# Preliminary study of neuroimaging and psychophysiology in adults with ADHD

Ni Chun Hung[1,2], MSc, Shih-Hsien Lin[3,4], PhD, Mei Hung Chi[3], MD, Po See Chen[3,4], MD, PhD, I Hui Lee[3,4], MD, Kao Chin Chen[3,4,5], MD, Yen Kuang Yang[3,4*], MD

[1]Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Psychiatry, Chi-Mei Foundation Medical Center, Tainan, Taiwan
[3]Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Addiction Research Center, National Cheng Kung University, Tainan, Taiwan
[5]Department of Psychiatry, National Cheng Kung University, Dou-Liou Branch, Yunlin, Taiwan
ykyang@mail.ncku.edu.tw

## Abstract

Attention Deficit Hyperactivity Disorder (ADHD) affects in both children and adults leading to poor executive functioning and quality of life. However, very little study focuses on neuroimaging and psychophysiology in the adults with ADHD. This preliminary study aimed to report neuroimaging and psychophysiology outcomes in the adults with ADHD. Participants in this study consisted of three groups: unaffected fathers of offspring with ADHD, adults with ADHD, and matched controls, were enrolled. A psychological battery was used in order to assess the participants' cool cognitive function. Levels of dopaminergic activity were assessed by using the single positron emission computed tomography (SPECT) with [99mTc] TRODAT-1. In a pilot test for further study, the Iowa gambling test in a mock functional MRI was conducted. Molecular neuroimaging indicated the pivotal role of dopaminergic activity altered as well as functional brain imaging demonstrated difference between cool and hot executive functions. Using the Event-Related Potentials (ERP), the P300 amplitude of adults with ADHD was found to be lower than healthy group. In conclusions, Neuroimaging and psychophysiology outcome were effectively identified in adult with ADHD. Further study of neuroendocrinological factors might be related.

**Keywords:** ADHD, Dopamine, Iowa gambling test, neuroimaging, P300 amplitude

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) seems to be a childhood psychiatric condition characterized by inattention, hyperactivity, and impulsivity. The ADHD continues across adolescence and adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002). Numerous follow-up studies indicate that around 66% of children with ADHD will still suffer from this condition during their adolescence and adulthood (S. J. Kooij, et al., 2010; Lara, et al., 2009). A meta-analysis reported that 15% of childhood ADHD patients retain the full diagnosis in adulthood, while only 50% achieve partial remission (Faraone, Biederman, & Mick, 2006).

The estimated prevalence of child ADHD is in the range of 5-10% (Faraone, Sergeant, Gillberg, & Biederman, 2003), with a 2-5% prevalence being reported for adult ADHD (Fayyad, et al.,

2007; Kessler, et al., 2005; J. J. Kooij, et al., 2005; Simon, Czobor, Balint, Meszaros, & Bitter, 2009), which supports the figure of a 66% rate of persistence given above. In a survey of incoming college students, 8.6% of the respondents was found to have high ADHD scores (Cheng et al., personal communication), and thus a significant number of people in the general population may suffer from adult ADHD in Taiwan. A range of negative psycho-social outcomes were reported to be associated with adult ADHD (Biederman, et al., 1995).

An important issue on the ADHD could be the executive functions, which may play a pivotal role in these negative outcomes. Although relatively less attention has been paid to the hot executive functions of adults with ADHD, abnormal cool executive functions have been reported, particularly with regard to response inhibition (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Murphy, Barkley, & Bush, 2001) and working memory (Dowson, et al., 2004; Murphy, et al., 2001). A study that examined adult ADHD and neurosurgical patients indicated that these abnormal cool executive functions might be associated with frontal cortex pathology (Clark, et al., 2007). Although studies have generally confirmed the role of cool executive functions among children and adolescents with ADHD, whether this is the only etiology of ADHD remains unclear. While a meta-analysis indicated that ADHD is associated with several cool cognitive functions, the moderate effect size and lack of universality in this earlier work suggests that cool cognitive functions may not be the only etiology of ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). On the other hand, another meta-analysis focusing on adult ADHD reported a homogenous cool cognitive deficit among the subjects (Schoechlin & Engel, 2005).

The neuropathology of adult ADHD remains to be investigated. It has been suggested that abnormalities in the structure and function of prefrontal cortex and cerebellum could be important to this condition. In particular, the dorsal part of the anterior cingulated cortex (dACC), which is involved in decision making and executive control, appear to related to the pathology of adult ADHD, along with the basal ganglia and cerebellum, which are involved in affect and cognition (Schneider, Retz, Coogan, Thome, & Rosler, 2006). Abnormal neurotransmitter activity is also an important part of the pathology of adult ADHD, with a higher binding potential of dopamine transporter (DAT) being found among such patients before methylphenidate (dopamine and norepinephrine reuptake inhibitor) treatment (Dresel, et al., 2000). Whether adults with ADHD have altered levels of dopaminergic activity remains unclear due to the clinical evidence is scarce. Lower levels of DAT have been found in drug naïve adults with ADHD, and the level of DAT in the putamen could be associated with the scores for inattention (Volkow, et al., 2007). This finding suggests that additional pathologies could play an important role in adult ADHD. Similar results were also found with regard to the binding potential of the dopamine D2/3 receptor and transporter in the reward pathway (Volkow, et al., 2009), which suggests that reward-motivational deficits are involved in adult ADHD. Indeed, an association between disruption of the dopamine reward pathway and motivation deficits was recently reported (Volkow, et al., 2011).

## Objectives

The aim of present article is to present some of the findings on psychological testing, neuroimaging, as well as the data from pilot study on the mock functional MRI from our team in National Cheng Kung University Hospital.

## Methods

The dopaminergic activity and psychophysiology was studied in adults with ADHD. Single photon

emission computerized tomography (SPECT) with [$^{99m}$Tc] TRODAT-1 was used to measure the in vivo dopaminergic activity. The performance of a decision-making task (in this case, the Iowa Gambling Task, IGT), which may involve hot executive functions, was measured in a mock functional MRI. This ongoing study has been sponsored by the National Science Council of Taiwan.

*Participants*

A small sample of adults with ADHD (N = 6), unaffected fathers of ADHD offsprings (N = 8), and their healthy controls, matched by age and gender, was enrolled in this study. The status of participants with ADHD, having met the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR) criteria, were confirmed by the adult ADHD Clinical Diagnostic Scale v1.2 (Adler & Cohen, 2004). The adult ADHD investigator symptom rating scale (AISRS) were used to assess the severity of ADHD (Spencer, et al., 2010). All the participants with ADHD were examined by a senior psychiatrist using the Mini International Neuropsychiatric Interview (MINI) (Sheehan, et al., 1998), in order to exclude other psychiatric comorbidity. The other inclusion criteria for the ADHD patients were as follows: (i). Within six months prior to screening the patients had met the DSM-IV-TR criteria for adult ADHD, and no medication of any kind had been taken for more than three months. (ii). Aged between 20 and 60 years old. (iii). Subjects must have signed an informed consent document, indicating that they understood the purpose and procedures of this study. The inclusion criteria for the fathers of children with ADHD were as follows: (i). Their children met the DSM-IV-TR criteria for childhood ADHD. (ii). The fathers did not have any psychiatric disorders, as confirmed by a senior psychiatrist using the MINI, and no medication of any kind had been taken for more than three months. (iii). The fathers were aged between 20 and 60 years old. (iv). Subjects must have signed an informed consent document, indicating that they understood the purpose and procedures of this study. Pregnant (known or suspected) or nursing woman, subjects with major physical and mental illnesses, drug or alcohol dependence or abuse in the past six months, those whose conditions presented contraindications for MRI and SPECT scanning, and who had pacemakers or any metal devices in their bodies, were excluded from the study.

*Instruments*

**1. TRODAT-1.**

A single bolus injection of 740 MBq (20 mCi) [$^{99m}$Tc] TRODAT-1(a radio labeled form of tropane derivative for selectively labeling DAT) was administered to the subjects, and a triple-headed rotating gamma camera (Multispect3; Siemens, Hoffman Estates, Illinois, USA) with ultra high-resolution fan-beam collimators was then be used, with an energy window of 15% centered on 140 keV for technetium-99m. Imaging was initiated approximately 240 minutes after injection of [$^{99m}$Tc] TRODAT-1.

SPECT and MRI imaging co-registration will be carried out using PMOD software (PMOD Technologies, Zurich, Switzerland). An experienced nuclear medicine specialist, who was blind to the patients' clinical data, was asked to draw the regions of interest in the individual magnetic resonance images. The ratio of radioactivity in the striatum to that in the cerebellum was derived by dividing the average counts per pixel in the striatum by the average counts per pixel in the cerebellum. The density of DAT was then assessed based on this.

**2. IGT in Mock function MRI**

We will conduct an fMRI assessment with IGT (Bechara, Damasio, Damasio, & Anderson, 1994) for ADHD starting from April. 2014. In a pilot test,

we enrolled a few subjects to test the IGT in a mock functional MRI. IGT is a gambling simulation that is used to assess real-world decision-making processes in a laboratory setting, and we used a computer version of this task. This task has sound construct validity (Buelow & Suhr, 2009), and had been applied to investigate issues related to substance abuse (Bechara & Martin, 2004). Only a few studies have used the IGT to investigate ADHD, and the findings were inconclusive (Geurts, van der Oord, & Crone, 2006; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007).

**3. Cognitive assessment**

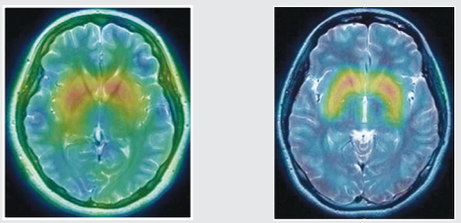
We used the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1986) to assess IQ, and this includes digital symbol, block design, object assembly, digit span, similarity, and arithmetic tests. Wisconsin Card Sorting Test (WCST) (Heaton, 1981), Continuous Performance Test (CPT) (Davies & R, 1982; Hsieh, et al., 2005), Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987), and Finger Tapping Test (FTT) (Prigatano, Johnson, & Gale, 2004) to assess other cool executive.

***Statistical Analysis***

The data were analyzed using SPSS software v17 (SPSS Inc. Chicago, IL., USA). Because the sample size was small, the Wilcoxon signed ranks test was used, and the level of significance was set at $P < 0.05$ (two-tailed).

## Results

SPECT with [99mTc] TRODAT-1 was used to measure the DAT availability (as shown in Figure 1). We discovered that the availability of DAT in adults with ADHD (left striatum: 1.25; right striatum: 1.27; average: 1.26) was lower than that in the health controls (left striatum: 2.22; right striatum: 2.03; average: 2.13), $Z = 2.02$ ($p = 0.04$). We also found out adults with ADHD had relatively poor performance in memory, IQ, and attention test (Table 1), but the fathers of children with ADHD did not.



Adult ADHD patient  Paired normal control

ADHD: attention deficit hyperactivity disorder

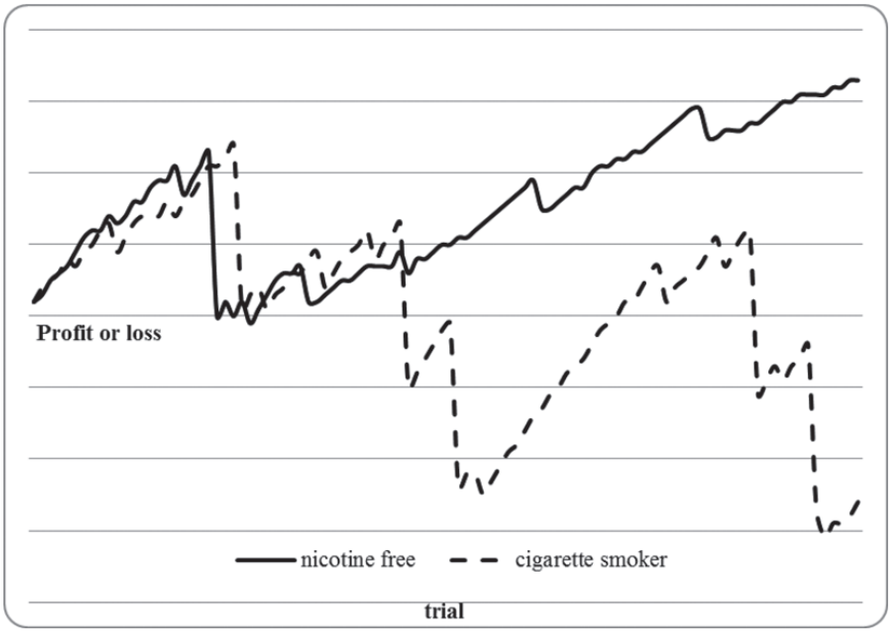
**Figure 1:** Availability of dopamine transporters in adults with and without ADHD

**Table 1:** Executive functions in adults with and without ADHD

| Outcomes | | ADHD | Non-ADHD | Statistic values | |
|---|---|---|---|---|---|
| | N | Mean±SD | Mean±SD | Z | p |
| Age | 8 | 26.88±4.52 | 27.02±4.38 | -0.94 | 0.35 |
| Educational year | 8 | 17.00±1.69 | 16.25±1.39 | -1.60 | 0.11 |
| WMS-R | | | | | |
| Verbal memory | 5 | 91.20±11.26 | 105.40±14.74 | -1.21 | 0.23 |
| Visual memory | 5 | 88.60±5.59 | 121.80±9.88 | -2.02 | 0.04 |
| General memory | 5 | 88.20±8.29 | 112.20±14.29 | -1.75 | 0.08 |
| Attention/concentration | 5 | 97.80±16.47 | 129.80±6.91 | -2.02 | 0.04 |
| Delayed recall | 5 | 89.80±6.76 | 117.80±13.86 | -2.02 | 0.04 |
| WAIS-R | | | | | |
| Performance IQ | 5 | 89.80±15.43 | 116.00±7.25 | -2.02 | 0.04 |
| Verbal IQ | 5 | 98.20±12.38 | 120.80±15.56 | -1.75 | 0.08 |
| Full IQ | 5 | 93.40±12.58 | 121.40±12.54 | -2.02 | 0.04 |
| FTT | | | | | |
| Dominant hand | 5 | 52.32±7.47 | 49.12±6.31 | -1.21 | 0.23 |
| Non-dominant hand | 5 | 45.28±6.54 | 47.32±5.12 | -0.94 | 0.35 |
| WCST | | | | | |
| Perseveration Errors | 5 | 10.60±7.2 | 5.60±2.3 | -1.48 | 0.14 |
| Categories Completed | 5 | 3.20±1.3 | 4.40±0.89 | -1.24 | 0.22 |
| CPT | | | | | |
| Unmask d’ | 5 | 3.72±0.54 | 4.68±0.12 | -2.02 | 0.04 |
| Mask d’ | 5 | 3.87±0.6 | 4.46±0.45 | -1.75 | 0.08 |

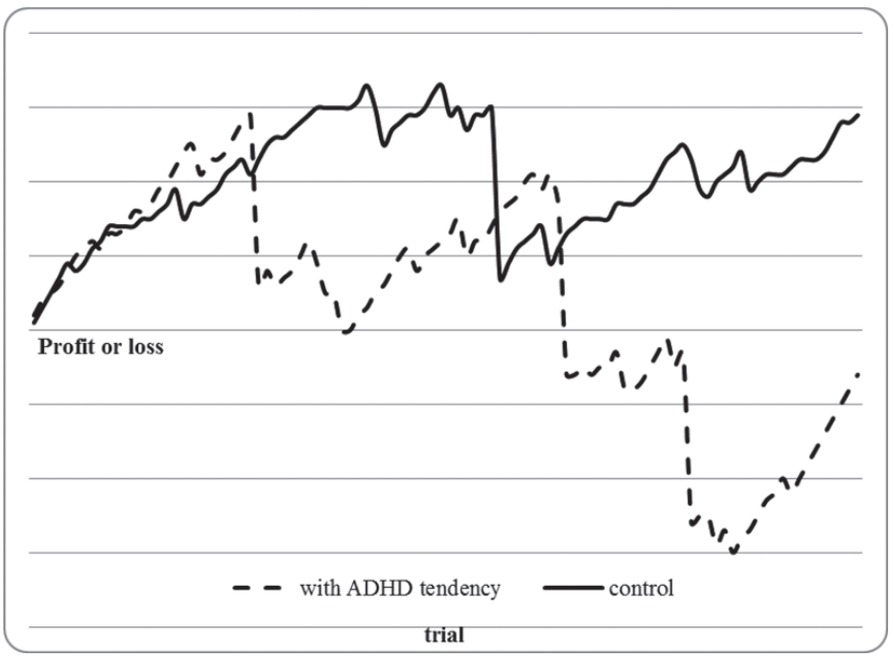
ADHD: attention deficit hyperactivity disorder; WMS-R: Wechsler Memory Scale-Revised; WAIS-R: Wechsler Adult Intelligence Scale-Revised; FTT: Finger Tapping Test; WCST: Wisconsin Card Sorting Test: CPT: Continuous Performance Test

In a pilot test, an IGT for the fMRI (event-related design) was conducted in a mock functional MRI. A total of 100 trials were carried out. Each task lasted 20-30mins, and five participants took part in the experiment. Based on the results of studies which found that additive behaviors are related dopamine hypoactivity (S.-H. Lin, Chiu, & Yang, 2013), and that smokers had poor performance in the IGT due to taking more risks in their decision making (Ert, Yechiam, & Arshavsky, 2013), we analyzed the performances of a male smoker and male ex-smoker in the IGT (Figure 2). The results showed that the smoker took more risky decisions in the later parts of the IGT than the health control. We also examined the results for one adult female with ADHD and another without it (Figure 3). At first there were no differences between then women, but then later in the IGT the adult female with ADHD made more risky decisions than the healthy control. This result is consistent with the hypothesis of the dual-pathway model (Sonuga-Barke, 2003) and a number of other studies (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Dickstein, Bannon, Castellanos, & Milham, 2006).




IGT: Iowa gambling task

**Figure 2:** Performance of IGT in men with smoking and ex-smoking.




ADHD: attention deficit hyperactivity disorder

**Figure 3:** Performance of IGT in women with and without ADHD

## Discussion

The results of our pilot study also confirmed the lower DAT availability among subjects with ADHD, as reported in earlier research (Volkow, et al., 2007). It should be noted that this deficit is quite significant, at a 40.8% reduction in total DAT availability in the striatum, which implies that altered dopaminergic activity could be a pivotal etiology of ADHD (Volkow, et al., 2009). In agree with literature (Schoechlin & Engel, 2005), some domains of cool executive functioning were found to be poor among adult patients with ADHD in our study.

It has been proposed that ADHD is characterized by poor performance in a range of executive functions, including working memory, self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution (Barkley, 1997; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). The stop signal paradigm, in which participants are instructed to respond to a stimuli as fast as they can and then inhibit the response when there is a stop signal, may be one of the most robust paradigms for assessing the cool executive functions among subjects with ADHD (Geurts, et al., 2006). Limited attention capacity, which is an important component of cool cognitive functions, has been found among children and adolescents with ADHD (Hwang, Gau, Hsu, & Wu, 2010). A study in Taiwan confirmed the role of executive dysfunction among subjects with ADHD and their unaffected siblings, implying that cool cognitive functions could be a potential endophenotype of ADHD (Gau & Shang, 2010).

Sounga-Bark (2003) proposed a dual-pathway model of ADHD. The first pathway is the executive dysfunction pathway, and the second is the motivational pathway. This model is in agreement with earlier ideas about cool and hot executive functions (Zelazo, Muller, Frye, & Marcovitch, 2003), and the theory presented in Nigg (2001), in which a distinction was proposed between behavior and motivational inhibition. Gambling tasks, such as the IGT (Bechara, et al., 1994; Bechara, Damasio, Tranel, & Damasio, 2005) and Soochow gambling task (C. H. Lin, Chiu, & Huang, 2009), have been applied to assess hot executive functions, and it has been reported that adolescents with ADHD have poor performance on the IGT (Ernst, et al., 2003). However, children with ADHD did not show any altered response inhibition or decision-making deficit in a study that combined hot and cool executive function tasks (Geurts, et al., 2006), and the role of hot executive functions in ADHD currently remains unclear. It was recently suggested that deficits in cool executive functions are a characteristic of ADHD, while deficits in hot executive functions are a characteristic of conduct disorders (Rubia, 2011). On the other hand, it was also proposed that altered hot executive functions could be a characteristic of ADHD (Castellanos, et al., 2006; Dickstein, et al., 2006).

Although we are still preparing for fMRI with the IGT, the pilot data support the validity of our instrument. It should be noted that a recent study focusing on substance abuse also reported an event-related design for IGT (Tanabe, et al., 2013), which suggests that such a design could be a useful tool to investigate mental disorders that are associated with hypodopaminergic activity. As yet, details of task performance in the IGT, hemodynamic response, and their association with DAT availability, remain to be revealed.

Other markers could be also associated with ADHD, and a study carried out in Taiwan indicated that it is associated with altered event related potentials (ERPs). It was also reported that children with ADHD have altered ERP performance associated with selective attention and inhibitory control (Shen, Tsai, & Duann, 2011). A meta-analysis indicated that P300 amplitude could be a potential endophentype for adult ADHD (Szuromi, Czobor, Komlosi, & Bitter, 2011). In addition, an altered early posterior negativity (EPN) value, which may

be with the SERT gene, was found among adults with ADHD during an emotional process (Herrmann, et al., 2009). A deficit in N170 emotion modulation for facial stimuli was also found among adults with ADHD (Fisher, Aharon-Peretz, & Pratt, 2011), while a recent study revealed altered ERP during decision making (including during the IGT) among adults with ADHD (Ibanez, et al., 2012). These results indicate that ERP is associated with hot executive functions among adults with ADHD. The dexamethasone suppression test (DST), which is a measure of sensitivity to HPA axis negative feedback, has been proposed as a compact measurement of stress (Mellsop, Hutton, & Delahunt, 1985). Several studies indicate that children with ADHD may have altered HPA axis functions (Kaneko, Hoshino, Hashimoto, Okano, & Kumashiro, 1993; Ma, Chen, Chen, Liu, & Wang, 2011), although much less work on this area has been done among adults with ADHD (Lackschewitz, Huther, & Kroner-Herwig, 2008). Other issues related to ADHD, such as how it affects sufferers in daily life, and especially their psychosocial functioning, are also worth examining, but beyond the scope of this study.

In sum, our study confirmed hypodopaminergic activity, and poor executive function could be associated with adult ADHD. Traits that associated with hypodopaminergic activity, such as addiction behaviors and a tendency of novelty seeking, should be noticed in clinical practice. These factors might be interacted with poor executive function, and result in negative outcomes. Pharmacological treatment targeting on dopaminergic system, and psychological treatment focus on above mentioned behavior trait, could be considered as a potential treatment for adult ADHD in the future. Meanwhile, our finding also indicate that hot executive function measured by IGT, might be an unrevealed factor that associated with adult ADHD. Identify the underlying interplay between hot and cool executive function as well as neuroactivity, could be a promising direction of future study. One limitation of this study was the small sample size analyzed. The potential gender differences was not able to confirmed. Furthermore, the study was cross-sectional; therefore the causal influence cannot be clarified.

## Conclusion

ADHD is a psychiatric disorder that not only affects children, but also adolescents and adults. Adult ADHD is associated with poor executive functioning, and may have very negative effects for the patients and their families. The literature review and preliminary data presented in this work highlight the important role of the dopamine system in ADHD. The findings also suggest that changes in brain activity and hot executive functions among ADHD sufferers are important issues that deserve more attention in future work.

## Acknowledgements

The authors wish to thank Ms. Tsai Hua Chang, Mr. Chien Ting Lin, and all of the research participants. This study was supported in part by grants from the National Science Council of Taiwan (NSC 102-2420-H-006-007-MY2).

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