same terrorist hit war zones not contemplating leaving the profession anymore. Prior to EMDR, his social and family life had almost come to being nonexistent and with EMDR he reported a significant boost in his self-esteem, lifting of mood, enhanced levels of mental wellbeing, feelings of being adjusted within the same harsh circumstances, significant reduction of night mares, reduced levels of hyper-arousal even with ongoing complex war against terror. He had become an improved person in terms of personal wellbeing.

The clinical efficacy of EMDR in post-traumatic stress disorder treatment for adults has been well established (Bisson et al., 2007). Efficacy of EMDR's to treat trauma has been demonstrated in approximately 20 controlled studies, in which EMDR was compared to psychopharmacology and various forms of psychotherapy, on the basis of which the practice guideline of the American Psychiatric Association and the Department of Veterans Affairs and Department of Defense classified EMDR as an effective treatment for PTSD. (American Psychiatric Association 2004),(Department of Veterans Affairs & Department of Defense 2004). The same status is also reflected in numerous international guidelines (Bleich et al., 2002),(Dutch National Steering Committee Guidelines Mental Health Care 2003),(National Collaborating Centre for Mental Health 2005),(Sjöblom et al., 2003).

The efficacy of EMDR for adults with PTSD symptoms has been demonstrated in several meta-analyses (Bradley et al., 2005)(Davidson & Parker 2001)(Seidler & Wagner 2006) but incremental efficacy, which means that a new treatment should add incremental value to established treatments, has not yet been supported (Rodenburg et al., 2009). EMDR, although a well established and well researched therapy still faces criticism and doubt as to its efficacy and effectiveness. Our study adds impetus

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to this incremental value of using EMDR as first line treatment in Pakistan as well, instead of just docking at pharmacological interventions.

EMDR has now being adapted as first line treatment for PTSD at par with trauma focused cognitive behavioural therapy (TF-CBT) by National Institute for Clinical Excellence (NICE 2009). One of the arguments to support why EMDR and cognitive behavioural therapy are effective is that they both share the same neurobiological objective and that is to down regulate the amygdala so as to allow the hippocampus and medial pre-frontal cortex to come back on line (D.P. Farrell et al., 2011). EMDR efficacy has been debated for several reasons, but mainly with reference to the absence of an empirically validated model proficiently explaining the effects of the EMDR method (Gunter & Bodner 2008)(Perkins & Rouanzoin 2002) and the role of the considered working mechanism in the form of the bilateral stimuli (Lohr et al.,1999). It has been demonstrated nevertheless that eye movements contribute to less vivid and unpleasant memories in people with non-clinical symptoms(Andrade et al,. 1997)(Barrowcliff et al., 2004)(Kavanagh et al., 2001). Besides, it has been found that eye movements decrease psycho-physiological arousal and increase parasympathetic activity in people with PTSD symptoms (Elofsson et al., 2008)(Sack et al., 2008). Several hypotheses that exist try to explain the mechanism of bilateral stimulation and the mechanism of the processing itself as posited with the AIP model (Shapiro 2007)(Shapiro 1995)(Shapiro 2001)(Solomon & Shapiro 2008). These hypotheses pertain to the EMDR inducing a REM sleep state-like condition(Stickgold 2008), the working memory account (Gunter & Bodner 2008), the investigatory reflex account Barrowcliff et al., 2004)(MacCulloch & Feldman 1996) the increased hemispheric communication account,(Christman et al., 2006) or the hypothesis of relaxation) (Shapiro, F. 2007). The case presented in this paper had multiple trauma forms and failed drug treatment and yet it was observed that EMDR provided marked improvement in all the domains of his deficits and this was at a prompt speed as compared to cognitive behavioural therapy (CBT) which usually takes longer duration of therapy and more sessions. The improvements in this individual were not short lived indicating permanent changes happening at neurobiological levels of brain.

In Pakistan, EMDR is still in its infancy and it's a novel treatment modality for mental health professionals, psychiatrists and psychologists alike. This case highlights the vast horizons of EMDRs cogency in complex man-made disasters and the promising future of EMDR for many mental health sufferers and stigmatized population as a substantial alternate to drug treatment. Further research in this direction in Pakistan would enable this type of non-pharmacological intervention (NPI) modality to be adapted as part of many treatment guidelines in Pakistan.

5. Conflict of interest

Authors declare no conflict of interest.

6. Grant support and financial disclosure

None declared.

7. Ethical considerations

This study was approved by the hospital ethical committee.

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LETTER TO THE EDITOR

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MULTIPLE SELF-MUTILATIONS IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER

YETİŞKİN DİKKAT EKSİKLİĞİ HİPERAKTİVİTE BOZUKLUĞUNDA ÇOKLU KENDİNE ZARAR VERME

Alper Evrensel*[1], Gökçe Cömert[1]

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Dear editor,

Self harm behavior is a frequently reported maladaptive behavior in the general population. The association of attention deficit hyperactivity disorder (ADHD) with self harm behavior is rare. In this paper, a case with ADHD was mentioned.

Twenty-four-year-old married male patient was admitted with complaints of irritability. Six years ago, he committed suicide by shooting to the right temporal region with a blank cartridge pistol. Scars which are in 1.3 cm diameter were present in his on the right temporal scalp (Figure1). In addition, there were self-mutilation incision scars on the arms, forearms, abdomen and chest (Figure 2). In order to close the incision scars he had tattoo in his left forearm. He had difficulty maintaining his attention at work. He worked disorganized and could not complete his work on time. Therefore, he has been warned by his boss. He suffered from forgetfulness, irritability, restlessness and losing his belongings. He talked excessively and interrupted others. He hated traffic congestion and was cutting in and out of traffic.

According to DSM-5 he was diagnosed adult ADHD. Right temporal bioelectrical disruption was detected in his EEG (electroencephalogram). After the suicide attempt, although he had no damage in his scalp it was thought that neuronal damage occurred due to the blast effect. No epileptic seizures were observed. Levatiracetam (1000 mg/day) treatment was prescribed to him. His impulsive behaviors have been decreased after treatment.

Figure 1: Scars which are in 1.3 cm diameter were present in his on the right temporal scalp.

Although abnormal impulsivity and poor self control are

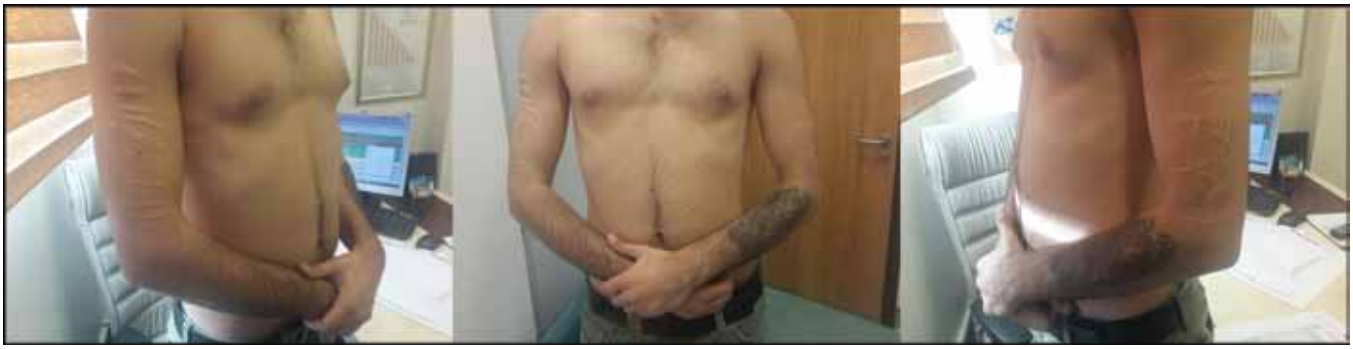

Figure 2: Self-mutilation incision scars on the arms, forearms, abdomen and chest.

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common, there are few studies about self-mutilation in ADHD. Only 15 studies were found in first review which were conducted by Allely (2014). According to these studies, ADHD is a risk factor for suicide attempts and self-mutilation (Hinshaw et. al., 2012; Hurtig et. al., 2012; Alley, 2014) Self-mutilation and suicide attempts were often seen together. Self-harm behavior might be in the form of open wounds on the skin with a razor blade. In this case, wounds have not been sutured. In this reason it was cause serious aesthetic problem. He closed part of scars on his left forearm with tattoo.

If there is self mutilation in patient, It should be noted that the possibility of suicide. ADHD may be a risk factor for suicidal ideation, suicidal behavior and self-mutilation. Correlation of suicidal behavior and self-mutilation are common. Antiepileptic drugs may treat impulsivity and aggression in ADHD.

Sincerely,

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CASE REPORT

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BILATERAL PEDAL EDEMA ASSOCIATED WITH OLANZAPINE TREATMENT: A CASE REPORT

OLANZAPİN TEDAVİSİ İLE ORTAYA ÇIKAN BİLATERAL AYAK BİLEĞİ ÖDEMİ: BİR OLGU SUNUMU

Hamiyet İpek Toz[1], Dilek Meltem Taşdemir[2], Ürün Özer*[3], Bahtiyar Toz[4], Güliz Özgen[5]

Abstract

Peripheric edema could be caused by various medical conditions as well as pharmacologic agents such as antihypertensives, nonsteroidal antiinflamatory drugs, endocrine agents and immunotherapies. Olanzapine is an atypical antipsychotic that is widely prescribed for the treatment of schizophrenia and bipolar affective disorder. Most common adverse reactions of olanzapine are weight gain, postural hypotension, constipation, dizziness, akathisia, sedation. Peripheral edema was reported as an infrequent side effect, which affected 3% of the olanzapine treated patients.

In this report, we aim to draw attention of psychiatrists on this rare adverse effect by presenting a 56-year-old case, who applied to our hospital with severe depressive and obsessive-compulsive symptoms and hospitalized because of suicide risk. Before psychiatric admission, he wasn't taking any medication. He was diagnosed as major depression with psychotic features and obsessive-compulsive disorder. He was started on olanzapine 10 mg/day, quetiapine 300 mg/day and fluoxetine 40 mg/day. Two weeks after initiation of olanzapine, he was found to have bilateral pedal edema without ulceration and temperature change but minimal redness was observed. He had no history suggestive of cardiac, renal and liver dysfunction or allergic reaction against to any drug that could explain his existing edema. Possible medical conditions which may cause edema were ruled out by laboratory tests and physical examination. Olanzapine was stopped immediately and the therapy was modified to risperidone 1 mg/day. After discontinuation of olanzapine, edema was gradually resolved within two weeks.

Because olanzapine associated edema has been seen rarely, it could be overlooked by psychiatrists in comparison to its more common side effects. Although it shows self-limited and benign course, patients may feel discomfort and their compliance to treatment may decrease. Also, it may interfere with differential diagnosis of other medical conditions which may cause edema. In conclusion, we suggest that patients should be observed carefully for edema during olanzapine treatment.

Keywords: Olanzapine, Peripheric Edema, Side Effect

Özet

Periferik ödem çeşitli tıbbi hastalıkların yanı sıra antihipertansifler, nonsteroidal antiinflamatuarlar, endokrin ilaçlar ve immünoterapiler gibi farmakolojik ajanlarla ortaya çıkabilir. Olanzapin şizofreni ve bipolar mizaç bozukluğu tedavisinde sıkça reçetelenen bir atipik antipsikotiktir. En sık yan etkiler kilo alımı, postural hipotansiyon, kabızlık, başdönmesi, akatizi ve sedasyon olarak bildirilmiştir. Periferal ödem, olanzapinle tedavi edilen hastaların %3'ünü etkileyen nadir bir yan etki olarak bildirilmiştir.

Bu yazıda, şiddetli depresif ve obsesif kompulsif belirtiler ile hastanemize başvuran ve intihar riski nedeniyle yatırılan 56 yaşında bir olgu sunularak, bu nadir yan etkiye psikiyatristlerin dikkatini çekmek amaçlanmıştır. Psikiyatri başvurusu öncesinde hastanın herhangi bir ilaç kullanımı yoktur. Hastaya psikotik özellikli major depresyon ve obsesif kompulsif bozukluk tanısı konmuştur. Tedavisine olanzapin 10 mg/gün, ketiyapin 300 mg/gün ve fluoksetin 40 mg/gün ile başlandı. Olanzapin başlandıktan iki hafta sonra, ülserasyon ve ısı değişikliği olmaksızın, minimal kızarıklıkla bilateral ayak bileği ödemi geliştiği gözlendi. Hastada ödemi açıklayabilecek, kalp, böbrek ve karaciğer yetmezliğini ya da bir ilaca alerjik reaksiyonu düşündüren öykü yoktu. Ödeme neden olabilecek olası tıbbi durumlar fizik muayene ve laboratuar testleri ile dışlandı. Olanzapin hemen kesildi ve risperidon 1 mg/gün tedavisine geçildi. Olanzapinin kesilmesinden sonra ödem iki hafta içinde giderek geriledi.

Olanzapinle ilişkili ödem, nadir görülmesi nedeniyle, psikiyatristler tarafından daha sık görülen yan etkilere kıyasla ihmal edilebilir. Kendini sınırlayan ve iyi huylu bir gidişi olmasına rağmen, hastalarda rahatsızlık yaratabilir ve tedaviye uyumlarını azaltabilir. Ayrıca, ödeme neden olabilecek diğer tıbbi durumların ayırıcı tanısını zorlaştırabilir. Sonuç olarak, olanzapin tedavisi süresince hastaların ödem açısından dikkatle izlenmesi yararlı olacaktır.

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1. Introduction

Edema is defined as a clinically apparent increase in the interstitial volume. Peripheric edema could be caused by various medical conditions, such as obstruction of venous or lymphatic drainage, congestive heart failure, nephrotic syndrome and other hypoalbuminemic states, cirrhosis and medication. Common pharmacologic agents known to cause edema are antihypertensives, nonsteroidal antiinflamatory drugs, endocrine agents and immunotherapies (Braunwald and Lascalzo, 2012). Olanzapine is a potent atypical antipsychotic that is widely prescribed for the treatment of schizophrenia and bipolar affective disorder. It does have antagonist properties at dopaminergic (D1,D2,D3), muscarinic (M1,M2), histaminergic (H1), seratonergic (5-HT2A,5-HT2C, 5-HT3,5-HT6) and adrenegic (alpha 1) receptors (Stahl, 2010). Although olanzapine is superior to typical antipsyhotics in its rare extrapramidal symptoms, it may lead to a significant weight gain and may impair glucose metabolism like other second generation antipsychotics (Al-Zoairy et al., 2013). Most common adverse reactions of olanzapine (≥5% and at least twice that for placebo) are weight gain, postural hypotension, constipation, dizziness, akathisia, sedation, headache, increased appetite, abdominal pain, extremity pain, fatigue, dry mouth, asthenia, tremor. According to premarketing trials, peripheral edema was reported as an infrequent side effect, which affected 3% of the 532 olanzapine treated patients, as compared to 1% of the 294 subjects on placebo (Lilly, 2005). There is limited information about peripheral edema associated with olanzapine in the literature. Because olanzapine associated edema shows self-limited and benign course, it could be overlooked by psychiatrists when compared to other side effects.

In this article, we report a case with bilateral pedal edema due to olanzapine treatment in order to draw attention of psychiatrists on this neglected side effect. Informed consent was obtained from the patient for this case report.

2. Case

56-year-old single, college educated male, was presented to our hospital with severe depressive symptoms for four months and obsessive-compulsive symptoms comorbid with hypochondriac concerns for two years. He was hospitalized to inpatient unit because of suicide risk on the same day. Before psychiatric admission, he wasn't taking any medication. He was diagnosed as major depression with psychotic features and obsessive-compulsive disorder with poor insight. He was evaluated also with Brief Psychiatric Rating Scale (BPRS) and total score on it was 34. He was started on olanzapine 10 mg/day, quetiapine 300 mg/day and fluoxetine 20 mg/day and titrated to 40 mg/day in a week. Two weeks after initiation of olanzapine treatment, the patient noticed bilateral swelling in his ankles which was more prominent on the left foot. Edema was barely evident on inspection and gradually worsened to grade 3 (following skin depression, indentation returns to normal 20-25 seconds) over the next 3 days at the 10 mg daily dose of olanzapine. There was no ulceration and temperature change but minimal redness was observed on the both edematous area (Figure 1). He had no history

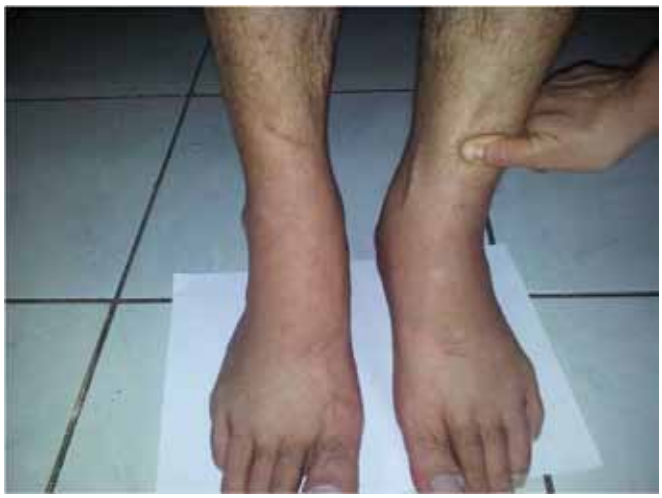

Figure 1: Minimal redness observed on the both edematous area.

suggestive of cardiac, renal and liver dysfunction or allergic reaction against to any drug that could explain his existing edema. He was evaluated by internalist to investigate the etiology of edema. Results of chest x-ray examination, echocardiography, complete blood count, electrolytes, chemistery profile and thyroid (TSH, f T3, f T4), renal (urea, creatinine), liver function (AST, ALT, GGT, alkaline phosphatase, total protein and albumin) tests were within normal limits. According to test results and consultation by internalist, all medical causes of edema were ruled out except for medication. Olanzapine was discontinued on day 15 and the therapy was modified to risperidone 1 mg/day. The edema regressed gradually within ten days without any medical intervention except for foot elevation and salt restriction in diet. At the end of hospitalization period of approximately 3 weeks, he showed substantial improvement in his depressive mood and was able to control his compulsive behaviours. The patient's obsessive thoughts was partly regressed. He had minimal edema, grade 1. He was discharged with risperidon 1 mg/day, fluoksetin 40 mg/day and seroquel 300 mg/day on day 22 and adviced to come for follow up one week after discharge. On subsequent follow up, 20 days after cessation of olanzapine, it was learn that his mood was euthymic, he has used same medication regularly and the edema did not recur. His BPRS score was 3. His laboratory tests (complete blood count, liver and renal function tests) were normal. It was seen that the edema resolved completely in physical examination.

3. Discussion

The case mentioned above was evaluated as olanzapine associated pedal edema because that edema gradually dissolved when the drug was discontinued. Also the absence of any systemic disease, clinical and laboratory findings explaining edema have supported our opinion. The mechanism of peripheral edema caused by olanzapine remains uncertain. It has been thought that this adverse effect related to olanzapine was attributed to its receptor profile. There are several possible hypotheses in the literature. Firstly, olanzapine antagonizes alpha-1 (α1) adrenergic receptors, resulting in peripheral vasodilation and decreased vascular resistance, which leads to edema (Ng et al., 2003). Secondly, stimulation of muscarinic

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(M1), histaminic (H1), serotonergic (5-HT2) receptors result in activation of Inositol 1-4-5 triphosphate (IP3) and diacylglycerol (DAG) post-receptor pathway. Increased IP3 leads to rapid calcium release by binding endoplasmic reticulum (ER). Calcium released from ER causes activation of ATP-dependent calcium pump. Blockage of these receptors by olanzapine inhibits the physiological increase in IP3, that causes downregulation of ATP- dependent calcium pump, ultimately resulting in smooth muscle relaxation and then vasodilation and edema (Katzung and Trevor, 1998). Thirdly, increased intracellular cyclic adenosine monophosphate levels due to blockage of HT2 recetors by olanzapine causes smooth muscle relaxation (Ganong, 1999). This mechanism is thought to be also involved in quetiapine associated edema (McSkimming et al., 2012). Previously, correlation between high plasma concentration of cAMP and idiopathic edema has been shown (Kuchel et al., 1975). Another mechanism, peripheric dopaminergic blockage by olanzapine might change renal regulation of fluid and electrolyte balance, resulting in edema. Finally, an allergic reaction against to olanzapine has been suggested as the cause of olanzapine induced edema. Although, in that case, immunoglobulin levels have been normal, allergic mechanism between the limb edema and olanzapine have been proven with histopathological findings and moderate eosinophilia (Honma et al., 2012). Similarly, Terao et al. (1988) and Conney and Nagy (1995) have explained the risperidone associated edema by allergic pathways.

In our case, as in the others in the literature, olanzapine was stopped after the development of edema and edema did not recur with risperidone treatment. These cases suggest that underlying pathophysiological mechanisms of olanzapine and risperidone associated edema may be different from each other. In addition to this hypothesis, the literature has reported that risperidone related edema could be dose-dependent and seen mostly (6 of 9 cases), in co-medication with valproic acid, benzodiazepine and / or dopamine receptor antagonists. According to the literature, there have been 14 cases of edema associated with olanzapine. In some of these cases, olanzapine was used in combination with valproic acid, albuterol, theophylline citalopram, benzodiazepine, gabapentin, bupropion. But, the edema had been attributed to olanzapine in these combined therapies. In our case, olanzapine was combined with quetiapine and fluoxetine simultaneously. Previously, quetiapine associated edema have been reported in a few cases (Kovela et al., 2009; McSkimming et al., 2012). Among them, one case documented that recurrence of the edema with quetiapine was seen after cessation of olanzapine (Kovela et al., 2009). In our case, the combination of olanzapine with quetiapine may have contributed this patient to developing edema. If considering their similar molecular structure and affected receptor groups between quetiapine and olanzapine, increase in the risk of developing edema is expected. Although quetiapine was continued at the same dosage, regression of edema gradually after discontinuing olanzapine showed that olanzapine was strongly the offending agent. According to former cases, edema has emerged as dose-dependent and at the dosage of 2.5-20 mg/day . In our case also, olanzapine dosage was consistent with the literature. In a case report, furosemide was started to treat the edema instead of stopping olanzapine (Deshauer et al., 2006). Although furosemide is effective in the treatment of olanzapine associated edema, there is not enough data on the long-term efficacy or safety of this intervention. After considering the alternatives, we preferred stopping possible agent, adviced the patient to leg elevation and salt restriction without any diuretic usage in the management of edema.

In a study, Ng et al (2003) have found that the frequency of edema in patients treated with olanzapine was 57 % of 49 patients. Of these patients, 10.2% had severe edema (Ng et al., 2003). The results of this study has contrasts with an incidence of 3% as reported in premarketing trials (Lilly, 2005). The discrepancy between this study and documented limited case reports suggests that milder cases of pedal edema may remain unrecognized as the complication of olanzapine. Because olanzapine associated edema has benign and self-limiting course , it could be overlooked by patients and psychiatrists in comparison to its more common side effects and appears less than actual incidence. Although it seems innocuous, patients may feel discomfort and their compliance to treatment may decrease especially in severe edema. Also, it may interfere with differential diagnosis of other medical conditions which may cause edema. In conclusion, we suggest that patients should be observed carefully and edema examination should be made by psychiatrists during olanzapine treatment in order to recognize this neglected side effect.

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LETTER TO THE EDITOR

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YELLOW SMOKE STAIN ON FINGERS IN PATIENT WITH SCHIZOPHRENIA

ŞİZOFRENİ HASTALARININ PARMAKLARINDAKİ SARI DUMAN LEKESİ

Alper Evrensel*[1], Mehmet Emin Ceylan[1], Barış Önen Ünsalver[1], Gökçe Cömert[1]

Dear editor,

A 27-year-old unmarried male patient with schizophrenia is treated for 8 years. Negative symptoms were the most prominent. He had poor self-care; long nails and oily hairs. He took bath once in two-three weeks and suffered from mental-motor retardation. He smoked 70-80 cigarettes per day and used to smoke until the end of the cigarettes. Therefore, depending on the tobacco smoke yellowing occurred in the second and third fingers of his right-hand (Figure 1).

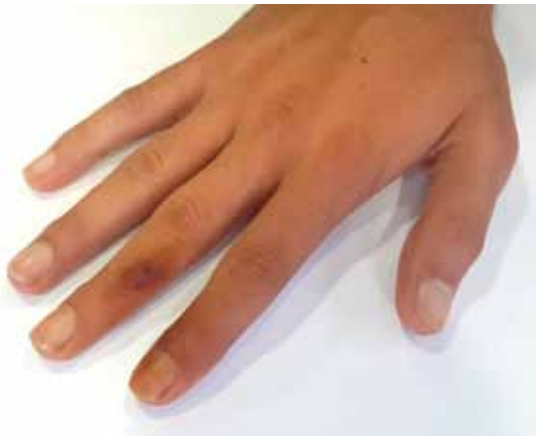

Figure 1: Depending on the tobacco smoke yellowing occurred in the second and third fingers of his right-hand

Although he did wash with soap, this yellow stain was not disappeared. He was treated with risperidone (8 mg/day), amisulpride (800 mg/day) and biperiden (4 mg/day). Therapeutic drug monitorization (TDM) of risperidone+9OH was determined as 7.8+20.0 (ng/ml) (therapeutic reference range, TRR: 20 to 60 ng/ml).1 TDM of amisulpride was determined 234.4 (ng/ml) (TRR: 100 to 320 ng/ml)1 and TDM of biperiden was determined 0.6 (ng/ml) (TRR: 1 to 6.5 ng/ml).1 Despite a high dose medicament, low drug levels in the blood were observed.

Smoking rates in patients with schizophrenia has been reported as 74-92%.2 It is assumed that smoking reduces negative symptoms and it is kind of self-medication for the patients with schizophrenia.3 It was observed that patients with schizophrenia smoke cigarettes which have higher nicotine and tar content and they used to smoke until the end of the cigarettes.3,4 Typically, this is linked to cognitive impairment and dementia. Also it has been suggested that the reason of it might be the presence of high level of nicotine at the end of the cigarette.4 It might say that the medical treatment of patients with smoke stains on their fingers is inadequate.

The prevalence of smoking in schizophrenia and cigarette consumption amount is higher than the normal population. In particular, patients with negative symptoms of schizophrenia may use nicotine as self-medication. Updating of medical treatment for patients with smoke stains on fingers due to low blood levels of the drug may be appropriate. TDM should be measured and pharmacotherapy treatment should be reviewed.

Yours sincerely,

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BUILDING BRIDGES IN THE COMMUNITY THROUGH MENTORING PROGRAMS

MENTÖRLÜK PROGRAMLARI İLE TOPLUMDA KÖPRÜLER KURMAK

Nadire Gülçin Yıldız*[1]

Dear Editor,

Mentoring is a form of structured trusting relationship, which aims to match disadvantaged at-risk youth with caring individuals who offer guidance, direction, support, motivation, encouragement and reassurance. The goal in mentoring programs is to develop the competence and character of the mentee (National Research Agenda, 2004). While traditionally parents fill this role, some children lack such a relationship. It is predicted that 20 % of youth lack a supportive relationship with a caring adult in their lives (Lawner & Beltz, 2013). When kind, concerned individuals serve as role models, it is more likely that youth will become healthy, successful adults who are integrated into society. Therefore, they are able to form perceptions about society through their observation and social interactions which will influence how they perceive their potential role in society.

Data gathered from a survey of 31,272 adolescents enrolled in high schools as part of the European School Survey Project reveal that youth who become drug addicted before age 15 are at the highest risk for chronic substance abuse and dependence (Pumariega, Burakgazi, Unlu, Prajapati & Dalkilic, 2014). Psychosocial variables, such as lower school grades, lower parental education, lower income, lower anxiety, higher irritability, higher antisocial traits, greater time with peers, less time with family and higher family substance abuse, may also contribute to adolescent substance abuse. In addition, according to the 2013 Adolescent Research Profile Report of Turkey (2014), 39 % of youth reported experiencing difficulty adapting to their developmental tasks. The same document indicates that 70 % of those who report being exposed to physical abuse at home were mainly abused by their fathers (37 %) and by their siblings (33 %), threatening family functioning. Being exposed to verbal abuse at school by teachers and administrators threatens the school climate and psychosocial development, highlighting the need for a systemic social support programs for youth.

This National Report offers recommendations based on study results with a sample size of 6,747 (i.e., survey with 12-18 years adolescents and their parents or custodians). Interestingly, the document recommends a mentoring system to promote readiness for learning academic materials. Findings also emphasize the development and sustainability of government-based national programs and United Nations or European Union-based international programs for girls with a lower socio-economic status family background. While the Ministry of Family and Social Policies document of 2014 Child Services General Administration statistics indicate that there are 62 Children Support Centers and 1,144 children received services (i.e., specialized in neglect, abuse and juvenile delinquency) there is no individualized psychosocial rehabilitation model developed nation-wide through the use of strengthening the social support system of at risk youth. Issues like violence and/or separation in the immediate family, increased divorce rate, socio-cultural (e.g., migration), economic and mental health problems place children at risk, while limiting adult supervision necessary for healthy physical, psychological and cognitive development.

Social relationships are strongly linked to wellness changing neuroplasticity. An fMRI-based handholding procedure examined the effectiveness of Emotionally Focused Therapy through the modification of social regulation of neural threat, which indicated changes on the brain's representation of threat cues if a partner is presented (Johnson, Moser, Beckes, Smith, Dalgleish, Halchuk et al., 2013). Similarly, active listening activates positive emotional brain regions (e.g., attending behavior, paraphrasing, reflecting feelings, summarizing), which affect the following areas: ventral striatum, right anterior insula and medial PFC & superior temporal sulcus found

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in an fMRI study (Kawamichi et al., 2014). Academic issues such as high stakes testing for high school and college entrance, social issues such as bullying and peer pressure, and community issues such as safety in the community only exacerbate the above-mentioned risk factors of disadvantaged youth in Turkey. Approximately 31.2 % of Turkey's population is under 18 (TUİK, 2013). Mentoring programs offer preventive relationships, which enhance social skills.

Mentoring programs can build trust and repair attachment bonds in children living in institutions serving at risk youth (e.g., those children with neglect and abuse, delinquent behaviors and living on the street). To support and guide disadvantaged youth in order to become responsible adults, mentoring-based community engagement programs may be critical. Such program activities provide opportunities to instill social skills in the context of relationships. One's ability to use necessary social skills determines his or her ability to succeed in life; and such social skills can only be attained in a relational context. Enabling teens to develop healthy social skills through mentoring relationships where they feel empowered restores their self-esteem, helping them gain greater self-confidence.

Previous research studies provide convincing evidence that mentoring programs are effective in the development of social skills and relationships. Making a Difference: The Impact Study of Big Brothers Big Sisters (Tierney, Grossman, & Resch, 1995) indicated reduced antisocial activities (violent behaviors, drug or alcohol use) and improved academic outcome and relationships with family and friends. DuBois D.L., Holloway, Valentine and Cooper's (2002) meta-analysis revealed similar results. Based on the review of 360 studies, Hair, Jager and Garrett (2002) identified programs that designed the promotion of quality relationships and good social skills. Results indicated that when youth engaged in these program' activities, they improved parent-child relationships, peer relationships, conflict resolution skills, self-control and behavior regulation, social confidence, social assertiveness, social self-efficacy and social initiative. Lawner and Beltz (2013) conducted a synthesis of experimental evaluations of 19 mentoring programs (e.g., Big Brothers Big Sisters) to study "how frequently these programs work to improve such outcomes as education, mental health, peer and parent relationships, and behavior problems, and what lessons can be learned to improve outcomes" (Lawner & Beltz, 2013, p. 1). Mentoring Programs such as Big Brothers Big Sisters of America have created and supported one-on-one relationships between adult volunteers and at-risk youth for more than a century. This organization is also one of the oldest, best-known and most elaborate, mentoring programs across the world (e.g., Australia, Austria, Canada, Ireland, Israel, Netherlands, New Zealand, Poland, Russia, and United States) and it fits with our collective cultural dynamics, which emphasize relational lifestyle.

The Turkish government is seeking to develop an Individualized Psychosocial Rehabilitation Model for children and adolescents who are living in institutions under government care. Relevant programs and social policies are regarded to be inadequate, while there is an increasing need to meet the psychosocial needs (aggression, addiction, neglect and abuse), of these youth. As a response to a request from the Ministry of Family and Social Policies (2013), Üsküdar University proposed an 8-week Individualized Rehabilitation Model where medical and clinical treatments were provided to a sample of 78 children. Similarly, an Evidence Based Mentoring Program sponsored by the Ministry of Youth and Sports (2014), targeted 45 teenage girls who were neglected and abused. Our rehabilitation approach includes an assumption that "the brain is built over time from the bottom up." Therefore, trauma treatment should focus on repairing attachment bonds, assuming that relationship building is at the core of therapeutic change. Consequently, it is important to provide supportive social relationships to help reduce the outcome of adverse childhood experiences. The Evidence Based Mentoring Program was designed to fulfill this goal where Üsküdar University undergraduate students served as mentors for one year. The outcome of the study has promising evidence that the program is effective. It would be judicious to consider these findings when designing future programs and making policies on the psychosocial rehabilitation of neglected and abused children living in institutions.

Sincerely,

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