https://doi.org/10.5664/jcsm.9032

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Different positron emission tomography findings in schizophrenia and narcolepsy type 1 in adolescents and young adults: a preliminary study

Wei-Chih Chin, MD[1,*]; Feng-Yuan Liu, MD[2,3,*]; Yu-Shu Huang, MD, PhD[1,†]; Ing-Tsung Hsiao, PhD[2,3,†]; Chih-Huan Wang, PhD[4]; Ying-Chun Chen MD[1]

*[1]Department of Child Psychiatry and Sleep Center, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan; [2]Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [3]Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan; [4]Department of Psychology, Zhejiang Normal University, Zhejiang, China; *W.-C.C. and F.-Y.L. contributed equally to this study; †Y.-S.H. and I.-T.H. contributed equally to this study.*

Study Objectives: The association between schizophrenia and narcolepsy has been controversial. We conducted a prospective case control study of schizophrenia and comorbid narcolepsy type 1 in adolescents compared with patients with either diagnosis alone and healthy controls using ^{18}F-fluorodeoxy glucose positron emission tomography, sleep studies, and neurocognitive tests.

Methods: We included 11 patients (9–20 years old) with schizophrenia and comorbid narcolepsy type 1, 11 with narcolepsy type 1, 11 with schizophrenia, and 11 controls. All groups were matched for age and sex. Participants were required to submit to clinical interviews for sleep and psychiatric disorders, sleep questionnaires, continuous performance test, Wisconsin card sorting test, sleep studies including polysomnography, multiple sleep latency test and actigraphy, and positron emission tomography studies. All data were analyzed to compare the differences between the 4 groups.

Results: The positron emission tomography results demonstrated significant differences in the dual diagnoses group compared with the 3 other groups. Compared with the controls, the dual diagnoses group had a significant presence of hypometabolism in the right mid-frontal, right orbital inferior frontal, and right posterior cingulum and a significant presence of hypermetabolism in the left amygdala, bilateral striatum, bilateral substantia nigra, bilateral basal ganglia, and bilateral thalamus. Continuous performance tests and Wisconsin card sorting tests showed that the dual diagnoses group had the worst performance.

Conclusions: Patients with schizophrenia and comorbid narcolepsy type 1 had different positron emission tomography findings than those with either schizophrenia or narcolepsy type 1 alone. They also had more neurocognitive impairments and required additional interventions.

Keywords: psychosis; hypersomnia; multiple sleep latency tests; image studies; neurocognitive function.

Citation: Chin W-C, Liu F-Y, Huang Y-S, Hsiao I-T, Wang C-H, Chen Y-C. Different positron emission tomography findings in schizophrenia and narcolepsy type 1 in adolescents and young adults: a preliminary study. *J Clin Sleep Med*. 2021;17(4):739–748.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The association between schizophrenia and narcolepsy has been controversial. We conducted a prospective case control study of schizophrenia and narcolepsy type 1 in adolescents and used 18-F-fluorodeoxy glucose positron emission tomography, sleep studies, and neurocognitive tests to evaluate the differences between patients with dual diagnosis and either diagnosis alone.

Study Impact: We found patients with schizophrenia and comorbid narcolepsy type 1 had different positron emission tomography findings than those with either schizophrenia or narcolepsy type 1 alone. They also had more neurocognitive impairments and required additional interventions.

INTRODUCTION

Narcolepsy type 1 is a sleep disorder associated with excessive daytime sleep, disrupted nocturnal sleep, and cataplexy. Cataplexy is characterized by the complete or partial loss of muscle tone after abrupt emotional changes.[1] Narcolepsy type 1 affects approximately 0.02% of adults and occurs early in adolescents and children.[2] The human leukocyte antigen (HLA) DQB1*06:02 allele can be confirmed in more than 92% of patients.[3] Narcolepsy type 1 has been found to be caused by an early loss of the hypothalamus neurons that produce hypocretin. One cerebrospinal fluid study showed pathologically low levels or even the absence of hypocretin,[4] and an autopsy revealed the destruction of the hypocretin neurons in the lateral hypothalamus.[5]

Schizophrenia is a psychiatric disorder with a lifetime prevalence rate of approximately 1%.[6] It is characterized by hallucinations, delusions, disorganized speech/behavior, and negative symptoms. Studies investigating the correlation of narcolepsy and schizophrenia have been limited and reported inconsistent results. In 1 study of patients with schizophrenia with comorbid narcolepsy, Douglass et al[7] reported that 7% of patients with refractory schizophrenia could have variants of HLA-associated narcolepsy. Five of their patients that responded poorly to antipsychotics showed improvement with stimulant treatment. HLA typing and sleep laboratory testing confirmed the diagnosis of narcolepsy in these cases.[7] However, another study screened patients with schizophrenia and further evaluated those with narcoleptic symptoms, but none of those participants were diagnosed with narcolepsy.[8]

In the study of patients with narcolepsy, the results of comorbid schizophrenia have also been controversial. A previous study of narcolepsy's psychiatric comorbidities found that patients with narcolepsy had more psychiatric comorbidities compared with the general population,[9] but no data of psychosis were mentioned. Another recent research using the research database in the United States also reported high rates of psychiatric comorbidity in narcolepsy,[10] and the prevalence of schizophrenia was 3.4% in patients with narcolepsy compared with just 0.9% in people without narcolepsy, which is a 4-fold increase. Patients with both schizophrenia and narcolepsy type 1 may have higher rates of obesity and depression than those with only schizophrenia or narcolepsy type 1 alone.[11] They may also have more difficulties and poorer prognosis, necessitating more clinical attention and help.

In recent years, more neuroimaging studies of schizophrenia and narcolepsy have been obtained, and 18F-fluorodeoxy glucose (FDG) positron emission tomography (PET) and ^{99m}Tc-ethyl-cysteinate dimer single photon emission computed tomography methods have been used to investigate the functional brain imaging of these patients. Most of these previous narcolepsy studies were conducted in adults, and very few studies evaluated brain function in younger populations. We found no image studies discussing the correlation of schizophrenia and narcolepsy type 1. Because onset of both diagnoses is often in adolescence,[6,12–14] comparing the young patients with the 2 diagnoses can assist in understanding their correlation and pathophysiology, and more studies are needed to investigate the differences of image studies and neurocognitive functions between schizophrenia and narcolepsy type 1.

METHODS

This is a prospective case control study of schizophrenia and comorbid narcolepsy type 1 in adolescents compared with patients with either diagnosis alone and healthy controls, using FDG PET, sleep studies, and neurocognitive tests.

Participants

Our sleep center is located in the largest hospital in northern Taiwan, which is also the referring center for children with abnormal sleep. We included 22 patients with narcolepsy type 1 (age range, 16–25 years) based on the criteria of the *International Classification of Sleep Disorders*, third edition.[15] Eleven of the 22 narcoleptic cases had also been diagnosed with schizophrenia. Furthermore, 11 age- and sex-matched patients with schizophrenia and 11 healthy controls were also included. Ultimately, this study consisted of 4 different groups: 11 with schizophrenia and narcolepsy type 1 (group A, the dual diagnoses group), 11 patients with narcolepsy type 1 (group B, the narcolepsy group), 11 with schizophrenia (group C, the schizophrenia group), and 11 healthy controls (group D, the healthy control group).

The study was approved by the Institutional Review Board of Chang Gung Hospital, Taiwan (103-7075A3), from January 8, 2015 to July 31, 2018. All individuals and their legal representatives received a detailed explanation and provided written informed consent before entering this study.

Narcolepsy type 1 evaluation

All participants underwent a clinical interview based on *International Classification of Sleep Disorders*, third edition, and also completed the Stanford narcolepsy questionnaire, Epworth Sleepiness Scale, Pediatric Daytime Sleepiness Scale, and 4 daily visual analog scales (scored 1–100) to evaluate excessive daytime sleep, the presence of hypnogogic/hypnopompic hallucination, and sleep paralysis. They also recorded sleep diaries for 14 continuous days, especially duration of cataplexy attacks after any possible triggers or influential situations.[16–18] Sleep examinations, including actigraphy, polysomnography (PSG), and multiple sleep latency test (MSLT) were arranged for every participant.

Actigraphy was applied for 2 weeks to observe the quantity of sleep inactivity duration the night and day. For PSG during sleep, a Neurovirtual BWIII PSG Plus Sleep System (Fort Lauderdale, FL) was used. The following variables were recorded: electroencephalography (C4/A1, C3/A2, Fp1/ T3, T3/O1, Fp2/T4, T4/O2, Fp1/C3, Fp2/C4), electro-oculogram, chin and leg electromyography, electrocardiography with a modified V2 lead, body-position sensor, nasal cannula/pressure transducer, mouth thermistor, thoracic and abdominal plethysmography bands, neck microphone, and finger pulse oximetry. MSLT was administered the following morning at 2-hour intervals, for a total of five 20-minute naps to obtain mean sleep-latency and number of sleep-onset rapid eye movement periods. Patients with narcolepsy have more than 2 sleep-onset rapid eye movement periods.[15] Scoring was performed by an individual not involved in the study who was blind to all conditions.

HLA typing was checked by blood sampling. A routine examination of height and weight was performed to calculate body mass index.

Schizophrenia evaluation

Schizophrenia was diagnosed by experienced child psychiatrists based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition.[19] The Schedule for Affective Disorder and Schizophrenia for school-aged children, adolescent version was performed in all participants.[20]

Neurocognitive measurement

The neurocognitive assessments included Conners' continuous performance test II (CPT) and the Wisconsin card sorting test (WCST). Both tests were carried out on a computer by trained technicians, and all participants underwent both tests. CPT measures attention and vigilance,[21] whereas WCST measures executive function.[22]

PET

All participants received an 18F-FDG PET scan. An intravenous injection of 5–10 mCi FDG was given in a quiet room with eyes closed to avoid stimuli. During the period until the PET scan, we asked participants to remain fully awake (holding a ball while staying in the waiting room after the injection) and not to move or talk. The environment was supervised by a researcher during the examination to make sure that they were alert and did not fall asleep.

Images were acquired for 10 minutes with a Siemens MCT PET/computed tomography camera 30 minutes after injection. To obtain standard uptake value ratio (SUVR) images, we

reconstructed images with a matrix size of 400 × 400 × 109 and a voxel size of 0.68 × 0.68 × 2.03 mm^3. Then we normalized spatially our data to a standard stereotactic space and format. We performed a voxel-based analysis of PET data using Statistical-Parametric-Mapping (SPM8) software.

Medications

All participants with narcolepsy type 1 received medication for excessive daytime sleep. They were initially treated with methylphenidate for the first 1–2 months after diagnosis at a dose of 20 mg daily. Then, methylphenidate was switched to 200 mg Modafinil (Cephalon, Inc., Frazer, PA) in the morning after the medication's application was approved. Furthermore, participants with cataplexy received anticataplectic medication, such as antidepressants. Patients with schizophrenia were treated with antipsychotic medications as necessary, including long depots. Before examination, all cases had a drug-free period of 7 days, except for antipsychotic medication. We arranged PSG, MSLT, PET, CPT, and WCST within 1–2 days after the drug-free period.

Image study

PET data analysis

We analyzed our data using PMOD image analysis software (version 3.2, PMOD Technologies Ltd, Zurich, Switzerland) and normalized individual ^{18}F-FDG images to the MNI PET template. Ultimately, 11 regions were selected for future analysis, including frontal, anterior cingulate, posterior cingulate, occipital, parietal, temporal, striatum, thalamus, hypothalamus, substantia nigra, and basal ganglia. Then, we used the mean value of regions with an intensity higher than 50% maximum as the reference value for calculating SUVR.

Voxel-wise analysis

Voxel-wise analysis of the SUVR parametric images was performed by SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) in Matlab2010b (MathWorks Inc., Natick, MA). The spatially normalized SUVR images were smoothed using an isotropic Gaussian kernel of 8-mm full-width half maximum. To compare the distribution pattern for patients with different disorders, a voxel-wise 2-sample *t* test was used to evaluate the statistical difference between healthy controls and the 3 other patient groups including patients with dual diagnoses: narcolepsy type 1 and schizophrenia. An uncorrected $P = .005$ with 50 extent voxels was selected as the threshold of statistical significance in each test.

Statistical analysis

All data were analyzed with SPSS, version 18. Variables were presented as either mean ± standard deviation or frequency. We adopted the Kruskal-Wallis test and Mann-Whitney test to compare the differences among the 4 groups with regard to demographic data, laboratory data, test scores, and PET data.

RESULTS

Our study included a total of 44 participants (62.8% male) with a mean age of 20.75 years, who were divided into 1 of the following 4 groups according to their diagnoses. Group A consisted of the patients with dual diagnoses (schizophrenia and narcolepsy type 1, n = 11). They were recruited from 18 dual diagnosis cases among 171 patients with type 1 narcolepsy, during the study period (10.5%). Group B of the patients had narcolepsy type 1 (n = 11), group C had patients with schizophrenia (n = 11), and group D was healthy control group (n = 11). There was no difference between the dual diagnosis group and the narcolepsy type 1 group in pharmacologic treatment of narcolepsy/cataplexy in this study. **Table 1** shows the demographic data, questionnaires' data, HLA typing, and *N*-methyl-D-aspartic acid receptor 1 antibody for the 4 groups. We observed significant differences in body weight and body mass index between the dual diagnosis group A and the other 3 groups, as well as a significant difference in body mass index between the narcolepsy type 1 group B and the control group D. Regarding the Epworth Sleepiness Scale, Pediatric Daytime Sleepiness Scale, and visual analog scales, we found significant differences between the 2 groups with narcolepsy type 1 (groups A and B) and the 2 groups without narcolepsy type 1 (groups C and D). Group C also had significantly higher Epworth Sleepiness Scale and visual analog scales scores than group D.

Table 2 shows the PSG and MSLT data. The PSG results showed that group A had significantly more rapid eye movement periods than the other 3 groups, less stage 2 sleep than group D, more slow wave sleep than group C, and higher periodic limb movement index (PLMI) than groups B and C. Furthermore, group B had significantly less stage 2 sleep than groups C and D and more slow wave sleep and higher oxygen saturation than group C. Group C had significantly less slow wave sleep and lower mean oxygen saturation than group D. Although group C also had significantly lower PLMI than group D, the mean PLMI of group D was within normal range (PLMI < 5).

The MSLT results showed that the 2 groups with narcolepsy type 1 (groups A and B) had lower mean sleep latency, more number of sleep latency < 5 minutes, and SOREM than the non-narcoleptic groups (groups C and D).

Table 3 and **Table S1** in the supplemental material show the PET results (**Figure 1**). Comparing group A, group B, and group C with group D, we found the following results (**Figure 2**):

- Group A had a significant presence of hypometabolism in the right mid frontal ($P = .006$), right orbital inferior frontal ($P = .011$), and right posterior cingulum ($P = .019$) and a significant presence of hypermetabolism in the left amygdala ($P = .012$), bilateral striatum (left: $P = .034$; right: $P = .041$), bilateral substantia nigra (left: $P = .028$; right: $P = .028$), bilateral basal ganglia (left: $P = .010$; right: $P = .010$), and bilateral thalamus (left: $P = .005$; right: $P = .004$).
- Group B had a significant presence of hypermetabolism in the bilateral striatum (left: $P = .009$; right: $P = .014$), bilateral basal ganglia (left: $P = .012$; right: $P = .012$), and right thalamus ($P = .015$).
- Group C had a significant presence of hypometabolism in the right mid-frontal ($P = .029$), right posterior cingulum ($P = .002$), right cuneus ($P = .010$), right lingual ($P = .011$),

Table 1—Demographic data between groups.

	S+N+C (n = 11): Group A	N+C (n = 11): Group B	S (n = 11): Group C	Normal (n = 11): Group D	*P*	Post Hoc *P*
Sex						
Male	8 (72.73%)	6 (54.55%)	7 (63.64%)	6 (54.55%)	.788	
Female	3 (27.27%)	5 (45.45%)	4 (36.36%)	5 (45.45%)		
Age (y)	22.30 ± 3.30 (18-25)	19.11 ± 5.34 (14-25)	21.82 ± 3.31 (18-25)	17.89 ± 5.37 (13-24)	.143	
Age onset (y)	14.20 ± 4.51	12.08 ± 3.83			.124	
Body weight (kg)	78.48 ± 12.93	58.06 ± 18.40	52.72 ± 11.06	47.57 ± 11.88	.004*	A/B: .012, A/C: .002, A/D: .001
Body height (cm)	161.34 ± 5.36	156.34 ± 16.69	159.82 ± 7.90	155.50 ± 19.14	.964	
BMI (kg/m^2)	28.81 ± 4.47	23.53 ± 4.17	20.53 ± 3.18	19.68 ± 2.34	.000*	A/B: .003, A/C: .002, A/D: .000, B/D: .004
ESS	17.70 ± 3.23	16.26 ± 4.79	5.91 ± 2.21	4.09 ± 1.58	.000*	A/C: .000, A/D: .000, B/C: .005, B/D: .000, C/D: .048
PDSS	25.40 ± 5.68	22.79 ± 4.62	10.09 ± 3.30	8.55 ± 2.73	.000*	A/C: .000, A/D: .000, B/C: .005, B/D: .000
VAS	86.00 ± 16.47	83.68 ± 11.25	21.82 ± 13.09	4.09 ± 3.75	.000*	A/C: .000, A/D: .000, B/C: .005, B/D: .000, C/D: .000
HLA DQB1 0602	N = 11	N = 11	N = 0	N = 0		
NMDA antibody	1 (+)	(−)	(−)	(−)		

*P < .05. Group A, S+N+C: schizophrenia and narcolepsy type 1, the dual diagnoses group; group B, N+C, narcolepsy type 1, the narcolepsy group; group C, S: schizophrenia, the schizophrenia group; group D, normal: healthy control, the healthy control group. BMI = body mass index, ESS = Epworth Sleepiness Scale, NMDA = *N*-methyl-D-aspartic acid receptor 1, PDSS = Pediatric Daytime Sleepiness Scale, VAS = visual analog scale.

Table 2—Sleep laboratory results between groups.

	S+N+C (n = 11): Group A	N+C (n = 11): Group B	S (n = 11): Group C	Normal (n = 11): Group D	*P*	Post Hoc *P*
PSG						
AHI (events/h)	6.08 ± 7.97	3.26 ± 4.95	5.78 ± 9.27	1.57 ± 1.50	.455	
Efficiency (%)	77.35 ± 10.91	82.53 ± 11.87	79.93 ± 10.12	86.93 ± 14.24	.104	
Awake (%)	17.25 ± 11.62	16.05 ± 11.14	14.87 ± 12.75	9.18 ± 12.38	.100	
REM (%)	25.82 ± 9.34	17.80 ± 6.12	16.83 ± 7.90	15.39 ± 5.78	.044*	A/B: .014, A/C: .034, A/D: .022
Stage 1 (%)	17.60 ± 8.29	16.58 ± 8.22	23.11 ± 23.79	10.10 ± 6.64	.171	
Stage 2 (%)	34.33 ± 12.24	37.10 ± 9.29	49.38 ± 15.52	45.88 ± 8.20	.009*	A/D: .034, B/C: .017, B/D: .017
SWS (%)	17.86 ± 10.31	21.90 ± 9.64	10.57 ± 17.03	19.66 ± 6.54	.036*	A/C: .041, B/C: .008, C/D: .050
TST (min)	352.95 ± 40.13	390.42 ± 53.48	395.13 ± 57.73	363.49 ± 58.37	.141	
PLMI	5.81 ± 8.92	4.01 ± 13.39	0.00 ± 0.00	0.65 ± 1.71	.044*	A/B: .045, A/C: .017, C/D:.037
Mean SaO_2 (%)	96.81 ± 1.25	96.84 ± 1.05	94.75 ± 2.38	97.08 ± 0.78	.037*	A/C: .040, B/C: .006, C/D: .013
MSLT						
Mean sleep latency (min)	3.35 ± 3.23	3.00 ± 2.36	13.33 ± 5.51	13.33 ± 4.09	.000*	A/C: .002, A/D: .001, B/C: .000, B/D: .000
Number of sleep latency < 5 min	3.40 ± 1.96	4.31 ± 0.84	1.13 ± 1.48	1.00 ± 1.22	.000*	A/C: .018, A/D: .011, B/C: .000, B/D: .000
SOREM	3.40 ± 1.43	3.94 ± 1.16	0.25 ± 0.70	0.11 ± 0.33	.000*	A/C: .001, A/D: .001, B/C: .000, B/D:.000

*P < .05. Group A, S+N+C: schizophrenia and narcolepsy type 1, the dual diagnoses group; group B, N+C, narcolepsy type 1, the narcolepsy group; group C, S: schizophrenia, the schizophrenia group; group D, normal: healthy control, the healthy control group. AHI = apnea-hypopnea index, mean SaO_2 = mean oxygen saturation, MSLT = multiple sleep latency test, PLMI = periodic limb movement index, PSG = polysomnography, REM = rapid eye movement period, SOREM = sleep-onset REM periods, SWS = slow wave sleep, TST = total sleep time.

right superior occipital (P = .030), left mid-occipital (P = .005), bilateral inferior occipital (left: P = .011; right: P = .016), left superior parietal (P = .006), and left inferior parietal (P = .011) and a significant presence of hypermetabolism in the left amygdala (P = .030), bilateral striatum (left: P = .007; right: P = .030), bilateral substantia

Table 3—Significant PET findings between groups.

	S+N+C (n = 11): Group A	N+C (n = 11): Group B	S (n = 11): Group C	Normal (n = 11): Group D	*P*	Post Hoc *P*
Mid-frontal L	0.88 ± 0.07	0.93 ± 0.04	0.91 ± 0.04	0.97 ± 0.06	.052	A/D: .019, C/D: .054
Mid-frontal R	0.90 ± 0.08	0.95 ± 0.05	0.94 ± 0.04	1.00 ± 0.06	.022*	A/D: .006, B/D: .079, C/D: .029
Mid-orbitofrontal L	0.84 ± 0.08	0.92 ± 0.05	0.90 ± 0.03	0.94 ± 0.07	.051	A/B: .021, A/C: .054, A/D: .023
Inferior orbitofrontal R	0.87 ± 0.07	0.91 ± 0.06	0.93 ± 0.03	0.94 ± 0.04	.032*	A/C: .015, A/D: .011
Posterior cingulum L	0.89 ± 0.07	0.92 ± 0.06	0.89 ± 0.04	0.97 ± 0.07	.075	A/D: .028, C/D: .049
Posterior cingulum R	0.80 ± 0.09	0.83 ± 0.07	0.80 ± 0.03	0.90 ± 0.06	.012*	A/D: .019, C/D: .002
Hippocampus L	0.58 ± 0.07	0.54 ± 0.05	0.55 ± 0.04	0.50 ± 0.04	.057	A/D: .015, C/D: .040
Amygdala_L	0.64 ± 0.09	0.59 ± 0.05	0.59 ± 0.04	0.55 ± 0.05	.028*	A/D: .012, B/D: .058, C/D: .030
Cuneus_R	0.91 ± 0.08	0.95 ± 0.03	0.89 ± 0.07	0.98 ± 0.06	.034*	A/D: .058, B/C: .040, C/D: .010
Lingual_L	0.85 ± 0.07	0.91 ± 0.05	0.81 ± 0.06	0.88 ± 0.05	.012*	A/B: .037, B/C: .003, C/D: .065
Lingual_R	0.85 ± 0.06	0.90 ± 0.05	0.81 ± 0.06	0.88 ± 0.05	.006*	A/B: .040, B/C: .003, C/D: .011
Superior occipital R	0.83 ± 0.09	0.84 ± 0.06	0.76 ± 0.05	0.82 ± 0.06	.055*	B/C: .007, C/D: .030
Mid occipital L	0.85 ± 0.08	0.89 ± 0.05	0.80 ± 0.05	0.88 ± 0.05	.015*	B/C: .002, C/D: .005
Inferior occipital L	0.79 ± 0.08	0.82 ± 0.05	0.74 ± 0.06	0.82 ± 0.05	.030*	B/C: .005, C/D: .011
Inferior occipital R	0.82 ± 0.09	0.85 ± 0.05	0.76 ± 0.06	0.82 ± 0.04	.037*	B/C: .007, C/D: .016
Superior parietal L	0.83 ± 0.08	0.82 ± 0.06	0.78 ± 0.04	0.87 ± 0.08	.050*	C/D: .006
Inferior parietal L	0.85 ± 0.09	0.87 ± 0.04	0.83 ± 0.05	0.92 ± 0.08	.049*	A/D: .054, C/D: .011
Striatum L	1.08 ± 0.10	1.07 ± 0.06	1.08 ± 0.07	0.98 ± 0.06	.021*	A/D: .034, B/D: .009, C/D: .007
Striatum R	1.06 ± 0.09	1.05 ± 0.05	1.05 ± 0.07	0.98 ± 0.06	.050*	A/D: .041, B/D: .014, C/D: .030
Substantia nigra L	0.82 ± 0.07	0.82 ± 0.07	0.86 ± 0.03	0.77 ± 0.04	.006*	A/D: .028, C/D: .000
Substantia nigra R	0.84 ± 0.06	0.79 ± 0.07	0.85 ± 0.04	0.78 ± 0.05	.025*	A/D: .028, B/C: .033, C/D: .016
Basal ganglia L	1.02 ± 0.07	1.01 ± 0.05	1.03 ± 0.05	0.93 ± 0.05	.007*	A/D: .010, B/D: .012, C/D: .002
Basal ganglia R	1.01 ± 0.07	1.00 ± 0.05	1.01 ± 0.06	0.93 ± 0.05	.016*	A/D: .010, B/D: .012, C/D: .009
Thalamus L	0.99 ± 0.03	0.97 ± 0.06	1.00 ± 0.05	0.91 ± 0.06	.009*	A/D: .005, B/D: .058, C/D: .002
Thalamus R	0.99 ± 0.04	0.98 ± 0.06	1.02 ± 0.07	0.90 ± 0.06	.004*	A/D: .004, B/D: .015, C/D: .003

*$P < .05$. Group A, S+N+C: schizophrenia and narcolepsy type 1, the dual diagnoses group; group B, N+C, narcolepsy type 1, the narcolepsy group; group C, S: schizophrenia, the schizophrenia group; group D, normal: healthy control, the healthy control group. L = left, R = right.

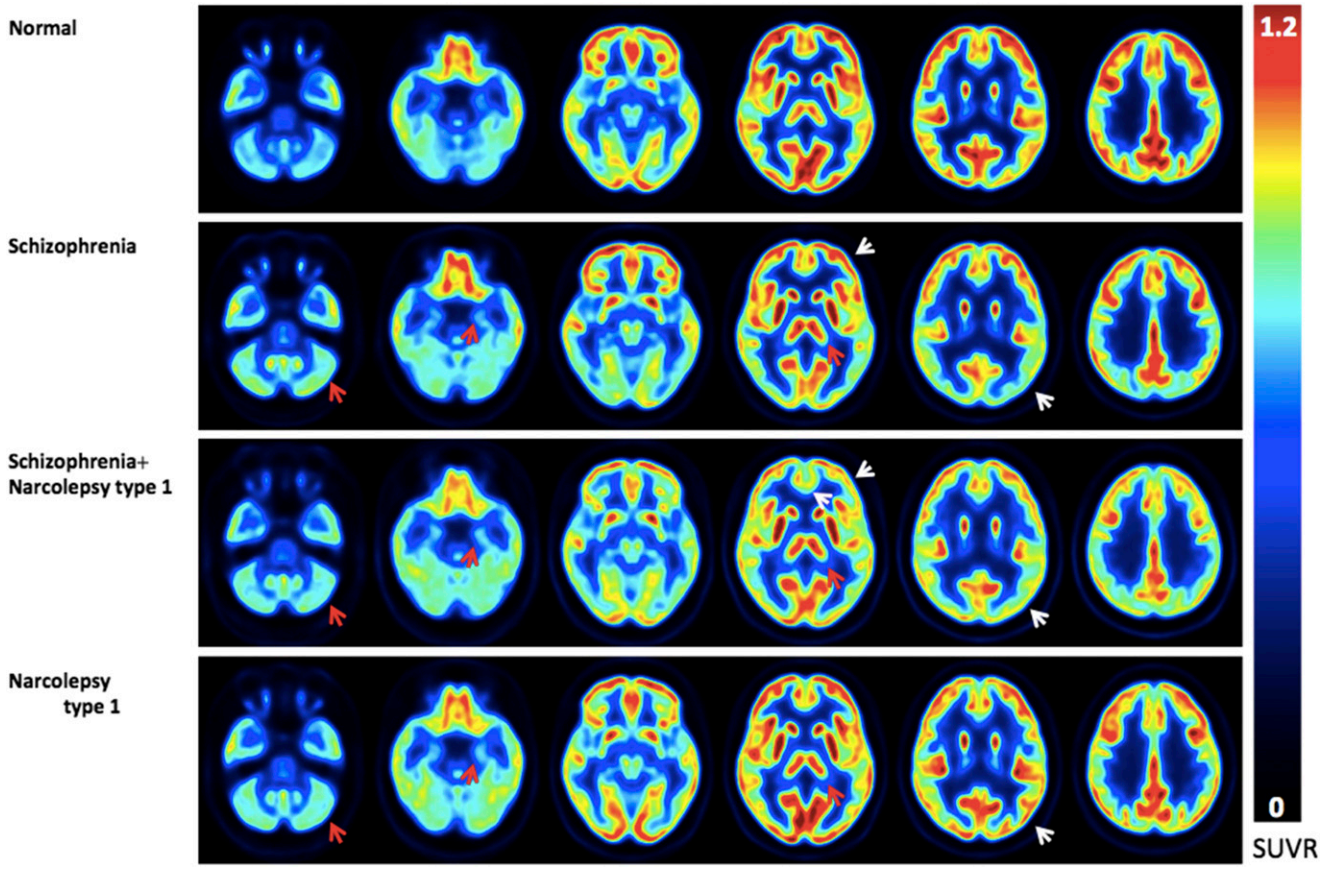
nigra (left: $P = .000$; right: $P = .016$), bilateral basal ganglia (left: $P = .002$; right: $P = .009$), and bilateral thalamus (left: $P = .002$; right: $P = .003$).

Comparing group A with groups B and C:

- Compared with group B, group A had a significant presence of hypometabolism in the bilateral lingual (left: $P = .037$; right: $P = .040$).
- Compared with group C, group A had a significant presence of hypometabolism in the right orbital inferior frontal ($P = .015$).

Table 4 shows the CPT and WCST data. Our CPT result showed that group A, group B, and group C were significantly worse in the clinical confidence index than group D. In other CPT variables, group A was significantly worse than group B in

Figure 1—Standard uptake value ratio (SUVR) images.



Mean standard uptake value ratio (SUVR) of the normal control group, the schizophrenia group, the schizophrenia and narcolepsy type 1 group, and the narcolepsy type 1 group. The SUVR scale shows from dark blue, which indicates slow metabolization, to bright red, which indicates fast metabolization. Clear differences can be noted among the 4 groups.

the hit rate standard error, detectability, and perseverations, significantly worse than group C in omissions and hit rate block change, and significantly worse than group D in the omission, hit rate standard error, detectability, and perseverations. Group B is significantly worse than group C in hit rate block change and significantly worse than group D in omissions and hit rate standard error. Group C was significantly worse than group B in perseverations and significantly worse than group D in hit rate standard error and perseverations.

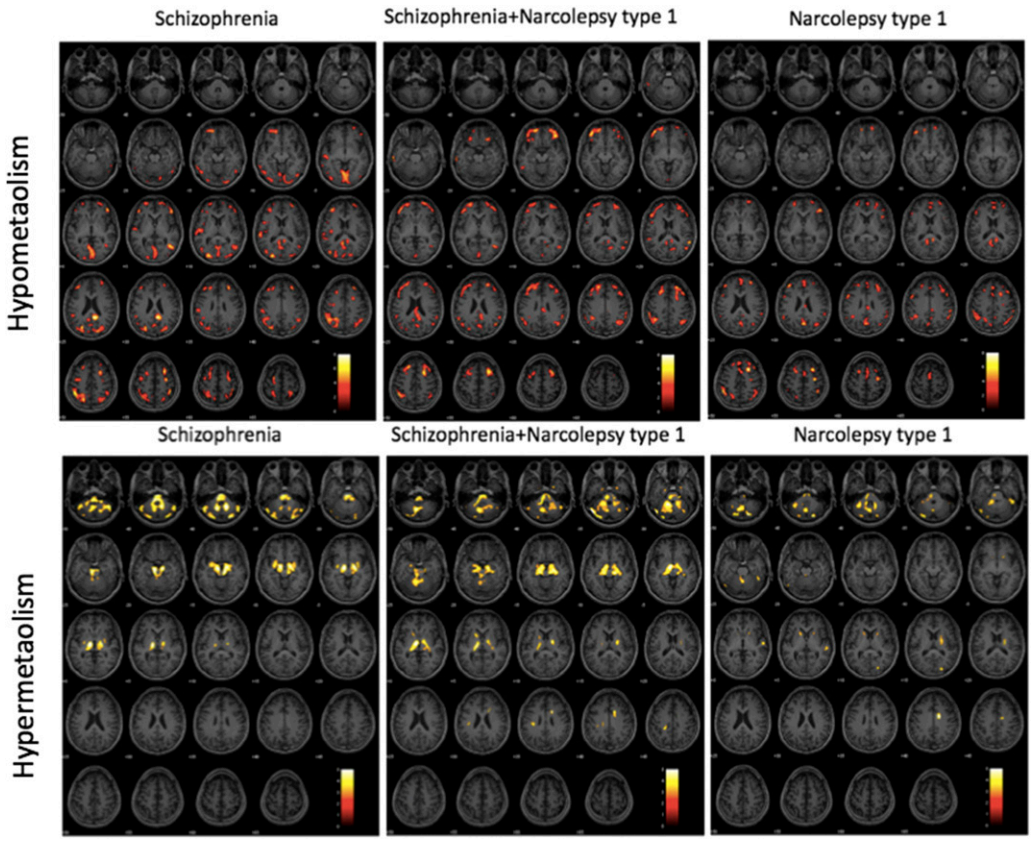
As for WCST, the 2 groups with narcolepsy (groups A and B) were significantly worse than group D in total errors, perseverative response, perseverative response errors, and conceptual level response. Group C was significantly worse than group D in total errors, perseverative errors, nonperseverative errors, and conceptual level response.

DISCUSSION

This study has several limitations. First, the sample size was small because of the rarity of schizophrenia and comorbid narcolepsy type 1. Second, we only included adolescent and young adult patients that were in the early stage of the disease course. Therefore, caution should be practiced when applying our results to different age groups. Third, we did not exclude patients receiving medication, because early intervention and treatment of narcolepsy type 1 and schizophrenia were crucial. Antipsychotic treatment of schizophrenia could not be discontinued. Medication use may have impacted the FDG-PET results, although we ensured an adequate drug-free interval before the examination for other medications. Fourth, inducing cataplexy during the PET scan was difficult, so we did not analyze PET cataplexy findings. Fifth, other psychiatric comorbidities of narcolepsy were not excluded, although such conditions like depression and attention deficit hyperactivity disorder may also contribute to neurocognitive impairment. Last, patients with narcolepsy could be very sleepy during the drug-free period. Although we had strategies (asking the patients to hold a ball, supervision by a researcher) to prevent patients falling asleep during the PET scan, it could still happen. Despite these limitations, our study is the first preliminary study to investigate the PET finding and neurocognitive function in patients with both schizophrenia and narcolepsy type 1 compared with patients with either diagnosis alone and healthy controls.

Our PET results showed that group A had significant hypometabolism in the right mid-frontal gyrus, right orbital

Figure 2—Hypometabolism of the schizophrenia group, the schizophrenia and narcolepsy type 1 group, and the narcolepsy type 1 group.



P < .005, extend voxel = 50, uncorrected, was selected as the threshold of statistical significance in each test. This figure shows the different hypometabolism and hypermetabolism areas between groups. Again, the differences can be clearly noted.

inferior frontal gyrus, and right posterior cingulum and significant hypermetabolism in the left amygdala, bilateral striatum, bilateral substantia nigra, bilateral basal ganglia, and bilateral thalamus compared with healthy controls. These brain regions, including the mid-frontal, orbital frontal, cingulum, and striatum, are related to such neurocognitive functions as attention, decision making, and working memory, and the abnormalities may explain the significantly worse performance of CPT and WCST of group A in our study. Substantia nigra and basal ganglia are closely related to psychotic symptoms and are associated with schizophrenia, whereas the thalamus can regulate the waking and sleeping states, which can explain our PSG and MSLT findings. Furthermore, the dual diagnosis group had significant more hypometabolism in the bilateral lingual than the narcolepsy type 1 group and in the right inferior orbital frontal gyrus than the schizophrenia group. The lingual gyrus relates to word processing, and the orbital frontal gyrus relates to decision making, indicating worse cognitive function in the dual diagnosis group than the narcolepsy type 1 group and the schizophrenia group.

Several investigators have observed hypofrontality of FDG-PET studies of schizophrenia, indicating a lower metabolism ratio of the frontal to occipital lobe.[23,24] Patients had lower metabolism in the frontal and temporal cortex but not in the parietal and occipital lobe regions.[25] However, not all studies could replicate the same finding,[26] and 1 study even found hyperfrontality.[27] In our study, we found hypometabolism in the frontal and especially the occipital region in the schizophrenia group. Both groups with schizophrenia had a similar pattern of hypermetabolism in the left amygdala, bilateral striatum, bilateral substantia nigra, bilateral basal ganglia, and bilateral thalamus compared with the control group. Different from group A, the schizophrenia group also showed significant hypometabolism in the right lingual, right superior occipital, left mid-occipital, bilateral inferior occipital, left superior parietal, and left inferior parietal, which may indicate that the 2 groups are still distinct. The different PET findings between the 2 groups with schizophrenia can assist the differential diagnosis of patients with schizophrenia from patients with narcolepsy type 1, because narcolepsy may also have perceptual changes such as hypnogogic or hypnopompic hallucinations or stimulant-related psychotic symptoms. In the future, additional studies are needed to confirm these findings.

Compared with healthy controls, only nonsignificant hypometabolism was noted in the right mid-frontal gyrus in the narcolepsy type 1 group, consistent with the findings of Dauvilliers et al,[28] who did not observe any significant hypometabolism. However, our previous PET study of patients with

Table 4—Neurocognitive function tests between groups.

	S+N+C (n = 11): Group A	N+C (n = 11): Group B	S (n = 11): Group C	Normal (n = 11): Group D	*P*	Post Hoc *P*
CPT						
Clinical confidence index	71.97 ± 34.31	52.82 ± 22.94	59.46 ± 31.25	32.81 ± 13.12	.010*	A/D: .015, B/D: .003, C/D: .036
Omissions	182.51 ± 143.11	58.74 ± 27.50	92.04 ± 132.50	44.20 ± 1.89	.003*	A/B: .004, A/C: .038, A/D: .001, B/D: .047
Commissions	54.11 ± 9.40	46.13 ± 11.60	56.76 ± 16.28	45.36 ± 12.12	.092	A/B: .041
Hit rate	72.19 ± 32.42	52.25 ± 11.40	46.90 ± 14.77	42.75 ± 8.28	.097	
Hit rate standard error	78.62 ± 33.35	50.71 ± 12.74	60.58 ± 25.72	42.78 ± 5.88	.009*	A/B: .023, A/D: .006, B/D: .027, C/D: .033
Variability	68.41 ± 24.27	51.51 ± 12.35	56.64 ± 20.71	44.56 ± 6.12	.069	A/B: .048, A/D: .016
Detectability	56.68 ± 7.66	47.13 ± 11.71	55.00 ± 9.46	45.77 ± 12.89	.018*	A/B: .006, A/D: .033
Response style	59.54 ± 17.18	53.92 ± 15.29	48.27 ± 4.68	48.07 ± 6.04	.180	A/D: .033
Perseverations	116.38 ± 110.23	54.01 ± 39.38	126.25 ± 178.17	48.55 ± 5.88	.001*	A/B: .002, A/D: .025, B/C: .002, C/D: .017
Hit rate block change	53.99 ± 11.27	53.19 ± 9.53	34.82 ± 22.68	48.29 ± 6.52	.012*	A/C: .024, B/C: .003
WCST						
Total error T score	37.44 ± 18.27	49.45 ± 11.28	40.30 ± 17.80	56.83 ± 10.85	.016*	A/B: .064, A/D: .027, B/D: .031, C/D: .013
Perseverative response T score	41.22 ± 18.12	50.81 ± 12.82	48.00 ± 18.62	62.08 ± 13.12	.047*	A/D: .019, B/D: .023
Perseverative errors T score	40.44 ± 13.42	50.55 ± 12.37	46.70 ± 17.44	62.25 ± 12.98	.021*	A/D: .010, B/D: .017, C/D: .032
Nonperseverative errors	40.67 ± 16.16	49.60 ± 9.62	42.90 ± 13.11	54.75 ± 12.58	.043*	A/D: .064, C/D: .017
% Conceptual level response T score	37.44 ± 17.22	49.52 ± 11.51	39.60 ± 16.62	57.08 ± 10.87	.007*	A/B: .055, A/D: .010, B/D: .035, C/D: .007
Learning to learn	-4.38 ± 6.92	0.90 ± 3.93	0.87 ± 2.29	-0.32 ± 3.65	.191	A/B: .065

*$P < .05$. Group A, S+N+C: schizophrenia and narcolepsy type 1, the dual diagnoses group; group B, N+C, narcolepsy type 1, the narcolepsy group; group C, S: schizophrenia, the schizophrenia group; group D, normal: healthy control, the healthy control group. CPT = continuous performance test, WCST = Wisconsin card sorting test.

narcolepsy type 1 showed significantly reduced metabolism in the frontal lobe and angular gyrus,[29] and it may be explained by this study's small sample size. Like in our previous study, we observed a significant presence of hypermetabolism in the bilateral striatum, bilateral basal ganglia, and right thalamus in the narcolepsy type 1 group, different from that of Dauvilliers et al,[28] who found hypermetabolism in the anterior and midcingulate cortex, right cuneus, and lingual gyrus. Our findings also differed from the study of Joo et al,[30] which found cerebral glucose hypometabolism of the hypothalamus-thalamus-orbitofrontal pathways in the narcoleptic brain. The different results between studies can relate to age differences in the patient population. The studies of Joo et al and Dauvilliers et al included patients much older than our participants. Because the onset of narcolepsy is often noted at an early age, longer disease duration and long-term medication use can have impacts on the PET findings. Besides, our control group included age- and sex-matched healthy participants, and control groups of other studies were patients with non-narcolepsy diseases.

The association between schizophrenia and narcolepsy type 1 is unknown, but several mechanisms are possible.[31] First, psychosis may develop in patients with narcolepsy because of stimulant therapy, although this is infrequent even in patients treated with high doses of stimulants.[32] Another possibility is that some narcoleptic symptoms, especially hypnogogic and hypnopompic hallucinations, may be misdiagnosed as an active psychotic state of schizophrenia. However, the clinical presentation can be quite different. Hyponogogic/hypnopompic hallucinations of narcolepsy are related to sleep and are usually visual/kinetic hallucinations,[33] instead of auditory hallucinations. We aimed to exclude these 2 possible mechanisms in our patients through careful evaluation of psychotic symptoms and the causal relationship between these symptoms and medication.

The third possibility is that both diseases may share similar physiopathologic factors, which can be partially supported by our PET finding of hypermetabolism of the striatum, basal ganglia, and thalamus in both the narcolepsy type 1 group and the schizophrenia group. A lack of hypocretin neurons has been shown to affect monoamine activities, including dopamine, norepinephrine, serotonin, histamine, and acetylcholine,[34] indicating an association between narcolepsy type 1 and the monoaminergic system. Dopamine not only plays a role in regulating sleep and wakefulness[35] but also significantly relates to the pathophysiology of schizophrenia. Furthermore, the pathophysiology of comorbid schizophrenia and narcolepsy

type 1 has been proposed in relation to the autoimmune system. One previous study found more narcolepsy-associated antigens, such as HLA DR15 and DQ6, in patients with schizophrenia than healthy controls.[36] In patients with narcolepsy, HLA DQ B1*06:02 suggests a basis for autoimmune reaction toward hypocretin neurons, along with other gene polymorphisms, including the T-cell receptor α locus, TNFSF4, Cathepsin H, the purinergic receptor P2RY11, and the DNA methyltransferase DNMT1.[37] However, Walterfang et al[38] pointed out that narcoleptic pathologic findings were largely absent in patients with schizophrenia, such as rapid eye movement sleep phenomena, HLA DQB1*0602, and evidence of hypocretin neuron disruption. As a result, no evidence can currently support this hypothesis, and further studies are needed in the future.

Our patients with dual diagnoses are the most obese among the 4 groups and sleepier than the schizophrenia group and healthy control group. It is well known that obesity is a common comorbidity of narcolepsy and schizophrenia. Hypocretin deficiency and lack of exercise because of sleepiness can contribute to obesity in patients with narcolepsy. The side effects of long-term antipsychotic use and negative symptoms play important roles in the obesity problem in patients with schizophrenia. Our study highlighted that obesity and related metabolic syndrome can be more severe in patients with dual diagnosis. With regard to neurocognitive function, the dual diagnosis group had the worst performance in most CPT and WCST scores. Previous studies concluded that patients with narcolepsy have cognitive deficits in attention and possibly in executive function and information processing.[39] Regarding the neurocognitive function of schizophrenia, numerous studies have proven the cognitive deterioration of patients with schizophrenia, including attention, executive function, memory, and information processing.[40,41] Because both diagnoses correlated with neurocognitive impairment, such impairment can be more exacerbated when the 2 disorders coexist. Interventions should be developed to assist this particular group of patients.

These patients who develop both narcolepsy and schizophrenia may have their diagnosis unrecognized or delayed. One reason is that sleepiness can be a side effect of the antipsychotic treatment.[42] Antidopaminergic medication for schizophrenia, such as sulpiride, can also mask or alleviate cataplexy.[43] Furthermore, overlapping symptomatology such as perceptual change or the possible side effect of stimulant treatment can further complicate diagnostic workup. In our practice, admission would be considered to closely monitor the symptoms and rule out medication effect when differential diagnosis is difficult. Clinicians should be aware of the possibility of the dual diagnosis of narcolepsy and schizophrenia, especially in adolescents and young adults. In our previous study, the comorbidity rate of schizophrenia in young patients with narcolepsy could be as high as 14.1%,[29] although the sample size is small, and 10.5% in this study. Thorough evaluation, psychiatrist or sleep specialist referral, and adequate treatments should all be provided.

In conclusion, patients with schizophrenia and comorbid narcolepsy type 1 had different PET findings than those with either schizophrenia or narcolepsy type 1 alone. They had significant more hypometabolism in the bilateral lingual than patients with narcolepsy type 1 and in the right inferior orbital frontal gyrus than those with schizophrenia. They also had worse performance in CPT and WCST, indicating more neurocognitive impairments. Further studies are warranted to confirm our preliminary results.

ABBREVIATIONS

CPT, continuous performance test
FDG, 18-F-fluorodeoxy glucose
HLA, human leukocyte antigen
MSLT, multiple sleep latency test
PET, positron emission tomography
PLM, periodic limb movement index
PSG, polysomnography
SUVR, standard uptake value ratio
WCST, Wisconsin card sorting test

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July 1, 2020
Submitted in final revised form November 11, 2020
Accepted for publication November 11, 2020
Address correspondence to: Yu-Shu Huang, MD, PhD, and Ing-Tsung Hsiao, PhD, Department of Child Psychiatry and Sleep Center, Chang Gung Memorial Hospital, 5, Fu-Shing Street, Kwei-Shan, Taoyuan 333, Taiwan; Tel: 886-3-328-1200, ext. 8541; Fax: 886-3-318-4541; Email: yushuhuang1212@gmail.com and ihsiao@mail.cgu.edu.tw

DISCLOSURE STATEMENT

All authors have seen and reviewed the manuscript. This study was partially funded by Chang Gung Memorial Hospital Research Grants CMRPG 3F1581 to Y. S. Huang and Taiwan's Ministry of Science and Technology Grant MOST 107-2314-B-182A-128-MY2 to Y. S. Huang. The authors report no conflicts of interest.