ISSN:2149-1909

# THE JOURNAL OF NEUROBEHAVIORAL SCIENCES

Year: 2015 Vol:2 No:2

## NÖRODAVRANIŞ BİLİMLERİ DERGİSİ



JNBS Published by Üsküdar University

JNBS
THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

ISSN:2149-1909

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**Printing office/Matbaa**
Armoninüans Görsel Sanatlar A.Ş.
Yukarıdudullu, Bostancı Yolu Cad. Keyap Çarşı
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# ABOUT THIS JOURNAL

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**Year :** 2015
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**Issue Number :** 2



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# EDITORIAL

İkinci yılının ikinci sayısı ile okuyucuyla buluşan Nörodavranış Bilimleri Dergisinin bu sayısında da hem ülkemizde hem de farklı ülkelerde çalışmalarını sürdüren araştırmacıların katkılarıyla hızla gelişmesinden ve hedeflediğimiz noktaya bir adım daha yaklaşmasından sevinç duyuyoruz. Bunun yanı sıra 9-13 Eylül 2015 tarihinde Münih'te gerçekleştirilmiş olan uluslararası katılımlı "The Annual Conference on Clinical Neurophysiology and NeuroImaging 2015/ Klinik Nörofizyoloji ve Nörogörüntüleme" kongresinde üniversitemizi ve ülkemizi temsil etmiş olmanın ve gelecek yıl 7-11 Eylül 2016 tarihinde gerçekleştirilecek olan kongreye Üsküdar Üniversitesi olarak ev sahipliği yapacak olmanın gururunu yaşıyoruz.

Bu sayımızda ilk olarak Nurmedov ve meslektaşlarının hazırladığı madde kullanım bozukluğu tedavisi gören hastalarda dikkat eksikliği ve hiperaktivitenin hastaların sosyodemografik ve klinik özellikleriyle karşılaştırıldığı geriye dönük çalışmalarını ve Karayün ve arkadaşlarının növrotik düzeyde kişilik örgütlenmesi olan bireylerdeki kişilik ve aile özelliklerinin sağlıklı bireylerle karşılaştırılmasını okuyucuya sunuyoruz. Bunun yanı sıra dergimizin bu sayısında Kaşıkçı ve arkadaşlarının serebellumun obsesif-kompulsif bozukluk ile ilişkili beyin ağı modeline eklenmesi konulu gözden geçirme makalesini ve Kaya ve Er'in, Çamkurt ve Şimşek'in, ayrıca Uvais ve Sreeraj'ın farklı özelliklerdeki olgu raporlarını bulabilirsiniz.

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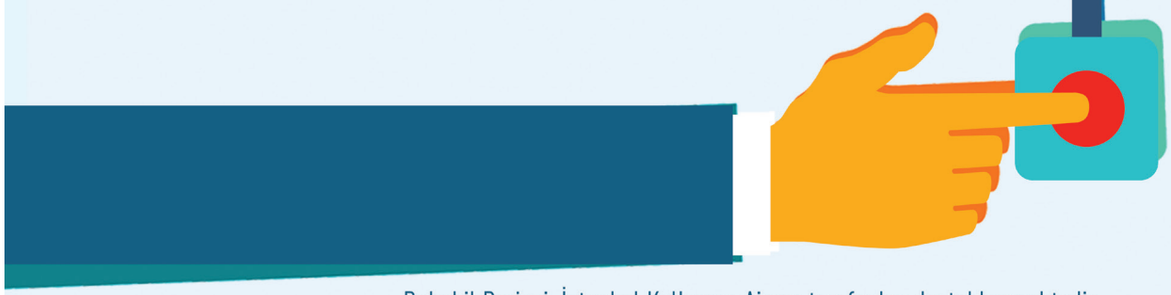

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ORIGINAL ARTICLE

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1434854695

**Article history:**
Received 20 June 2015
Received in revised form 28 June 2015
Accepted 3 August 2015

# DIAGNOSIS OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AMONG PATIENTS WITH SUBSTANCE USE DISORDER AND ASSOCIATION WITH SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS: A RETROSPECTIVE STUDY

## MADDE KULLANIM BOZUKLUĞU OLAN HASTALARDA DİKKAT EKSİKLİĞİ VE HİPERAKTİVİTE BOZUKLUĞU TANISI VE SOSYODEMOGRAFİK VE KLİNİK ÖZELLİKLERLE İLİŞKİSİ: RETROSPEKTİF BİR ÇALIŞMA

Serdar Nurmedov*[1], Onur C Noyan[1], Aslı E Darçın[2], Onat Yılmaz[3], Nesrin Dilbaz[4]

### Abstract

**Objective: Substance use disorders (SUD) are chronic, relapsing disorders in which compulsive behaviors persist despite severe negative consequences. SUD is frequent among patients with ADHD and ADHD is frequent among patients with SUD. The aim of this study was to investigate the prevalence of ADHD among patients with substance abuse/dependence according to DSM-IV TR retrospectively, and to demonstrate whether the diagnosis of ADHD is associated with sociodemographic and clinical characteristics of these patients. Method:We analyzed the medical records of 485 patients. All participants were diagnosed as having alcohol or substance abuse/dependence.Socio-demographic and data regarding clinical characteristics were derived from patient records. Results: Of the included 395 participants, 37 (9.4%) were female and 358 (90.6%) were male. The mean age was 31.53±10.44 years. Comorbid ADHD was diagnosed among 82 (20.8%) of all participants. The mean age in ADHD group was significantly lower than that of the group without ADHD (27.10± [7.87] versus 32.69± [10.73], p<0.05).Also, rate of remission was significantly lower in the group without ADHD (%48.8 vs. %33.2, p<0.05). Cannabis and derivatives abuse/dependence were found to be higher in the group with ADHD, whereas alcohol or multidrug abuse/dependence were higher in the group without ADHD comorbidity (p<0.05). Conclusion: In conclusion, we found that in the majority of the participants with ADHD had their diagnosis after the substance use problems had developed. This finding suggests that ADHD can be underdiagnosed in adults and we should be aware of this diagnosis.**

**Keywords:** ADHD, Comorbidity, Addiction

### *Özet*

***Amaç: Madde Kullanım Bozukluğu (MKB), olumsuz sonuçlarına karşın kompulsif madde kullanımının devam ettiği yineleyen, kronik bir hastalıktır. MKB, DEHB'si olan bireylerde, DEHB de MKB'si olan bireylerde daha sıktır. Bu araştırma, DSM-IV TR'ye göre madde bağımlılığı/kötüye kullanımı olan bireylerde DEHB sıklığının ve sosyodemografik ve klinik özellikleri ile ilişkisinin araştırmayı amaçlamıştır. Yöntem: Bu araştırmada 485 hastanın tıbbi kayıtları incelenmiştir. Hastaların hepsi alkol veya madde kötüye kullanımı/bağımlılığı tanısını almıştır. Sosyo-demografik ve klinik özellikleri ile ilgili veriler tıbbi kayıtlardan elde edilmiştir. Bulgular: Araştırmaya dâhil edilen 395 hastanın 37 (%9.4)'si kadın, 358 (%90.6)'sı erkek olduğu ve ortalama yaşlarının 31.53 ±10.44 olduğu tespit edilmiştir. DEHB komorbiditesi 82 (%20.8) hastada tespit edilmiştir. DEHB komorbiditesi olan grupta ortalama yaş DEHB komorbiditesi olmayanlara göre daha düşük olduğu tespit edilmiştir (27.10± [7.87] ile 32.69± [10.73], p<0.05). DEHB'si olmayan grupta remisyon oranı daha düşük bulunmuştur (%48,8 ile %33,2, p<0.05). Esrar ve türevleri DEHB'si olan grupta daha fazla kullanılıyor iken, alkol ve çoğul madde kullanımı DEHB'si olmayan grupta daha sık olduğu tespit edilmiştir (p<0.05). Sonuç: DEHB'si olan hastaların büyük bir kısmının tanısı madde kullanımına başlandıktan sonra konduğu tespit edilmiştir. Bu bulgular, erişkinlerde DEHB tanısının yeterince bilinmediği ve bu konuda daha dikkatli olmamız gerekiğini akla getirmektedir.***

***Anahtar Kelimeler:*** *DEHB, Komorbidite, Bağımlılık*

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## 1. Introduction

Substance use disorders (SUD) are chronic, relapsing disorders in which compulsive behaviors persist despite severe negative consequences. Substance use usually begins during adolescence and has a worse progress in the presence of accompanying psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), mood disorders or conduct disorder. ADHD is a common, childhood-onset neurodevelopmental disorder with adverse consequences during adulthood. Prevalence of ADHD in children varies between 3 to 12% and the disorder persists through adolescence and adulthood in the 75% of these subjects. Although symptom severity is lower in adults with ADHD, functionality is affected at almost a similar level to children's (Polanczyk et al., 2007; Rappley, 2005; Biederman & Faraone, 2005; Adler, 2004; Matthys et al., 2014). There is a significant and clinically relevant overlapping between ADHD and SUD (Arias et al., 2008). SUD is frequent among patients with ADHD and ADHD is frequent among patients with SUD. ADHD and SUD have common neurobiological alterations that may predispose an individual to develop both conditions. The dopaminergic dysfunction in the dopaminergic circuits in basal and frontal cortex with consequent defects in executive function and reward system have been found in ADHD and SUD patients (Seidman et al., 2005). In recent years, studies conducted in clinical samples revealed that adolescents and adults with substance use disorder showed ADHD more frequently than healthy individuals and the mean occurrence rate in this group varies between 15-50% (Biederman et al., 2011; Wilson, 2007; Oortmerssen et al., 2012; Szobot et al., 2007; Wilens & Morrison, 2012). There are studies reporting that, ADHD occurs in 17-45% of patients with alcohol use disorder and in 9-30% of the patients with SUD (Oortmerssen et al., 2012; Wilens, 2006; Wilens, 2004; Wilens & Upadhyaya, 2007). It has been stated that the risk of substance use problems in adults with ADHD is four times higher than in the general population (Fayyad et al., 2007).

Whereas some of the authors have stated that the diagnosis of ADHD in adulthood is difficult and ADHD is underdiagnosed, the others have stated that ADHD is overdiagnosed among adults. In fact there are limited materials for the screening, diagnosis and treatment of adult ADHD among SUD. Age-specific and strict criteria of ADHD in the DSM IV-TR and cognitive deficits associated with substance abuse is making difficult to diagnose ADHD among adults with SUD regarding underdiagnoses. On the other hand, SUD symptoms may mimic ADHD symptoms, which can lead to an overdiagnosis of ADHD in the SUD population (Matthys et al., 2014).

Most of the studies investigating comorbidity of ADHD and substance use disorder were conducted in adolescents, and reported that the age onset of substance use was younger in the presence of ADHD comorbidity. The presence of ADHD also impacts the characteristics of substance usage. In this group, progression from "use" to "abuse" and addiction is faster and compliance to treatment is worse with frequent relapses. It is also more difficult for these patients to maintain sobriety (Oortmerssen et al., 2012; Wilens, 2011; Wilens, 2006). Comorbid ADHD has a negative effect on the course of SUD. Patients with both ADHD and SUD become addicted at a younger age, use more substances and are hospitalized more often than SUD patients without ADHD (Arias et al., 2008).

The treatment of ADHD should be integrated into the treatment of addiction, thus symptoms of ADHD as impulsivity, hyperactivity, inattention and disturbed planning and organization can interfere with the addiction treatment (Matthys et al., 2014; Mariani & Levin, 2007). It has been noticed that the treatment of the ADHD symptoms can make the addiction easily treatable. Early treatment for ADHD decreases the risk for subsequent SUD in adolescence and adulthood (Wilens et al., 2003). In some other studies report that treatment of childhood ADHD with stimulants results in a 50–70 % reduction in the symptoms of SUD. Goksøyr and Nøttestad (2008) showed that occurrence of substance abuse and tendency to crime were higher in untreated adult ADHD patients. The aim of this study was to investigate the prevalence of ADHD among inpatients with substance abuse/dependence according to DSM-IV TR retrospectively, and to demonstrate whether the diagnosis of ADHD is associated with sociodemographic and clinical characteristics of these patients.

## 2. Method

We analyzed the medical records of 485 patients who were hospitalized in Neuropsychiatry Istanbul Hospital Addiction Treatment Center between January 2013 and December 2014. Medical records of 90 patients were excluded due to lack of sufficient data or other Axis-I comorbidity. All participants were diagnosed as having alcohol or substance abuse/dependence, based on DSM-IV TR, by two psychiatrists separately. The ADHD diagnosis was also made due to and confirmed with the Adult Attention Deficit Disorder/Attention Deficit and Hyperactivity Disorder (ADD/ADHD) Scale scores. Socio-demographic data including sex (male/female), age, marital status, employment status, duration of education (years) and data regarding clinical characteristics such as the age at first substance use, number of hospitalizations, presence of criminal records, rates of remission and rate of drop out were derived from patient records. The study was approved by Ethics Committee of Uskudar University. Information about remission and adherence to treatment was obtained via self-reports through outpatient visits and telephone interviews after discharge. Remission was defined as staying sober at least 12 months after admission. Patients who could not be followed up longer than six months were accepted as dropped out the treatment.

### *2.1. Statistical analysis*

Obtained data were analyzed using Statistical Packet for Social Sciences (SPSS) version 15.0. Descriptive analysis included means and standard deviations. Intergroup comparisons were made by Chi-square and t-test. Statistical significance was adjusted to $p<0.05$. Descriptive statistics were also calculated as frequency or percent.

### 3. Results

Of the included 395 participants, 37 (9.4%) were female and 358 (90.6%) were male. The mean age was 31.53±10.44 years. Among the participants, 272 were (68,9%) single and 123 (31.1%) were married. The mean of the duration of education were 11.34±2.79 years among participants. Comorbid ADHD was diagnosed among 82 (20.8%) of all participants due to DSM-IV TR. Participants with substance abuse/dependence were grouped into two groups based on the presence of ADHD and compared in terms of sociodemographic characteristics such as age, gender, marital status, employment, duration of education, and characteristics of substance use such as age of the first substance use, number of hospitalizations, lifetime legal problems, rates of remission and drop out. The mean age in ADHD group was significantly lower than that of the group without ADHD (27.10± [7.87] versus 32.69± [10.73], p<0.05). Also, rate of remission was significantly lower in the group without ADHD (%48.8 vs. %33.2, p<0.05). A Table 1 summarizes sociodemographic variables and clinical characteristics of the participants.

We also compared the sociodemographic and clinical characteristics of participants who had the diagnosis of ADHD before or after the onset of substance abuse/dependence. Patients who had the diagnosis of ADHD prior to the onset of substance use had lower mean age and higher rate of unemployment. This group also had the diagnosis of substance abuse/dependence at a younger age and their lifetime legal problems were at a lower level (p<0.05). A table 2 summarizes the sociodemographic variables and clinical characteristics of the participants in terms of association with ADHD comorbidity and the time of diagnosis.

The groups with and without ADHD comorbidity were also compared in terms of preference of substance that was abused. Cannabis and derivatives abuse/dependence were found to be higher in the group with ADHD, whereas alcohol or multidrug abuse/dependence were higher in the group without ADHD comorbidity (p<0.05). Assosciation of ADHD comorbidity and preference of the substance abused are presented in Table 3.

### 4. Discussion

There is growing evidence that ADHD is seen among adolescents and adults with substance use disorders more frequently, and the mean of prevalence in this group varies between 15-50% (Wilens & Morrison, 2011). In this study 82 (20.8%) of all participants with a substance use disorder met DSM-IV TR criteria for comorbid ADHD. This finding is supported by the findings of Oortmerssen et al. (2012), who have reported that the estimated

**Table 1:** Sociodemographic variables, clinical characteristics of the participants

| | | ADHD (+) (n=82) | ADHD (-) (n=313) | t/ $\chi$2 | p |
|---|---|---|---|---|---|
| Age (mean±SD) | | 27.10±(7.87) | 32.69±(10.73) | -4.421 | 0.003* |
| Sex | Female n (%)<br>Male n (%) | 3 (3.7)<br>79 (96.3) | 34 (10.9)<br>279 (89.1) | 3.972 | 0.046* |
| Duration of education (years) | (mean ± SD) | 10.7±(2.60) | 11.51±(2.81) | -2.367 | 0.597 |
| Marital Status n (%) | Single<br>Married | 56 (68.3)<br>26 (31.7) | 216 (69)<br>97 (31) | 2.970 | 0.227 |
| Occupation n (%) | Inoccupied<br>Occupied | 31 (37.8)<br>51 (66.2) | 159 (50.8)<br>154 (49.2) | 5.526 | 0.063 |
| Age at first substance use | (mean±SD) | 17.29 ±4.23 | 18.16±4.052 | -1.709 | 0.736 |
| Lifetime legal problems n (%) | No<br>Yes | 39 (47.6)<br>43 (52.4) | 120 (38.3)<br>193 (61.7) | 5.330 | 0.021* |
| Number of hospitalizations | (mean±SD) | 1.24±1.65 | 1.93±2.11 | -2.747 | 0.713 |
| Remission (n,%) | Yes<br>No | 40 (48.8)<br>42 (51.2) | 104 (33.2)<br>209 (66.8) | 8.830 | 0.009* |
| Drop out n (%) | Yes<br>No | 29 (35.4)<br>53 (64.6) | 133 (42.5)<br>180 (57.5) | 1.364 | 0.243 |

* Statistically significance level is <0.05

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**Table 2:** Comparison of sociodemographic variables and clinical characteristics of participants with comorbidity in terms of diagnosis antecedence

| | | Diagnosed ADHD before SUD diagnosis (n=15) | Diagnosed ADHD after SUD diagnosis (n=67) | t/ $\chi$2 | p |
|---|---|---|---|---|---|
| Age (mean±SD) | | 21.73±(5.93) | 28.3±(7.78) | 0.193 | 0.003* |
| Sex | Male | 15 (100) | 64 (95.5) | 0.697 | 1,000 |
| | Female | 0 (0) | 3 (4.5) | | |
| Duration of education (years) | (mean ± SD) | 10.6±(2.59) | 10.6±(2.59) | -0.156 | 0.877 |
| Marital status (n, %) | Single | 12 (80) | 44 (64.7) | 2.485 | 0.289 |
| | Married | 3 (20) | 23 (34.3) | | |
| Occupation n (%) | Inoccupied | 11 (73.3) | 20 (29.9) | 9.953 | 0.007* |
| | Occupied | 4(26.7) | 47 (70.1) | | |
| Age at first substance use | (mean±SD) | 16.13±1.55 | 17.55±4.59 | -1.177 | 0.243 |
| Lifetime legal problems n (%) | No | 11 (73.3) | 28(41.8) | 4.889 | 0.044* |
| | Yes | 4 (26.7) | 39 (58.2) | | |
| Number of hospitalizations | (mean±SD) | 1.00±1.25 | 1.30±1.73 | -0.630 | 0.530 |
| | | 16.13±1.55 | 17.55±4.59 | -1.177 | 0.243 |
| Time of SUD diagnosis (in age) | (mean±SD) | 19.20±3.61 | 22.87±6.08 | -2.242 | 0.028* |
| Remission (n,%) | Yes | 8 (53.3) | 32 (47.8) | 0.152 | 0.779 |
| | No | 7 (46.7) | 35 (52.2) | | |
| Drop out n (%) | Yes | 5 (33.3) | 24 (35.8) | 0.033 | 1.000 |
| | No | 10 (18.9) | 43 (64.2) | | |
| Adult ADD/ADHD subscales (mean ± SD) | Total score | 70.80±19.38 | 72.13±22.87 | -0.209 | 0.835 |
| | Attention deficit | 13.00±6.08 | 13.03±5.54 | -0.019 | 0.985 |
| | Hyperactivity/Impulsivity | 12.07±5.27 | 14.61±6.11 | -1.492 | 0.140 |
| | Related features | 45.07±13.28 | 44.58±14.05 | 0.122 | 0.903 |

* Statistically significance level is <0.05

**Table 3:** Association of ADHD comorbidity and preference of the substance abused

| | ADHD (+) (n=82) | ADHD (-) (n=313) | t/ $\chi$2 | p |
|---|---|---|---|---|
| Alcohol use disorder (n, %) | 12 (14.6) | 99 (31.6) | 31.075 | 0.000* |
| Cannabis use disorder (n, %) | 39 (47.6) | 72 (23,0) | | |
| Heroin use disorder (n, %) | 2 (2.4) | 14 (4.5) | | |
| Cocaine use disorder (n, %) | 7 (8.5) | 7 (2.2) | | |
| Polisubstance use disorder (n, %) | 22 (26.8) | 121 (38.7) | | |

* Statistically significance level is <0.05

overall prevalence of ADHD among those with a SUD has been found 23%.

Although ADHD is a well-known disorder by child psychiatrists, adult ADHD is not well-known and can be underdiagnosed and undertreated in clinical practices (Buitelaar, 2001). An important reason for missed diagnosis of ADHD among adults is alterations in symptomatology of the disorder. Another factor is comorbid psychiatric disorders such as substance use disorder which is not rare and also can mimic or mask the diagnosis of ADHD (Wender et al., 2001; Wilens & Upadhyaya, 2007).

Furthermore, unrecognized ADHD symptoms may be consequences of poor treatment in the comorbid disorders. It has been stated that SUD patients are more likely to have a previous or current diagnosis of ADHD. Screening for adult ADHD is not a routine practice in many clinical conditions (McAweeney et al., 2009). However, in this study, 82 patients had ADHD comorbidity and only 15 of them were diagnosed with ADHD prior to their diagnosis of substance use disorder. The remaining patients had their ADHD diagnosis after admission due to alcohol/substance use disorder.

When the sociodemographic and clinical data of the groups with or without ADHD comorbidity were examined, there was no significant difference in the age of first substance use, but patients with ADHD comorbidity had an attempt to have a treatment for substance use disorder at an earlier age. This may suggest that, in the presence of ADHD, symptoms and problems according to substance use may be more severe and the progression of substance use may be faster. Also parental awareness might be increased with presence of ADHD. Thus, the need for treatment occurs at an early age. In fact, the study of Wilens (2004), verified this explanation.

In our study, prevalence of remission was lower in the group without ADHD comorbidity. This finding is not supported by the literature. Wilens (2004) reported that the remission rate was around 80% in SUD either with or without ADHD comorbidity. This contradictory finding may be due to the fact that, in our sample most of the ADHD diagnosed patients were treatment naive for ADHD, and subsequent treatment was given immediately after the admission. In our study, better remission rates among individuals with ADHD may be associated with effects of pharmacological treatment of ADHD. Therefore by virtue of treating their ADHD we might have provided a protective effect in terms of abstinence. Muld et al. (2015) indicated that pharmacological treatment of ADHD may improve the long-term outcomes of individuals with SUD and comorbid ADHD. Initiation of pharmacological treatment to improve daily functioning and facilitate a treatment after stabilization of SUD may decrease the risk for relapse and may ensure the recovery through increasing motivation and a well-structured treatment compliance. Existence of this putative effect needs further verification through studies with prospective designs with treatment and control outputs for ADHD.

The groups with or without an ADHD comorbidity were compared in terms of preference among substances that have abused. Some studies have reported that individuals with ADHD use mixed substances more prevalent compared to individuals without ADHD. It has been proposed that individuals with ADHD prefer stimulants due to the relieving effects on symptoms of ADHD (Lee et al., 2011). Cannabis and derivatives have been preferred to be used more prevalently in the group with ADHD, whereas alcohol or polysubstance use have seen in the group without ADHD more often. This finding is not surprising, when we consider that participants with ADHD comorbidity may be more impulsive and have higher risk taking behaviors. On the other hand, higher rates of cocaine dependence in ADHD group suggest that cocaine might be used as a self-medication in this group. Another important finding was prevalent lifetime legal problems in the group whose diagnosis of substance abuse/dependence was prior to the ADHD diagnosis. This finding is supported by the findings of Goksøyr and Nøttestad (2008). This suggests that early diagnosis and treatment of ADHD may prevent legal issues in individuals with substance use disorder.

All treatment seeking SUD patients should be screened for ADHD and, after confirmed diagnosis they should have a treatment for ADHD. Thus the current literature indicates poor prognosis of patients with SUD and comorbid ADHD.

## 5. Conclusion

In conclusion, we found that in the majority of the participants with ADHD had their diagnosis after the substance use problems had developed. This finding suggests that ADHD can be underdiagnosed in adults and we should be aware of this diagnosis. At the same time, a delayed ADHD diagnosis may increase the risk of legal issues. In addition, substance preference can differ between the patients with or without ADHD comorbidity in patients with SUD.

Limitations of this study include retrospective design, insufficient number of female patients, and lack of severity scales for addiction. Further studies should be focused on the effect of ADHD on severity of addiction. Prospective, large-scaled, comparative studies should be conducted about this comorbidity.

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JNBS 2015 Published by Üsküdar University www.jnbs.org

ORIGINAL ARTICLE

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1437481824

**Article history:**
Received 21 June 2015
Received in revised form 3 September 2015
Accepted 9 September 2015

# THE COMPARISON BETWEEN PERSONALITY CHARACTERISTICS AND FAMILY RELATIONS OF THE SUBJECTS WITH NEUROTIC LEVEL OF PERSONALITY ORGANIZATION WITH CONTROL GROUP

## NEVROTİK ORGANİZASYONLU BİREYLERİN KİŞİLİK ÖZELLİKLERİNİN VE AİLE İLİŞKİLERİNİN KONTROL GRUBUNA GÖRE KIYASLANMASI

Deniz Karayün[1], Tonguç Demir Berkol[*2], Habib Erensoy[3], Ebru Kırlı[4], Serkan Islam[5], Doğan Şahin[6]

### Abstract

**Studies to explain neurotic personality organization is no more. Studies emphasize the early family relationships are important in formation of this structure. Our study aims to assess personality traits and family relations of individuals with neurotic personality organization. 31 patients assessed in neurotic personality organization according to SCID-I and SCID-II followed by social psychiatry unit (Structured Clinical Interview for DSM Disorders), 31 control groups not taking diagnostic in the same tests were included in study. Socio-demographic data form was filled by interviewer, Beck Depression Inventory, MMPI (Minnesota Multiphasic Personality Inventory), State-Trait Anxiety Inventory, Family Assessment Scale, Sheehan Disability Scale by the participants. Control group was created from, of volunteers, subjects not taking any psychiatric diagnosis. Compared to neurotic patient group with control group; Shehan Disability Scale for Beck Depression Inventory scores; Family Assessment Scale for social life and family environment, business subscale and household responsibilities, for State-Trait Anxiety Inventory; hypochondria, depression, hysteria, and social introversion subscales for problem solving and behavior control subscale scores between groups and Minnesota Multiphasic Personality Inventory. Neurotic group was taking significantly diagnosis compared to control group for depressive disorder, anxiety disorders and avoidant personality disorder. Considered that avoidant personality structuring of neurotic individuals are at the forefront, the secondary anxiety and depressive symptoms progress. Said all these processes impair domestic problem-solving, behavior control skills of these individuals. Supports this process that the average score of neurotic patients are higher than control group for hypochondria, depression, hysteria, and social introversion subscales as results of MMPI.**

**Keywords:** Neurotic organization, personality characteristics, family interaction.

### *Özet*

***Çalışmamız nevrotik kişilik organizasyonu olan bireylerin kişilik özellikleri ve aile ilişkilerini değerlendirmeyi hedeflemektedir. Çalışmaya, sosyal psikyatri biriminden takipli SCID-I (Structured clinical interview for DSM disorders) ve SCID-II' ye göre nevrotik kişilik örgütlenmesi içinde değerlendirilen 31 hasta ve 31 kontrol gurubu alındı. Kontrol grubu rastlantısal bir şekilde, gönüllüler arasından, psikiyatrik açıdan herhangi bir tanı almayan deneklerden oluşturuldu. Sosyodemografik Veri Formu görüşmeci tarafından, Beck Depresyon Ölçeği, MMPI (Minnesota Multiphasic Personality Inventory), Durumluk-Sürekli kaygı Envanteri, Aile Değerlendirme Ölçeği, Sheehan Yeti Yitimi Ölçeği çalışmaya katılanlar tarafından doldurduldu. Nevrotik hasta gurubunun kontrol gurubuna göre; Beck Depresyon Ölçeği puanları açısından, Shehan Yeti Yitimi Ölçeğinin; sosyal yaşam ve aile ortamı, iş alt ölçeği ve evdeki sorumluluklar açısından, Durumluk-Sürekli Kaygı Envanteri açısından, Aile Değerlendirme Ölçeğinin; gruplar arasında problem çözme ve davranış kontrolü alt ölçekleri ve Minnesota Çok Yönlü Kişilik Envanteri açısından; hipokondri, depresyon, histeri ve sosyal içe dönüklük alt ölçekleri anlamı bulundu. Çalışmada nevrotik grup en çok depresif bozukluklar, anksiyete bozuklukları ve kaçıngan kişilik bozukluğu açısından kontrol grubuna göre anlamlı tanı alıyordu. Nevrotik bireylerin kaçıngan kişilik yapılanmalarının daha ön planda olduğu, buna sekonder anksiyete ve depresif semptomlarının geliştiği ve bu nedenle bu bireylerin aile içi problem çözme ve davranış kontrolü yetilerinin bozduğu söylenebilir. Yine MMPI sonuçları olarak hipokondri, depresyon, histeri ve sosyal içe dönüklük alt ölçekleri açısından nevrotik hasta grubunun ortalama puanları kontrol grubundan anlamlı olarak yüksek olması bu süreci desteklemektedir.***

***Anahtar Kelimeler:*** *Nevrotik organizasyon, kişilik özellikleri, aile ilişkileri*

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THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

JNBS 2015 Published by Üsküdar University www.jnbs.org

## 1. Introduction

Mental structure according to the dynamic theory; can be seen in three different ways, as psychotic organization, borderline personality organization and neurotic personality organization. There are not much studies conducted to explain neurotic and borderline personality organization. The studies emphasize on the formation of these structures that early family relationships are of great importance. According to Kernberg spiritual organization can be seen in three ways (Kernberg, 1997), these are; Neurotic personality organization, borderline personality organization, psychotic personality organization.

According to Kernberg, the distinction between these organizations is performed based on three qualities including identity integration, defense mechanisms, and reality testing

In the neurotic personality organization; it is distinguished from other personality organization with being full of identity integration, being high level defense mechanisms and being full of reality testing. A sufficient anxiety tolerance, impulse control and sublimation capacity is observed in neurotic organization.

All self-image in the neurotic structure (both good and bad ones) is integrated to a comprehensive self and also "good" and "bad" image of others is integrated to the concept of a comprehensive others. People have a solid sense of self and the capacity to thoroughly understand others. The capacity that Neurotic person has to live in ''all'' object relations, reflects the integration of the contrasting properties related to both its own and the others.

In the neurotic person, ego defense organization generates advanced or high level defense mechanisms such as reaction formation, isolation, making-breaking, intellectualization and rationalization especially repression. Urges not approved through these defense mechanisms are removed from the conscious ego and thus the ego would be protected from intrapsychic conflicts (Kernberg, 1997).

According to Hornet, neurosis; does not completely separate from the community generally people living within a certain community, and is the behavioral disorders affecting adversely people's health, efficiency and effectiveness. Neurosis arises from a socio-psychic conflict; and the disorders and the conflicts in human relations. They are important determinants socio-cultural factors in the formation of neurosis for which human relationships vary according to specific communities and cultures (Horney, 1993).

Neurosis is a mental disorder that the basic disorder is a symptom or group of symptoms afflicting people. These symptoms are defined as unacceptable by person and foreign ego (ego-dystonic); reality testing is largely preserved. Behavior does not create significant impairment in social dimensions. The disorder is more than just a temporary react against the stress factors and shows a chronic and recurrent course to the extent that it is not treated. (Kaplan&Sadock, 2007).

## 2. Material and Methods

The Study was conducted Istanbul University Faculty of Medicine Department of Psychiatry in Social Psychiatry Unit.

31 patients followed by social psychiatry unit and evaluated in the neurotic personality organization according to SCID-I (Structured clinical interview for DSM-III-R) and SCID-II were included in the study. In addition, 31 healthy controls attempted to be compatible with the patient group in terms of age, gender and education were included in the study. In order to determine the healthy control group, SCID-I and SCID-II tests were applied to this person. The control group did not receive any diagnostic from these tests. Thus, 31 healthy control groups were created.

After people were informed about the study and their written approvals were obtained, two interviews were planned with people in the patient and control groups. During the first interview, Sociodemographic data form by the interviewer and Beck Depression Scale, MMPI (Minnesota Multiphasic Personality Inventory), State- Trait Anxiety Inventory, Family Assessment Scale, Sheehan Disability Scale were filled by the study participants. At the first interview, SCID-I form was given after applying SCID-II and at the second interview, SCID-II was performed.

It was defined as inclusion criteria in patients with the condition of being at least primary school graduates, being at least 18 years, responding to the tests to be applied, taking diagnosis of SCID-I in the neurotic personality organization. The exclusion criteria; was determined as taking diagnosis of SCID-II (except for cluster C) alcohol, substance abuse or addiction, bipolar disorder, psychotic disorders, depressive disorders other than depressive disorders developing depending on neurotic conflicts from diagnosis of SCID, psychiatric disorders due to general medical condition or substance use. The control group was created of subjects without taking any psychiatric diagnosis among from volunteers in a random way. It was tried to be consistent in terms of age, sex and education with patient group.

The obtained data was entered into the computer by using SPSS 11.0 for Windows program, Kolmogorov Smirnov test was used to determine the distribution of the variables and normally distributed variables were evaluated using in dependent t-test while Mann Whitney U test was used in evaluation of the abnormally distributed variables. The qualitative data were compared using Yates Continuity Correction Test. There results were evaluated by accepted significance level of $p<0,05$.

All participants gave a written informed consent and the Local Ethics Committee approval was obtained for the study.

The tests we used in this study;

***2.1. SCID-I:*** According to DSM-III-R classification is a method of the structured interviews applied individually to diagnose on 1st axis (Spitzer et al., 1987). Validity and reliability studies were conducted in Turkey (Sorias et al., 1988).

***2.2. SCID-II;*** is personality disorder screening test structured according to DSM-III-R consisting of 120 questions and conduct disorder additional section (Spitzer et al., 1990). The validity and reliability studies were conducted in Turkey (Sorias, 1990).

***2.3. Socio-demographic Data Form;*** is the version prepared by Istanbul University, Istanbul Faculty of Medicine, Department of Psychiatry, Social Psychiatry Service Team and revised by being shortened Social Psychiatry Service Application Evaluation Form. It was administered by an interviewer.

***2.4. State-Trait Anxiety Inventory (STAI);*** was developed to determine state and trait anxiety levels (Spielberger et al., 1970). STAI is a self-assessment questionnaire containing two scales composed of a total of 40 articles. The reliability and validity studies were conducted in Turkey (Öner, 1994) It can be considered that anxiety level has exceeded the normal limits on the values of 60 or above.

***2.5. Beck Depression Scale;*** is a self-assessment questionnaire used to measure emotional, somatic, cognitive, and motivational symptoms seen in depression (Beck et al., 1961). It was stated that the cut-off point of the scale is 17 in reliability and validity article for Turkish. The adaptation and validity and reliability of the scale was made in Turkey (Tegin, 1980).

***2.6. Family Assessment Scale (FAS);*** This scale has been defined to distinguish healthy and unhealthy the structural and organizational features of the family and the interaction between family members. The validity and reliability study of the scale was conducted in our country. (Bulut, 1990).

***2.7. Shehan Disability Scale (SDS);*** a scale developed to measure the life quality (Leon et al., 1995). Disability is measured with three items. (work, social life and leisure pursuits, family life and household responsibilities). In each item, 0-10 [no [0] light [1, 2, 3], medium [4, 5, 6], evident [7, 8, 9] and excessive [10]) assessment point is given. Total scores range varies between 0-30.

***2.8. MMPI (Minnesota Multiphasic Personality Inventory);*** was used for the first time in 1943, created by the University of Minnesota. It is an objective personality inventory developed by Psychologist Stark R. Hathawey and Neuropsychiatrist J. Charnley Mc Kinley. Turkish adaptation and standardization was made. (Savaşır, 1981). Profiles were rearranged according to Turkish standards and neurotic and psychotic patient norm profiles were performed as well as the normal male and female profiles by making the validity research on psychiatric patients.

## 3. Results

The ages of 62 people included in the study (31 patients and 31 Control Group) were between 18 and 43. The mean age of the control group was 25.59 and the mean age of the patient group was 26.35. The average number of siblings in the patient group was 2.61. The average number of siblings in the control group 3.90 ± 2.28 was found statistically significantly higher than the study group 2.61±1.05. The average place in sibling order of the patient group was 1.84. The average place in sibling order of the control group was 2.58. There was a significant difference between groups (see Table 1).

**Table 1:**

| | Neurotic Group(N=31) | Control Group(N=31) | P |
|---|---|---|---|
| **Sociodemographic data** | | | |
| Gender (Female) | 21 (67,70%) | 20 (64,52%) | [a]0,998 |
| Age | 26,35±7,16 | 26,39±6,06 | [b]0,981 |
| **Education level** | | | |
| Uneducated | 0 | 0 | |
| Primary-secondary school/High school | 22 (71,00%) | 20 (64,52%) | |
| University | 9 (29,00%) | 11 (35,48%) | [a]0,785 |
| **Marital status** | | | |
| Single | 22 (71,00%) | 25 (80,60%) | [a]0,554 |
| Married/shacking | 9 (29,00%) | 6 (19,40%) | |
| Mean number of siblings | 2,61±1,05 | 3,90±2,28 | [c]0,005 |
| Mean birth order among siblings | 1,84±0,89 | 2,58±1,80 | [c]0,044 |

[a]YatesContinuity Correction Test
[b]Independent-t Test
[c]MannWhitney U Test

In terms of SCID-I and SCID-II features, there were significant differences in terms of whether the current and past major depressive episodes, panic disorder (agoraphobia or without agoraphobia), social phobia, anxiety disorder not otherwise specified (NOS), undifferentiated somatoform disorder, avoidant personality disorder, any SCID-I or SCID-II diagnosis were taken between patient and control group.

Between women of both groups; there were significant differences in terms of whether the current and past major depressive episodes, undifferentiated somatoform disorder, avoidant personality disorder, or any SCID-I, SCID-II diagnosis were taken.

**Table 2:**

| | Neurotic Group (N=31) | Control Group (N=31) |
|---|---|---|
| **SCID-I** | | |
| Between groups; current and past | | |
| M. Depressive episode (current) | 7 | 0 |
| M. Depressive episode (past) | 16 | 0 |
| Panic disorder | 6 | 0 |
| Social phobia | 6 | 0 |
| Anxiety disorder NOS | 7 | 0 |
| Undifferentiated somatoform disorder | 6 | 0 |
| Whether diagnosed any SCID-I disorder | 31 | 0 |
| Between female subjects of both groups; current and past | | |
| M. Depressive episode (current) | 6 | 0 |
| M. Depressive episode (past) | 10 | 0 |
| Undifferentiated somatoform disorder | 6 | 0 |
| Whether there was any diagnosis of SCID-II | 21 | 0 |
| Between male subjects of both groups; past | | |
| M.depressive episode (past) | 6 | 0 |
| Whether diagnosed any SCID-I disorder | 10 | 0 |
| **SCID-II** Between groups; current and past | | |
| Avoidant personality disorder | 7 | 0 |
| Between female subjects of both groups; current and past | | |
| Avoidant personality disorder | 5 | 0 |

Between men of both groups; there were significant differences in terms of whether the current and past major depressive episodes, any SCID-I, SCID-II diagnosis were taken.

Statistic analysis was not made in these parameters, because it was necessary that these diseases were not available in the control group. Therefore we only specified the differences in the patient group.

In terms of Beck depression scale, the average score of the patient group was 14.45 (indicates mild depression) and it were statistically significantly higher than the control group 4.94. (points to a value below major depression).

Compared to female patients and control group: an average score of female patients in the study group; 13.95, was statistically significantly higher than the average score of female in the control group 4.04.

Compared to male patients and control group: an average score of male patients in the patient group; 15.50, was statistically significantly higher than the average score of male in the control group 6.80.

In terms of Sheehan disability scale, the average of SDS- business subscales the patient group, the average of SDS-social life subscale, the average of SDS- family atmosphere and of the household responsibilities subscale and the total average scores were statistically significantly higher than the control group.

The average of SDS-business sub-scale of the female patient group, the average of SDS-social life subscale, the average of SDS-family atmosphere and household responsibilities subscale, SDS total average scores were statistically significantly higher than the female control group.

The average of SDS-business sub-scale of the male patient group, the average of SDS-social life subscale, the average of SDS-family atmosphere and household responsibilities subscale, SDS total average scores were statistically significantly higher than the male control group.

In terms of trait anxiety inventory, STAI- trait anxiety scores of the patient group was statistically significantly higher than the control group. Female and male STAI-Trait anxiety scores of the patient group were statistically significantly higher than the control group.

In terms of family assessment scale, problem-solving subscale of the patient group was significantly lower than the control group; the control behavior scale scores were significantly higher. While the female problem-solving subscale scores of the patient group was statistically identical than the control group, female behavior control scale scores of the patient group was statistically significantly higher than the control group.

While the male behavior control scale scores of the patient group was statistically identical than the control group, male problem-solving subscale scores of the patient group was statistically lower than the control group.

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**Table 3:**

| | Neurotic Group(N=31) | Control Group(N=31) | P |
|---|---|---|---|
| **Beck depression inventory** | | | |
| Mean scores | 14,45±9,85 | 4,94±5,12 | [c]0001 |
| In female subjects | 13,95±10,08 | 4,09±4,21 | [c]0,001 |
| In male subjects | 15,50±9,68 | 6,80±6,51 | [c]0,001 |
| **Sheehan disability scale** Betweengroups | | | |
| Mean scores of work subscale | 3,90±3,13 | 0,81±1,35 | [c]0,0001 |
| Mean scores of social life subscale | 4,41±3,38 | 1,00±1,67 | [c]0,0001 |
| Mean scores of family life and home responsibilities subscales | 3,65±3,14 | 0,84±1,63 | [c]0,0001 |
| Mean scores of whole subscales and total scores | 11,71±8,54 | 2,65±4,11 | [c]0,0001 |
| Between female patients | | | |
| Mean scores of work subscale in female subjects | 3,29±3,2 | 0,67±1,19 | [c]0,0001 |
| Mean scores of social life subscale in female subjects | 3,48±3,34 | 1,14±1,85 | [c]0,001 |
| Mean scores of family life and home responsibilities subscales in female subjects | 2,90±3,06 | 0,67±1,19 | [c]0,004 |
| Mean scores of all subscales and total scores in female subjects | 9,67±7,34 | 2,48±4,13 | [c]0,0001 |
| Between male patients | | | |
| Mean scores of work subscale in male subjects | 5,20±2,44 | 1,10±1,66 | [c]0,0001 |
| Mean scores of social life subscale in male subjects | 5,60±3,16 | 0,70±1,25 | [c]0,0001 |
| Mean scores of family life and home responsibilities subscales in male subjects | 5,20±2,86 | 1,20±1,93 | [c]0,0001 |
| Mean scores of all subscales and total scores in male subjects | 16,00±7,62 | 3,00±4,26 | [c]0,0001 |
| **State-Trait and Continuous anxiety inventory** | | | |
| Mean scores (continuous anxiety scale) | 46,26±14,04 | 36,77±10,53 | [c]0,003 |
| Mean female scores (continuous anxiety scale) | 44,24±14,74 | 36,00±7,49 | [c]0,007 |
| Mean male scores (continuous anxiety scale) | 50,50±12,03 | 38,40±9,57 | [c]0,0001 |
| **Family Assessment Scale** | | | |
| Problem solving subscale between groups | 1,73±0,57 | 2,06±0,48 | [c]0,016 |
| Behavior control subscale between groups | 2,09±0,32 | 1,85±0,29 | [c]0,010 |
| Behavior control subscale between female subjects | 2,07±0,37 | 1,85±0,31 | [c]0,013 |
| Problem solving subscale between male subjects | 1,67±0,76 | 2,25±0,35 | [c]0,003 |

[b]Independent-t Test [c]MannWhitney U Test

In terms of Minnesota Multiphasic Personality Inventory, Hs-hypochondria, D-depression, Hy-hysteria, Si-social introversion subscale scores of the patient group were statistically significantly higher than the control group. K-advocacy subscale score was statistically significantly lower than the control group.

**Table 4:**

| Interms of Minnesota multiphasic personality inventory | Neurotic Group(N=31) | Control Group(N=31) | P |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| K-defensiveness | 50,03±9,36 | 56,81±14,01 | [b]0,028 |
| Hs-hypochondriasis | 57,26±8,48 | 48,90±8,07 | [b]0,002 |
| D-depression | 58,45±11,54 | 48,35±8,22 | [b]0,002 |
| Hy-hysteria | 58,45±10,28 | 52,52±7,73 | [b]0,013 |
| Si-social introversion | 54,81±12,92 | 44,84±9,62 | [b]0,001 |
| Between female groups | | | |
| D-depression | 56,05±10,02 | 46,90±6,95 | [b]0,0001 |

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| | | | |
|---|---|---|---|
| Hs-hypochondriasis | 57,24±7,95 | 49,19±7,15 | [b]0,0001 |
| Si-social introversion | 52,00±13,46 | 42,43±8,68 | [b]0,001 |
| Between male groups | | | |
| K-defensiveness | 45,40±8,26 | 54,00±13,30 | [b]0,003 |
| D-depression | 63,50±13,41 | 51,40±10,12 | [b]0,002 |
| Si-social introversion | 60,70±9,86 | 49,90±9,94 | [b]0,0001 |

[b]Independent-t Test

D-depression, Hs-hypochondria and Si-social introversion scores of female patient group were significantly higher than the female control group.

D-depression, Hs-hypochondria and Si-social introversion subscale scores of male patient group were significantly higher than the female control group. K-advocacy subscale score was statistically significantly lower than the control group.

## 4. Discussion

There was no statistically significant difference between groups in terms of socio-demographic characteristics; it was an indicative that a comparison of these two groups was balanced.

There was no significant difference between the two groups in terms of averages of age. The averages of age were appropriate for the ages that psychiatric disorders were more seen. (Kaplan&Sadock, 2007). The ratio of male and female was 3/1 in the group. These data were close to previous studies (Pedersen et al., 2014, Stevenson et al., 2011).

In terms of marital status, the number of singles in both groups was greater, but there was no significant difference between the two groups. Although it is found that psychiatric disorders are lower than divorced and grass widow in married people in the studies on the relationship of psychiatric disorders with marital status, the number of married people in general psychiatric population is greater. (Kaplan&Sadock, 2007).

Considering the distribution of psychiatric disorders in terms of SCID I, it was observed that neurotic group is mostly depressive disorder, anxiety disorder and undifferentiated somatoform disorder. There was no undifferentiated somatoform disorder in male neurotic group. It is supported in the studies on the subject that the majority of patients with undifferentiated somatoform disorder were of female, and stressful life events would be a risk factor in the emergence of the disease (Kaplan&Sadock, 2007, Pribor et al., 1993).

The prevalence of personality disorders were found between 3.9% 22.3% by different studies (Kaplan&Sadock, 2007, Zimmerman et al., 2008, Dereboy et al., 2014, Coid et al., 2006) Cluster C personality disorders also known as neurotic cluster are the most common disorders (1 in 10 people)in the general population (Torgersen et al., 2001).

In terms of SCID-II, the neurotic group significantly was taking high diagnosis compared to the control group in terms of avoidant personality disorder. Subjects in the control group consisted of those not receive a diagnosis of personality disorder and therefore there was no one taking diagnosis.

Secondary anxiety (particularly social phobia), and depressive symptoms improvements to the avoidant personality disorder basic of neurotic patients group is an expected finding for the patient profiles of avoidant personality disorder (Kaplan&Sadock, 2007). Also it is known that neurotic patients express their unconscious conflicts through depressive anxious and somatic ways. (Kaplan&Sadock, 2007).

In terms of Beck Depression Scale, the average scores were 4.94 in the control group and 14.45 in the neurosis group. The neurotic group scores were significantly higher than the control group. Reason for the high level of neurotic group score was that almost all of them were probably in an active Axis I disorder and avoidant personality disorder were more frequent. There are also evidence that people with high neuroticism feel more lonely themselves. (Iacoviello et al, 2007). In general, depression combination with psychiatric disorders is a common frequent. (Tümkaya et al., 2005).

Cluster B personality disorders were associated with the severity of depression and Cluster C personality disorders with the chronicity of depression in a depression study and it was said that those having cluster C personality disorders were more anxious.(Levin&Stokes, 1986).

In terms of State-Trait Anxiety Inventory, the average of neurotic patients was significantly higher than the control group. It was an expected finding in terms of our present study. We indicated for SCID I in our study, the neurotic group showed mostly the significance for depressive disorders and anxiety disorders. (1 axis) anxiety disorders or anxiety semptoms are a finding frequently observed in psychiatric disorders, (Kessler et al., 2005) and it was reported in several studies that depression and anxiety disorders were most frequently observed diagnoses. (Zimmerman et al., 2008, Kessler et al., 2005).

In terms of Sheehan disability scale, the average of neurosis group was significantly higher than the control group. The lowest average in terms of family life and household responsibilities was in the control group. It was seen that the disabilities were in middle level in male neurotic group while there were mild disabilities in general neurotic group and female neurotic group in Sheehan disability. In our study, Beck depression scores had been significantly higher in the neurosis group, this may be a condition that affects the functionality. In a study conducted, it was observed that there was an important functional loss in depressed patients (Kongsakon et al, 2005). Also, neurotic organizing patients were more evident compared to the control group at any diagnoses point in SCID-I, the reduction of functionality in psychiatric disorders is a known state. (Kırkpınar&Oral, 2012).

Considered the Family Assessment Scale, There is a direct correlation between the increase in unhealthiness with the rise of points in the family assessment scale. The control group was significantly than neurosis group in the items problem solving and problem solving among men between these scale groups. So especially problem solving ability of men and of the neurotic group was significantly lower than the control group. Considered avoidant personality disorder and anxiety and depressive features of the neurotic group, it is is understandable that the abilities to solve problems are low.

Considering the work done by FAD, the families where there are members with mental problems have been found unhealthy than controls. (Bulut, 1990). In this study problem solving and behavior control are unhealthy commonly seen in people with neurotic personality organization, problem-solving is indicative of insufficient, masked or transposed communication among the family members. Behavior control shows the inability to set standard and to provide the discipline to the behaviors of family members. Unhealthy function observed in these two areas can be considered support each other.

In terms of Minnesota Multiphasic Personality Inventory, any subscale did not exceed 70 points in both groups, when groups are compared to one another: The average score of neurotic patient group was significantly higher than the control group in terms of Hypochondriasis, depression, hysteria, and social introversion subscales. Hypochondria subscale indicates the somatic defense and the presence of somatic symptoms relation with psychological uneasy. In our study, somatoform disorders in neurotic patients have a high rate.

Being high of depression subscale was consistent with our study. Beck depression scores we mentioned earlier was significantly compared to the control group in the neurotic group. Obviously, the presence of social introverted personality characteristics was important for patients in these diagnostic groups. In the remark of MMPI, social introversion may point the presence of symptoms such as shyness, withdrawal of social relationships, self-humiliation, self-distrust, feelings of guilt, sensitivity to others' ideas, instability and pessimism. In our study, social introversion item of the MMPI results were extremely significant when compared to the control group with the neurotic group. In addition, in our study in line with this data, SCID-II avoidant personality disorder and SCID-I anxiety and depression features were significantly found in the neurotic people compared to the control group.

In our study, Hysteria subscale was significantly in the neurotic group compared to the control group. Hysteria subscale reflects the tendency to apply to physical symptoms due to escape from responsibility and problems, as known physical symptoms are common in neurotic patients. (Kaplan&Sadock, 2007).

As a result, it may be considered that avoidant personality structuring of neurotic individuals is more prominent and accordingly the secondary anxiety and depressive symptoms improve. It can be said that all of these processes impair disability of these individuals, domestic problem solving and behavior control abilities. Again, as a result of MMPI, the average scores of neurotic patient group in terms of hypochondriasis, depression, hysteria, and social introversion subscales are significantly higher than the control group and it supports this process.

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JNBS 2015 Published by Üsküdar University www.jnbs.org

ORIGINAL ARTICLE

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1433794984

**Article history:**
Received 14 June 2015
Received in revised form 2 September 2015
Accepted 7 September 2015

# AN INVESTIGATION OF NEURAL CORRELATES IN ADULTS WITH DEVELOPMENTAL DYSCALCULIA USING FMRI

## GELİŞİMSEL DİSKALKULİ SAHİBİ YETİŞKİNLERDE NÖRAL BAĞLANTILARIN FMRI İLE İNCELENMESİ

E. Seylan Şahin[*1]

### Abstract

**Developmental dyscalculia is a specific learning difficulty which reflects deficits in arithmetical skills. The cause behind this disorder is not known. Recent studies provide evidence in favor of believing that the disorder is somehow tied with specific brain regions' roles. These regions include the intraparietal sulcus (IPS), the angular gyrus (ANG) and the supramarginal gyrus (SMG) in developmental dyscalculia. The present study investigates the role of these regions in adults with developmental dyscalculia. Brain images were collected from 10 participants with developmental dyscalculia and 10 control participants using fMRI while conducting number comparison, multiplication and subtraction tasks. The results revealed the activation of the intraparietal sulcus during number comparison and the activation of both the angular gyrus, the supramarginal gyrus, and the intraparietal sulcus during calculation tasks. These results suggest that the IPS activation was not less than the developmental dyscalculia group than in the control group when conducting the number comparison task; and that there were activation in the ANG, SMG and IPS regions of the brain in participants' brains during both the multiplication and subtraction tasks.**

**Keywords:** cognitive neuroscience, developmental dyscalculia, fmri, angular gyrus, supramarginal gyrus, intraparietal sulcus.

### *Özet*

***Gelişimsel diskalkuli matematik yeteneğini etkileyen bir özel öğrenme güçlüğü formudur. Bu bozukluğa neden olan faktörler kesin olarak bilinememektedir. Son çalışmalar, diskalkulinin ortaya çıkmasında beyindeki spesifik bölgelerin etkili olabileceği yönünde kanıt ortaya koymaktadır. Bu beyin bölgeleri arasında; intraparyetal oluk, angular girus ve supramarjinal girus yer almaktadır. Bu çalışma, bu bölgelerin gelişimsel diskalkulideki rollerini araştırmaktadır. Çalışmaya 10 gelişimsel diskalkuli sahibi yetişkin, 10 da kontrol grubu olmak üzere 20 katılımcı dahil olmuştur. Katılımcılar sayı kıyaslama, toplama ve çıkarma işlemlerini yaparken fMRI ile beyin aktiviteleri görüntülenmiştir. Sayı kıyaslama esnasında intraparyetal olukta beyin aktivasyonu tespit edilmiştir. Toplama-çıkarma esnasında intraparyetal oluk, angular girus ve supramarjinal girusda beyin aktivasyonu tespit edilmiştir. Sayı kıyaslama esnasında IPS de gözlenen aktivasyon diskalkulik grupla kıyaslandığında kontrol grubunda daha az saptanmamıştır. Ayrıca, toplama-çıkarma esnasında da ANG, SMG ve IPS'de de aktivasyon gözlenmiştir.***

***Anahtar Kelimeler:*** *kognitif nörobilim, gelişimsel diskalkuli, fmri, angular girus, supramarjinal girus, intraparyetal oluk*



### Introduction

The term "Developmental Dyscalculia" refers to a specific learning difficulty which affects mathematical abilities and mathematical learning. Individuals with developmental dyscalculia may have difficulties in understanding simple number concepts, acquiring mathematical skills, and learning number facts and procedures (Hannell, 2013).

In recent years, there is an increasing agreement that developmental dyscalculia has a neuropsychological basis which is characterized by deficits in basic numerical skill; for instance, number comparison and number sense, such as to be able to calculate mathematical problems in your head and number fluency (Landerl, Bevan & Butterworth, 2004; Rubinsten & Henik , 2005; Butterworth, 2005; Gersten & Chard, 1999). Even research on developmental dyscalculia has increased recently, the causes of which are still not known. On the other hand, there are two different hypotheses which try to explain the cause of such deficits; the first suggests an abnormally developed specialized brain system and deficits in number sense (Butterworth, 1999; Dehaene et al., 2003; Aster and Shalev, 2007) while the second suggests general deficits in cognitive abilities (Geary, 1994).

According to Dehaene (2001), every person is born with number sense. This refers to an ability to quickly understand basic numerical concepts, the ability to approximate and manipulate numerical quantities, and the ability to acquire and represent numerical quantities. Further, it is suggested that a specific cerebral system which is located in the intraparietal cortex of both hemispheres is responsible for number sense and number processing. Especially, the intraparietal sulcus (IPS) has an importance for number

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processing, particularly for processing numerosity when arraying things (Butterworth, Varma, & Laurillard, 2011) and for number comparison (Kadosh et al., 2005). Due to early damage to their inferior parietal cortex, children with developmental dyscalculia might have defects in the number sense which results in their inability to grasp numbers intuitively (Butterworth, 2005). A great deal of research has supported this hypothesis by using a range of tasks (Hanich eet al., 2001; Jordan & Hanich, 2003; Landerl, Bevan, & Butterworth, 2004). In addition, neuropsychological studies conducted on patients with left parietal lesions as well as normal subjects support that calculation or number comparison tasks activated the horizontal segment of IPS (Cappelletti, Butterworth & Kopelman, 2001; Dehaene and Cohen 1997; Dehaene et al., 1999). Moreover, in their study, Molko et al. (2003), found out that, a number of comparison tasks caused the bilateral activation of the intraparietal sulcus.

On the other hand, the second hypothesis suggests a non-numerical explanation which focuses on general cognitive deficits, such as those with regards to to working memory (Geary, 1993; 1994). According to Geary (1993), children with developmental dyscalculia might have computational and memory-retrieval errors which might be related to their using working-memory resources. Indeed, working-memory might have a central role in developmental dyscalculia. This is evidenced in several studies, all of which indicate that working memory functions have an essential role in cognitive arithmetic in children and adults (De Rammelaere & Vandierendonck, 2001; LeFevre et al., 2005) as well as well as in children with developmental dyscalculia (Geary & Brown, 1991; Gray, 1991).

### *1.1. Neural Basis of Developmental Dyscalculia*

It has been found that the ability to understand and manipulate numerosities has a direct relationship with the parietal lobes, mainly with the IPS (Piazza et al., 2002; Dehaene et al., 2003; Castelli, Glaser, & Butterworth, 2006). This is because activation was detected in the parietal lobes, including the horizontal segment of the IPS when healthy adults were solving mathematical problems (Dehaene et al., 2003; van Eimeren et al., 2010). In addition, the superior parietal lobule (SPL), the angular gyrus (ANG) and the supramarginal gyrus (SMG) regions are the other brain regions that were found to have a relation with number processing and mathematical abilities (Grabner et al., 2009; Wu et al., 2009). The supramarginal gyrus (especially the left SMG) showed activation in the studies using a calculation task (Rivera et al., 2005); likewise, the SMG with ANG have been found to be activated in mental mathematic tasks (Rickard et al., 2000).

On the other hand, the results found from healthy adults have been found to be similar with those retrieved from children with developmental dyscalculia in terms of the relationship between IPS and numerical distance (Ansari, 2008). Neuroimaging studies have shown that the parietal cortices, including the IPR and SMG, have abnormal activity related with the number's size and difficult tasks (Molko et al., 2003; Rivera et al., 2002). Evidence in favor of IPS activation modulated by numerical distance was provided by the study by Price et al. (2007). According to the results of this study, non-symbolic number processing led to a stronger activation in the right IPS of the control group than in the children with developmental dyscalculia.

According to Kucian et al. (2006), arithmetical problems in children with developmental dyscalculia are related with defects in the parietal areas. Further, a significant blood flow increase in the prefrontal and parietal cortices, as well as bilateral activation in the ANG, were found during subtraction tasks (Roland & Friberg, 1985). Grabner et al. (2007) found a relation between brain activation in the left ANG and complex multiplication tasks in their study with adults who had lower and higher mathematical-numerical skills. Furthermore, Lee suggested that the left SMG and ANG were responsible for single digit multiplication facts.

The present study investigates the neural correlates of developmental dyscalculia in adults based on fMRI data. For this purpose, adults with developmental dyscalculia were scanned while conducting tasks testing number comparison, multiplication and subtraction. The aim was to examine the brain activations related to the tasks being tested for in adults with developmental dyscalculia and the differences between the developmental dyscalculia group and the controls. It was predicted that adults with developmental dyscalculia would show less brain activation than in the control group in the IPS with relation to the tasks that tested for number comparison, more activation than in the control group in the ANG and in the SMG during the tasks that tested for multiplication, and bilateral IPS activation during the tasks that tested for subtraction.

## 2. Methods

### *2.1. Participants*

Twenty adults aged between 19 and 36 (15 females and 5 males, mean age= 22.17, SD= 3.4, range= 19-36) voluntarily participated in this study. All subjects were undergraduate and postgraduate students from the University of York. All 20 subjects were both native speakers of English and right-handed. None of the subjects had any history of psychiatric or neurological illnesses.

All participants were assessed using behavioral tests including general cognitive ability (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), arithmetic skill (Wide Range Achievement Test 4; Wilkonson & Robertson, 2006), reading skill (Test of Word Reading Efficiency; Torgesen, Wagner, & Rashotte, 1999) and speed calculation tests in order to identify whether they had low arithmetic skills. Clinical diagnoses of the participants were not made by the investigators. After behavioral test section, brain image data was collected from all participants by using fMRI while they were having fMRI tasks.

10 of participants constituted the developmental dyscalculia group (6 females and 4 males, mean age= 21.79, SD= 1.7 years, range= 19-24). Participants met the present research criteria for developmental dyscalculia only if they had an IQ at or above 90, a Wide Range Achievement Test (WRAT) arithmetic score below 85, and

**Table 1:** Background variables for participants with developmental dyscalculia and controls

| | DD | | | Control | | | Effect Size | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *N*[a] | *Mean* | *SD* | *N*[a] | *t* | *p** |
| Age | 21.50 | 1.650 | 10 | 22.70 | 4.945 | 10 | | |
| Cognitive ability (IQ) | 115.10 | 9.608 | 10 | 125.80 | 8.664 | 10 | -2.615 | .018* |
| Sight Word Reading Efficiency (TOWRE) | 100.30 | 10.100 | 10 | 100.80 | 12.246 | 10 | -.100 | .922 |
| Phonemic Decoding Efficiency (TOWRE) | 110.20 | 8.817 | 10 | 107.40 | 13.501 | 10 | .549 | .590 |
| Reading (WRAT) | 113.30 | 7.675 | 10 | 113.30 | 6.413 | 10 | .000 | 1.000 |
| Spelling (WRAT) | 108.40 | 4.351 | 10 | 110.50 | 4.994 | 10 | -1.003 | .329 |
| Arithmetic (WRAT) | 86.30 | 3.020 | 10 | 110.20 | 7.983 | 10 | -8.855 | .000* |
| Handedness | 68.89 | 27.25 | 9 | 64.70 | 25.95 | 10 | .343 | .736 |

*Note:* DD= Developmental Dyscalculia, TOWRE = Test of Word Reading Efficiency. WRAT = Wide Range Achievement Test.
[a] Number of participants varies due to technical problems with participants' medical situations and experimenters' errors.
* Bonferroni-corrected significance level; $p < .05$, independent-samples t test, two-tailed.

a difference between their IQ and WRAT arithmetic scores of at least 10 points.

The other 10 participants constituted the control group (9 females and 1 male, mean age= 22.7 years, SD= 4.9 years). Control participants were matched as far as possible with regards to the IQ, age and gender of the experimental groups. Control participants met the present research criteria if they had an IQ at or above 90 and a WRAT arithmetic score of above 100.

### *2.2. Procedure*

Participants were tested usually during one—maximally two—sessions. All subjects were assessed in the Numerical Cognition Laboratory of the Psychology Department of the University of York. The tests were conducted in the following order: first, reading and arithmetic skills tests; second, handedness inventory; finally, general cognitive ability measurement.

### *2.3. fMRI Tasks*

The fMRI scanning part of the study consisted of a motor cortex localizer task, a number comparison task, a multiplication task and a subtraction task.

#### *2.3.1. Motor cortex localizer*

The paradigm which was used in the study was a finger-to-thumb opposition paradigm. The image of the task was shown to the participants on the screen during the scanning. The image included two hands with a red dot being projected on the fingers of the image. Participants were asked to touch their left or right thumb synchronously in correspondence with the finger on which the red light was being projected on. The stimuli included white hands placed on a black background.

#### *2.3.2. Number comparison*

The number comparison task consisted of white double-digit Arabic numbers (31-99, never 65; Arial, font size 60; number 65 presented in Arial, size 24) which were demonstrated centrally on a black screen one by one. Participants were required to determine whether the demonstrated number was smaller or larger than 65. This is called a distance effect and was used to compare a set of target numbers with a fixed standard number in order to reflect participants' reaction times (Zhang & Wang, 2005).

Participants pressed one of two response buttons so as to give their decisions; while the left index finger was to be used for smaller numbers, the right index finger was used for larger numbers. According to Aster & Shalev (2007), while making judgements about numbers, the left hand is quicker for smaller numbers and the right hand is faster for larger numbers; this is known as the "spatial numerical association of response codes" (SNARC) effect.

#### *2.3.3. The rationale behind the inter-stimulus interval (ISI) randomization:*

(Also applies to both multiplication and subtraction tasks)

The purpose of using the make_random_timings.py command from the AFNI suite was in order to choose stimulus timings within a particular block. For each set of parameters, 100 timing randomizations were applied. The stimulus block which had lengths of 75, 150, 240, 300, 450 and 600 seconds were assessed. While the ISI was jittered, the timing of the stimuli presentation remained stable.

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Several conditions were used, such as Multiplication/Subtraction correct (Mc, Sc), Multiplication/Subtraction incorrect (Mi, Si), Number Comparison Close (C)/Far (F) were used within a block. In order to assess the design matrix, a gamma convolution was used. Afterwards, custom scenarios were used in order to obtain the sets of randomizations from a single block and to combine them into the full experimental design using multiple blocks. The 3dDeconvolve command from AFNI was used for this purpose.

#### *2.3.4. Multiplication*

The multiplication block consisted of presenting a multiplication problem with single digit operands and a suggested response (e.g. 2 × 8 = 16) to participants. White digits (Arial, size 30) placed on a black background were used. The stimuli included fifty per cent incorrect answers (e.g. 2 × 8 = 14) and fifty per cent correct answers. Participants were asked to decide if the equation was solved correctly and respond by pressing one of two response buttons (right index finger for correct items, left index finger for incorrect items). Half of the incorrect equations were table-related (e.g. 2 × 8 = 14) while the other half were unrelated (e.g. 2 × 8 = 15).

#### *2.3.5. Subtraction*

The subtraction block consisted of presenting a subtraction problem with a suggested response (e.g. 16 – 9 = 7) to participants. White digits (Arial, size 30) placed on a black background were used. In the first part of the block, the stimuli included fifty per cent double digit equations ranging from 11 to 19 and presented first, and fifty per cent single digit equations ranging from 3 to 9 and presented second. The other half of the block consisted of fifty per cent double digit equations ranging from 52 to 91 and presented first, while the other fifty per cent were double digit equations ranging from 23 to 76 and presented second. The first half had a small problem size that could be solved by fact retrieval (e.g. 16 - 9 = 7) while the other half had a large problem size that needed to be calculated (e.g. 88 – 35 = 53). Participants were asked to decide if the equation was solved correctly and respond by pressing one of two response buttons (right index finger for correct items, left index finger for incorrect items).

#### *2.3.6. fMRI Procedure and Design*

Before the scanning session, there was a training period in which participants had a chance to exercise the tasks by receiving full instructions. In the training period, participants could see a shorter example of the tasks on a computer screen. They were asked to make decisions about the stimuli and respond by pressing response buttons on the keyboard quickly. This was an exact copy of the process that would take place during the scanning. After completing the training period, participants completed a motor cortex localizer task, a number comparison task, a multiplication task, and a subtraction task during the scanning period.

For all fMRI tasks, the Presentation 13.1 program was used in order to present and control the stimuli as well as acquiring reaction times (RTs). A mirror which was placed to the head coil helped participants to see the stimuli which was shown on a screen. Before each block, the upcoming task was announced on the screen. The fMRI scanning session consisted of two consecutive parts which took approximately 40 minutes for each and a 10 min break between these two parts. Each part included either a motor cortex localizer task or a number comparison task, two blocks of multiplication and two blocks of subtraction. The presentation order was randomized.

### *2.4. Data acquisition*

Imaging data were collected at the York Neuroimaging Centre (YNiC) using a 3 Tesla Signa HDx Excite MRI system (General Electric) with an eight channel phased array head coil (GE Signa Excite 3.0T, High Resolution Brain Array, MRI Devices Corp., Gainesville, FL). In order to reduce head movement, a foam insert was placed in the scanner.

The following functional imaging parameters were used to obtain the functional MR imaging in the present study: a T2*-weighted gradient echo EPI sequence (echo time (TE) = 34.3 ms, repetition time (TR) = 3 s, flip angle = 90°, field of view (FOV) =256 mm, matrix = 128 x 128). 38 para-axial slices (which were parallel to the corpus callosum), each with a thickness of 3.5 mm thickness, were obtained per volume with no inter-slice spacing. The voxel size of the images was 2 x 2 x 3.5 mm.

The following functional imaging parameters were used to obtain high resolution anatomical images in the present study: a T1-weighted sequence (TE = 3.6ms, TR = 9.0ms, flip angle=8°, FOV = 256mm, matrix = 256 x 256). The voxel size of the structural images was 1 x 1 x 1 mm.

### *2.5. Data Analysis*

#### *2.5.1. Behavioral Data*

Performance measures on accuracy and the RTs of the cognitive ability, reading skills, handedness and the arithmetic skills tests, the motor localizer, the number comparison, the multiplication and the subtraction tasks were analyzed using descriptive statistics firstly. Then, individual trials of each task were analyzed using independent t-tests for between-group differences. In addition, for each task, the effects of trial types (close/far, correct/incorrect, correct large & small/incorrect large & small) were analyzed using repeated measures analysis of variance (one-way within-subject ANOVA).

#### *2.5.2. fMRI Data*

Pre-processing and statistical analyses were carried out using FEAT (FMRI Expert Analysis Tool version 5.98) which is part of FSL (the software library of the Oxford Centre for Functional MRI of the Brain (FMRIB); www.fmrib.ox.ac.uk/fsl). At the first-level analysis, irst-level analysis, MCFLIRT (Jenkinson, 2002) was used in order to apply motion corrections. Pre-statistics processing

included slice-timing correction using Fourier-space time-series phase-shifting and non-brain removal using the BET Brain extraction tool, version 3.3 (Smith, 2002).

In order to smooth the images spatially, a Gaussian kernel of FWHM 5mm and a grand-mean intensity normalization of the entire 4D dataset with a single multiplicative factor were used. To take away the low frequency drifts, a high-pass temporal filter (Gaussian-weighted least-squares straight line fitting, with sigma of 25.0s for multiplication/subtraction and 30.0s for both motor cortex localizer and number comparison tasks) was used. FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson & Smith, 2001) was utilized in order to register high-resolution structural images of a standard brain (MNI 152).

During the second-level analysis, in order to perform group analysis for mixed-effects across participants, FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann, 2003; Woolrich, 2004) was used. Trials with inaccurate responses for Subtraction/Multiplication blocks were not analyzed.

Both single- and second-level analyses were done at single-subject-level and images were thresholded using clusters settled in Z> 2.3 and a corrected cluster significance threshold of p = 0.05.

The contrasts, as well as whole brain analyses of each contrast, were analyzed at single-subject-level. This was done in order to determine the brain areas involved in the mathematical processes.

## 3. Results

### *3.1. Number Comparison*

Four clusters were detected for participants with developmental dyscalculia and the controls in the close distance contrast (numerical distance to 65 was small, as mentioned in fMRI section), encompassing areas in the angular gyrus in the left hemisphere, intraparietal sulcus in the both hemisphere and in the superior frontal gyrus. Similarly, this activation pattern was identical for the far distance contrast (numerical distance to 65 was large, as mentioned in fMRI section); five clusters were detected encompassing areas in the angular gyrus in the left hemisphere and intraparietal sulcus in the left hemisphere (see Figure 1, Table 2). The IPS activation was stronger in the close distance contrast than in the far distance contrast and stronger in the left hemisphere than in the right hemisphere.

### *3.2. Multiplication*

Multiplication correct items activated the bilateral network of the brain regions, including the angular gyrus, supramarginal gyrus, neighboring areas of the intraparietal sulcus and also, the inferior frontal gyrus in the left hemisphere and the superior frontal gyrus (see Figure 2, Table 3). Similar activation patterns were observed when multiplication incorrect items were considered, with bilateral activation in the intraparietal sulcus, the angular gyrus, the supramarginal gyrus and also, the superior frontal gyrus and the inferior frontal gyrus in the left hemisphere (see Figure 2, Table 3). Activations were more extensive in the left hemisphere compared to the right in both tasks.

| | | | Peak Coordinates In MNI | | |
|---|---|---|---|---|---|
| *Brain areas* | *Voxels* | *Z-MAX* | *X (mm)* | *Y (mm)* | *Z (mm)* |
| Close | | | | | |
| Angular Gyrus | 1723 | 5.13 | -6 | 6 | 42 |
| IPS | 1158 | 5.04 | 42 | -46 | 38 |
| IPS | 11463 | 5.06 | -40 | -6 | 8 |
| Superior Frontal Gyrus | 2134 | 4.76 | 38 | 18 | 10 |
| Far | | | | | |
| Angular Gyrus | 3270 | 4.56 | -2 | -66 | -22 |
| Angular Gyrus | 2397 | 4.89 | -44 | -4 | 8 |
| Angular Gyrus | 1845 | 4.09 | 34 | -28 | 38 |
| IPS | 696 | 4.2 | 22 | 4 | 8 |
| IPS | 671 | 4.26 | -44 | -40 | 36 |

*Only first three peak activations of each contrast can be seen (the first three is close > far contrast, the second three is far > close contrast).
Z= 2.3

**Table 2:** Number comparison (close distance, far distance and close versus far contrasts), showing cluster index, number of voxels within each cluster, maximum z-score and peak cluster coordinates for the two groups.

**Table 3:** Number comparison (close distance, far distance and close versus far contrasts), showing cluster index, number of voxels within each cluster, maximum z-score and peak cluster coordinates for the two groups.

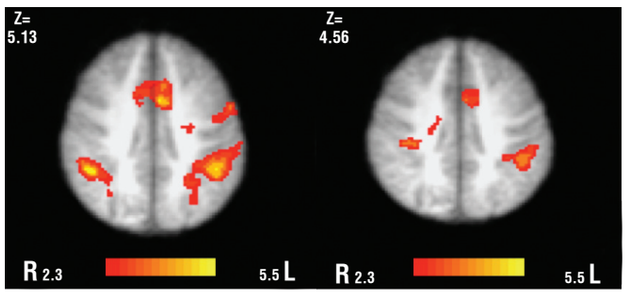


**Figure 1.** Brain activation in the close distance contrast (left image) and the far distance contrast (right image) in the number comparison task for participants with dyscalculia and the controls.

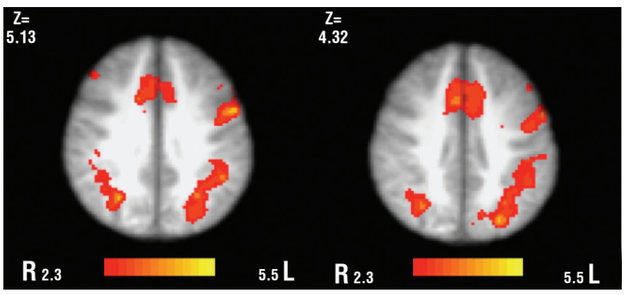


**Figure 2.** Brain activation in the incorrect item contrast (left image) and the correct item contrast (right image) in the multiplication task for participants with dyscalculia and the controls.

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| Brain areas | Voxels | Z-MAX | Peak Coordinates In MNI X (mm) | Y (mm) | Z (mm) |
|---|---|---|---|---|---|
| Correct | | | | | |
| Angular Gyrus | 8781 | 4.32 | -26 | 24 | 0 |
| Supramarginal Gyrus | 4290 | 4.58 | 44 | -86 | -12 |
| IPS | 7011 | 4.81 | -22 | -92 | -16 |
| Inferior Frontal Gyrus | 2883 | 4.46 | -48 | 24 | 20 |
| Incorrect | | | | | |
| IPS | 3273 | 5.1 | -32 | 26 | -4 |
| Angular Gyrus | 2227 | 4.56 | 32 | 20 | -4 |
| Supramarginal Gyrus | 6618 | 4.88 | 24 | -88 | -8 |
| Inferior Frontal Gyrus | 3743 | 5.09 | -46 | 20 | 24 |

Z= 2.3

### *3.3. Subtraction*

As with the multiplication task, subtraction task's correct items led to bilateral activation in the angular gyrus, the supramarginal gyrus, neighboring areas of the intraparietal sulcus and also, the superior frontal gyrus as well as the inferior frontal gyrus in the left hemisphere (see Figure 3, Table 4). A similar pattern of activation was observed when subtraction incorrect items were considered, with bilateral activation in the intraparietal sulcus, the angular gyrus, the supramarginal gyrus and also activation in the superior frontal gyrus and the inferior frontal gyrus (see Figure 3, Table 4). Likewise, activations were more extensive in the left hemisphere when compared to the right in both tasks.

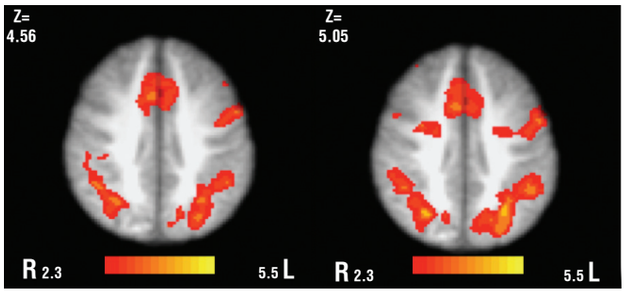


**Figure 3.** Brain activation in the correct item contrast (left image) and the incorrect item contrast (right image) in the subtraction task for participants with dyscalculia and the controls.

**Table 4:** Subtraction (correct and incorrect item contrasts), showing cluster index, number of voxels within each cluster, maximum z-score and peak cluster coordinates for the two groups.

| Brain areas | Voxels | Z-MAX | Peak Coordinates In MNI X (mm) | Y (mm) | Z (mm) |
|---|---|---|---|---|---|
| Correct | | | | | |
| Angular Gyrus | 3273 | 5.1 | -32 | 26 | -4 |
| Supramarginal Gyrus | 2127 | 4.56 | 32 | 20 | -4 |
| IPS | 3743 | 5.09 | -46 | 20 | 24 |
| Incorrect | | | | | |
| IPS | 29543 | 5.05 | -26 | 20 | 0 |
| Angular Gyrus | 2777 | 4.98 | 28 | -64 | 36 |
| Supramarginal Gyrus | 39996 | 5.48 | -24 | -92 | -16 |

Z= 2.3

## 4. Discussion

The present study examined the neural correlates in adults with developmental dyscalculia during number comparison and calculation (multiplication and subtraction) tasks. The results confirmed IPS, ANG and SMG activity in subjects when they exercised their mathematical skills. This supports previous studies' results (Grabner et al., 2009; Wu et al., 2009; Ansari, 2008).

We predicted that the IPS activation would be less in developmental dyscalculia during the number comparison task. The results support the role of the IPS during number comparison and agree with previous studies (Pesenti et al., 2000). However, there was no activation when the two groups were compared. It was found that close and far distance led to a similar activation pattern. However, the activation was stronger when the number was close to the comparison number. In addition, the activation was stronger in the left hemisphere. A series of studies indicate that the IPS holds the representation of number distance (Dehaene et al., 2003; Dehaene, Dehaene-Lambertz, & Cohen, 1998). In their study, Pinel et al. (2001) examined the examined the relation between numerical distance and brain activity in the comparing of two-digit numbers and found that numerical distance affected IPS activity. In addition, it was discovered that the distance had an inverse relation with activation; i.e. when the distance was small, the activation was stronger. Other studies have found differences between the controls and the developmental dyscalculia group with regards to the activation of IPS (Price et al., 2007; Kucian et al., 2006; Ansari et al., 2005). However, these studies either compared children with other children or children with adults. Only a few studies were done with adults. This is the major contribution of the study. Even though the IPS region of the brain was activated during the number comparison task, there is still a debate about their role. This study tried to find a solution to this debate by underlying the role of IPS in the number comparison task.

Furthermore, we predicted that there would be activation in the left ANG and the left SMG during multiplication. Multiplication led to the activation in the ANG, SMG and IPS regions of the participants' brains. Correct and incorrect items did not show a difference in the activation pattern and the activation was stronger in the left hemisphere for both items. When the two experimental groups were compared, no activation was observed. These results show similarities with the literature which suggests that the left ANG activates during multiplication tasks (Chochon et al., 1999; Dehaene et al., 1999). In their study, Ischebeck et al. (2006) examined the examined the learning process of multiplication and subtraction. Half of the participants took multiplication/subtraction training before fMRI scanning. The results showed that trained multiplication led to higher activation in the IPS and the left inferior frontal gyrus which were presumed to have a role in quantity processing (Fias et al., 2003; Piazza et al., 2002; Ischebeck et al., 2006) and verbal working memory (Ischebeck et al., 2006). On the other hand, untrained multiplication led to activity in the left ANG which was related with mathematical fact retrieval (Lee, 2000). Moreover, the SMG was found to be related with

multiplication in children with developmental dyscalculia (Mussolin et al., 2009). It can be said that over-activation in the ANG and SMG regions was not examined in adults with developmental dyscalculia. This study tries to fill this gap in the literature by examining the ANG and the SMG activation in adults with developmental dyscalculia by using several multiplication tasks (correct-incorrect, table related-unrelated).

In addition, we predicted that there would be bilateral activation in the IPS during subtraction. The results confirmed this prediction. Additionally, the same brain regions that were found to be activated during multiplication were active during subtraction and there was no difference between the two groups. The final analysis compared subtraction and multiplication in order to find differences in activation patterns; however, no activation was detected. Thus, the prediction, which suggested that we would find different activation patterns between the two groups, was not confirmed. Brain imaging studies provided evidence in favor of different representations in the brain for different mathematical operations due to different types of knowledge (Dagenbach & McCloskey, 1992; Dehaene & Cohen, 1995) and different number mechanisms (Lemer et al., 2003; Dehaene et al., 2004). According to Dehaene et al. (2004), damage in the ANG region resulted in multiplication deficits while damages in the IPS region caused subtraction deficits. However, subtraction tasks showed a similar activation pattern and did not show a difference when subtraction and multiplication tasks were compared.

The study included some weaknesses. The main limitation was that the data from participants with developmental dyscalculia belonged to the previous project while the control data belonged to a project conducted during the 2012-2013 academic year. Even though the data collection procedure was the same, it was not known whether there were conditions that could affect the data. In addition, 4 or 5 participants with developmental dyscalculia also had reading difficulties which could affect the results. The bottom line is, however, that more research on investigating neural correlates is needed.

To conclude, neural correlates in developmental dyscalculia were investigated in this study. It was predicted that the IPS region of the brain would show less activation during the number comparison task in the adults with developmental dyscalculia. However, the findings showed that adults with developmental dyscalculia did not show less brain activation than in the control group in the IPS with relation to the tasks. Additionally, it was discovered that the activation of the left ANG, as well as the left SMG, during the multiplication task while there was activation in the bilateral IPS during the subtraction task.

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REVIEW ARTICLE

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1432919387

**Article history:**
Received 30 May 2015
Received in revised form 20 July 2015
Accepted 23 July 2015

# DISTINCT ROLES OF GAMMA-AMINOBUTYRIC ACID TYPE A RECEPTOR SUBTYPES: A FOCUS ON PHASIC AND TONIC INHIBITION

## GAMA AMİNOBÜTİRİK ASİT TİP A RESEPTÖR ALT TİPLERİNİN FARKLILAŞMIŞ FONKSİYONLARİ: FAZİK VE TONİK INHİBASYON

Ayla Arslan[*1]

### Abstract

**The gamma-aminobutyric acid type A receptors ($GABA_A$Rs), belonging to the superfamily of Cys-loop receptors, responsible for the inhibitory transmission in the vertebrate central nervous system. Assembled from a pool of 19 subunits, the subunit composition of heteropentameric $GABA_A$Rs impacts on receptor's function, physiology, cellular and subcellular localization in the cell membrane, i.e., synaptic or extrasynaptic. γ2 containing $GABA_A$Rs (γ2-$GABA_A$Rs) are clustered in the synapses and mediate classical fast synaptic inhibition called phasic inhibition. δ subunit containing $GABA_A$Rs (δ-$GABA_A$Rs) are located extrasynaptically and mediate a different form of inhibition called tonic inhibition critical for the threshold of action potential generation and neuronal excitability. Thus, distinct physiological roles of synaptic and extrasynaptic $GABA_A$R subtypes lead to the question to ask about the possibility of subtype selective drugs. In the light of accumulating data from X-ray crystal structures of vertabrate, invertabrate and prokaryotic Cys-loop receptor family members, new opportunities arise for the development of novel drugs targeting specificaly these subtypes of $GABA_A$Rs for the treatment of various neuropathological conditions.**

**Keywords:** GABAA Receptors, GABA, phasic inhibition, tonic inhibition, gamma2 (γ2) subunit, delta (δ) subunit, Cys-loop receptors, synaptic, extrasynaptic

### *Özet*

***Memelilerde beyinde inhibasyonun iletiminden sorumlu birincil reseptör olan gama amino butirik asit tip A reseptörleri ($GABA_A$Rs), Cys-loop reseptörleri familyasina baglidir. 19 alt uniteden olusan bir havuzdan belirli kombinasyonlarla pentamer olarak organize olan bu reseptörlerin kompozisyonu, reseptörün fonksiyonu, fizyolojisi, bulundugu hücre tipi ve sinaptik ya da ekstra-sinaptik gibi hücre zarinda belirli bir lokalizasyonda bulunmasına etki eder. γ2 alt ünitesini bulunduran $GABA_A$R alt tipi (γ2-$GABA_A$Rs) sinaptik olarak lokalize olup fazik inhibasyon olarak bilinen tipik hizli inhibasyonun iletiminden sorumludurlar. δ alt ünitesini bulunduran $GABA_A$Rs (δ-$GABA_A$Rs) ekstrasinaptik olarak lokalize olup fazik inhibasyondan daha farkli bir inhibasyon türü olan ve aksiyon potansiyelinin olusmasi için gereken eşik değerinde ve hücre uyarılabilirliğinde rol oynayan tonik inhibasyonun iletiminden sorumludurlar. Sinaptik ve ekstrasinaptik $GABA_A$R tiplerine özgü bu farklılaşmış fizyolojik görevlerin gittikçe daha belirgin hale gelmesi, ilgili reseptör tiplerine yönelik özel ilaçlarin geliştirilebilmesi ile ilgili ihtimalleri de akla getirmektedir. Zira, son yıllarda omurgali, omurgasiz ve prokaryot kaynaklardan elde edilen Cys-loop reseptör ailesine ait reseptörlerin X-isini kristal yapılarina dair yeni verilerin birikmesiyle çesitli nöropatolojilere yönelik olarak sinaptik ve ekstrasinaptik $GABA_A$R tiplerini seçici olarak hedefleyebilen yeni ilaçlarin geliştirilmesi mümkün olabilecektir.***

***Anahtar Kelimeler:*** *GABA (A) reseptörleri, GABA, fazik inhibasyon, tonik inhibition, gama2 (γ2) , delta (δ), Cys-loop reseptörleri, sinaptik, extrasynaptik*



### 1. Introduction

Neural circuits mediate brain information processing by the integration of excitatory and inhibitory signals generated by neurotranmitters like Glutamate and GABA respectively. The actions of GABA is mediated by different receptors, including gamma-aminobutyric acid type A receptors (GABAARs) which play a significant role by means of its spatiotemporal activity during brain information processing (Koch et al., 1983). Belonging to family of "Cys-loop receptors", GABAARs are heteropentameric chloride channels responsible for the inhibitory transmission in the vertebrate central nervous system (reviewed in Lester et al., 2004; Unwin, 2005; Sine & Engel, 2006). These GABA-gated heteropentameric channels are permeable to HCO3- and Cl- ions (reviewed by Sieghart and Sperk 2002). Depending on the intracellular Cl- concentration, GABAAR activation can lead to Cl- influx or efflux. In adult neurons, upon activation of the receptor by GABA binding, Cl- usually moves into the cell, causing a strong inhibitory hyperpolarization (Kaila et al., 1997; Rivera, et al., 2005).

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### *1.1. The structure of the GABAARs*

Initially, the atomic structure of a GABAAR subunit complex was determined by the studies based on the snail acetylcholine receptor binding protein (AChBP) and muscle nicotinic acetylcholine receptor from the electric organ of the Torpedo ray fish (Brejc et al., 2001; Cromer et al., 2002; Ernst et al., 2003; Unwin, 2003, 2005; Sine and Engel, 2006). Recently, the crystallized structure of homeric β3 subunit containing GABAAR (GABAAR -β3cryst ) at 3A° resolution has been reported (Miller and Aricescu, 2014). This study provides a direct overview for the receptor structure for the first time (Figure 1) which confirms the characteristic elements of eukaryotic Cys-loop receptors (reviewed by Lynagh and Pless, 2014). Thus GABAARs are arranged as heteropentameric structures by which five subunits co-assemble around a central pore. Each subunit has a large extra-cellular N- terminus, four transmembrane domains (TM1–TM4), and a small extracellular C-terminal. There is a large intracellular loop between the third and fourth transmembrane domains.

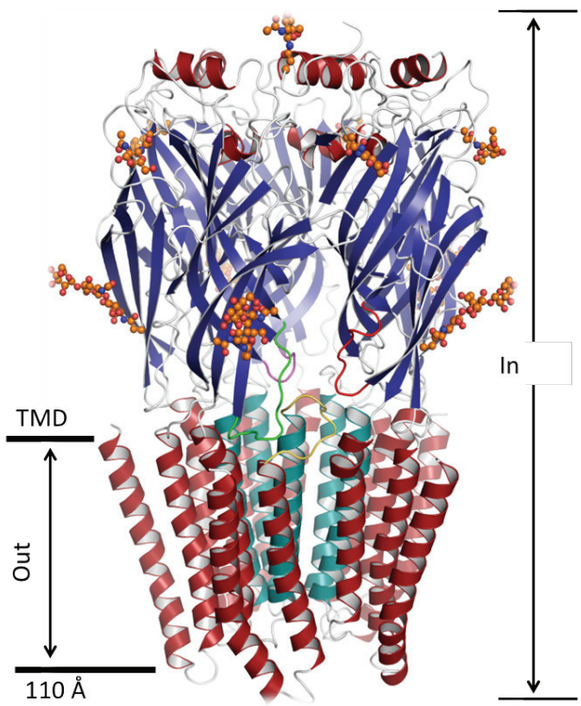


**Figure 1:** Crystal structure of the human GABA (A) receptor composed of β3 homopentamer (GABA(A)R-β3cryst ). α-helices are shown in red, excluding the pore-lining second transmembrane domain, shown in green; β-strands are shown in blue and the loops are shown as grey. Orange ball-and-stick model illustrates the N-linked glycans. (TMD: Transmembrane domain). (Reproduced from Miller & Aricescu, 2014)

### *1.2. Subunit composition: Tonic and Phasic Inhibition*

The GABAARs are assembled from a subunit pool of 19 subunits. These subunits are named as α1–α6, β1–β3, γ1–γ3, δ, ε, θ,π, ρ1–ρ3 (Schofield et al., Korpi et al., 2002a; Rudolph and Mohler, 2006; Whiting, 2006) and expressed in age and anatomy dependent manner (Wisden et al., 1992; Laurie et al., 1992a, b; Fritschy and Mohler, 1995; Schwarzer et al., 2001). Also cell type is a critical factor for the subunit co-assembly. It is known that the δ subunit co-assemble specifically with the α4 and α6 subunits in the forebrain (Cope et al., 2005) and cerebellum respectively (Jones et al., 1997; Peng et al., 2002). The δ represents a rare isoform of GABAAR subunits specifically located at the extrasynaptic sites (Nuser et al., 1998; Wei et al., 2003) in the dentate gyrus granule cells of hippocampus (Sun et al., 2004) and ventrobasal nucleous of the thalamus and neocortex (Chen et al., 2005; Cope et al., 2005; Glykys et al., 2007) besides to cereballar granule cells (Jones et al., 1997; Jehlinger et al., 1998). These δ containing GABAARs receptors (δ-GABAARs) have higher affinity for GABA (Fisher and Macdonald, 1997) and mediate the tonic inhibition (Petrini et al., 2004; Farrant and Nusser, 2005), which is activated by GABA diffusing out of the synaptic cleft (Hamann, et al., 2002). Tonic inhibition is critical for the synaptic integration besides to its role in setting the threshold for the action potential generation and controlling the excitatory synaptic signalling (Hausser and Clark, 1997; Hamann, et al., 2002, Semyanov et al., 2004). It is also important to mention that tonic inhibition is not only mediated by δ-GABAARs, α5 containing GABAARs also mediate the tonic inhibition (Glyks, et al., 2008) which is not the focus of this study. Another GABAARs subtype is the one, that is most abundant in brain: the γ2 containing GABAARs (γ2-GABAARs) are composed of αβγ2 subunits and mediate fast synaptic inhibition (Ernst et al., 2003). They are abundantly clustered in the postsynaptic sites besides to nonsynaptic sites (Somogyi et al., 1996; Nuser et al., 1996, 1998; Fujiyama et al., 2000, 2002, Kullman et al., 2005). Figure 2 shows the phasic and tonic inhibition mediated by synaptic and extrasynaptic GABAARs in the forebrain (Goetz et al., 2007).

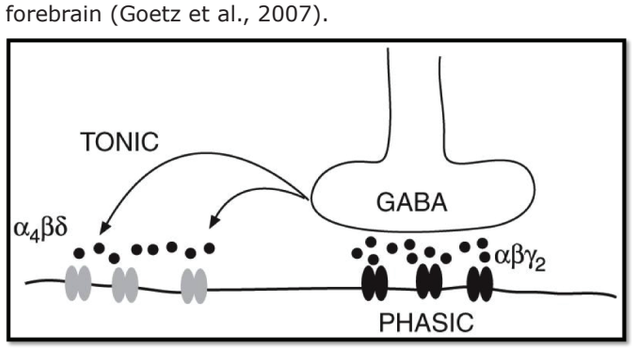


**Figure 2:** γ2-GABAARs are concentrated at the postsynaptic sites that contain α, β and γ2 subunits (shown as black receptors at the postsynaptic site). They mediate classical fast synaptic inhibition (phasic inhibition) in response to GABA release (black dots in the synptic cleft). δ-GABAARs contain α, β and δ subunits (shown as gray receptors at the extrasynaptic site) and mediate tonic inhibition in response to GABA spillover from the synaptic cleft (arrowed black dots). (Reproduced from Goetz et al., 2007).

### *1.3. Distinct physiological functions, distinct modulation*

As described so far, synaptic and extrasynaptic GABAARs mediate two physiologically distinct forms of GABAergic signalling (Fisher and Macdonald, 1997; Mody and

Pearce, 2004; Farrant and Nusser, 2005). This is also well reflected in the level of their modulation. For example the γ2-GABAARs are sensitive to Benzodiazepines (BZ) (Prittchett et al., 1989; Wingrove et al., 1997 Sigel and Buhr, 1997). Among the specific combinations of γ2-GABAARs, there are also further differential modulatory effects. Sedative effects of etomidate is mediated by γ2-GABAARs with β2 subunits, and anesthetic effects of etomidate is mediated by γ2-GABAARs with β3 subunit (Reynolds et al., 2003). Etomidate also affects δ-GABAARs similar to allosteric modulatory effect of this anesthetic on γ2-GABAARs (Feng et al., 2014), but by a different kinetic mechanism than that of γ2-GABAARs. The etomidate potentiation of δ-GABAARs occurs by a prolonged deactivation and reduced desensitization of the receptor (Liu et al., 2015) where as the etomidate potentiation of γ2-GABAARs does not involve receptor desensitization (Zhong et al., 2008).

δ-GABAARs are specifically sensitive to physiologically relevant ranges of alcohol a feature that is not found in γ2-GABAARs (Deitrich et al., 1989; Sundstrom-Poromaa et al., 2002; Wallner et al., 2003; 2014; Liang and Olsen 2014). Another difference between the γ2-GABAARs and δ-GABAARs is their modulation by neurosteroids, steroids synthesized in the brain. The most widely explored neurosteroids are allopregnanolone, allotetrahydrodeoxycorticosterone, androstanediol which enhance the activity of both receptor subtypes but this enhancement is stronger for the latter as δ-GABAARs are more senitive to neurosteroids (Wohlfarth et al., 2002; Stell et al., 2003; Carver and Reddy, 2013, Romo-Parra, et al., 2015) As a result, interaction of δ-GABAARs with neurosteroids have a critical status in terms of the potentiation of tonic inhibition and thus impacting on neuronal network excitability, seizure susceptibility, and behavior (Carver and Reddy, 2013). This has already been shown by the studies of δ subunit knock-out mice, which have a reduced inhibition and neurosteroid sensitivity (Spigelman, et al., 2003).

Recent studies in the literature continusously address the differential modulation. An interesting study not only report the differential modulation of γ2-GABAARs and δ-GABAARs but also further dissect δ-GABAARs the in this context (Hoestgaard-Jensen, et al., 2014). The ligand 4,5,6,7-tetrahydroisothiazolo[5,4-c]pyridin-3-ol (Thio-THIP) was found to have a negligible antagonist activity at the α4β2δ subtype unlike its effect on α4β1δ and α4β3δ among δ-GABAARs Moreover, the Thio-THIP displayed weak antagonist activity at α1,2,5β2,3γ2 containing receptors. Some other new studies report the differential modulation in terms of phasic and tonic inhibition. One study reports the potentiation of phasic and tonic currents following the inhibition of nitric oxide synthase (Gasulla and Calvo, 2015), while others suggest phosphorylation related modulation of phasic and tonic currents by CaMKII and PKC, respectively (Joo et al., 2014), or potentiation of tonic inhibition by serotonin (Jang, et al., 2015). However the subunit composition of the receptors that mediate phasic or tonic inhibition in these electrophysiological studies is not known except for the case of Gasulla and Calvo (2015), may be. Since there are many different GABAAR subunits (see the section "Subunit composition: Tonic and Phasic Inhibition"), electrophsiological recordings of phasic and tonic inhibition, without molecular profiling, will only provide a limited understanding of receptor subtype specific modulation. The focus of the present study is only γ2−GABAARs and δ− GABAARs, which mediate phasic and tonic inhibition. On the other hand there is another GABAAR subtype that mediate tonic inhibition for example: the α5 containing extrasynaptic GABAARs (Prenosil et al., 2006; Glyks, et al., 2008). Thus, the studies of electrophsiological recording of phasic and tonic inhibition and their modulation requires further molecular investigation in this context. Nevertheless, accumulating data address the modulation of δ− GABAARs by kinase A and C (phosphorylation) and regulation of tonic inhibition by G-protein coupled receptors (see Conelly et al., 2013 for a detailed review). Modulation of γ2− GABAARs by phosphorylation is already a better explored subject (Kittler and Moss, 2003) and the current emerging data about the modulation of δ− GABAARs by phosphorylation as well as by other ligands described so far will add a new dimension for the distinct modulation of phasic and tonic inhibition mediated by these receptor subtypes for their significance as potential targets of subtype selective drugs.

## 2. Conclusion

Assembled from a large subunit pool, the rich molecular, cellular and functional diversity of GABAARs is well known (Seeburg et al., 1990; Mody and Pierce, 2004). This diversity manifests itself in the form of distinct physiological functions. Phasic and tonic inhibition mediated by synaptic and extrasynaptic GABAARs is one example of this phenomenon. What is new in the agenda is the emerging data: Studies from X-ray crystal structures of ligand-gated ion channels from prokaryotic and invertebrate organisms (Lynagh and Pless, 2014), together with the crystal structure of human GABAAR (Miller and Aricescu, 2014) and serotonin receptor (Hassaine et al., 2014) accumulate. These accumulating data will trigger the studies of molecular dynamics and homology modeling which will boost the development of new drugs for selective modulation of the GABA receptor subtypes for the treatment of various neuropathological states such as epilepsy (Rogawski et al., 2013), premenstrual dysphoric disorder (Staley and Scharmann, 2005) or alcohol use disorders (Liang and Olsen, 2014).

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JNBS 2014 Published by Üsküdar University www.jnbs.org

MINI REVIEW

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1442584377

**Article history:**
Received 18 September 2015
Received in revised form 4 October 2015
Accepted 7 October 2015

# CEREBELLUM INVOLVEMENT IN OBSESSIVE-COMPULSIVE DISORDER RELATED BRAIN NETWORK MODEL

## SEREBELLUMUN OBSESİF-KOMPULSİF BOZUKLUK İLE İLİŞKİLİ BEYİN AĞI MODELİNE EKLENMESİ

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JNBS 2015 Published by Üsküdar University www.jnbs.org

### Abstract

**Conventional obsessive-compulsive disorder related brain network model relies mainly on cortico-striato-thalamo-cortical areas. However, recent findings consistently point cerebellar structural and functional differences in obsessive-compulsive disorder patients compared to healthy controls. Here we briefly reviewed these studies and argued that cerebellum should be involved in obsessive-compulsive disorder related brain network model for a better understanding of the nature of this disorder.**

**Keywords:** Obsessive-compulsive disorder, OCD, cerebellum.

### *Özet*

***Geleneksel obsesif-kompulsif bozukluk ile ilişkili beyin ağı modelleri temel olarak kortiko-striato-talamo-kortikal bölgelere dayanır. Ancak, son bulgular istikrarlı olarak obsesif-kompulsif bozukluk hastalarında sağlıklı kontrollere göre yapısal ve işlevsel serebellar değişiklikler olduğuna işaret ediyor. Bu yazıda ilgili çalışmaları kısaca taradık ve hastalığın doğasının daha iyi anlaşılabilmesi için serebellumun obsesif-kompulsif bozukluk ile ilişkili beyin ağı modeline eklenmesi gerektiğini savunduk.***

***Anahtar Kelimeler:*** *Obsesif-Kompulsif Bozukluk, OKB, serebellum*

Obsessive-compulsive disorder (OCD) is a chronic mental disorder typically characterized by the presence of recurrent, persistent and intrusive thoughts (obsessions) leading to intentional repetitive behaviors or mental acts (compulsions) to avoid anxiety. OCD was classified under the anxiety disorders spectrum in DSM-4-TR, but is grouped under a new spectrum that is called the obsessive-compulsive and related disorders in the new DSM-5 (APA, 2013). Theoretical models suggest that OCD is related with functional and structural abnormalities in cortico–striato–thalamo–cortical (CSTC) network in general (Eng et al., 2015) and orbitofronto-striatal circuits in particular (Menzies et al., 2008). However in several studies, posterior brain regions including cerebellum is consistently reported as areas manifesting structural and functional changes in OCD patients. Therefore a number of recent research and review papers suggest the involvement of cerebellum in OCD related brain network model (Menzies et al., 2008; Hou et al., 2012; Ping et al., 2013; Kim et al., 2015).

Cerebellum is well known as the center crucial for movement related functions such as movement coordination and motor learning. On the other hand, many recent studies revealed its role in cognitive functions and that the functional or anatomical abnormalities of cerebellum is associated with a variety of psychiatric disorders (see Phillips et al., 2015 for review). In the light of these evidences in neuroimaging study on OCD, increasing attention have now been paid to the cerebellum (Hou et al., 2012)

Ample evidence suggests the neuroanatomical and functional changes in OCD as compared to heathy controls (HCs). A majority of the structural studies used voxel based morphometry (VBM) as the main method of investigation and most of them consistently reported increased gray matter (GM) volume (Pujol et al., 2004; Kopřivová et al., 2009; Okada et al., 2015) with a few exceptions that found decreased GM volume (Kim et al., 2001) in cerebellum. A recent study that used a fusion of canonical correlation analysis (CCA) and independent component analysis (ICA) for source localization of grey and white matter networks in patients with OCD pointed cerebellum as one of the main areas that distinguished OCD patients from HCs (Kim et al., 2015). Studies of white matter (WM) changes in OCD revealed that compared to HCs, patients had significantly higher fractional anisotropy (FA) values

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in various tracts in left cerebellar and brainstem white matter (Zarei et al., 2011). Despite all these studies some studies did not find cerebellar abnormalities in OCD (see Piras et al., 2015 for a review).

Regarding the functional projections of aforementioned structural abnormalities in cerebellum, some studies has investigated patients with OCD. In brief, fMRI studies reported decreased activation in the cerebellum during task switching (Woolley et al., 2008) and interference inhibition (Nabeyama et al., 2008; Woolley et al., 2008) which increased with the clinical improvement and task performance (Nabeyama et al., 2008). Regarding functional connectivity, patients with OCD presented decreased amplitude of low frequency fluctuations (ALFF) (Hou et al., 2012) and increased intra-regional synchronized activity (ReHo) in the bilateral cerebellum (Ping et al., 2013; Hou et al., 2014). However, some other studies found decreased cerebellar connectivity in OCD as compared to heathy controls (Zhang et al., 2011). Taken as a whole, it appears to be that there is no clear consensus about the direction of functional changes in OCD, though abnormal activity was present for most of the studies.

Cerebellar findings are also shown to be related with OCD disease severity. GM volume in cerebellum was found to be correlated with severity level and again the results are not unidirectional; both positive (Zarei et al., 2011) and negative correlations were found (van den Heuvel et al., 2009). Cerebellar abnormalities and their relation with treatment response was investigated in a few studies. In a single-photon emission-computed tomography (SPECT), researchers found that responders showed a decrease in regional cerebral blood flow (rCBF) in cerebellar vermis and an increase in cerebellum tonsil compared to HCs (Wen et al., 2013). The same study pointed that the reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score was positively correlated with pre-treatment rCBF in cerebellum. Another study reported an inverse correlation between the ReHo of the cerebellum and the Y-BOCS compulsive scores (Ping et al., 2013).

Taken as a whole, in light of these recent studies, it may be plausible to include cerebellum to the traditional CSTC network in OCD. Thus, it may be necessary to revisit the CSTC model (Menzies et al., 2008; Hou et al., 2012; Ping et al., 2013; Kim et al., 2015). In fact, a few studies have already has shown the relationship between cerebellum and CSTC network. (see Eng et al., 2015 for a review). Besides, some other studies have argued that cerebellum may contribute to the regulation of CSTC network (Tobe et al., 2010).

CSTC model worked quite well for understanding OCD related brain changes and their relation with the behavioral manifestations of OCD, but recent findings point alterations in other brain regions and suggested to extend CSTC model. One drawback of neuroimaging studies in general is the exclusion of cerebellar regions in data acquisition stages. Therefore, it is not entirely clear whether or not cerebellar abnormalities were consistent for previous neuroimaging work in OCD. Besides, there is the well-known registration error in cerebellum due to the restraints of VBM techniques. The exclusion of cerebellum from the models of psychiatric disorders may cause imperfect understanding of the nature of those disorders. A suggestion for future studies may be the segmentation of cerebellum separately and evaluating the association between symptoms, treatment response and prognosis of patients suffering from OCD. Lastly, further research is required to reveal whether the supervisory role of cerebellum over CSTC circuit is consistent together with their implications in OCD to place cerebellum in the right spot in OCD related brain network model.

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THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
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JNBS 2015 Published by Üsküdar University www.jnbs.org

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1437674679

**Article history:**
Received 23 July 2015
Received in revised form 28 July 2015
Accepted 03 August 2015

# COINCIDENCE OF DELUSIONAL DISORDER, SUBCLINICAL HYPOTHYROIDSM AND HIRSUTISM: A CASE REPORT

## HEZEYANLI BOZUKLUK, SUBKLİNİK HİPOTİROİDİZM VE HİRSUTİZMİN EŞZAMANLI GÖRÜNÜMÜ: OLGU SUNUMU

Fatma Duygu Kaya[*1], Ramazan Erdem Er[2]

### Abstract

**In this report, we present a 51 year old postmenopausal woman with clinical presentation of "delusional disorder-somatic type" and also facial hirsutism and subclinical hypothyroidism. Blood tests revealed thyroid gland dysfunction with high TSH and anti-TPO levels but other blood tests and radiological investments were found to be normal. The relationship between thyroid dysfunction, hirsutism and psychosis is discussed in the context of this particular case. In presence of limited case reports in literature indicating a relationship with subclinical hypothyroidism and psychotic symptoms, we think that our case is important for reminding clinicians to consider endocrine disorders providing a basis for psychiatric disorders and to investigate thyroid function deficiency not only in patients with depression but with other psychiatric presentations like psychosis.**

**Keywords:** subclinical hypothyroidism; hirsutism; postmenopausal; delusional disorder

### *Özet*

***Burada "delüzyonel bozukluk-somatik tip" kliniği ile başvuran, aynı zamanda yüzde hirsutizmi ve subklinik hipotiroidisi olan 51 yaşında postmenapozal bir olgu sunulmaktadır. Hastanın kan testlerinde yüksek TSH ve anti-TPO seviyeleri mevcut olup diğer kan testleri ve radyolojik incelemeler normal sınırlardadır. Tiroid işlev bozukluğu, hirsutizm ve psikoz arasındaki ilişki bu olgu çerçevesinde tartışılmıştır. Subklinik hipotiroidi ve psikotik belirtiler arasındaki ilişkiye işaret eden az sayıdaki literatür varlığında bu olgunun; klinisyenlere, endokrin bozuklukların psikiyatrik bozukluklara temel oluşturabildiğini düşünmelerini ve sadece depresyonu olan hastalarda değil psikoz gibi diğer psikiyatrik tablolarda da tiroid işlevlerini incelemelerini hatırlatması bakımından önemli olduğunu düşünmekteyiz.***

***Anahtar Kelimeler:*** *subklinik hipotiroidizm; hirsutizm; postmenapozal; delüzyonel bozukluk*



### 1. Introduction

Hypothyroidism as an endocrine disorder that is often seen in elderly females, mostly leads to affective and cognitive symptoms in patients (Heinrich & Grahm, 2003). Even patients may present to physicians with psychiatric symptoms only before emergence of physical symptoms related to thyroid function deficit. On the other hand, psychotic disorders with delusions and hallucinations might be seen in case of hypothyroidism (Haggerty et al., 1986; Westphal, 1997; Lehrmann & Jain, 2002). It was indicated that emergence of psychotic symptoms is not related to the level of thyroid hormone deficiency and these symptoms may accompany to subclinical hypothyroidism that free T3 and free T4 values are not significantly impaired (Lehrmann & Jain, 2002).

Hirsutism is another endocrine disorder that affects mental health of women negatively and decreases quality of life (McGaffee et al., 1981). Hirsutism, which might indicate an underlying disease, is mostly idiopathic. There is also a known relation between hypothyroidism and hirsutism.

In this report, we present a postmenopausal woman who was referred to our psychiatry department with clinical presentation of "delusional disorder-somatic type" and with comorbid facial hirsutism and subclinical hypothyroidism.

### 2. Case

51 year old S.E., a married postmenopausal woman with 4 children, was brought to department of internal medicine of our hospital with facial hirsutism by her daughter

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and was consulted to psychiatry. She was complaining about anxiety, difficulty in breathing, insomnia, poor appetite, fatigue, sleepiness, the hair growth on her chin underneath her skin, deformation of her chin, growing of her nose hair thorough her eyes, sliding of her face skin, narrowing of her forehead, continuous move of her body hair and facial hair, contraction of her mouth, dimpling of her chin and sliding of her nose for nearly two months. It was learned that her brother, who lived abroad, went to jail for selling illegal gasoline two months ago and after this event, anxiety of the patient began and was followed by psychotic symptoms two weeks later.

### *2.1. Mental Status Examination*

At the time of examination, her personal care was a bit poor and she was wearing a hospital mask to cover her chin. She was unable to sit because of her anxiety and had difficulty in breathing. She showed to the clinician 3-4 cm long hair on her chin, how the shape of her face was distorted and her skin was slided. She was asking for help from the doctor and complaining about somatic symptoms. Her psychomotor activity was noted to be increased. She was dysphoric and anxious, her affect was congruent with her mood and contained no lability. She was oriented to person, place, time, situation and her intellectual functioning was estimated to be average. She appeared not to maintain attention and concentration to the interviewer's tasks so the short term memory could not be assessed but long-term memory was intact. Her flow of thought was coherent and her thought content revealed somatic delusions as well as kinesthetic hallucinations. Speech was fluent and speech volume was normal. Insight and judgment were poor. Impulse control appeared to be intact.

### *2.2. Physical Examination*

There was 3-4 cm long facial hair on her chin but no other male-type distributed hair on her body or sign of virilism was present. Body mass index of the patient was 25.1, indicating a normal weight range. Her skin examination revealed no pathology. A postoperative scar was evident on her neck relating to thyroid nodule excision. Neurological examination was normal.

### *2.3. Background*

She had no past psychiatric history, alcohol or drug abuse and did not take concomitant medication. She had been smoking 20 cigarettes daily for thirty five years. It was learned from the patient, her daughter and medical records that her menopause started five years ago, she had a thyroid nodule excision surgery four years ago and her excess hair growth on her chin was present for twenty five years.

### *2.4. Family History*

One of her daughters had a history of brief psychotic disorder while the other had a history of anxiety disorder.

### *2.5. Clinical Progress*

Brief Psychiatric Rating Scale (BPRS) score of the patient was 49. She was consulted to neurology and neurological examination and cranial magnetic resonance imaging were found to be normal. She was started escitalopram 5 mg/day and pimozide 2 mg/day for psychiatric symptoms.

The patient was consulted to an endocrinologist for a detailed investigation. Results of the blood tests were; morning cortisol: 20 µg/dL (6,7-22,6), fasting blood glucose: 86 mg/dL (74-100), TSH:8,51 µIU/mL (0,34-5,6), anti-TPO: 1070,1 IU/mL (0-9), fT4: 8,91 pmol/L (7-16), FSH: 81,6 mIU/mL (16,7-114 for menopause), LH: 23,95 mIU/mL (10,9-58,6 for menopause), DHEA-SO4: 122,6 µg/dL (7-188), free estriol: 0,042 ng/mL ($^{<}$ 2), total testosterone: 22,04 ng/dL (10-75). Her laboratory findings showed normal hemogram, lipid profile, electrolyte, creatinine and liver enzyme levels. Thyroid ultrasound revealed a decreased volume of thyroid gland and parenchymal heterogeneity and roughness which was consisted with Hashimoto's thyroiditis. After two weeks that she was started psychiatric drugs her delusions and anxiety was still evident so escitalopram was increased up to 10 mg/day and she was started 25 mcg/day levothyroxine sodium by the endocrinologist.

Ten days later her delusions were weakened and functionality was improved but we couldn't associate her well-being only with levothyroxine because of other used drugs. Her gynecologic examination and transvaginal ultrasound revealed no pathology. After a brief hospitalization she was discharged with escitalopram 20 mg/day, pimozide 2 mg/day and levothyroxine sodium 25 mcg/day where her anxiety totally disappeared and her delusions were not fully improved but weakened (BPRS score 25). Written informed consent was obtained from the patient and her family allowing her medical data to be used for academic purposes.

## 3. Discussion

We think that a two dimensional discussion can be conducted for this particular case.

### *3.1. Hirsutism and thyroid dysfunction*

Hirsutism is the excess growth of terminal hair in women on androgen sensitive body areas and caused by polycystic ovary syndrome, congenital adrenal hyperplasia, ovarian-adrenal tumors and some medications or could be idiopathic (Escobar-Morreale, 2010). Although there is no clear definition of idiopathic hirsutism (IH), it is diagnosed when normal ovulatory function and androgen levels are detected. Mostly increase in skin 5α-reductase activity, androgen receptor polymorphisms or altered androgen metabolism is thought to be responsible for IH (Azziz et al., 2000). Ferriman-Gallwey scoring system is a classification method for determining degree of hirsutism at 11 different body sites (a score of 0 through 4). The total score of our patient was 4 (extensive terminal hair growth) only for her chin. Presence of previous regular menstrual cycle and normal ovulatory function, normal androgen levels, normal pelvic ultrasound, no evidence

of virilism, no cranial pathology in MRI together with excluding other hirsutism causes made us diagnose IH in this patient. Thyroid dysfunction is one of causes of hirsutism, especially for congenital hypothyroidism but there is not enough evidence in literature to interrelate subclinical hypothyroidism and hirsutism (Somani et al., 2008). Because this patient's hirsutism history localized to her chin (25 years) was older than hypothyroidism history, two situations were not thought to be related. However a possible relationship between subclinical hypothyroidism and hirsutism must be taken into account when considering the well-known complex relation between thyroid hormones, sex hormone binding globulin and estrogen metabolism (Poppe & Velkeniers, 2004). On the other hand it is well-known that hirsutism with or without subclinical hypothyroidism is a challenging situation for women (McGaffee et al., 1981). Previous studies reported that psychiatric symptoms are more common among women with hirsutism (Sonino et al., 1993). Likewise content of delusions of our patient was primary about her facial hirsutism and appearance but not about other body parts.

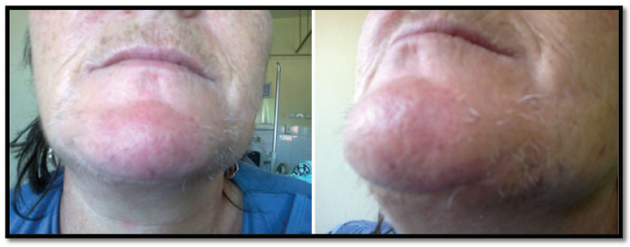

**Figure 1:** The patient with hirtuism localized on the face

### *3.2. Hypothyroidism and psychosis*

In past years when hypothyroidism wasn't treated well and myxedema presentation was more often; cases of psychotic disorders with delusions and hallucinations were reported that improved with thyroid replacement therapy (Asher, 1949). We know that our patient had been having high TSH levels for at least four years from the medical reports. Subclinical hypothyroidism prevalence is 10% and it increases to 20% for women who are 60 years and older (Haggerty et al., 1993). It was previously indicated that subclinical hypothyroidism may be responsible for thought disorders, therefore psychotic symptoms may be unrelated to level of thyroid hormone deficiency (Lehrmann & Jain, 2002).

Considering the relation of subclinical hypothyroidism with psychotic symptoms and subclinical hypothyroidism with hirsutism; we assessed this case in the light of her family history for psychiatric disorders and a vulnerable endocrine basis with stressful life events that precipitate delusional disorder. This delusional disorder was considered as a psychiatric presentation that hirsutism determined the delusional content and was precipitated by negative life events with underlying untreated chronic subclinical hypothyroidism.

To our knowledge, in literature there are only three case reports indicating a relationship with subclinical hypothyroidism and psychotic symptoms (Haggerty et al., 1986; Lehrmann & Jain, 2002; Madhusoodanan et al., 2014). Our case is important for reminding clinicians to consider endocrine disorders providing a basis for psychiatric disorders and to investigate thyroid function deficiency not only in patients with depression but with other psychiatric presentations like psychosis.

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CASE REPORT

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1423170020

**Article history:**
Received 4 July 2015
Received in revised form 23 July 2015
Accepted 3 August 2015

# SERTRALIN INDUCED NORMOPROLACTINEMIC GALACTORRHEA

## SERTRALİNİN İNDÜKLEDİĞİ NORMOPROLAKTİNEMİK GALAKTORE

Mehmet Akif Camkurt*[1], Nadya Şimşek[2]

### Abstract

**Galactorrhea is defined as non-puerperal lactation and frequently occurs as an adverse drug reaction due to typical antipsychotics. Furthermore, antidepressants, especially SSRIs, cause galactorrhea since the introduction of imipramine to psychiatry practice. Although galactorrhea usually accompanies increased prolactin levels, in some cases prolactin levels could be within the normal range. To date there are two case reports of normoprolactinemic galactorrhea due to sertraline and here we report a patient who developed normoprolactinemic galactorrhea 1 month after initiating sertraline 50 mg/day.**

**Keywords:** Sertraline, Galactorrhea, Normoprolactinemic

### *Özet*

***Galaktore psikiyatri pratiğinde sıklıkla tipik antipsikotiklerin bir yan etkisi olarak ortaya çıkmaktadır. Öte yandan imipraminin antidepresan olarak kullanılmaya başlanmasından beri, antidepresanlara bağlı da galaktore gelişebileceği bildirilmiştir. Galaktore klinikte sıklıkla artmış prolaktin düzeyleri ile karşımıza çıkmakla beraber bazı durumlarda prolaktin düzeyleri normalken de gelişebilmektedir. Bu güne kadar sertralinle ilgili 2 tane prolaktin düzeyleri normal sınırlarda iken gelişen galaktore olgusu bildirilmiştir. Bu vakamızda sertralin 50 mg/gün başlandıktan 1 ay sonra gelişen galaktore olgusunu sunmayı amaçladık.***

***Anahtar Kelimeler:*** *Sertralin, Galaktore, Normoprolaktinemik*



### 1. Introduction

Galactorrhea- in other terms, non-puerperal lactation- is a condition that usually occurs in the presence of hyperprolactinemia. The most frequent cause of galactorrhea is prolactinoma. Other medical conditions related with galactorrhea may be sorted as hypothyroidism, liver and renal failure. In psychiatry practice it usually occurs as an adverse drug reaction due to typical antipsychotics. As is known, dopaminergic antagonism of typical antipsychotics is responsible from hyperprolactinemia and galactorrhea (Egberts et al., 1997). After imipramine came out to psychiatry practice, antidepressant induced galactorrhea is present as an adverse drug reaction since 1964 (Klein et al., 1964). Most of the cases were reported with serotonergic antidepressants thus far. Although increased serum prolactin levels frequently accompany galactorrhea, thirty percent of patients could be normoprolactinemic. Normoprolactinemic galactorrhea is a rare side effect of antidepressants and its mechanism in not fully understood, even though role of prolactin in galactorrhea is not clear(Kaye, 1996).

Here we report a patient who developed normoprolactinemic galactorrhea 1 month after commencing sertraline 50 mg/day.

### 2. Case

A 40-year-old female was admitted to our clinic with complaints of anhedonia, unwillingness, increased sleep, decreased appetite, feeling sad and loss of energy. Her symptoms were present through 3 months. Routine biochemical tests were normal. Thus, the patient was diagnosed as major depressive disorder. We commenced sertraline 25 mg/day and recommended the patient to increase dose to 50 mg/day after one week. One month after initiating sertraline (three weeks after increasing dose to 50mg/day), the patient stated that she was feeling very well, severity of her symptoms decreased significantly but she was complaining of galactorrhea. Her prolactine level was 10,8. Thyroid, renal and liver function tests, and serum cortisol level were within normal range. Magnetic resonance of brain was carried out to determine whether galactorrhea was due to pituitary adenoma, and it was normal. Consultation of obstetry and gynecology,

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endocrinology, general surgery and neurology were asked. Nothing significant was found related with galactorrhea. Therefore, galactorrhea was considered to be related with sertraline and we recommended stopping medication. We asked the patient to visit our clinic regularly. Four weeks after discontinuation galactorrhea stopped.

### 3. Discussion

Escitalopram, citalopram, fluoxetine, paroxetine and sertraline may cause galactorrhea. Clinical presentation of SSRI induced galactorrhea could be different. Although in some cases prolactin levels could be high, there are few case reports of normoprolactinemic galactorrhea. Furthermore, onset of galactorrhea may vary from patient to patient. A report describes acute onset within three days and the other mention late onset up to 8 months(Nebhinani, 2013; Polat and Turan, 2014).

There are two case reports of normoprolactinemic galactorrhea with sertraline. Nebhinani presented a 32 year-old female, experienced normoprolactinemic galactorrhea 2 days after increasing sertraline from 25 mg/day to 50 mg/day. Prolactine level was 15,3 (normal range:2.8-29.2). They switched to desvenlafaxine to manage this condition. Eight weeks after discontinuation galactorrhea stopped(Nebhinani, 2013). Other case was reported by Sayar et al, in which patient developed galactorrhea 1 week after increasing sertraline from 25 mg/day to 50 mg/day. They stopped sertraline and followed patient closely. In this case, galactorrhea stopped 16 days after discontinuation(Ozten et al., 2015). Although they didn't measure prolactine level Bronzo et al reported galactorrhea in a 37-year-old woman after taking 100 mg/day for 5 weeks. Twenty one days after discontinuing sertraline, this patient recovered completely(Bronzo and Stahl, 1993). Our case is consistent with previous reports that support sertraline probably induce normoprolactinemic galactorrhea.

The mechanism of SSRI induced normoprolactinemic galactorrhea is elusive. A probable mechanism is direct stimulation of prolactin release in hypothalamus by serotonin with mediation of postsynaptic 5-HT receptors(Mondal et al., 2013). Furthermore serotonin may inhibit tuberoinfindibular dopaminergic neurons indirectly(Arya, 1994). In addition, serotonin interacts with prolactin-releasing factors. One of them is vasoactive intestinal protein (VIP) , which increases prolactin gene expression(Wanke and Rorstad, 1990). Oxytocin also participates VIP-induced pathway of prolactin release and inhibits tuberoinfundibular dopaminergic pathway(Samson et al., 1989).

In conclusion, increasing data point out that SSRIs cause both hyperprolactinemic and normoprolactinemic galactorrhea. Psychiatrists should be aware of that patients who take not only antipsychotics but also antidepressants (especially SSRIs) could develop galactorrhea as an adverse drug reaction.

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CASE REPORT

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1443357705

**Article history:**
Received 27 September 2015
Received in revised form 3 October 2015
Accepted 7 October 2015

# OLANZAPINE INDUCED SEIZURES: A CASE REPORT

## OLANZAPİN İLE İNDÜKLENMİŞ NÖBETLER

N.A. Uvais[1], V.S. Sreeraj[2]

### Abstract

**Galactorrhea is defined as non-puerperal lactation and frequently occurs as an adverse drug reaction due to typical antipsychotics. Furthermore antidepressants, especially SSRIs, cause galactorrhea since the introduction of imipramine to psychiatry practice. Although galactorrhea ususally accompany increased prolactin levels, in some cases prolactin levels could be in normal range. To date there are two case reports of normoprolactinemic galactorrhea due to sertraline and here we report a patient who developed normoprolactinemic galactorrhea 1 month after initiating sertraline 50 mg/day.**

**Keywords:** Sertraline, Galactorrhea, Normoprolactinemic

### *Özet*

***Galaktore doğuma bağlı olmaksızın süt salgılanması olarak tanımlanır ve tipik antipsikotiklere bağlı advers ilaç reaksiyonu olarak sıklıkla ortaya çıkar. Ayrıca, imipraminin psikiyatri pratiğine girişiyle birlikte antidepresanlar, özellikle SSRI'lar, da galaktoreye sebep olmaktadır. Genellikle galaktore prolaktin seviyesindeki artışa eşlik ederken, bazı olgularda prolaktin seviyesi normal aralıkta olabilir. Bugüne kadar sertraline bağlı iki normoprolaktinemik galaktore olgu raporu vardır ve bu çalışmada günde 50mg sertralin başlandıktan bir ay sonra normoprolaktik galaktore geliştirmiş bir hasta rapor edilmiştir.***

***Anahtar Kelimeler:*** *Sertralin, Galaktore, Normoprolaktinemik*



### 1. Introduction

Olanzapine is one of the most commonly used atypical antipsychotic agents. Though closely related to Clozapine structurally, the seizurogenic potential of olanzapine is limited. The premarketing trials have found incidence of seizures at 0.88% which is comparable to other conventional antipsychotics (Alper, Schwartz, Kolts, and Khan, 2007). But, few case reports of fatal status epilepticus (Wyderski, Starrett, Abou-Saif, 1999) and myoclonic status ( Camacho, García-Navarro, Martínez, Villarejo, and Pomares, 2005) have attributed olanzapine as the causative agent. Hereby we are reporting a case of seizure in a patient receiving Olanzapine.

### 2. Case

A 58-year-old female was brought to the Emergency Department (ED) with "alteration of mental state." She reportedly experienced a single generalized tonic-clonic seizure 2 hrs back. She had recurrence of generalized tonic clonic seizure within half an hour of reaching Emergency Department. Her psychiatric history revealed that she was diagnosed as paranoid schizophrenia 2.5 years back and was on T. Olanzapine 7.5 mg/day. Informant reported that she missed medicine for previous three days and restarted the same day. Within one hour of taking medicine she had this first seizure attack. This was the first seizure in her life time. There was no history of alcohol and other substance use or any significant medical illness.

On examination in the ED, she was confused. The neurological examination was otherwise, unremarkable. Her vital signs were stable. Complete blood count, electrolytes, and liver function tests were in the normal range. MRI brain showed no abnormalities. EEG showed generalized epileptiform discharge.

Olanzapine was discontinued and was treated with anti epileptics Phenytoin and Lacosamide and. T Haloperidol 5 mg was started. Since she tolerated the drug and showed no further seizure, she was discharged on the same dose after 4 days.

### 3. Discussion

The present case suggests precipitation of seizures by Olanzapine which was restarted rapidly at relatively higher previously prescribed dose. The occurrence of seizure when patient was on Olanzapine and no recurrence during the brief follow up period of stopping

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it rules out other alternative explanations. The trial for attribution by stopping and restarting the medicines could not be done owing to high fatal risk of the seizure. The objective evidence in the means of abnormal EEG was noted. According to Naranjo Algorithm (Naranjo et al., 1981) with a score of 6, the seizure occurring in our case was probably due to olanzapine.

Among second generation antipsychotics no drug is out of risk in inducing seizure. A possible mechanism postulated includes Dopamine D2 receptor antagonism, Histaminergic H1 antagonism, Alfa 1 antagonism, Chronic Alfa 2 receptor and sigma 1 receptor changes, and reduction of GABA neurotransmission as a common final pathway (Torta, and Monaco, 2002).

Olanzapine is known to cause highest EEG changes, in 35-45% of cases (Centorrino et al., 2002), among the nonclozapine newer antipsychotics. An abnormal EEG could be seen in most of the reported cases of seizure including our case. No prospective data regarding mean duration of appearance of changes have been done. But dose and duration both were not found to be correlating with the EEG changes. Abrupt changes in doses are noted to increase the risk (Lee, Crismon, and Dorson, 1999). As seen in our case, patient had long term Olanzapine use and had discontinued and restarted which led to seizures.

No consensus exists regarding ideal way of managing these seizures. Stopping Olanzapine with monitoring for the possible cholinergic rebound effects and starting a typical antipsychotic like Haloperidol (Behere, Anjith, Rao, Venkatasubramanian, and Gangadhar, 2009) could be recommended. Considering persistence of abnormal EEG and rare risk of fatal status epilepticus, cover of anticonvulsants at least until the normalization of EEG could also be recommended. Moreover, it would be beneficial to monitor EEG as a seizure preventive strategy in high risk patients on olanzapine like Old age, organicity, epilepsy, hypertension, bipolar disorders, comorbid OCD (Behere, 2009), after the cost effectiveness being evaluated.

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JNBS 2015 Published by Üsküdar University www.jnbs.org

LETTER TO EDITOR

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

**Year :** 2015
**Volume :** 2
**Issue Number :** 2
**Doi Number :** 10.5455/JNBS.1433937530

**Article history:**
Received 10 June 2015
Received in revised form 1 August 2015
Accepted 4 August 2015

# MEDROXYPROGESTERONE ACETATE-INDUCED MANIC EPISODE IN A PATIENT WITH BIPOLAR AFFECTIVE DISORDER-I

## BİR BİPOLAR DUYGUDURUM BOZUKLUĞU HASTASINDA MEDROKSİPROGESTERON ASETAT İLE İNDÜKLENMİŞ MANİK EPİZOD

Filiz İzci*[1], Sümeyye Kurtuluş Çallı[2], Yağmur Sever[2]



Dear Editor,

Medroxyprogesterone acetate (MPA) is a methyl acetyloxy derivative of progesterone. It shows direct and indirect anti-estrogenic effects by inhibiting gonadotropin secretion. In higher doses, it acts as androgen and glucocorticoid reseptor agonist (Kayaalp, 2000; Sitruk, 2002). Side effects include galactorrhea, menstrual changes, weight instability, jaundice and psychiatric conditions such as depression, insomnia, fatigue, and irritability (Sitruk, 2002). In bipolar affective disorder reinforcement treatment, it can be used as a mood stabilizer, but it can increase depressive symptoms (Kulkarni et al., 2006). So in this article, we aimed to emphasize that although MPA can cause anti-manic and depressive effects, it may also induce manic symptoms in some cases. although MPA can cause effects such as anti-manic symptoms and increase depresive symptoms, it may also induce manic symptoms in some cases

A 34-year old female patient was prescribed MPA for irregular menstrual cycles. She was single, high school graduated, and unemployed. After using MPA 5 mg twice a day for only 2 days,After using for only 2 days, 5 mg twice a day, she admitted to psychiatry emergency department with irritability, insomnia, increase in speech. According to the history taken from patient and relatives, she was diagnosed with bipolar affective disorder-I 15 years ago she has been diagnosed with bipolar affective disorder-I 15 years ago and she was prescribed valproate 2000 mg/day, paliperidone 6 mg/day, quetiapine 50 mg/day for the last year. Her blood valproic acid level was 69.8 mg/L. She used her medications regularly, yet she passed four manic episodes without hospitalization. She has no family history of any psychiatric or organic disorder. In her mental examination, mood was elevated, affect was irritable, thinking processes was accelerated, association of idea was accelerated, psychomotor activity was increased, sleep and appetite was decreased.starvation were decreased. Her speech rate and amount were increased, she had grandiose delusions she had delusions such as grandiosity but no hallucinations. Young Mania Rating Rate Scale (YMRS) score was 27. Her complete blood count, biochemistry tests, thyroid hormone levels, full urinalysis, urine substance metabolite levels (cannabis, canabis, heroin,etc.) were all normal.With the initial diagnose of manic episode due to drug usage, MPA was stopped and she was given haloperidol 10 mg/day and biperiden 5 mg/day IM for stabilization. Lorazepam 3 mg/ day was added to her present treatment and one week after her manic symptoms were alleviated she was discharged with lorazepam 2mg/day, valproate 2000 mg/ day, paliperidone 6mg/day, quetiapine 50 mg/day. She was referred to gynecology and also psychiatry outpatient clinics for follow ups. In her first follow-up visit one week after discharge; it was seen that her mood elevation, psychomotor activity and speech rate were reduced and her YMRS score was 11. The lorazepam therapy dose was reduced and she was invited for the second follow up. With initial diagnose of manic episode due to drug usage, she was given haloperidol 10 mg/day, biperiden 5 mg/ day IM according to DSM-IV TR diagnostic criteria for bipolar affective disorder-I. After she was stabilized by intramuscular injectionlorazepam 3 mg/ day was added for maintenance. She was discharged with lorazepam 2mg/day, valproate 2000 mg/day, paliperidone 6mg/ day, quetiapine 50 mg/day one week later. She was recommended to go to out-patient clinic of gynecology and obstetrics again, after her mood was euthymic, as MPA was stopped. One week later, in her follow-up visit, her mood elevation, psychomotor activity and speech rate were reduced. YMRS score was 11. The lorazepam therapy was reduced and for redetermination she was invited for control after ten days.

One of the main reasons for termination of hormone replacement treatments including MPA during perimenopausal and early post-menopausal periods is its effects on mood (Li et al., 2000). In a study where

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estrogen receptor modulators (tamoxifen) and progestins (medroxyprogesterone acetate) were added to mood regulators of 51 manic female patients, it was seen that manic symptoms responded faster to treatment and more patients responded to the drug in MPA group compared to tamoxifen group therefore MPA has been considered as a new additional treatment in manic patients (Kulkarnietal., 2006).

On the other hand, MPA treatment was also implicated to worsen depressive symptoms in women (Nupur, 2001). In a study of 80 female patients who received MPA treatment, long-term treatment was found to increase depressive symptoms whereas short term treatment did not (Westhoff, 1995). In another study; psychiatric symptoms such as anger and hostility feelings, and physiologic signs such as eating and sleep disorders was increased in MPA using group at the 6th month compared to baseline (Kıyak, 2004). In a follow-up study, depression level was found significantly higher in patients who were receiving MPA (Civic et al.,2000). On the contrary, in a study where depressive symptoms were evaluated before and after MPA use in female patients with or without depression, MPA was considered safe in these patient groups (Rogines Velo et al., 2012). So, it has been suggested that MPA was not primarily related to depression and may increase depressive symptoms in patients with mood problems. It is suggested to be careful when using these drugs in patients with a known history of mood disorders (Westhoff, 1998).

Based on the above-mentioned considerations, studies indicated that MPA may be used in treatment of manic disorder, it may increase or may not affect depressive symptoms. But as we mentioned here, we observed symptoms of manic disorder following MPA administration in our bipolar patient who was on remission. To our knowledge, this is the first case report of MPA-induced manic episode in a patient with bipolar affective disorder. It should be kept in mind that MPA containing hormone preparations may lead to manic symptoms besides affecting depressive symptoms in patient groups with or without mood disorders.

One of the main reasons for termination of hormone replacement treatment during perimenopausal and early post-menopausal periods is its effects on mood (Lİ et al., 2000). These treatments include MPA. In a previous study, estrogen receptor modulators (tamoxifen) and progestins (medroxyprogesterone acetate) added to mood regulators were compared in 51 manic female patients (Kulkarni et al.,2006). Manic symptoms responded faster and larger in MPA group when compared to tamoxifen group. MPA has been considered as a new additional treatment in manic patients (Kulkarni et al.,2006). In contrast, we observed symptoms of manic disorder following MPA administration in our patient with bipolar affective disorder. She was on remission. Besides, MPA treatment worsened depressive symptoms in women (Nupur, 2001). In a study of 80 female patients who received MPA treatment, long-term treatment affected depressive symptoms whereas short term treatment was ineffective (Westhoff, 1995). Depressive symptoms were evaluated before and after MPA use in female patients with or without depression, and MPA was considered safe in those patient groups (Rogines Velo et al., 2012). Similarly, it has been suggested that MPA was not primarily related to depression and may increase depressive symptoms in patients with mood problems. However, there are other opinions suggesting to be careful when using these drugs in patients with a known history of mood disorders (Westhoff, 1998). Conversely, In MPA using group at the 6th month compared to baseline (0.month), psychiatric symptoms such as anger and hostility feelings, and physiologic signs such as eating and sleep disorders increased (Kıyak, 2004). In a follow-up study of 6 months and 3 years, depression level was found significantly higher in patients who were receiving MPA (Civic et al.,2000). Based on the above-mentioned considerations, studies indicated that MPA may be used in treatment of manic disorder, it may increase or may not affect depressive symptoms. To our knowledge, this is the first case report of MPA-induced manic episode in a patient with bipolar affective disorder. It should be kept in mind that MPA containing hormone preparations may lead to manic symptoms besides affecting depressive symptoms in patient groups with or without mood disorders.

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JNBS 2015 Published by Üsküdar University www.jnbs.org

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