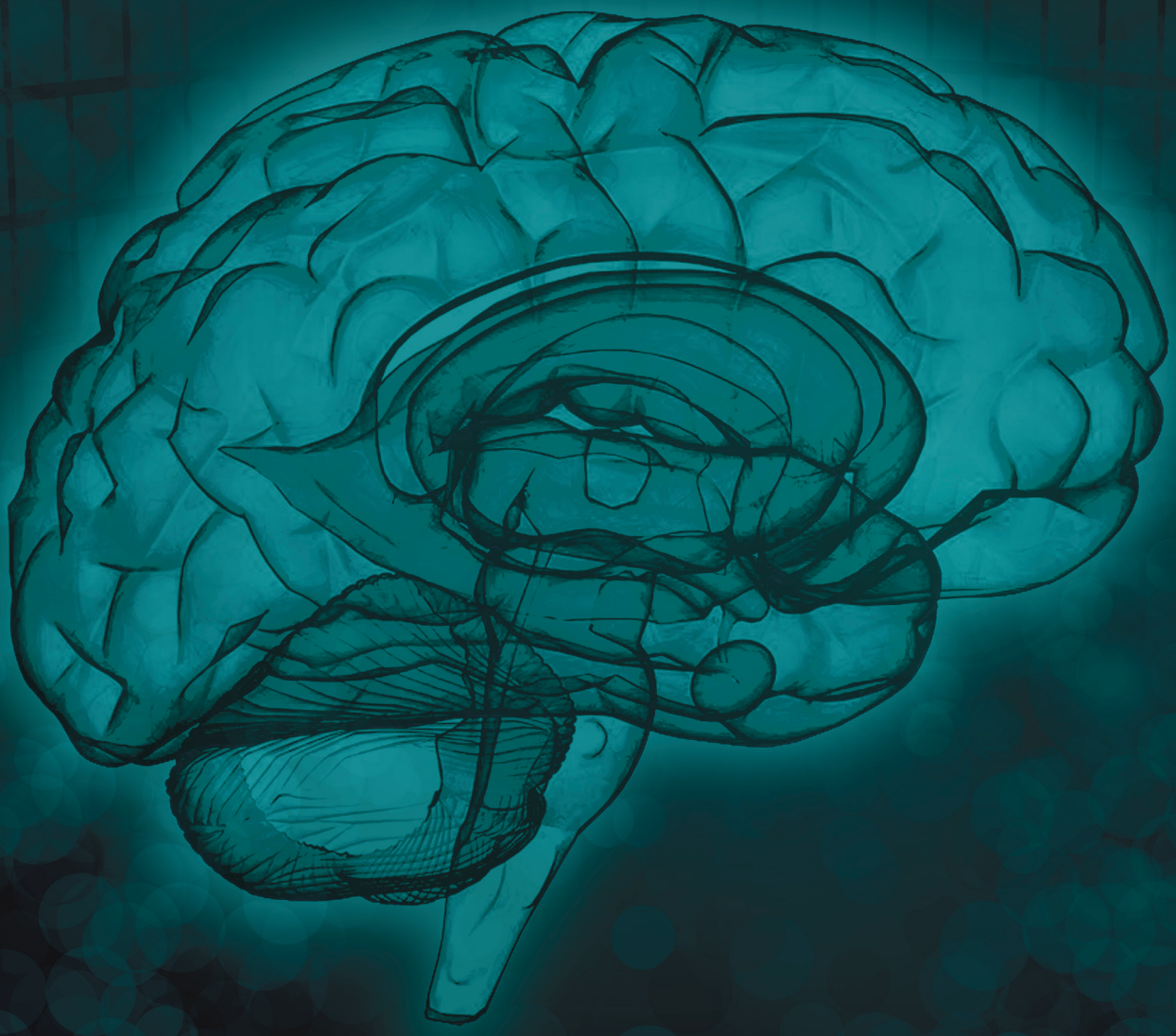
ISSN: 2147-5709

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES

Year: 2014 Vol:1 No:1

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ



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JNBS Published by Uskudar University

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

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The scope of the journal is broad. It covers many disciplines and spans molecules

(e.g., molecular neuroscience, biochemistry) through systems (e.g., neurophysiology, systems neuroscience) to behavior(e.g. cognitive neuroscience) and clinical aspects

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JNBS AND SCIENCE VOYAGE

In the first week of April in 2013, the President of the USA Mr. Obama started a new project with the president of NIH (National Institutes of Health). The name of the project was **'Brain Initiative and American Innovation'**, and briefly it was a press release on the declaration of a reformist and an advanced project support protocol which uses neurotechnology on brain studies. President Obama declared that "After Human Genome Project that has been followed by Post-genomic Era, resolving the mysteries of human brain promises a lot for future." He added that "by means of new treatment and diagnosis techniques to be found, American economy will get the best of it, and the investment in science will provide us with a greater profit."

The year was 1998. We attempted to bring the teleneuropsychiatry practices from the USA to Turkey. Since ISDN data transfer lacked the necessary substructure at that time, we failed to achieve our goal. However, we set up "the QEEG Brain Mapping system" as the diagnostic protocol for both children and adults. As for the treatment protocol, we pioneered measurability in treating neuropsychiatric diseases along with treatability by measuring the brain functions with the help of 'Neurobiofeedback and Computerized Cognitive Rehabilitation (Rehacom)' for the first time in Turkey. In the following years, we formed the treatment protocols of rTMS, tDCS and CES in the Brain Stimulus Laboratory. We still apply these systems successfully.

The year was 2011 and Üsküdar University was established as a thematic university in the field of "Behavioral Sciences and Health". Today, we have carried out some important substructures as the R&D Unit. In our Neuroscience Center: Functional MRI, EEG compatible with MR, 9 Neurobiofeedbacks, 5 Rehacom systems, 4 QEEG Brain Mapping systems are existing. In the Molecular Biology and Genetics Laboratory, Real Time PCR systems and DNA isolation substructure are now able to analyse 61 drug molecules and 13 toxic substances in the Clinical Pharmacogenetics and Toxicology Laboratory. By establishing Neuropsychopharmacology Research and Application Center, which is the third in the world, we have begun studies on experimental animals to search for drugs which will treat addiction and be an innovator for the treatment of schizophrenia.

Üsküdar University has added a course named "Project Culture" to all the departments including associate degree programs for the first time in Turkey to contribute to help Turkey be a science community because we expect every graduated student to have a universal perspective in the sense of project perception.

While making progress on this science voyage, NPISTANBUL Neuropsychiatry Hospital, which is the strategic partner of our university, supported us morally and financially. It is not only a well-known hospital for treating intractable and resistant disorders, but it has also made a lot of investments in R&D Unit. It published a periodical called 'NPAKADEMI'. Following its foundation, Üsküdar University decided to publish JBNS, and along with the first issue I desire it will bring about beneficial and useful results on science voyage.

20.04.2014
Prof. Dr. Nevzat TARHAN

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JNBS VE BİLİM YOLCULUĞU

Yıl 2013 ve Nisan'ın ilk haftası ABD Başkanı Obama NIH (Ulusal Sağlık Enstitüsü) başkanını yanına alıp bir proje başlatıyor. Projenin adı **'Brain Initiative and American Innovation'**, özetle beyin araştırmalarında nöroteknolojiyi kullanan yenilikçi ve ileri bir projeler destek protokolunun beyanı amaçlı basın açıklaması. Başkan Obama 'İnsan Genom' projesinden sonra post genomik çağa girildiği bu çağda insan beyninin sırlarının çözülmesinin çok şey vaad ettiğini deklare etti. Böylece bulunacak yeni tedavi ve tanı teknikleri ile ABD ekonomisi kazançlı çıkacak, bilime yapılacak yatırım bize fazlası ile geri döneceğini söyledi.

Yıl 1998, Türkiye'ye ABD'den Telenöropsikiyatri uygulamalarını getirmek için girişimde bulunmuştuk. O tarihte ISDN veri aktarımı alt yapısı olmadığı için başarılı olamamıştık. Ancak aynı zamanda hem çocuklara hem de erişkinlere tanı protokolu olarak 'QEEG, Beyin Haritalaması' sistemini kurduk. Tedavi protokolü olarak da Türkiye'de ilk defa 'Neurobiofeedback ve Kompüterize kognitif rehabilitasyon (Rehacom)' ile nöropsikiyatrik hastalıkların tedavisinde ölçülebilirliği, beyin işlevlerini ölçerek tedavi edilebilirliğin öncülüğünü yaptık. Sonraki yıllarda Beyin Uyarım Laboratuvarı'nda rTMS, tDCS, CES tedavi protokollarını oluşturduk. Halen bu sistemleri başarı ile uyguluyoruz.

Yıl 2011 ve Üsküdar Üniversitesi "Davranış Bilimleri ve Sağlık" alanında tematik bir üniversite olarak kuruldu. Bugün ARGE birimi olarak önemli alt yapıları gerçekleştirdik. Nörobilim merkezimizde; fonksiyonel MRI, MR uyumlu EEG, 9 adet Nerubiofeedback, 5 Adet Rehacom sistemi, 4 adet QEEG Brain Mapping sistemi mevcut. Molekuler Biyoloji ve Genetik Laboratuvarı'nda Real Time PCR sistemleri ve DNA izolasyon alt yapısı, Türkiye'de ilk olan Klinik Farmakogenetik ve Toksikoloji Laboratuvarı'nda 61 adet ilaç molekülü 13 adet uyuşturucu (Toksik) madde analizi yapar hale geldik. Nöropsikofarmakoloji Uygulama Araştırma Merkezi'nin dünyada üçüncü örneğini kurarak deney hayvanlarında şizofreni tedavisi öncüsü veya bağımlılık tedavisi amaçlı ilaç araştırmalarına başladık.

Üsküdar Üniversitesi Türkiye'nin Bilim toplumu olmasına katkı sağlamak için Türkiye'de ilk önlisans dahil bütün bölümlere proje kültürü dersini koydu. Mezun olan her öğrenci proje algısı açısından evrensel bir bakışa sahip olmalıydı.

Çıktığımız bilim yoculuğunda ilerlerken Üniversitemizin stratejik ortağı NPİSTANBUL Nöropsikiyatri Hastanesi, anlamlı maddi ve manevi destek oldu. Zor vakaları, tedaviye dirençli olguları tedavi etmekle ünlenmiş bir hastane iken ARGE'ye de yatırım yapmayı ihmal etmedi. NPAKADEMİ isimli bir dergi çıkardı. Üsküdar Üniversitesi, kurulması ile birlikte JBNS'ı çıkarma kararı aldı, ilk sayı ile birlikte bilim yolculuğunda hayırlı ve faydalı sonuçlara sebep olunmasını diliyorum.

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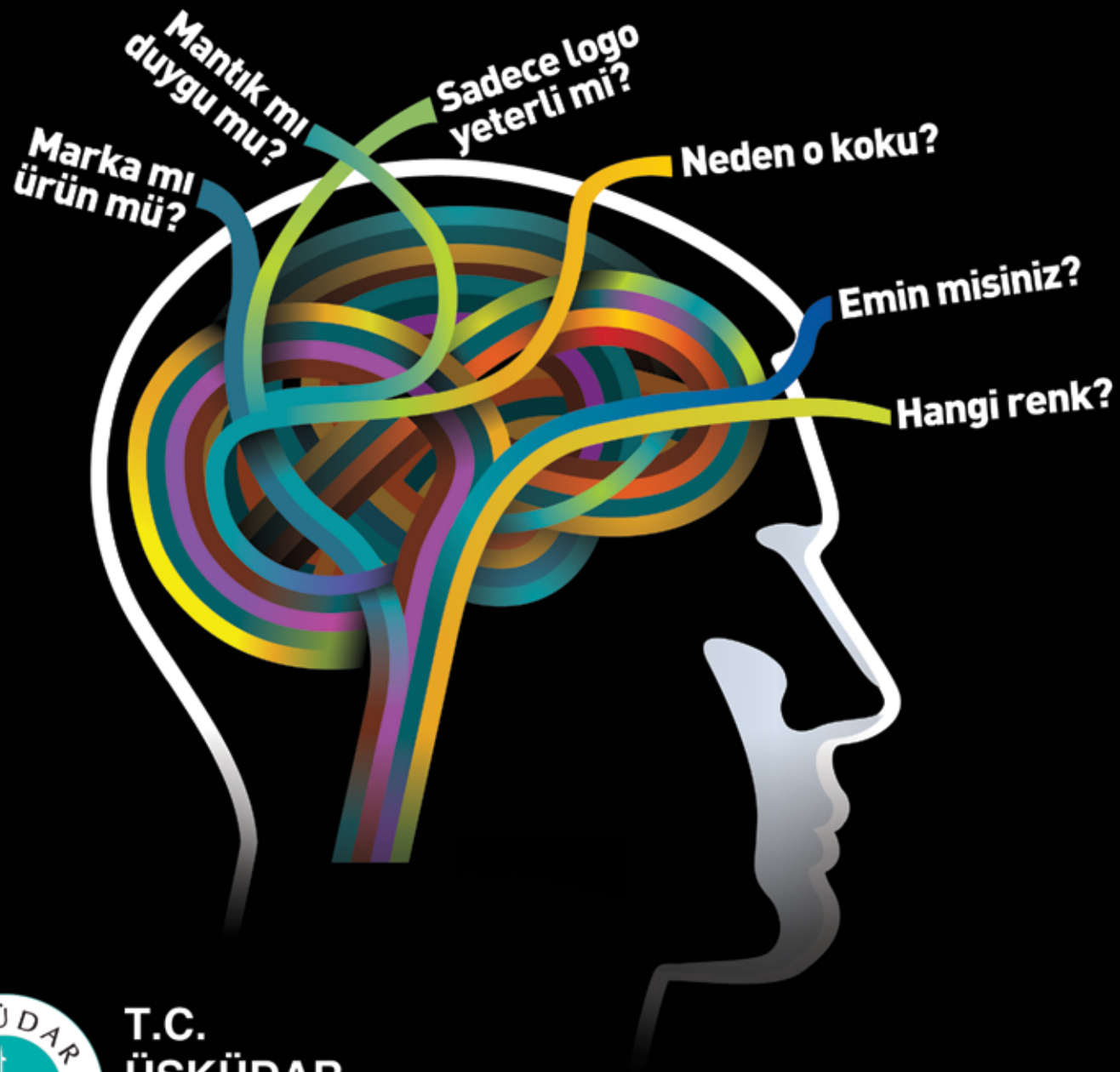

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MINI-REVIEW

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1386758794

Article history:
Received 24 December 2013
Received in revised form 31 December 2013
Accepted 10 January 2014

CEREBELLAR MUTISM
SEREBELLAR MUTİZM

Gökşin Şengül [*1], Mehmet Hakan Şahin [1]

Abstract

Cerebellar mutism has been a well-known clinical entity that develops in a subset of patients who have undergone resection of posterior fossa tumors. It is characterized by severely diminished or absent speech output as well as other neurological, cognitive, and behavioral impairments. Though increasing numbers of case reports and literature reviews that indicate the cerebellar mutism, the mechanism of occurrence and best therapeutic approaches are not established. This article reviews current status of this devastating complication with respect to epidemiology, anatomical substrate, pathophysiology, risk factors, treatment options, prognosis and prevention.

Keywords: Cerebellar, complication, mutism, posterior fossa, tumor

Özet

Serebellar mutizm arka çukur tümörlerinin çıkarılması sonrasında bir grup hastada geliştiği bilinen bir klinik tablodur. Bu tablo, konuşmanın bozulması veya hiç konuşamama ile birlikte diğer nörolojik, bilişsel ve davranışsal bozukluklar ile karakterizedir. Literatürde serebellar mutizmle igili vaka raporları ve derlemelerdeki artışa rağmen oluşum mekanizması ve etkin tedavi yaklaşımları henüz belirlenememiştir. Bu makalede, bu yıkıcı komplikasyonun görülme sıklığı, anatomik temeli, patofizyolojisi, risk faktörleri, tedavi seçenekleri, sonucu ve korunması açısından güncel durumu gözden geçirilmiştir.

Anahtar Kelimeler: arka çukur, komplikasyon, mutizm, serebellar, tümör

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1. Introduction

Cerebellar mutism (CM) has been defined as muteness following lesion of the cerebellum as opposed to the cerebrum or the lower cranial nerves. It is characterized by delayed onset, limited duration, and usually long-term linguistic sequellae. It occurs rarely isolated but often together with other neurological, emotional and behavioral disturbances. Cerebellar mutism most frequently occurs in pediatric population following surgical treatment of posterior fossa tumors (Gudrunardottir et al., 2011, Küper&Timmann, 2013). It can also be seen following trauma, vascular events, infection, pineal gland tumor removal of pineal gland tumors, or in adults (Baillieux et al., 2007, Ellis et al, 2011, Ersahin et al., 1997, Frassanito et al., 2009, Ildan et al., 2002, Papavasiliou et al., 2004). It was first anecdotally reported by Stein et al. in 1972, and later by Hirsch et al. and Pierre-Kahn et al. However, Yonemasu and Rekate et al. are generally considered the first who have reported this peculiar syndrome in more detail. Since 1985, more than 400 cases of CM have been described in the literature (Gudrunardottir et al., 2011, Küper&Timmann, 2013, Pitsika&Tsitouras, 2013).

2. Epidemiology

The incidence of cerebellar mutism after posterior fossa surgery in children is reported to range between 8%-39% in the recent literature (Pitsika&Tsitouras, 2013). Mean ages were 6-7 years in these reports. In adults, the incidence of postoperative cerebellar mutism is less frequent and was present in 1% of the reported cases. Brainstem involvement by the tumor, tumor type, midline location and preoperative language impairment were determined as risk factors for development of cerebellar mutism (Di Rocco et al., 2011, Law et al., 2012, Tasdemiroglu et al., 2011).

3. Pathophysiology

The exact reason for cerebellar mutism has not been agreed upon. Bilateral interruption of the dentato-thalamo-cortical pathway is suggested to be the main cause of cerebellar mutism. Interruption of this pathway results in cerebro-cerebellar diaschisis which has been described as a temporary functional deactivation of an intact brain region remote from the lesion area. Delayed onset and resolution of the mutism suggest that a secondary pathophysiological mechanism initiated by the tumor resection mediates the cerebellar mutism. Proposed mechanisms involve cerebellar perfusional disturbances, postoperative edema, transient dysregulation of neurotransmitter release and functional disruption of the white matter bundles containing efferent axons within the superior cerebellar peduncles (Gudrunardottir et al.,

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2011, Ozgur et al., 2006, Pollack et al., 1995, Puget et al., 2009).

4. Clinical features

Cerebellar mutism has three characteristic features. First, cerebellar mutism is not present directly after surgery, but develops within a time interval of hours to several days after the surgical intervention (Robertson et al., 2006). Second, mutism is always transient. The duration is variable, lasting from a few days to several months (Ildan et al., 2002). Recovery of mutism occurs spontaneously and can occasionally be rapid and complete (Gelabert-González&Fernández-Villa, 2001). Finally, after the mutistic phase, symptoms of motor speech and language impairments, cognitive, emotional and behavioral disturbances remain to various extends.

5. Treatment

There is no established treatment modality exists for cerebellar mutism. Pharmacological and speech therapy has been used to reverse the symptoms of mutism. Bromocriptine, zolpidem and fluoxetine were found to beneficial in sporadic cases but have not been systematically assessed (Akhaddar et al., 2012, Caner et al., 1999, Shyu et al, 2011). But there is a complete lack of trials that explore the efficacy of both pharmacological and speech therapy during the recovery phase.

6. Prevention

Preventive strategies to protect dentate nucleus and superior cerebellar vermis can be effective for reducing the incidence of cerebellar mutism. Several surgical strategies are recommended to avoid from this complication. Piecemeal removal of the tumor, access to the tumor without splitting the vermis by telovelar approach and short-lasting retraction of the cerebellar vermis were reported to provide significant advantages in the prevention of cerebellar mutism (Aguiar et al., 1995, Frassanito et al., 2009, Mussi&Rhoton, 2000).

7. Prognosis

Prognosis is variable in patients suffering from cerebellar mutism. The duration of symptoms after surgery seems to be correlated with functional prognosis. If the symptoms persist for more than four weeks, patients will have a high risk of suffering language dysfunction at postoperative 1st year (Robertson et al., 2006). Patients have improved quality of life if they receive pharmacological, speech therapy and individual educational support with psychiatric examination. There are no reports in the literature in regards to a recurrence of cerebellar mutism with subsequent surgeries.

8. Conclusion

Over the past 30 years, more than 400 cases of mutism and associated behavioral and personality changes have been reported after the removal of posterior fossa tumors. Advanced neuroimaging techniques could contribute to identification of high-risk patients preoperatively and allow for more effective surgical planning that should focus on maximal tumor resection with minimal risk to important neural structures. Properly designed multicenter trials are needed to provide stronger evidence regarding effective prevention of cerebellar mutism and the best therapeutic approaches for such patients with a combination of pharmacological agents and multidisciplinary speech and behavior augmentation.

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RESEARCH ARTICLE

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1389129470

Article history:
Received 08 January 2014
Received in revised form 2 February 2014
Accepted 12 February 2014

MECHANISMS OF SHORT-TERM FALSE MEMORY FORMATION
KISA SÜRELİ SAHTE BELLEK FORMASYONLARININ MEKANİZMALARI

Achille Pasqualotto[123*], and Michael J. Proulx[1]

Summary

False memories are the erroneous recollection of events that did not actually occur. False memories have been broadly investigated within the domain of long-term memory, while studies involving short-term memory are less common and provide a far less detailed 'picture' of this phenomenon. We tested participants in a short-term memory task involving lists of four semantically related words that had to be matched with a probe word. Crucially, the probe word could be one of the four words of the list, it could be semantically related to them, or it could be semantically unrelated to the list. Participants had to decide whether the probe was in the list. To this task we added articulatory suppression to impair rehearsal, concurrent material to remember, and changes to the visual appearance of the probes to assess the mechanism involved in short-term memory retrieval. The results showed that, similarly to the studies on long-term memory, false memories emerged more frequently for probes semantically related to the list and when rehearsal was impaired by concurrent material. The visual appearance of the stimuli did not play an important role. This set of results suggests that deep semantic processing, rather than only superficial visual processing, is taking place within a few seconds from the presentation of the probes.

Keywords: false memories; short-term memory; consciousness; semantic processing.

Özet

Sahte anılar aslında meydana gelmemiş/yaşanmamış olayların hatalı bir şekilde hatırlanmasıdır. Kısa süreli belleği içeren çalışmalar daha az yaygın ve bu fenomenin çok daha az detaylı bir "resmini" ortaya koymaktayken, sahte anılar uzun süreli belleğin alanı içerisinde geniş kapsamda araştırılmıştır. Çalışma kapsamında, katılımcıları birbiriyle semantik olarak ilişkili ve araştırılan kelime ile eşleştirilme zorunluluğu olan dört kelimelik listeleri içeren bir kısa süreli hafıza görevi ile test ettik. Kritik olarak, araştırılan kelime listedeki dört kelimeden biri, listedeki kelimelerle semantik olarak ilişkili, ya da listedeki kelimelerle semantik olarak ilişkisiz olabilirdi. Katılımcıların araştırılan kelimenin listede olup olmadığına karar vermeleri gerekmekteydi. Bu ödeve, kısa süreli bellekten geri çağırma mekanizmasını değerlendirmek için tekrarlamayı/prova etmeyi bozacak fonolojik baskılama, hatırlamayı eşzamanlı materyal ve araştırılan kelimenin görsel görünümüne değişiklikler ekledik. Sonuçlar, uzun süreli bellek çalışmalarına benzer şekilde, tekrarlama eşzamanlı materyallerle bozulduğunda ve araştırılan kelimeler listeyle semantik olarak ilişkili olduğunda sahte anıların daha sıklıkla ortaya çıktığını göstermiştir. Uyaranın görsel görünümünün önemli bir rolü yoktur. Bu sonuçlar kümesi, yüzeysel görsel süreçler yerine, derin semantik işlemenin araştırılan kelimelerin gösterilmesinden sonraki birkaç saniye içerisinde gerçekleştiğini göstermektedir.

Anahtar Kelimeler: sahte anılılar, kısa süreli bellek, bilinç , semantik işleme

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1. Introduction

Memory can be fallible. Information in long-term memory (LTM) can either be successfully recalled or forgotten. Besides failing to remember events that actually occurred, two interesting errors can arise during recall or recognition: remembering events that did not happen or remembering them differently (Clancy et al., 2002; Loftus, 1996). In particular, a class of the former is referred to as 'false memories' (Deese, 1959; Jou & Flores, 2013; Pasqualotto et al., 2013; Robinson & Roediger, 1997; Roediger & Mcdermott, 1995; Roediger et al., 2001). Theories of false memory generally consider LTM, including associative activation or source monitoring failures (Collins & Loftus, 1975; Flegal et al., 2010; Quillian, 1967). False long-term memories are reliably produced with the Deese-Roediger-McDermott (DRM) paradigm (Deese, 1959; Roediger & Mcdermott, 1995).

In classic DRM experiments, participants listen to lists of words semantically related to a single non-studied theme, or 'related lure' (e.g Roediger et al., 2001). For example, participants may hear (or read): *thread, pin, eye, etc.,* all semantically associated to the related lure needle. Then participants attempt to recall the list, usually through a free-recall or a recognition test, which includes studied words, non-studied related words and non-studied unrelated words. The results from most DRM experiments (e.g. Roediger & Mcdermott, 1995) demonstrate that participants falsely recall non-studied related words. Moreover Roediger and colleagues found that confidence ratings, or remember-know (where 'remember' entails that an individual can consciously remember the occurrence of an episode, or whether s/he can only vaguely 'know' that it happened), indicate that participants are fairly confident in recognizing the non-studied related word as a studied word (Rajaram & Roediger, 1997).

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Although the majority of research on false memory has been focused on LTM, research on short-term memory (STM) illustrates that this system is also vulnerable to various interferences such as phonological and visual similarity (Nairne, 2002; Neath, 2000). Recent studies have established that robust false memories also exist in STM (Atkins & Reuter-Lorenz, 2008; Coane et al., 2007; Flegal, et al., 2010). These findings indicate that the mechanisms underlying false memories formation might be delay invariant. Interestingly, the findings are consistent with unitary models of memory which consist of delay-invariant storage and retrieval processes (Jonides et al., 2008; Nairne, 2002). In other words, both LTM and STM are affected by this type of distortion.

The aim of this experiment is to investigate the mechanisms of false memory formation within STM in a study that replicates and extends those by Flegal et al. (2010) and Macé and Caza (2011). On the one hand, Flegal et al. highlighted that there was no difference between false memories in both STM and LTM tasks, however they did not take into account the processing differences across these two memory stores (e.g. articulatory suppression to impede rehearsal of the material). In particular, rehearsal is an important factor for the creation and maintenance of STM (Atkinson & Schiffrin, 1968) and this was not explored in their study using mathematical verification, which does not requires rehearsal. In contrast, we asked participants to remember a pair of numbers as a concurrent memory task, where the digits had to be sub-vocally rehearsed to be maintained together with the words of the list (Baddeley et al., 1984; Atkins et al., 2011). On the other hand, Macé and Caza did use auditory presentation and took into account articulatory suppression, yet they used 'mixed' lists of words (i.e. where words where associated to a common or not). Additionally, they were using lists of six words, which are toward the high-end of the STM span of 7 ± 2 (Miller, 1956). Therefore, long lists may have triggered memory processes beyond STM. Additionally, we investigated the role of the visual appearance of the stimuli by changing their font across presentation and testing. An effect of this manipulation would suggest that words underwent a very superficial processing based on visual appearance rather than 'deeper' semantic processing (Craik & Lockhart, 1972; Craik & Tulving, 1975).

In sum, here we employed a visual presentation of 'purely' themed 4-word lists, investigated the role of articulatory suppression (Baddeley & Hitch, 1974; Baddeley & Lewis, 1981), and of the visual appearance of the probes (i.e. font). We predict that probes semantically related to the list will be falsely recognised at a higher rate than those unrelated (Deese, 1959; Roediger & McDermott, 1995; Brainerd et al., 1995; Gallo & Roediger, 2002). Moreover, we predict that articulatory suppression would lead to an increase in the false recognition of related probes and decrease in the correct recognition of target probes.

To infer the level of stimulus processing, throughout the experiment the font of the probes was either maintained lowercase as within the list, or changed to uppercase. Prior studies on semantic memory have changed the font of the probe to infer the level of processing (i.e. visually and superficial, or semantically and deep), however such a manipulation has not been tested in the domain of false short-term memory (J.H. Coane, personal communication). Thus, in case of superficial processing, a font change from the lowercase of list to the uppercase of the probe would, for example, trigger more rejections of the related lures. In case of deeper processing (Craik & Tulving, 1975; Rhodes & Castel, 2008) we should not find such effect.

We also included the remember-know rating (Tulving, 1985) to investigate participants' phenomenological experience associated to the generation of false memories. In particular we want to determine whether false memories are more associated to a conscious 'remembering' of seeing the probe among the words of the list, or whether it is more connected to a vague 'knowing' that it was there –that is, without a conscious memory, but with a 'feeling' (see Slotnick & Schacter, 2004).

2. Method

Participants

We tested 66 undergraduate students (21 were males) of the Queen Mary University of London. Their age ranged from 19 to 22. Participants signed the consent form that was approved by the local Ethics Committee, thus complying with the Declaration of Helsinki on research ethics.

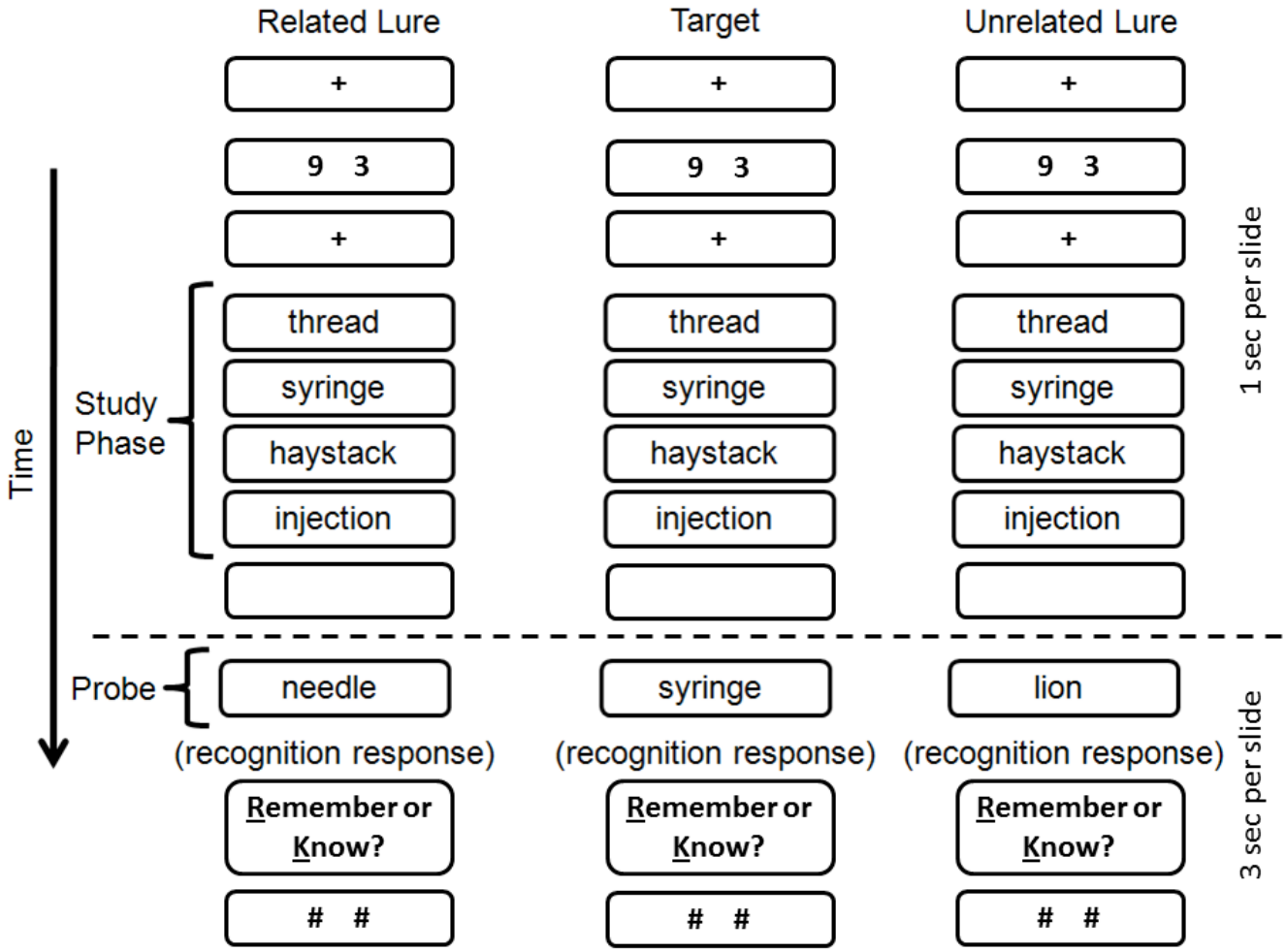
Procedure

Each participant was provided with a blank booklet containing seven pages. The first page was used for the age, sex, and answers to the two practice trials. Pages 2-6 contained the space for answering the 96 trials. The final page contained questions about their overall impression of the experiment. Participants were all seated in a lecture-theatre where they viewed the screens on which the words were presented.

Each trial containing four semantically related words. Each list was followed by a Related, a Target, or an Unrelated probe (32 probes for each of the three types; see Figure 1). Lists were extracted from Flegal et al. (2010). The stimuli were presented in PowerPoint using the timing controls within the program to control stimulus duration.

In Block 1, in each trial participants were presented with a pair of numbers that they had to sub-vocally rehearse and then recall at the end of each trial. Then it followed the list of four words where each word was presented for one second on the screens. After a one-second pause, a probe word was presented for three seconds. Participants wrote down whether the probe word was 'Old' (i.e. present in the list) or 'New'. The font of the probe was either Lowercase (as for the words of the list) or Uppercase. After the probe was presented, participants were prompted for three seconds to write whether they 'Remembered' the probe being showed on the screen (i.e. they could consciously remember it as displayed on the screen) or whether they more simply 'Knew' that it had been shown. The remembered-known statement was required only when the probe was considered Old. Finally, the '# #' on the screen prompted participants to write down the two numbers presented at the beginning of the

Figure 1: The depiction of a trial in Block 1



Notes: Related Probes were words that had not been presented in the preceding list but that were semantically related to them, Target Probes were words that had been presented in preceding list, and Unrelated Probes were words that had not been presented in the preceding list and that were unrelated to them. In Block 2 there was not neither the presentation of the pair of digits (i.e. "9 3") nor their test (i.e. "# #").

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trial (see Figure 1).

After the completion of Block 1, participants had a longer break before performing Block 2. Here participants were not presented with digits to rehearse; all the remaining details were the same is in Block 1, except that new lists were showed. The entire experiment took about 1 hour.

3. Results

For each participant we calculated the average number of errors across the twelve conditions (e.g. if the probe was judged as 'New' when it was actually 'Old' this was recorded as an error). Mean errors across participants are reported in Table 1. As a control for number rehearsal, we discarded the trials where participants could not remember the two rehearsed numbers. This was quite rare and involved less than 1% of the total number of trials. Our statistical approach involved an analysis of variance with the main factors covering the experimental design (e.g. type of rehearsal, type of probe, etc.); additionally interactions among main factors were further investigated by using Bonferroni-corrected post-hoc analyses.

We performed a 2x3x2 within-subjects ANOVA on the average error rates with Block (articulatory suppression, or rehearsal), Probe Type (Related, Target, or Unrelated) and Case (Uppercase or Lowercase) as variables. We found a significant effect of the Block [$F(1,64)=28.09$, $p<.01$] where rehearsed lists were better performed (0.19 average error) than when there was articulatory suppression (0.47 average error). Probe Type was significant too [$F(2,63)=41.46$, $p<.01$] with Unrelated probes generating least errors (0.04 average error), Target probes being in between (0.34 average error), and Related probes generating most errors (0.61 average error). The Case was not significant [$F(1,64)=1.76$, $p>.05$]. Finally we found a significant interactions between Block and Probe Type [$F(4,61)=13.21$, $p<.01$], and across Block, Probe Type, and Case [$F(6,60)=5.47$, $p<.05$]. No other interaction reached the significant level.

We corrected for the multiple comparisons by using the Bonferroni post-hoc analysis (see Figure 2). Block by Probe Type revealed that Related probes and articulatory suppression produced more errors than any other condition (0.90 average error), that Target probes with articulatory suppression produced the second biggest error rates (0.5 average error), while Unrelated probes

The results for Block 1 and 2

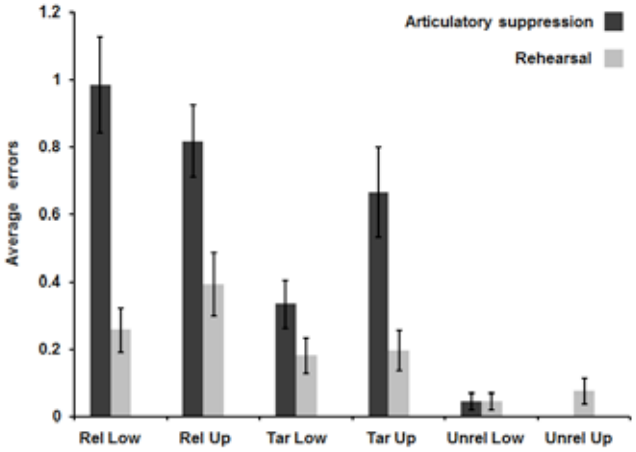
		Block 1		Block 2	
		Lower Case	Upper Case	Lower Case	Upper Case
Related	Mean	0.98	0.82	0.26	0.39
	(SD)	(1.16)	(0.88)	(0.53)	(0.76)
Target	Mean	0.33	0.67	0.18	0.20
	(SD)	(0.59)	(1.09)	(0.43)	(0.47)
Unrelated	Mean	0.05	0	0.05	0.08
	(SD)	(0.21)	(0)	(0.21)	(0.32)

Notes: Mean and standard deviations error rates associated to the Block 1 (articulatory suppression) and Block 2 (rehearsal) across the three types of probes (Related, Target, and Unrelated) and the two type of case (Lowercase and Uppercase).

in both Block 1 and 2 where the best performed (0.02 and 0.06 average error respectively) [all $p<.05$]. In sum, post-hoc contrasts confirmed that articulatory suppression and Related probes produced more errors –namely, false memories. Finally, the interaction Block by Probe Type by Case confirmed that Related probes both Uppercase and Lowercase in Block 1, together with the Target Uppercase probes in Block 1 were those generating more errors [all $p<.05$] (see Figure 2).

We further analysed the phenomenological experience relative to the creation of false memories, thus focusing on the errors produced by the participants. Therefore, for the trials that *did* generate false memories across the Related and Unrelated conditions (i.e. when a New probe was judged as Old) we calculated how many times these erroneously chosen probes were experienced as Remembered and how many were experienced as Known. In other words we tried to determine the conscious experience associated to trials generating false memories. On these means it was performed a 2x2x2x2 within-subjects ANOVA with Attribution (Remembered or Known), Block (articulatory suppression, or rehearsal), Probe Type (Related or Unrelated), and Case (Uppercase or Lowercase) as variables. Attribution was not significant [$F(1,64)=1.62$, $p>.05$]. Block was significant [$F(1,64)=21.49$, $p<.01$] indicating that articulatory suppression produced more Remember-Know judgements (i.e. errors) (2.79 on average) than when rehearsal was allowed (1.07 on average). Ultimately, this confirms that articulatory suppression produced more false memories (errors) than when rehearsal was allowed. We found a significant effect of the Probe Type [$F(1,64)=89.23$, $p<.01$], where Related probes triggered higher Remember-Know ratings (3.72 on average) than Unrelated probes (0.14 on average), thus confirming that Related probes produced more false memories. The case was not significant [$F(1,64)<1$]. The interaction Attribution by Probe Type was marginally significant [$F(3,62)=2.79$, $p=.10$]. We investigated this interaction with the Bonferroni post-hoc analysis and found that Related probes (i.e. those generating most of the false memories) were more often judged as 'known' rather than 'remembered' [$p<.05$]. Finally, the interaction Block by Probe Type was significant [$F(3,62)=32.73$, $p<.01$], that further confirmed that articulatory suppression and Related probes generated more Remember-Know judgements and thus more false memories. No other interaction was significant.

Figure 2: Recognition task results



Notes: Average errors associated to the recognition task where 'Articulatory suppression' indicates Block 1 and 'Rehearsal' Block 2. Additionally, 'Rel' stands for Related probes, 'Tar' for Target probes, 'Unrel' for Unrelated probes, 'Low' for Lowercase, and 'Up' for Uppercase. Error bars represent the ± SE.

4. Discussion

In the present study we investigated the factors influencing the generation of false memories in STM. We found that the main factors were: the Probe Type and the possibility to use sub-vocal rehearsal. Related probes generated more false memories than Unrelated probes. This is consistent with previous studies such as that by Atkins and Reuter-Lorenz (2008), Flegal et al. (2010), and Coane et al. (2007) who all observed a strong effect of Related lures in STM memory tasks. This suggests that semantic processing does occur at the STM level, thus that deep semantic processing occurs rapidly after stimulus presentation. These results expand the scope of theories such as the fuzzy trace theory (Brainerd et al., 1995) and the activation monitoring theory (Gallo & Roediger, 2002). The fuzzy trace theory hypothesises that the memory traces of the lists are actually fuzzy, and false memories are generated by the semantic relation shared by probes and the fuzzy traces of the list (Arndt, 2011). The activation monitoring theory (Gallo & Roediger, 2002) proposes that the presentation of a probe causes an activation which spreads to the 'neighbouring' items stored within semantic memory (Collins & Loftus, 1975; Quillian, 1967). The spread of activation is monitored by processes which determine its 'authenticity' (i.e. that is, which distinguish between 'real' activation and the mere spread of activation from neighbours). False memories occur when a probe triggers a level of activation sufficient to bypass the monitoring processes (Gallo, 2006). Therefore, our results suggest that the same theories on false memories formation in LTM are valid for STM as well. In particular, considering the activation monitoring theory, the monitory process can be represented by the central executive component of the STM/working memory (Baddeley, 1986).

Additionally, another main result was the crucial role played by rehearsal in the accuracy of STM (see Macé & Caza, 2011). Thus, when participants were prevented from sub-vocally rehearsing the words of the list, this had an overall negative impact on STM performance.

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Baddeley's working memory model (Baddeley, 1986) uses rehearsal to consolidate memory traces, thus articulatory suppression results in the failure of proper memory formation. Therefore, our results can be explained by the general cost produced by articulatory suppression, which can be even more deleterious when coupled with probes Related to the words of the list.

There was a weak effect of the font manipulation, suggesting that words underwent deep semantic processing (Craik & Tulving, 1975). The sole significant effect was to render more difficult the recognition of Target probes (i.e. words that were actually on the list) when sub-vocal rehearsal was suppressed (see Figure 2). In this case, participants relied more on the visual features of the words to encode them in STM. Aside this effect, the significant level of false memories for Related probes implies that participants mainly encoded the words non-visually. This processing rapidity is supported by behavioural data on both semantic and non-semantic material (Kovács, 1996; Longtin &Meunier, 2005; Marr & Marr, 1976) and electrophysiological evidence (Penolazzi et al., 2007; Hinojosa et al., 2004).

The phenomenological experience more associated to false memories formation was of vaguely Knowing, rather than Remembering, that the probe was in the list. This is different from previous results (e.g. Flegal et al., 2010), reporting that false memories are more associated to consciously Remembering a Related probe being in the list. This difference perhaps arises from the more extensive manipulations to the stimuli: here participants had to deal with articulatory suppression, remembering antagonist material (pair of numbers), and changes in typeface in addition to the remembering the list of words and rejecting incorrect probes. This may have triggered a higher cognitive effort, resulting in the feeling that that the task was quite demanding and thus making participants less assertive in their judgements – thus, preference for Knowing over Remembering. In fact, in support of this line of reasoning, Knowing was chosen more in the more demanding conditions (i.e. Related probes and articulatory suppression).

In sum, the present study provides further evidence that the creation of false memories can occur in STM (Coane et al., 2007; Flegal et al., 2010) by showing that semantic processing is already taking place and that visual cues associated to the stimuli are irrelevant, thus supporting the hypothesis that semantic processing occurs early. Future studies should address if such early 'high level' processing is performed at the level of primary sensory cortices, which are thought to be involved only in basic perceptive aspects. This may not be too surprising as the attribute of the sensory specificity (e.g. primary visual cortex specific for visual input) seems to fade (Ghazanfar & Schroeder, 2006; Pasqualotto & Proulx, 2012).

Acknowledgements

This work was supported by a Marie Curie IEF (grant number: PIEF-GA-2010-274163) and a grant from the EPSRC (EP/J017205/1). We thank Ms B. Ogbodo for helping with testing.

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Legends

Figure 1: The depiction of a trial in Block 1. Related Probes were words that had not been presented in the preceding list but that were semantically related to them, Target Probes were words that had been presented in preceding list, and Unrelated Probes were words that had not been presented in the preceding list and that were unrelated to them. In Block 2 there was not neither the presentation of the pair of digits (i.e. "9 3") nor their test (i.e. "# #").

Figure 2: Average errors associated to the recognition task where 'Articulatory suppression' indicates Block 1 and 'Rehearsal' Block 2. Additionally, 'Rel' stands for Related probes, 'Tar' for Target probes, 'Unrel' for Unrelated probes, 'Low' for Lowercase, and 'Up' for Uppercase. Error bars represent the ± SE.

Table 1: Mean and standard deviations error rates associated to the Block 1 (articulatory suppression) and Block 2 (rehearsal) across the three types of probes (Related, Target, and Unrelated) and the two type of case (Lowercase and Uppercase).

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CASE SERIES

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1392036730

Article history:
Received 02 January 2014
Received in revised form 21 January 2013
Accepted 30 January 2014

QEEG RELATED CHANGES FOLLOWING THE TREATMENT OF ANXIETY DISORDERS: CASE SERIES

ANKSİYETE BOZUKLULUKLARINDA TEDAVİSİ SONRASINDA QEEG DEĞİŞİKLİKLERİ: OLGU SERİSİ

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Abstract

Patients with anxiety spectrum disorders are a highly heterogeneous group, requiring new therapeutic strategies and individualized treatment monitoring. Today, there is a growing interest for implementing biological approaches to clinical practice in psychiatry. Quantitative EEG is an excellent tool in this regard, though it has been widely underestimated when compared to recent neuroimaging techniques. In this case series, we presented four cases with a different diagnosis of anxiety spectrum disorder and evaluated their qEEG changes before and after the treatment. In addition, we also calculated the so-called EEG cordance values as an index of cerebral perfusion and cingulate cortex activity. According to the results, there appears to be an increase in the frontal beta and theta band in our cases, which has responded to treatment. In regards to the cordance values, we found that there was a reduction in the prefrontal regions up to %38 percent following the treatment. Based on previous studies, this may also indirectly suggest reduction in the cingulate cortex activity. The possible implications of these findings were discussed. Taken together, this case series highlighted the potential use of qEEG power values, normative z-scores and cordance values in treatment response monitoring of anxiety spectrum disorders.

Keywords: Anxiety disorders, qEEG, cordance, treatment monitoring

Özet

Anksiyete bozuklukları yeni tedavi ve bireye özel izlem stratejilerinin geliştirilmesi gereken heterojen bir hastalık grubudur. Günümüzde biyolojik yaklaşımların psikiyatri klinik pratiğine aktarılmasına her geçen gün artan bir ilgi olmaktadır. Bu bağlamda kantitatif EEG, diğer nörogörüntüleme yöntemlerine göre değeri görece olarak göz ardı edilse de oldukça etkin bir araçtır. Bu olgu serisinde, farklı anksiyete spektrum bozukluklarına sahip dört olgunun tedavi öncesi ve sonrası qEEG ölçümlemelerisunulmuştur. Buna ek olarak, "EEG kordans" değeri olarak tanımlanan, beyindeki yerel kan akımının ve singulat korteks aktivitesinin göstergesi olarak kabul edilen değerlerin, teta frekans bandındaki sayısal değerleri hesaplanmıştır. Sonuçlara göre, tedavi öncesinde vakalarda frontal bölgede teta ve beta bandında izlenen artış tedavi sonrası normale dönmüştür. Ayrıca, prefrontal bölgedeki teta kordans değerlerinin tedavi sonucunda %38 oranında azaldığı saptanmıştır. Önceki yapılmış çalışmalar ışığında bu azalma singulat korteks aktivitesindeki tedavi sonrası azalma ile ilişkili olabilir. Bulguların olası sonuçları makalede tartışılmıştır. Bütün olarak ele alındığında, bu olgu sersi qEEG güç, z-skoru ve kordans değerlerinin anksiyete bozukluklarında kullanılmasının potansiyel faydalarının altını çizmektedir.

Anahtar Kelimeler: Anksiyete bozuklukları, qEEG, tedavi izlem, kordans değeri

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1. Introduction

When the perception of fear becomes disproportioned than the actual source of worry and higher levels of arousal due to fear hinders normal social functioning, then the criteria for an anxiety spectrum disorder is met (APA,2000). Within this definition, it is plausible to expect the range of people diagnosed with anxiety spectrum disorders to be highly heterogeneous. However, systematic evaluation of treatment response for anxiety disorders has relied only on a handful of subjective self-report measures. Nowadays, researchers have devoted substantial efforts in an attempt to use biological measures to monitor treatment response, though many of these efforts are still experimental and have not yet reached clinical practice. With this in mind, quantitative electroencephalogram (qEEG) has become a popular tool to explore potential biomarkers of pathological anxiety by classifying electrical activity of the brain in different frequency bands (Kropotov et al.,2009).

With regards to qEEG research, a number of studies have concluded that anxiety disorders are accompanied by increased signs of hyperactivation of the frontal cortex. For instance, patients with obsessive compulsive disorder (OCD) have shown an increase in the theta band at frontotemporal regions (Karadag et al., 2003). Bucci et al., (2004) found a relative decrease in alpha band activity in a group of patients with OCD, when compared to healthy participants, which was then

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normalized following treatment. In addition, decreased alpha activity was accompanied by an increase in the power of the beta band activity, which has also been shown to be in close relationship with the characteristics of anxiety disorders in other studies. For instance, Tot et al., (2002) found that OCD patients with increased alpha and decreased beta activity during hyperventilation had superior treatment response than those with the converse pattern. Furthermore, many studies have highlighted differences in frontal alpha band asymmetry in depression and anxiety spectrum disorders (Kropotov et al.,2009). Notably, frontal asymmetries shifted from greater right to greater left alpha band activity following treatment in patients with social anxiety disorder (Moscovitch et al., 2011).

Nevertheless, the locations of the source of these differences in electrical activity cannot be reliably identified with conventional qEEG techniques. Therefore researchers have turned their focus to alternative techniques using EEG source density methods, such as low resolution brain electromagnetic tomography (LORETA), to localize the source of the activity. A thought-provoking LORETA study demonstrated that increased beta band activity in patients with anxiety disorders was associated with posterior cingulate cortex activity, and has potential to predict treatment response in depression and anxiety disorders (Sherlin and Congedo, 2005). In addition, Leuchter and his colleagues developed a qEEG method (EEG cordance) by using a formula that gives us an index of the absolute and relative EEG power of each band separately. They also used a different electrode montage to make power values more informative for specific brain regions (Leuchter et al., 1999). A few studies have demonstrated that increased frontal theta cordance is due to an overactive anterior cingulate cortex activity (Pizzagalli et al., 2003; Korb et al., 2009). In addition, an intriguing pharmacological clinical trial found that "ketamine", a pharmacological agent which is thought to reduce the metabolism in the anterior cingulate cortex (Salvadore et al., 2009), reduced the severity of depressive symptoms. Interestingly, the same study also found decreased levels of theta cordance in the prefrontal region following ketamine administration (Horacek et al., 2010). Although it is important to note that we are not aware of any studies evaluating EEG cordance values in anxiety spectrum disorders. However, focusing on individual changes in the qEEG could be informative for the development of individualized, biological treatment response criteria of these patients.

Given all, the aim of this case series is to illustrate the potential use of qEEG and cordance changes in a small group of patients with anxiety spectrum disorders as an index of treatment response. Here, we present four different cases with different types and severities of anxiety disorder. We recorded resting state qEEGs and calculated the theta cordance values before and six months after treatment with antidepressant medication. All patients provided written informed consent and all procedures met institutional ethical review.

2. EEG recordings and Cordance calculations

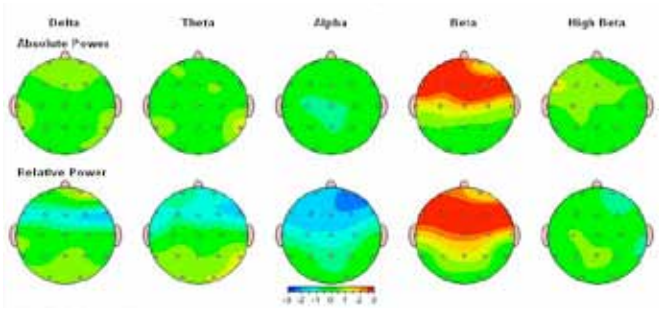
All subjects were instructed to rest with eyes-closed in a quiet room with subdued lighting. Three minutes of eyes-closed resting state EEG was acquired using a Scan LT EEG amplifier and electrode cap (Compumedics/Neuroscan, USA), with the sampling rate of 250 Hz. Nineteen sintered Ag/AgCl electrodes were positioned in the cap according to the 10/20 International System with binaural references. The raw EEG signal was filtered through a band-pass filter (0.15-30 Hz) before artifact elimination. Artifact-free EEG data epochs (minimum 2 minutes) were manually selected based on visual inspection. Cordance calculations and age referenced z-score deviations based on a commercially available normative qEEG database (NeuroGuide Deluxe 2.5.1 ; Applied Neuroscience; St. Petersburg, FL). A Fast-Fourier-Transform was used to calculate absolute and relative power in each of two non-overlapping frequency bands: delta (1-4 Hz) and theta (4-8 Hz) by using NeuroGuide Deluxe 2.5.1 software (Applied Neuroscience; St. Petersburg, FL). The comparisons were made based on the absolute and relative powers of each electrode referenced to the left ear. All spectral analyses were completed by using Neurostats software (Applied Neuroscience; St. Petersburg, FL).

The cordance values were calculated in several steps. First, we used a bipolar montage which is based on the calculation of electrical differences of the electrodes which are topographically close to each other. Second, we reattributed the power from bipolar pairs of electrodes to individual electrodes. Third, we normalized the absolute and relative power across brain areas by calculating their z values. Forth, we summed the z score of the absolute power and the relative power of each electrode. The value could be either a positive or a negative value which was attributed as cordant and discordant respectively.

3. Case series

3.1. Case one

Figure 1: Z-scored topographical brain mapping of Case-1 before the treatment



Case R.S was 21 years old, male and a university student. He admitted to the Istanbul Neuropsychiatry Hospital in May 2012 with fear of death, obsessions with religion, perceived anxiety, palpitation and sleep problems. Following the psychiatric interview, he was diagnosed with obsessive compulsive disorder according to the DSM-IV-TR. Prior to treatment, he had a Beck Anxiety Scale total score of 33, and a Yale-Brown Scale total score of 35. Six months after the selective serotonin reuptake inhibitor treatment augmented with aripiprazole (effective dose titrated by plasma drug monitorization), his Beck Anxiety and Yale-Brown Scale total scores

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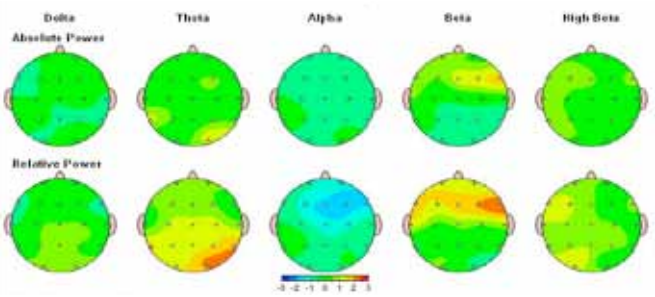
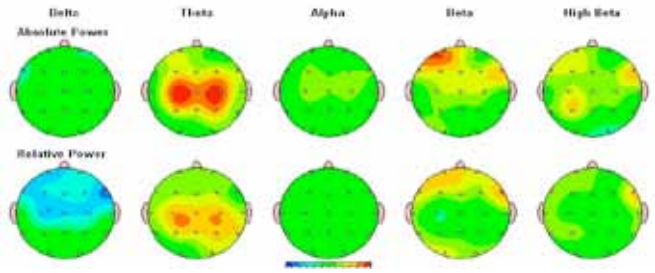
dropped down to 7 and 20, respectively. The topographical analyses based on the z-score deviations before and after the training are illustrated in figure 1 and 2. Accordingly, in comparison with the normative database of z-scores, there was an increased left dominant beta band activity, that was changed to normal level for his age following the treatment. Notably, we also observed relatively decreased alpha band activity in frontal regions before the treatment.

Figure 2: Z-scored topographical brain mapping of Case-1 after the treatment.



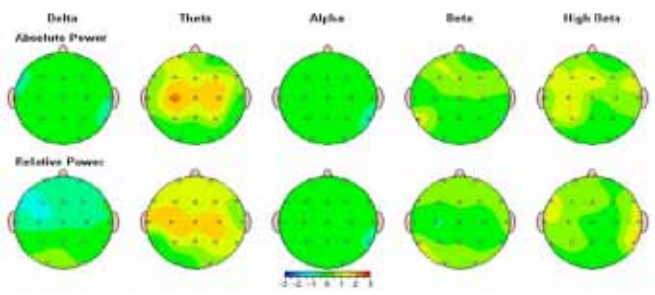
3.2. Case two

Figure 3: Z-scored topographical brain mapping of Case-2 before the treatment.



Case S.C. was 22 years old and a female university student. She admitted to the Istanbul Neuropsychiatry Hospital in May 2013 with fear of death, overthinking, hypochondriac thoughts and behaviors, sleep problems, perceived anxiety and palpitations. Following the psychiatric interview, she was diagnosed with anxiety disorder not otherwise specified according to the DSM-IV-TR. Prior to treatment, she had a Beck Anxiety Scale total score of 36. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization) her Beck Anxiety Scale total scores dropped down to 12.

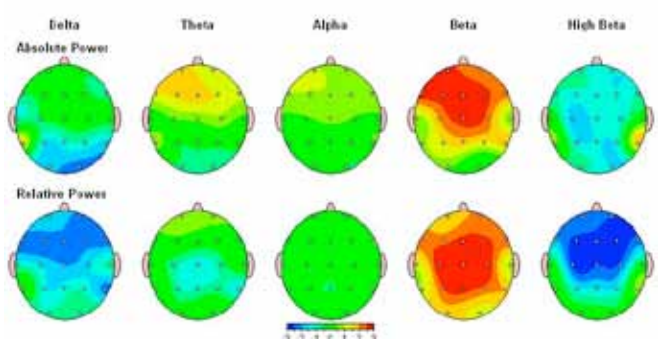
Figure 4: Z-scored topographical brain mapping of Case-2 after the treatment.



The topographical analyses based on the z-score deviations before and after the treatment are illustrated in figure 3 and 4. According to the qEEG, an increased fronto-central theta activity was resolved following the treatment. In addition, we observed increased left fronto-central beta power, which was was changed to normal level for his age following the treatment.

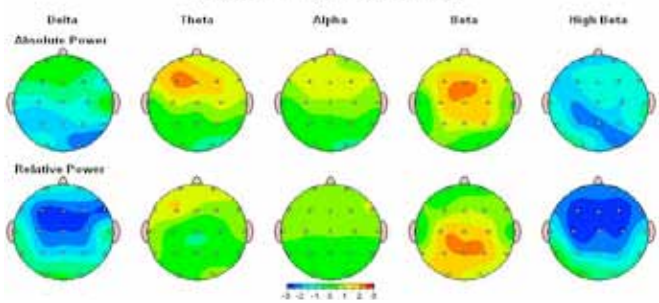
3.3. Case three

Figure 5: Z-scored topographical brain mapping of Case-3 after the treatment.



Case Z.S was 43 years old, female and a factory worker. She admitted to the Istanbul Neuropsychiatry Hospital in October 2012 with palpitation, sweating, hypochondria and depressive mood. Following the psychiatric interview, she was diagnosed with anxiety disorder not otherwise specified according to the DSM-IV-TR. Prior to treatment, she had a Beck Anxiety Scale total score of 38. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization) her Beck Anxiety Scale total scores dropped down to 11. The topographical analyses based on the z-score deviations before and after the training are illustrated in figure 5 and 6. Here we observed an increased absolute power in the beta band, together with lower relative power in the delta band before treatment. We also found a decreased relative power in the high beta band. The relative power of the high beta and delta activity were not affected by the treatment. Nevertheless, the absolute power in the beta band was changed to normal level for her age after the treatment. Lastly, there was a moderate increase in the theta band relative to the normative data, which was not affected by treatment.

Figure 6: Z-scored topographical brain mapping of Case-3 after the treatment.



3.4. Case four

Case P. K. was 19 years old, female and a university student. She admitted to the Istanbul Neuropsychiatry

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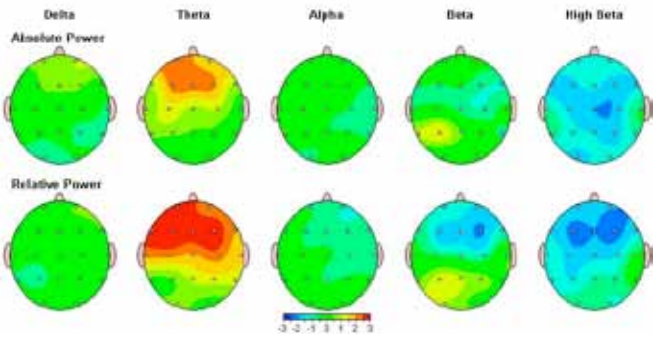
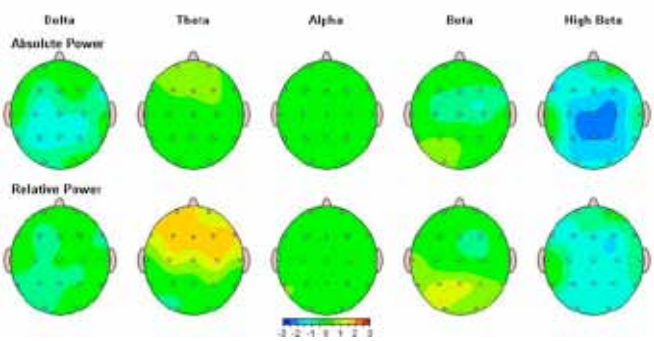
Figure 7: Z-scored topographical brain mapping of Case-4 after the treatment.



Hospital in June 2013 with a previous diagnosis of generalized anxiety disorder (GAD) according to the DSM-IV-TR. Following the psychiatric interview, in addition to GAD, a comorbidity of cannabis abuse was also determined. Prior to treatment, she had a Beck Anxiety Scale total score of 38. Six months after the selective serotonin reuptake inhibitor treatment (effective dose titrated by plasma drug monitorization,) together with treatment from 30 sessions of repetitive transcranial magnetic stimulation (rTMS), her Beck Anxiety Scale total scores dropped down to 12. The topographical analyses based on the z-score deviations before and after the treatment are illustrated in figure 7 and 8. Here, we found a significantly increased deviation of the absolute and relative theta power compared with the normative database. Notably, theta activity had resolved following the treatment.

Figure 8: Z-scored topographical brain mapping of Case-4 after the treatment.



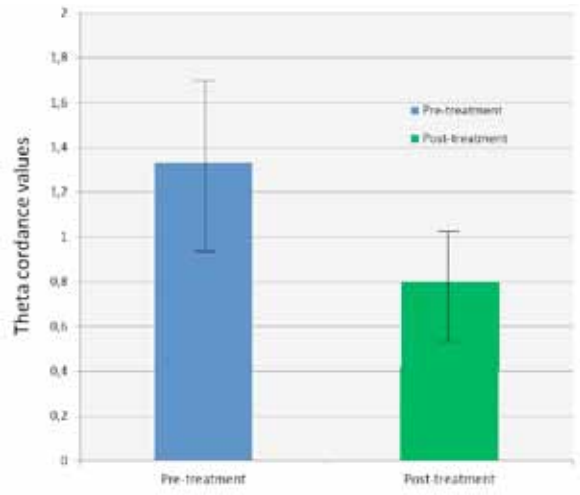
3.5. Theta cordance results

Here we pooled the prefrontal theta cordance values of all cases and calculated mean values. Accordingly, we found a moderate reduction of theta cordance values following the treatment (see figure 9). Specifically, the cordance values reduced approximately 38,3% percent six months after the treatment. Due to the small number of cases, we did not perform hypothesis tests here in this step.

3.6. Discussion

The ultimate goal of this case series was to highlight the different topographical EEG power spectrums of anxiety spectrum disorders and their change following the treatment. In addition to this, we presented theta cordance values, which appeared to be a reliable and consistent measure across different types of anxiety

Figure 9: Prefrontal theta cordance values before and after the treatment



spectrum disorders and thus, may be considered for treatment monitoring of anxiety spectrum disorders in the future. In line with the literature, we found an increased theta and beta activity in the frontal areas. As expected, these activities successfully responded to the treatment. Regarding theta cordance, we replicated the cordance findings of patients with depression (Hunter et al., 2007). Specifically, previous studies calculating cordance values of depressive patients demonstrated an approximately 20% percent of reduction 2 weeks after the treatment (Bares et. el., 2007, 2008).

In our cases, we observed a non-specific increase in the beta band accompanied by a decrease in alpha band. These changes may indirectly suggest that using the absolute and relative power values could not be sufficient to classify anxiety disorders. However, this could not be stressed for the observed changes following the treatment. Because, all power deviations from the normative database disappeared following treatment and thus provided important insights for the clinicians to observe the effects of their treatment.

Previous studies underlined the potential use of cingulate cortex (CC) activity to predict treatment response for depression and anxiety disorders. Greater CC activity was associated with poor improvements following the treatment of patients with post-traumatic stress disorder (Bryant et. al., 2008). In a fMRI study, grater pre-treatment activity of CC in response to the fearful faces has predicted the magnitude of treatment response in patients with generalized anxiety disorder (Whalen et al., 2008). In addition, subsequent to a surgical procedure for removing right posterior CC, OCD patients with higher CC metabolism before operation had a significantly better post-operative outcome than those with smaller metabolism in a neurosurgery study (Rauch et al., 2001). Here we used theta cordance values as an index of cingulate cortex activity. The observed reduction in the theta power suggests that although these patients had different diagnoses, theta cordance may be utilized as an easy to use, non-invasive tool for anxiety disorders.

In light of our cases, although speculatively it would be

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legitimate to expect similar spectral changes in the qEEGs of a patient in his or her subsequent episodes, which may require medication or hospitalization. In such occasions, clinicians may consider using the previous qEEG's of their patients in order to follow up the progress. Taken together, although qEEG methods may still require development, the current approaches provide us the initial steps on the way to biological, individualized treatment monitoring for patients. Lastly, theta cordance values may be useful to use to monitor treatment response in anxiety spectrum disorders.

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"German-Turkish Year of Research, Education and Innovation 2014" supported by The Scientific and Technological Research Council of Turkey (TUBITAK)

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CASE REPORT

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1386249156

Article history:
Received 01 December 2013
Received in revised form 15 December 2013
Accepted 31 December 2013

A CREUTZFELDT-JAKOB DISEASE CASE PRESENTING WITH PSYCHIATRIC SYMPTOMS

PSİKİYATRİK BELİRTİLERLE SEYREDEN BİR CREUTZFELDT-JAKOB HASTALIĞI OLGUSU

Aslı Akın Aslan[1], Arda Karagöl[2], Gökben Hızlı Sayar[*3], Ebru Bilge Dirik[4]

Abstract

Creutzfeldt Jakob Disease is an incurable and invariably fatal degenerative brain disease. Sporadic and variant forms of the disease can be observed among patients. We report on a patient for calling attention to clinical features and laboratory findings of Creutzfeldt-Jakob Disease and the psychiatric prodromal symptoms. This case demonstrates that psychiatric symptoms may also be a presenting symptom of Creutzfeldt-Jakob Disease and this diagnosis should be considered when rapid deterioration in cognition is observed with presence of psychiatric and neurological symptoms.

Keywords: Creutzfeldt-Jakob disease; diagnosis; psychiatric presentation

Özet

Creutzfeld Jakob Hastalığı, tedavisi mümkün olmayan ve kaçınılmaz şekilde ölümle sonlanan dejeneratif bir beyin hastalığıdır. Hastalar arasında sporadik ve varyant formları gözlemlenmektedir. Bu olgu sunumunda Creutzfeld Jakob Hastalığının klinik belirtilerine, laboratuar bulgularına ve prodrom döneminde izlenen psikiyatrik belirtilerine dikkat çekmeyi amaçladık. Bu olgu sunumu, psikiyatrik belirtilerin Creutzfeld Jakob Hastalığında da izlenebileceğini ve psikiyatrik-nörolojik belirtilerin yanı sıra bilişsel işlevlerde hızlı bir bozulma izlendiğinde Creutzfeld Jakob Hastalığı tanısının düşünülmesi gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Creutzfeldt Jakob Hastalığı; tanı; psikiyatrik prezentasyon

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1. Introduction

Creutzfeldt-Jakob Disease (CJD) is an incurable and invariably fatal degenerative brain disease. It is a well-known cause of rapidly progressive dementia. Most victims die six months after initial symptoms appear, often of pneumonia due to impaired coughing reflexes. About 15% of patients survive two or more years (Puoti et al., 2012). Definite diagnosis of CJD requires tissue diagnosis showing spongioform degeneration, astrocytic gliosis, amyloid plaques and lack of inflammatory response (Ozen, 2007). The symptoms of CJD are caused by the progressive death of the brain's nerve cells, which is associated with the build-up of abnormal prion proteins forming amyloids (Poser et al., 2000). It is not feasible to conduct a tissue biopsy in all suspected cases so various diagnostic criteria have been proposed (Newey, Sarwal, Wisco, Alam, & Lederman, 2013).

CJD is the most common prion disease with an incidence of about 1-2 persons/million people/year (Branden, Salomon, Capek, Vaillant, & Alpérovitch, 2009). Sporadic (85% of cases), genetic (10-15%) and variant (iatrogenic and acquired, more likely to be acquired, result from transmission of causative agent by contaminated surgical equipment or as a result of cornea, dura mater transplants or administration of human derived pituitary growth hormones) forms exist (Ironside, Ritchie, & Head, 2005). We would like to report the clinical characteristics of a "probable" CJD case to demonstrate the diagnostic workup and to call attention to clinical presentation with early psychiatric symptoms.

2. Case

A 60-year-old male, married, farmer, referred by a general practitioner with a two months history of agitation, restlessness, increased speech, distractibility, insomnia and increased self-esteem. According to his family, several months before the other complaints, he suffered from personality changes, insomnia and talkativeness. For the last 10 days, he had severe insomnia, increased sexual arousal, transient disorientation, short term memory impairment and confabulation. He presented grandiose and paranoid delusions as fear of being killed by the ones jealous of his work. He had not any history of smoking or alcohol/substance abuse. He didn't have any medical history and there were not any psychiatric or neurological disease in his family.

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His family stated that he was diagnosed as "anxiety disorder" and was put on citalopram 20 mg/day treatment 4 weeks ago. But after a week, due to failure in improvement of his complaints, general practitioner referred him to psychiatric unit. Psychiatric examination revealed increased psychomotor activity, pressured and increased speech, labile affect, grandiose thoughts and overinvolvement of routine daily events. Computerized tomography of brain and EEG revealed normal findings. His Mini Mental Test score was 15. He was prediagnosed as "Bipolar affective disorder, manic episode" and a treatment of olanzapine 10 mg/day was initiated. Olanzapine dose was increased to 20 mg/day soon after. Unfortunately, the complaints did not relieve. His neurological symptoms, such as disorientation, bilateral dysmetria and cerebellar ataxic gait added to clinical presentation so he was hospitalized in neurology department to investigate the etiology. Quetiapine dose was increased to 900 mg/day as there was no significant reduction of agitation and insomnia at the end of the first week.

Contrasted cerebral MRI in T2 sequences showed frontal periventricular ischemic-gliotic areas and bilateral hyperintensity at caudate and putaminal nuclei. Moreover, diffusion MRI revealed hyperintensity in right lentiform nucleus. In EEG tracing bilateral periodic sharp wave complexes observed. The laboratory workup did not show any autoimmune, metabolic or infectious etiology. Complete blood count, thyroid function tests, complete urine analysis, tumor markers including PSA, CEA, CA 19-9, CA-125, CA 15-3, hepatitis markers, anti HIV, VDRL, TPHA, Anti dsDNA, anticardiolipin IgM and IgG, antigliadine IgM and IgG, antitransglutaminase IgM and IgG, anti CCP, vitamin levels were within normal range. Cerebrospinal fluid (CSF) screening was also normal and tested negative for the P 14.3.3 protein. Gram staining, mycobacterium PCR, CSF culture and Wright staining did not revealed any significant results as well.

During the tenth day of the hospitalization he experienced generalized sudden jerks provoked by sounds and soon after sounds and soon after he had a focal motor seizure obseved as tonic clonic contractions in his left upper extremity while he was asleep. his left arm while asleep. He presented ataxia, which worsened in a week. Visual hallucinations, akinetic mutism, urinary incontinence were added to the clinical course. At the end of the third week of hospitalization; cardiac failure occurred. Hepatic and renal function tests rapidly deteriorated. Unfortunately he died on the 32nd day of hospitalization in a state of akinetic mutism.

Patient's symptoms, laboratory findings and clinical diagnosis in different phases of the disease were presented on Table 2.

3. Discussion

The clinical features of this case were consistent with previous descriptions of CJD. The final diagnosis was "probable sporadic CJD" according to the WHO and European MRI-CJD consortium criteria (WHO, 1998; Zerr et al., 2009). MRI-CJD consortium criteria for sporadic CJD are given on Table 1. Psychiatric symptoms, mainly depression and anxiety, occur in the clinical course in about one third of cases of sporadic CJD (Kurne et al., 2005). Rapidly progressing neurological symptoms including ataxia, myoclonus, cognitive impairment and akinetic mutism might be presented after the psychiatric symptoms. Clinical reports have described the early appearance of psychiatric symptoms in sporadic CJD, including paranoid psychosis (Dunn, Alfonso, Young, Isakov, & Lefer, 1999), mania (Lendvai, Saravay, & Steinberg, 1999), and depression (Jardri, DiPaola, Lajugie, Thomas, & Goeb, 2006). Schizophreniform disorders have been described during the clinical course, with auditory and visual hallucinations and paranoid delusions (Ali, Baborie, Larner, & White, 2013).

Table 1. MRI-CJD Consortium criteria for sporadic CJD

I. Clinical Signs	• dementia • cerebellar or visual • pyramidal or extrapyramidal • akinetic mutism
II. Tests	• periodic sharp wave complexes in EEG • 14-3-3 detection in CSF (in patients with a disease duration of < 2 years) • high signal abnormalities in caudate nucleus and putamen or at least two cortical regions
Probable CJD: two out of I and at least one out of II	
Possible CJD: two out of I and duration less than 2 years	

In this case in the prodromal phase psychiatric symptoms of the CJD (pressured speech, increased sexual arousal, increased energy, and decreased sleep) are prominent. Although there is only one CJD patient in the literature that was presented with manic symptoms, Lendvai et al suggested that familial predisposition could be the cause

Table 2. Patient's symptoms, laboratory findings and clinical diagnosis in different phases of the disease

	Prodromal	Early phase	Late phase
Duration	3 months	3 weeks	3 weeks
Psychiatric symptoms	Personality changes, irritability, emotional lability	Insomnia, increased speech and sexual arousal, delusions, transient memory impairment	Rapid progressive dementia, disorientation hallucinations
Neurological symptoms	-	Ataxia	Myoclonic jerks urinary incontinence, akinetic mutism
Investigationsv	-	Normal Brain CT, Normal EEG	Brain MRI: hyperintensity of putamen EEG: Periodic sharp wave complexes
Diagnosis	Anxiety disorder	Bipolar affective disorder, manic episode	CJD

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of manic presentation on that case (Lendvai, Saravay, & Steinberg, 1999).

Our patient did not have any depressive or manic episode history; so his mood state was considered as secondary mania. Secondary mania can occur with physical illness; medications (e.g., bronchodilators, corticosteroids); metabolic disturbances (e.g., vitamin B12 deficiency, thyrotoxicosis); neoplasms, central nervous system diseases (e.g., Parkinson disease, cerebritis due to lupus, multiple sclerosis, epilepsy, cerebrovascular accident); and infections (e.g., neurosyphilis, HIV, influenza) (Price, & Marzani-Nissen, 2012). Nakimuli-Mpungu et al. reported that in the majority of HIV-positive patients presenting with mania, the mania is secondary to HIV infection and that its presentation and correlates differ from those of HIV-negative patients with primary mania (Nakimuli-Mpungu, Musisi, Mpungu, & Katabira, 2006).

Although the 14-3-3 test negativity did not support our diagnosis, it is suggested to evaluate the test with clinical correlation since the test can be false negative or false positive and cannot rule out the CJD (Cuadrado-Corrales et al., 2006). EEG is the best available auxiliary means of diagnosing sporadic CJD, with a reported sensitivity of around 60% (Collins et al., 2006). The typical EEG in sporadic CJD is characterized by periodic or pseudoperiodic sharp wave complexes. These complexes tend to arise in the middle and late stages of disease; diffuse slowing and frontal rhythmic delta activity are often recorded in early stages (Hansen, Zschocke, Stürenburg, & Kunze, 1998). The finding of asymmetric hyperintensity on diffuse weight imaging in at least three cortical non-contiguous gyri or in the striatum (caudate and rostral part of the putamen), or both, is highly suggestive of sporadic CJD. On the basis of these criteria, MRI has proven to be an accurate diagnostic test (1).
This case reminds us that sporadic CJD patients may initially present with psychiatric symptoms. Clinicians should pay attention to subtle neurological signs in patients with atypical mood disorder. Utilizing investigations including EEG, 14-3-3 protein detection in CSF and MRI could help clinicians to make more precise and earlier diagnosis of CJD.

4. Conclusion

The first symptoms of this patient were purely psychiatric and difficult to distinguish from common psychiatric disorders. As sporadic CJD can present with psychiatric symptoms, this diagnosis should be considered when there is rapid deterioration in cognition with fleeting psychiatric symptoms and the presence of neurological symptoms.

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CASE REPORT

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1394035079

Article history:
Received 08 January 2014
Received in revised form 12 February 2014
Accepted 30 January 2014

HABIT REVERSAL TRAINING IN TRICHOTILLOMANIA

TRİKOTİLLOMANİDE ALIŞKANLIĞI TERSİNE ÇEVİRME EĞİTİMİ

Gökben Hızlı Sayar[1*], Gaye Kağan[2]

Abstract

Trichotillomania is a psychiatric disorder that involves repetitive hair pulling to the point of apparent loss. No approved treatment algorithm is available for trichotillomania. We present a case report of a 28-year-old female diagnosed as trichotillomania, with complaints of recurrent hair pulling resulting in noticeable hair loss. She was treated with Habit Reversal Training and a selective serotonin reuptake inhibitor (sertraline) over a period of 6 weeks. Habit reversal training includes self-monitoring, awareness training, competing response training, and homework assignments. The aim of this case report is to provide a brief description of habit reversal training, which is unfamiliar to many professionals.

Keywords: habit reversal training, hair pulling, trichotillomania

Özet

Trikotillomani, tekrarlayan saç yolmalar sonucu belirgin saç kaybı ile sonuçlanan bir psikiyatrik bozukluktur. Kabul görmüş bir tedavi algoritması bulunmamaktadır. Bu yazıda tekrarlayan saç koparmaları sonucu belirgin saç kaybı olan trikotillomani tanılı, 28 yaşında bir kadın olgu sunulacaktır. Olgu alışkanlığı tersine çevirme eğitimi ve seçici serototnin gerialım inhibitörübir ilaç (sertralin) ile 6 hafta boyunca izlenmiştir. Alışkanlığı tersine çevirme eğitimi, kendini izleme, farkındalık eğitimi, karşıt cevap eğitimi ve ev ödevlerini kapsayan bir tekniktir. Bu olgu sunumunun amacı birçok profesyonelin aşine olmadığı alışkanlığı tersine çevirme eğitiminin kısa bir tanımını yapmaktır.

Anahtar Kelimeler: alışkanlığı tersine çevirme eğitimi, saç koparma, trikotillomani

JNBS 2014 Published by Uskudar University www.jnbs.org

1. Introduction

Trichotillomania (TTM) is characterized as a psychiatric disorder in which individuals fail to resist urges to pull out their own hair, and is associated with significant functional impairment and psychiatric comorbidity across the developmental spectrum. Lifetime prevalence rates of TTM have been estimated to be from 0.6% to 1.0% (Duke et al., 2010). TTM has been found to be related with feelings of isolation, shame, embarrassment, and low confidence, along with avoidance of activities such as medical exams, haircuts, swimming, social relationships, and intimate interpersonal relationships to hide their symptoms (Diefenbach et al., 2005). Individuals may pull their hair for up to several hours a day or require extraordinary attempts to conceal hair loss, either of which can significantly interfere with daily living.

The DSM-IV diagnosis of trichotillomania is now termed trichotillomania (hairpulling disorder) and has been moved from a DSM-IV classification of impulse-control disorders not elsewhere classified to obsessive-compulsive and related disorders in DSM-5 (APA, 2013). After pulling hair, more than half of the patients use the hair in an odd manner (biting the hair, touching the hair to the lips and even swallowing the hair). Swallowing of hair may lead to the formation of hairballs in the intestine known as trichobezoars which can lead to intestinal ulceration, obstruction and even perforation (Walsh & McDougle, 2001). Management of trichotillomania is challenging. A number of treatment modalities have been used including psychotherapy, hypnotherapy, and pharmacotherapy; though treatment response is variable and relapses are frequent (Chawla et al.2013; Franklin et al., 2011).

In 1973, Azrin and Nunn developed Habit Reversal Therapy (HRT) to treat various habits (Azrin & Nunn, 1973). HRT is commonly used to treat disorders involving repetitive, body-focused, unwanted behaviors, such as Tourette's Syndrome (Woods & Miltenberger, 1995), trichotillomania, nail biting, temporomandibular disorder, thumb sucking, finger and lip biting (Roberts et al., 2013). These disorders all characterized the variety of

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problems as habit behaviors, each with clear potential for development of a competing muscle movement (Bate et al., 2011). Studies on the pharmacotherapy of trichotillomania remain inconsistent with no particular drug or group of drugs found to be clinically effective constantly (Stewart & Nejtek, 2003; Voth, 2006). Behavior therapy in the form of HRT has been found to be an effective treatment in several reports (Bloch et al., 2007; Crosby et al., 2012; Woods et al., 2006). HRT has some key components like awareness training, stimulus control, competing response training and social support which are delivered on several therapy sessions (Kar & Kumar, 2012; Mouton & Stanley, 1996).

We present a case report detailing clinical data taken during the course of outpatient treatment of a patient with a diagnosis of TTM. The patient was resistant to a range of drugs and was started on treatment with HRT. Informed consent was obtained from the patient by using a written form.

2. Case

Ms E, twenty-eight years old, high school graduated, divorced, a saleswoman, admitted to psychiatric interview with complaints of hair pulling and apparent hair loss. She has been pulling her hair since she was 13 years old. She used to do it when alone or under stress. There was significant hair loss on her scalp, which was more marked in the left side, due to repeated pulling. After pulling the hair, she used to chew the ends of her hair and even swallow it. She used to develop both an urge and a sense of tension immediately before pulling out the hair, or when attempting to resist the behavior on which she felt relieved while pulling out the hair. Hair pulling was not only localized to the scalp but also to the eyebrows. She totally lost her whole eyebrows, so she drew an artificial eyebrow with a make-up pencil. The patient started using a scarf, which she was wearing throughout the day, because of the baldness arising due to her hair pulling. She developed decreased confidence owing to her problems and started avoiding social gatherings. She was diagnosed as TTM. Her treatment history revealed various antidepressants including fluoxetine, escitalopram, clomipramine, risperidone, sulpiride, with no significant improvement. There was no relevant family history of any psychiatric illness. Physical examination revealed patchy baldness all over the scalp. Hair loss was also observed on her eyebrows. Laboratory tests revealed normal hemogram, liver function and thyroid functions and abdominal ultrasoundography.

She was started on sertraline 50mg/day which was then gradually escalated to 100mg/day over a period of 6 weeks, along with risperidone 1 mg/day. Behavior therapy in the form of HRT was planned. The therapy was structured as six sessions, each lasting for 40 to 45 minutes on a weekly basis.

In the first session, she was educated about the diagnosis of trichotillomania, its prevalence, etiology, and course. The concept of HRT was explained. She completed a focused questionnaire related to her hair-pulling behaviors, antecedents, and consequences. A self-monitoring form was given, and she agreed to fill it on a daily basis and maintain it throughout the therapy period.

In the second session, awareness training was given by making the patient realize that the behavior of hair pulling was abnormal, and by identifying different situations during which she used to pull her hair. Environmental, sensory, cognitive, and effective cues that have been conditioned to trigger hair-pulling are identified through self-monitoring. She concluded that she pulled it when she was feeling bored or relaxed, therefore, she needed something to do with her hands.

In the third session, feedback of the last session was taken, and self-monitoring form was assessed. She had developed an awareness of habit and often resisted pulling. Skin sensations provided significant cues for pulling. Efforts then are aimed at breaking or interrupting these conditioned sequences and replacing the hair-pulling behavior with more adaptive responses. The patient was taught progressive muscular relaxation and diaphragmatic breathing and was asked to do both on a daily basis. She was advised to replace her behaviors including cue for hair pulling with other postures, such as placing her hands behind her back while working or putting her hand under the pillow while sleeping. Imaginal exposure techniques were used during the session to encourage patient in practicing the relaxation techniques in high-risk situations. She was asked to close her eyes and imagine herself in a high-risk situation and notice the urge to pull hair become stronger until she wanted to pull her hair acutely. Afterwards, she was asked to use relaxation strategies to restrict the hair-pulling urge by both breathing and postural adjustment.

The fourth session constituted of teaching the "competing response" which is acquiring of a muscle tensing activity which is opposite to, and incompatible with hair pulling. She was taught to make a clenched fist with the hand she uses to pull hair, to bend the arm at the elbow 90, and to press the arm and hand firmly against her side at her back. She was then instructed that whenever and wherever she would get the urge to pull, she was to (in order) relax herself, do diaphragmatic breathing for 60 seconds, and the competing response for 60 seconds. She was encouraged to perform these techniques in front of the therapist, thereafter her family members and then in different social situations. She was asked to do rehearsal of these techniques at home.

In the fifth session, she reported that the deep breathing and doing competing muscle exercises almost entirely eliminated her urge to pull. The patient's parents were instructed to help her to practice the competing responses and appreciate her efforts. Review of the rationale and types of replacement or competing behaviors that would help reduce her symptoms were done with the patient and her family.

In the concluding session, the patient's improvement after HRT sessions was analyzed. She reflected upon her experiences and progress over the 6-week period. Despite some hesitancy at treatment onset, she concluded that increasing awareness of behavior was the key to change hair pulling behavior.

With the combination of pharmacotherapy and HRT technique, there was a significant improvement. During follow-ups, over a period of six months, her hair pulling habit was reduced from several times in a day to 1 – 2 times in a week and hair started growing on the scalp and she stopped using her scarf to cover her head.

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3. Conclusion

HRT is a highly effective, well-structured and simple behavioral therapy approach for patients with TTM. Although HRT appears to be an effective method of treatment for TTM, conducting is not enough due to the possibility of non-adherence to the strategic approach after the end of psychotherapeutic sessions. Therefore, it is required to follow the case and review the HRT technique and hair pulling symptoms in regular intervals.

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LETTER TO EDITOR

THE JOURNAL OF NEUROBEHAVIORAL SCIENCES
NÖRODAVRANIŞ BİLİMLERİ DERGİSİ

Year : 2014
Issue : 1
Number : 1
Doi Number : 10.5455/JNBS.1388568708

Article history:
Received 02 January 2014
Received in revised form 21 January 2013
Accepted 30 January 2014

THE FUTURE OF PHARMACOGENOMICS: GOING BEYOND SINGLE NUCLEOTIDE POLYMORPHISMS

FARMAKOGENOMİĞİN GELECEĞİ: TEK NÜKLEOTİD POLİMORFİZMLERİNİN ÖTESİNE DOĞRU

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To editor;

Human genome project (HGP) opened the era of personalized medicine. It not only identified the number, location and structure of genes, but also revealed the mechanism underlying the regulation of several genes. On the other hand, single nucleotide polymorphisms, shortly SNPs, just lie under the genetic variations between individuals, and are also believed to affect how individuals respond to chemicals, drugs, special treatments, and even to diseases. Today's technologies are now trying to integrate the identified SNPs into the number of omics like transcriptome, proteome or metabolome. In addition, genomic technologies have profound roles in diagnosis and treatment in relation to personalized medicine, rotating general treatment to patient oriented approach.

Pharmacogenomics (pharmacology + genomics) is the science which links the genetic make-up of an individual and probable drug therapy and aims to develop rational means to optimize drug treatment, with respect to personal genome in order to assure the maximum efficacy with minimal adverse effects. These approaches are now being implemented in treatments of cancer, diabetes, and psychiatric diseases.

To date, as of July 2013, there have 62,676,337 listed SNPs in humans (1). Due to developing technologies and decreasing costs, the past decade has made considerable progress for human genome information. Array based and next- generation sequencing technologies have led many scientists to analyze relatively much more amounts of genomes. In addition to these, genome- wide association studies (GWAS) have identified too many genomic variations, some of which are associated with drug response. These findings have led us understand the underlying genetic mechanism of inter- individual differences in drug response or predisposition to certain diseases.

Most interdisciplinary studies now try to integrate the genomic information into clinical practice in order to improve the diagnosis and treatment of the related diseases. Some SNPs have an accurate prediction rate in certain drug responses and in some psychiatric therapies, and identifying these SNPs in the related illnesses increases the chance of benefit from drugs used in treatment. For most drug companies, personalized drugs will be the most highlighted feature. Producing SNP- based drugs will be more effective than just producing one type of drug for genomic varied- diseases.

New treatment models will have a considerable impact on future medicine. New programs, sources and education tools will lead most pharma- market members like insurance and drug companies or clinicians to customize the treatment for patients. With the improvements in sequencing or integrating array- based technologies, it is going to be possible for individuals to have their own genetic sequence. By use of this unique information, geneticists or genetic counselors, who must be members of a clinician team, should be able to provide enough accessible information to patients about the way their genetic information will guide their treatments.

Another point in integrating genomic information in drug treatments is the possibility of reducing adverse events that will also speed up recovery. The genetic blueprint in pharmacokinetics will allow clinicians to start the appreciate therapy at the right time, disabling further tries.

In conclusion, due to the decrease in the costs and accuracy of the genetic tests in pharmacogenetics, new therapeutic approaches will include genetic counseling in broad terms with extensive applications.

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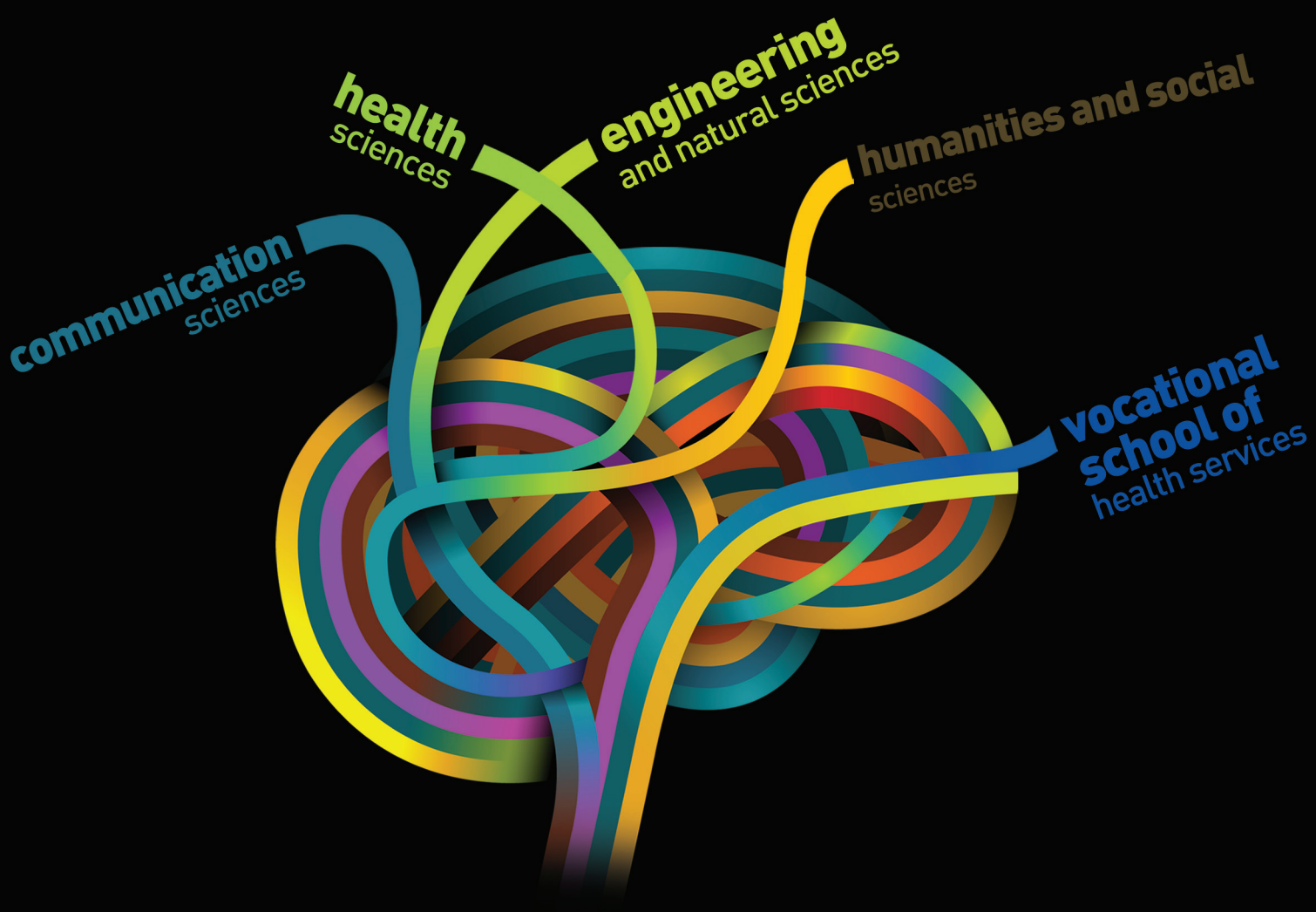

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