

# The Effect of Comorbid with Attention-Deficit/Hyperactivity Disorder Symptoms on Face Encoding and Retrieving in Children with Autism Spectrum Disorder

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## Research

**Keywords:** ASD, ADHD, face encoding, face retrieving, visuospatial working memory, executive function

**Posted Date:** May 14th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-28414/v1>

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# Abstract

## Background

Visuospatial working memory (VSWM) impairments were common in Autism Spectrum Disorder (ASD). However, the detailed processing characteristics when facing face stimuli has not been studied. The present study aimed to explore the deficits of face encoding and retrieving, two processing periods of VSWM, in children with ASD. Furthermore, the influence of comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms and executive function (EF) on VSWM were discussed.

## Methods

A sample of 98 children were analyzed in the present study including ASD- (ASD-only,  $n = 24$ ), ADHD ( $n = 23$ ), ASD+ (with ADHD symptoms,  $n = 23$ ) and neurotypical controls (NTC,  $n = 28$ ). Social Responsive Scale (SRS) and Swanson, Nolan, Pelham-IV rating scales (SNAP-IV) were applied to measure autistic and ADHD-related symptoms. We employed face encoding and retrieving task to examine the ability of VSWM as well as Wisconsin Cart Sorting Test (WCST) to assess the EF.

## Results

We found that the children with ASD- exhibited lower accuracy in both face encoding and retrieving, while subjects with ASD + showed lower accuracy in the face retrieving. No evidence implied a deficit of VSWM in ADHD group. We also found diverse indices of EF contributed to the individuals' differences of VSWM performance in different clinical groups: categories completed (CC) predicted the accuracy of face retrieving in ASD- group; perseverative responses errors (RPE) predicted the response time (RT) of face retrieving in ADHD and ASD + group; while failure to maintain set (FMS) and RPE predicted the RT of face encoding in ASD + group.

## Limitations

The sample size is still small and the sample mainly comprised of intellectually able participants. Therefore, our findings should not be overinterpreted.

## Conclusion

Our findings indicate that comorbid with ADHD symptoms and EF may modulate the deficit of face encoding in children with ASD. The study shed lights on the transdiagnostic neurocognitive basis and re-emphasize the importance of considering ADHD-comorbid condition in ASD.

Qi Chen and Zengjian Wang contributed equally to this work as the joint first authors.

# Background

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in social communication and interaction, as well as restricted, repetitive behaviors [1]. Beyond the core symptoms, ASD was also accompanied by cognitive deficits, specifically the visuospatial working memory (VSWM) including face perception [2–4]. Despite a strong tradition of VSWM research in ASD, only relatively few studies have been carried out to investigate the effect of comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms on the VSWM performance in children with ASD [5].

VSWM is a cognitive system with limited resource applying for temporary storage and manipulation of visual information [6], which plays an important role in navigating social interaction [7, 8]. In recent studies, researchers have found that the ability of VSWM in ASD was correlated with the attention condition [9], and it would be influenced by comorbidity with ADHD. Same as neurodevelopmental disorder, children with ADHD were also reported to have social problems and VSWM impairments [10, 11], but the features differed with ASD [12, 13]. Moreover, subjects comorbid ASD and ADHD manifested as an additive condition with the difficulties of both groups [14, 15]. Notably, the subclinical symptoms of ADHD observed in school-aged children with ASD were very common which reached appropriately 30–60% [16, 17]. Co-occurring with ADHD symptoms would worsen the cognition, behaviors, brain function and core symptoms of ASD [18, 19]. Thus, it's essential to consider the condition of ADHD-comorbid in ASD study, irrespective formal diagnosis [20, 21].

For the underlying mechanism of cognitive impairments in ASD and ADHD, executive dysfunction (EF) is one of the robust findings [22–24]. There is a close relationship between VSWM and EF: it was found that individuals needed to employ resources of working memory during executive control [25], meanwhile the process of working memory also needed the support of EF [26, 27]. Recent studies have further suggested that the deficiency of VSWM observed in ASD and ADHD may be attributable to the disruptions in EF such as sustained attention and strategy use rather than the capacity of VSWM per se [28, 29]. For example, the experience of short-term VSWM in ASD showed that the reducing efficiency of process was associated with the deficit of planning [30]. Importantly, ASD and ADHD may have overlap but distinct characteristics in the domain of EF [31, 32]. Moreover, varying subtypes of EF could contribute to distinguish and better understand the cognitive characteristics [12, 33]. Therefore, it's significant to explore the potential effect of EF on VSWM deficits in children with ASD and ADHD.

In our former study, we found that children with ASD performed worse than neurotypical controls (NTC) during VSWM task (tapping test), but there were no differences between ADHD and NTC [34]. More importantly, we found different indices of EF measured by Wisconsin Cart Sorting Test (WCST) made

contributions to the VSWM in children with ASD and ADHD respectively. Beyond these findings, there are some doubts still unsolved. Firstly, successful VSWM relies on the process of encoding, maintaining and retrieving the information. However, which process of VSWM was impaired in ASD is yet unknown. In spite of the sparse direct studies, the relevant findings seemed to prompt that VSWM of ASD might be injured in early encoding period [35, 36], while ADHD were more likely to be affected in retrieving [36, 37]. Secondly, since the profile of VSWM differed in ASD and ADHD and predicted by diverse component of EF, then how comorbid with ADHD symptoms would influence the VSWM in children with ASD merit further study.

The aim of our study was to verify whether the ability of face encoding or retrieving are injured in children with ASD, especially the effect of comorbid with ADHD symptoms on the VSWM processing. We compared the differences of performances during face encoding and retrieving among the four groups: ASD- (ASD-only), ADHD, ASD+ (ASD with ADHD symptoms) and NTC. Our hypotheses were: 1) The function of VSWM would be significantly defected in ASD- group, but relative slighter in ADHD; 2) Children with ASD + may demonstrate worse social function, cognitive ability and VSWM; 3) Performance of face encoding and retrieving would be associated with different EF indicators for respective groups.

## Methods

### Participants

One hundred and six right-handed children aged 6–12 years old were recruited from November 2018 to December 2019 in the present study. All study procedure was approved by the medical ethics committee of the affiliated institute of the authors (consistent with the Declaration of Helsinki) before the recruitment. Written informed consent was obtained from guardians after we explained the purposes and procedure of the study. All parents of children with ASD or ADHD were instructed not to administer medication in 24 hours prior to the test.

Children with ASD or ADHD were all previously diagnosed by professional pediatricians in licensed hospitals in Guangzhou City or Shenzhen City and then confirmed by two pediatrics and psychiatrist experienced in ASD and ADHD assessment according to DSM-IV-TR [38]. Then participants with ASD were divided into two groups: ASD- group (ASD-only, without ADHD symptoms) and ASD + group (with ADHD symptoms) based on their scores of Swanson, Nolan, Pelham-IV rating scales (SNAP-IV). Children with NTC were recruited through primary school, only children using no medication were included.

The Chinese version of Wechsler Intelligence Scale for Children, fourth edition (C-WISC-IV), were used to assess the cognitive profile of all participants which induced full intellectual quotient (FIQ) and 4 sub-indices: verbal comprehensive index (VCI), perceptual reasoning index (PRI), working memory index (WMI) and processing speed index (PSI).

### In/exclusion criteria

General in criteria were: 1) aged 6–12 years old, right-handed; 2)  $FIQ \geq 70$ , with normal naked vision or corrected-vision; 3) the ability to speak and comprehend Mandarin. In addition, children with NTC were required to have normal (not clinical or subclinical) scores on any rating scales for ASD and ADHD symptoms.

Exclusion criteria were: 1) with history or present neurological or severe medical illness, such as learning disorder, schizophrenia, bipolar disorder, major depression disorder, anxiety disorder and so on; 2) could not complete the behavioral tasks.

### Clinical characteristics

Child Autism Rating Scale (CARS) and Social Responsive Scale (SRS-2) were applied to assess participants' autistic symptoms. The CARS, with 15 items, have been the most widely used implement for ASD [39] and it was measured by two well-trained postgraduates in the present study. While SRS-2 is a 65-item parent-rating measure which consists of 5 subdomains: social awareness, social cognition, social communication, social motivation and autistic behaviors [40]. As for ADHD symptoms, they were measured by the Chinese version of SNAP-IV (18-items) [41]. The first 9 items described the symptoms of attention deficit, and the latter 9 items were used to assess the symptoms of hyperactivity. The subjects would be judged to have corresponding symptoms when they have 6 items (or more than 6 items) scored equal to or higher than two. In addition to CARS, parents were instructed to rate their children's psychological and behavioral status without medication according to performance of the latest half years.

### Face encoding and retrieving task

The modified paradigm was consisted of a face encoding task (FET) and a face retrieving task (FRT) in different sessions to assess the performance of VSWM (see Fig. 1). Both tasks have already been applied successfully in different samples [42–44]. We used block design in the present study, the participants were instructed to complete the FET firstly and then the FRT. The two sessions were divided by a short break for appropriately 2 minutes.

*Face encoding task (FET)* Each trial was preceded by a fixation (a character of '+') presented on the center of the screen for 1000 ms. Then either single pictures of neutral faces were presented for 4000 ms in a pseudo-randomized order, and participants were required to distinguish the gender of facial images. They were instructed to press the 'F' button if the person is woman and press 'J' button when the person is man. Following this, stimulus was replaced by a blank screen for another 1000 ms to complete the trial.

*Face retrieving task (FRT)* Similar to FET, each trial of FRT began with a fixation for 1000 ms. Then a target stimulus was presented on the center of the screen for 1000 ms and participants were asked to actively memorize each face for the later response to probe stimulus. In the probe stimulus, two

pictures of faces (comprising one presented previously and another new) were presented simultaneously side by side for 4000 ms, subjects were requested to select the previously presented face by pressing 'F' button if the face appeared in the left while pressing 'J' button if on the opposite. As we modified, during the interval between target stimulus and probe stimulus (1000 ms), the subjects were asked to read out the two numbers appeared in the screen. Same as FET, the trail was ended by a blank screen for another 1000 ms.

In addition, we also used the mask blocks as baseline-condition. The stimulus were grey scrambled images which required participants to press 'J' button within 4000 ms. Either tasks consisted of 5 blocks including 6 trials of target stimulus and 6 mask stimuli so that FET would be completed within 6 minutes and FRT would be ended within 7 minutes. There were 2 practice blocks before formal experience for children to learn the rules. Mean response time (RT) and accuracy (ACC) were recorded.

The face images were selected from the Chinese Facial Affective Picture System [45]. The paradigm was designed using E-prime 2.0 and displayed on a 20-inch LCD screen (1920 × 1080 pixels resolution). Visual stimuli subtending 0.5-1° of visual angle were presented in the horizontal plane at eye-level.

## Executive function

Wisconsin card sorting test (WCST) is a well-established measurement of EF [46]. Here we examined EF by a computerized WCST which comprises 128 reaction cards. The stimuli cards differ in colors, shapes and numbers while the response card would combine these factors so that a response card would match different stimuli cards based on diverse rules. It would generate 11 familiar scores and 4 indices were used in present study: 1) categories completed (CC) reflecting the conceptual ability, 2) errors responses (RE) reflecting the ability of switching, 3) perseverative errors responses (RPE) revealing the ability of flexibility, 4) failure to maintain set (FMS) representing sustained attention.

## Statistical analysis

The data analysis was carried out using SPSS 25.0 software. Firstly, we conducted Shapiro-Wilk tests to inspect the distribution of variables. Based on the results, parametric tests were employed for normally distributed variables and non-parametric tests for non-normally distributed ones (including age, PSI, score of CARS, score of SRS and indices of EF, RT of mask).

Secondly, one-way analysis of variance (ANOVA) or Kruskal-Wallis test was performed to determine the group differences of demographic characteristics, related symptoms, performance of VSWM and indices of EF, and further Bonferroni correction was used for multiple comparisons. In addition, analysis of covariance (ANCOVA) was applied to compare VSWM performance among the four groups after controlling for age and PSI.

Finally, Pearson/Spearman correlation analysis was carried out to test the relationship between VSWM and symptoms of ASD and ADHD. Furthermore, multi-level linear regression analysis was employed to explore the relationship between EF and VSWM. Size of the test was set at  $\alpha = 0.05$ .

## Results

### Sample characteristics

Six participants including children with ASD- ( $n = 2$ ), ADHD ( $n = 1$ ), and ASD+ ( $n = 3$ ) were excluded as they could not accomplish the behavioral tasks. Furthermore, an initial screening based on omission rate of mask-task was conducted to yield 2 outlier subjects ( $Z$  score beyond  $\pm 3$  of the sample as a whole). As a result, a total of 98 subjects (24 ASD-, 23 ADHD, 23 ASD+, 28 NTC) were available for final analysis.

Table 1 showed the sociodemographic, clinical and performance information of all the participants. There were no significant differences in age ( $H_{(3,94)} = 0.412, p = 0.745$ ) and sex distribution ( $\chi^2 = 2.048, p = 0.562$ ) among the four groups. There were group differences in FIQ ( $F_{(3,94)} = 5.395, p = 0.002$ ) and PSI ( $H_{(3,94)} = 5.625, p = 0.001$ ), and the *post hoc* test showed that ASD + group presented lower FIQ than NTC ( $p = 0.001$ ), and all clinical groups scored lower PSI than NTC (all pairwise comparisons,  $p \leq 0.005$ ).

Table 1  
Demographic characteristics of the participants(n = 98)

|  | ASD-          | ADHD          | ASD+          | NTC           | Statistic | P       | Post hoc (Bonferroni corrected)     |
|--|---------------|---------------|---------------|---------------|-----------|---------|-------------------------------------|
| N(female)  | 24(3)         | 23(2)         | 23(3)         | 28(6)         | 2.048     | 0.562   | -                                   |
| Age  | 7.83 ± 0.36*  | 8.34 ± 0.29   | 7.97 ± 0.38*  | 8.18 ± 0.33*  | 0.412     | 0.745   | -                                   |
| FIQ#   | 97.75 ± 3.61  | 98.61 ± 3.29  | 92.09 ± 3.60  | 108.71 ± 1.80 | 5.395     | 0.002   | ASD + < NTC                         |
| VCI#   | 97.17 ± 3.33  | 103.65 ± 2.81 | 93.09 ± 3.81  | 111.25 ± 1.98 | 7.429     | < 0.001 | ASD-, ASD + < NTC                   |
| PRI#   | 104.13 ± 3.73 | 104.00 ± 3.66 | 98.39 ± 3.64  | 110.18 ± 2.06 | 2.276     | 0.085   | -                                   |
| WMI  | 100.79 ± 3.81 | 95.39 ± 2.95  | 94.17 ± 3.17  | 101.75 ± 2.63 | 1.469     | 0.228   | -                                   |
| PSI  | 87.50 ± 2.77* | 88.57 ± 2.95  | 86.78 ± 4.01* | 100.71 ± 1.85 | 5.625     | 0.001   | ASD-, ADHD, ASD + < NTC             |
| CARS#  | 31.44 ± 0.45  | 20.00 ± 0.37  | 31.37 ± 0.55  | 16.71 ± 0.29* | 80.265    | < 0.001 | ASD-, ASD + > ADHD > NTC            |
| <b>SNAP-IV</b>   |               |               |               |               |           |         |                                     |
| total score  | 18.29 ± 1.05  | 28.70 ± 1.38  | 35.78 ± 1.37  | 15.29 ± 1.16  | 35.030    | < 0.001 | ADHD, ASD + > ASD-, NTC             |
| Inattention  | 11.38 ± 0.54  | 17.00 ± 0.89  | 17.13 ± 0.45  | 10.07 ± 0.61  | 31.226    | < 0.001 | ADHD, ASD + > ASD-, NTC             |
| hyperactivity  | 6.67 ± 0.76   | 11.70 ± 0.94  | 12.65 ± 1.23  | 5.21 ± 0.70   | 16.232    | < 0.001 | ADHD, ASD + > ASD-, NTC             |
| <b>SRS</b>   |               |               |               |               |           |         |                                     |
| total score  | 69.38 ± 4.52  | 62.52 ± 3.79  | 96.78 ± 3.89  | 45.57 ± 3.29  | 30.821    | < 0.001 | ASD + > ASD-, ADHD > NTC            |
| awareness  | 9.54 ± 0.59   | 9.78 ± 0.51   | 12.35 ± 0.46  | 8.00 ± 0.37   | 14.148    | < 0.001 | ASD + > ASD-, ADHD, NTC             |
| cognition  | 13.13 ± 0.99  | 12.83 ± 0.88  | 19.57 ± 0.85  | 8.75 ± 0.78   | 26.515    | < 0.001 | ASD + > ASD-, ADHD > NTC            |
| communication  | 23.92 ± 1.77  | 19.87 ± 1.45  | 31.52 ± 1.61  | 13.36 ± 1.38* | 24.698    | < 0.001 | ASD + > ASD-, ADHD > NTC            |
| motivation   | 10.38 ± 0.70  | 9.96 ± 0.72*  | 13.52 ± 4.51* | 9.43 ± 0.81*  | 5.171     | 0.002   | ASD + > ADHD, NTC                   |
| autistic behavior#   | 12.42 ± 1.28  | 10.09 ± 1.21  | 19.83 ± 5.47  | 6.04 ± 0.61   | 46.217    | < 0.001 | ASD + > ASD-, ADHD, NTC; ASD- > NTC |
| Note: # variance inequality; * distributed non-normally; ASD-, autism spectrum disorder (without ADHD symptoms); ADHD, attention-deficit/hyperactivity disorder; ASD+, ASD children with ADHD symptoms; NTC, neurotypical controls; FIQ, full intellectual quotient; VCI, verbal comprehensive index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index. |               |               |               |               |           |         |                                     |

As for clinical characteristics, *Kruskal-Wallis* test and *ANOVA* showed between-group differences from the score of CARS ( $H_{(3,94)} = 80.265, p < 0.001$ ), SRS ( $F_{(3,94)} = 30.821, p < 0.001$ ) and SNAP-IV ( $F_{(3,94)} = 35.030, p < 0.001$ ). Multiple comparisons indicated that in CARS, ASD- and ASD + scored higher than ADHD and NTC (all pairwise comparisons,  $p < 0.001$ ), and ADHD scored higher than NTC ( $p = 0.04$ ). In SRS total and subdomain scores, children with ASD + were higher than other three groups (all pairwise comparisons,  $p < 0.001$ ), and both ASD- and ADHD groups were higher than NTC (ASD- vs NTC,  $p < 0.001$ ; ADHD vs NTC,  $p = 0.013$ ). In SNAP-IV, *post hoc* test demonstrated ADHD and ASD + scored higher than ASD- and NTC group (all pairwise comparisons,  $p < 0.001$ ).

## The ability of face encoding and retrieving

The *ANOVA* results showed the group differences on face encoding and retrieving performance (see **Table S1**). In the FET, RT of mask ( $H_{(3,94)} = 18.185, p < 0.001$ ), RT of encoding ( $F_{(3,94)} = 3.868, p = 0.012$ ) and ACC ( $F_{(3,94)} = 7.027, p < 0.001$ ) were statistically different among the four groups. Multiple comparisons illustrated that the RT-mask of ASD- and ASD + were longer than NTC (ASD- vs NTC,  $p = 0.005$ ; ASD + vs NTC,  $p = 0.001$ ), and the result was similar in the RT-encoding (ASD- vs NTC,  $p = 0.027$ ; ASD + vs NTC,  $p = 0.045$ ). While children with ASD- and ASD + presented smaller ACC-encoding than NTC (ASD- vs NTC,  $p < 0.001$ ; ASD + vs NTC,  $p = 0.014$ ), and children with ASD- had a smaller ACC-encoding than ADHD ( $p = 0.024$ ). In the facet of FRT, we found there were group differences in RT of mask ( $H_{(3,94)} = 8.809, p = 0.032$ ) and ACC ( $F_{(3,94)} = 12.118, p < 0.001$ ). Multiple comparisons indicated

that children with ASD- had a longer RT-mask than NTC ( $p = 0.029$ ), and children with ASD- and ASD + had smaller ACC-retrieving than ADHD and NTC (all pairwise comparisons,  $p < 0.005$ ).

In order to control the influence of participants' age span and the basic response speed, we further conducted analysis of covariance (ANCOVA) after controlling age and PSI [47]. The results revealed that there were no significant interactions between group and age ( $F_{(3,94)} = 1.131, p = 0.341$ ), neither between group and PSI ( $F_{(3,94)} = 1.215, p = 0.309$ ). Moreover, only group differences of ACC-encoding ( $F_{(3,94)} = 5.145, p = 0.002$ ) and ACC-retrieving ( $F_{(3,94)} = 9.641, p < 0.001$ ) remained significant. In FET, children with ASD- showed a smaller ACC than children with ADHD ( $p = 0.026$ ) and NTC ( $p = 0.003$ ). In FRT, both children with ASD- and those with ASD + presented a lower ACC than ADHD and NTC (ASD- vs ADHD,  $p < 0.001$ ; ASD- vs NTC,  $p = 0.001$ ; ASD + vs ADHD,  $p = 0.003$ ; ASD + vs NTC,  $p = 0.023$ ) (see Fig. 2).

## The correlation between VSWM performance and symptoms of ASD and ADHD

Table 2 exhibited the results of *Pearson correlation analysis* (or *Spearman analysis* for variables that couldn't meet the prerequisite of normal-distribution and homogeneity of variance) between VSWM performance and the score of SRS and SNAP-IV. In ASD- group, the RT-encoding was negatively correlated with scores of SRS including total score ( $r = -0.411, p = 0.046$ ), social awareness ( $r = -0.462, p = 0.023$ ), social cognition ( $r = -0.455, p = 0.025$ ) and autistic behaviors ( $r = -0.418, p = 0.042$ ); while the ACC-retrieving ( $r = -0.418, p = 0.042$ ) and RT-retrieving ( $r = -0.406, p = 0.049$ ) was associated with social cognition. By contrast, in ADHD group, only ACC-retrieving was negatively correlated with social motivation ( $r = -0.428, p = 0.041$ ). As for children with ASD+, the ACC-encoding was associated with score of SRS including total score ( $r = -0.433, p = 0.039$ ) and social motivation ( $r = -0.521, p = 0.011$ ); the RT-encoding was correlated with total score ( $r = -0.497, p = 0.016$ ) and hyperactivity ( $r = -0.550, p = 0.007$ ) of SNAP-IV; and RT-retrieving was associated with social awareness ( $r = -0.593, p = 0.003$ ). Moreover, NTC group didn't exhibit significant correlations of VSWM with the score of SRS and SNAP-IV.

Table 2  
The correlation between VSWM performance and core symptoms of ASD and ADHD.

|                   | ASD- (n = 24) |                |                |                | ADHD (n = 23) |        |                |       | ASD+ (n = 23)  |                 |            |                 |
|-------------------|---------------|----------------|----------------|----------------|---------------|--------|----------------|-------|----------------|-----------------|------------|-----------------|
|                   | Encoding      |                | Retrieving     |                | Encoding      |        | Retrieving     |       | Encoding       |                 | Retrieving |                 |
|                   | ACC           | RT             | ACC            | RT             | ACC           | RT     | ACC            | RT    | ACC            | RT              | ACC        | RT              |
| <b>SRS</b>        |               |                |                |                |               |        |                |       |                |                 |            |                 |
| total score       | -0.271        | <b>-0.411*</b> | -0.219         | -0.366         | -0.124        | 0.012  | -0.278         | 0.231 | <b>-0.433*</b> | -0.108          | -0.403     | -0.313          |
| awareness         | -0.154        | <b>-0.462*</b> | 0.045          | -0.245         | 0.036         | -0.273 | -0.135         | 0.196 | -0.129         | -0.314          | 0.151      | <b>-0.593**</b> |
| cognition         | -0.339        | <b>-0.455*</b> | <b>-0.418*</b> | <b>-0.406*</b> | -0.118        | -0.032 | -0.061         | 0.101 | -0.372         | 0.000           | -0.317     | -0.243          |
| communication     | -0.194        | -0.294         | -0.227         | -0.324         | -0.072        | 0.000  | -0.263         | 0.174 | -0.286         | -0.183          | -0.395     | -0.210          |
| motivation        | -0.202        | -0.107         | -0.033         | -0.199         | 0.100         | 0.132  | <b>-0.428*</b> | 0.412 | <b>-0.521*</b> | 0.210           | -0.382     | -0.230          |
| autistic behavior | -0.244        | <b>-0.418*</b> | -0.138         | -0.307         | 0.290         | 0.097  | -0.200         | 0.113 | -0.337         | -0.157          | -0.331     | -0.164          |
| <b>SNAP</b>       |               |                |                |                |               |        |                |       |                |                 |            |                 |
| total score       | -0.266        | -0.199         | -0.254         | -0.260         | -0.345        | 0.129  | -0.077         | 0.423 | 0.167          | <b>-0.497*</b>  | 0.160      | -0.389          |
| inattention       | -0.089        | -0.131         | -0.317         | -0.295         | -0.280        | 0.016  | 0.014          | 0.298 | 0.317          | -0.002          | -0.011     | -0.197          |
| hyperactivity     | -0.307        | -0.183         | -0.122         | -0.147         | -0.239        | 0.174  | -0.127         | 0.337 | 0.071          | <b>-0.550**</b> | 0.181      | -0.360          |

Note: \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; VSWM, visuospatial working memory; ASD-, autism spectrum disorder (without ADHD symptoms); ADHD, attention-deficit/hyperactivity disorder; ASD+, ASD children with ADHD symptoms; ACC, accuracy; RT, response time.

## The relationship between EF and VSWM

In the comparison of EF, all clinical groups had lower score of CC than NTC ( $H_{(3,94)} = 18.781, p < 0.001$ ; all pairwise comparison,  $p < 0.05$ ). Participants with ADHD and those with ASD + scored higher than NTC in the index of RE ( $H_{(3,94)} = 16.886, p = 0.001$ ; ADHD vs NTC,  $p = 0.001$ ; ASD + vs NTC,  $p = 0.006$ ). There existed no group differences in RPE and FMS (see Table S2).

The *Spearman correlation analysis* (see Table S3) illustrated that ACC-retrieving was positively associated with CC in ASD- group ( $r = 0.444, p = 0.030$ ). In addition, RT-retrieving was correlated with CC ( $r = -0.501, p = 0.015$ ), RE ( $r = 0.425, p = 0.043$ ) and RPE ( $r = -0.583, p = 0.018$ ) in ADHD group. And for children with ASD+, RT-encoding showed positive relationship with CC ( $r = 0.546, p = 0.007$ ) and FMS ( $r = 0.463, p = 0.026$ ). No significant relationship between EF and VSWM performance was found in NTC.

To explore how different indices of EF predicted the performance of face encoding and retrieving, we employed multi-linear regression analysis (stepwise) adjusting for age and FIQ. The results showed in Table 3 illustrated that CC predicted 22.5% individual variation of ACC-retrieving in ASD-

group ( $F_{(1,22)} = 7.660, p = 0.011, R^2_{adjusted} = 0.225$ ), and RPE could predict 23.3% individual difference of RT-retrieving in ADHD group ( $F_{(1,21)} = 7.672, p = 0.011, R^2_{adjusted} = 0.233$ ). While in ASD + group, RPE and FMS predicted 27.2% performance of RT-encoding ( $F_{(1,20)} = 5.104, p = 0.016, R^2_{adjusted} = 0.272$ ), and RPE predicted 32.2% performance of RT-retrieving ( $F_{(1,21)} = 11.438, P = 0.003, R^2_{adjusted} = 0.322$ ). None indices of EF predicted the performance of face encoding and retrieving in NTC group.

Table 3  
Multiple regression analysis between EF and VSWM in different groups

| Group | Dependent      | Independent | <i>B</i> ( <i>SE</i> ) | <i>b</i> ' | <i>t</i> | <i>P</i> | <i>R</i> <sup>2</sup> | <i>R</i> <sup>2</sup> <i>changed</i> |
|-------|----------------|-------------|------------------------|------------|----------|----------|-----------------------|--------------------------------------|
| ASD-  | ACC-Retrieving | CC          | 0.043 (0.016)          | 0.508      | 2.768    | 0.011    | 0.285                 | 0.258                                |
| ADHD  | RT-Retrieving  | RPE         | -40.781(14.724)        | -0.517     | -2.770   | 0.011    | 0.268                 | 0.268                                |
| ASD+  | RT-Encoding    | FMS         | 163.741 (72.155)       | 0.414      | 2.269    | 0.034    | 0.338                 | 0.145                                |
|       |                | RPE         | 15.541 (7.435)         | 0.381      | 2.090    | 0.050    |                       |                                      |
|       | RT-Retrieving  | RPE         | 23.284 (6.855)         | 0.594      | 3.382    | 0.003    | 0.353                 | 0.353                                |

*Abbreviation:* ASD-, autism spectrum disorder (without ADHD symptoms); ADHD, attention-deficit/hyperactivity disorder; ASD+, ASD children with ADHD symptoms; CC, categories completed; RE, errors responses; RPE, perseverative responses errors; FMS, failure to maintain set; ACC, accuracy; RT, response time.

## Discussion

In this study, we directly compared the ability of face encoding and retrieving among the four groups (ASD-, ADHD, ASD + and NTC) to investigate the influence of comorbid with ADHD symptoms on VSWM of children with ASD. Our findings showed that children with ASD- exhibited lower accuracy than NTC in both face encoding and retrieving, and subjects with ASD + performed worse than NTC only in the face retrieving. But no evidence implied a deficiency in VSWM for ADHD group. Besides, we also found varying indices of EF made contributions to the VSWM performance in respective groups.

Our study replicated the well-documented findings that individuals with ASD had significant deficits on VSWM [48–52], and further suggested the impairments were both manifested on face encoding and retrieving. Previous studies have demonstrated that subjects with ASD showed general difficulties on face perception [53–55]. And in recent neurological studies, Tye *et al.* [36] found that the N170 amplitude (component of ERP) of ASD was reducing during presentation of emotional face stimuli which indicated an alteration at the encoding period. Cooper *et al.*[56] discovered that participants with ASD exhibited lower accuracy and attenuated hippocampal functional connectivity during episodic memory retrieving. We also found the VSWM performance of children with ASD was correlated with their social function impairments, which imply that VSWM may be an endophenotype for ASD [8, 57]. Combined these findings, more research works are needed to disclose the relationship between the deficit of VSWM and social attention bias in ASD.

Consistent with our former finding [34], the present study didn't support the deficits of VSWM in ADHD group. By contrast, several previous studies revealed that children with ADHD had impairments on VSWM [10, 11, 58]. In our study, the result implied the ability of VSWM would be less invasive in children with ADHD, which is also consistent with study from Hyun *et al.* [37]. Some literatures illustrated that individuals with ADHD performed well as NTC in the behavioral tasks but the efficiency of neural processing was decreased [59, 60]. Moreover, we also found that the VSWM performance of children with ADHD was correlated with social problems but not ADHD-related symptoms. From our data, although social difficulties were also observed in children with ADHD, the deficits were slighter than ASD what was observed to lie in the intermedia point between ASD and NTC. We thus speculated that children with ADHD may own more knowledge of social skills which supported by relative better cognitive function [12, 13].

Furthermore, this study showed that ASD with ADHD symptoms presented worse cognitive ability and severer social problems than children with ASD-only. The result was in line with previous findings emphasizing the importance of considering the ADHD-comorbid condition in ASD [20, 51]. While inconsistent with our hypothesis, compared with ASD-only group, ASD with ADHD symptoms manifested deficiency only in the face retrieving after controlling age and PSI. In addition, our study also indicated that the ability of face encoding was correlated with social dysfunction as well as ADHD-related symptoms, and the performance of face retrieving was only associated with social awareness. We thus inferred that ADHD symptoms may influence the process of face encoding but not retrieving. Recent studies have also proposed that children with ASD may 'compensate' for their underlying difficulties [61, 62]. In order to orienting the challenge against worse core dysfunction, they may mobilize more other cognitive resources such as EF. Through fMRI data, children and adolescents with ASD were found to exhibit increased activation within multiple prefrontal cortex areas when responding to WM load and facing faces [63, 64]. Based on that, more direct evidence was needed to analyze the changes of neurocognitive function in ASD.

Importantly, previous studies have revealed the closely relationship between EF and VSWM impairments in ASD and ADHD respectively [25, 28, 30]. Our data showed that the different EF indicators contributed to predict the ability of face retrieving in all clinical groups. Concretely, to the children with ASD-only, categories completed (CC) effectively predicted the accuracy of face retrieving which is consistent with our former study [34]; and the perseverative responses errors (RPE) predicted the individual differences of face retrieving in both ADHD and ASD with ADHD symptoms group. Moreover, some scholars suggested that the ability of EF may have an important compensation function in patients with ASD [62, 65, 66]. Interesting, only to ASD with

ADHD symptoms, we found the performance of face encoding was predicted by failure to maintain set (FMS) and RPE. And notably, the ability of RPE and FMS were normal in children with ASD comorbid ADHD symptoms. Combining with above findings, we deduced that subjects with ASD comorbid ADHD symptoms may mobilize the resource of EF to show relative complete performance in face encoding. Since diverse components of EF made contributions to the face encoding and retrieving in ASD and ADHD, it's worth further study to extend the knowledge that would have a guiding role in the effective intervention.

## Limitations

There were also several limitations in this study. Firstly, the sample size is still small which would affect the validity and reliability of the findings, so we compared the results with other studies and analyzed the difference to make the inference cautiously. Secondly, to be strict, the process of face retrieving in our task also included the course of encoding. Although the result has disassociated the different process periods of VSWM, study combines with ERP may better distinguish the neural responses of encoding and retrieving. Finally, considering the related studies were rare, our findings should not be overinterpreted. More precise experiment conditions and larger sample size would increase the degree of explanation.

## Conclusion

By comparing the performance of face encoding and retrieving among ASD-only, ADHD, ASD with ADHD symptoms and NTC group directly, our study was able to investigate the influence of ADHD-comorbid condition on VSWM of children with ASD. Our study suggested that ADHD symptoms and executive function may modulate the deficits of face encoding in children with ASD. Our findings stress the importance of trans-diagnostic approach to the relationship between behavior and neuropsychology. Future work needs to clarify the role of VSWM and visual attention bias in ASD.

## Abbreviations

ASD  
Autism Spectrum Disorder  
ADHD  
Attention-Deficit/Hyperactivity Disorder  
ASD-  
children with ASD-only  
ASD+  
ASD with ADHD symptoms.  
NTC  
neurotypical controls  
VSWM  
visuospatial working memory  
EF  
executive function  
WCST  
Wisconsin Cart Sort Test  
CC  
categories completed  
RPE  
perseverative responses errors  
RE  
response errors  
FMS  
failure to maintain set  
CARS  
Child Autism Rating Scale  
SRS-2  
Social Responsive Scale, 2th edition  
SNAP-IV  
Swanson, Nolan, Pelham-IV rating scales  
C-WISC-IV  
The Chinese version of Wechsler Intelligence Scale for Children, fourth edition  
FIQ  
full intellectual quotient  
VCI  
verbal comprehensive index

PRI  
perceptual reasoning index  
WMI  
working memory index  
PSI  
processing speed index  
FET  
face encoding task  
FRT  
face retrieving task  
ACC  
accuracy  
RT  
response time  
ANOVA  
analysis of variance  
ANCOVA  
analysis of covariance

## Declarations

## Ethics approval and consent to participate

The study was approved by the medical ethics committees of Sun Yat-sen University and written informed consent was obtained from guardians before the onset of the experience.

## Consent for publication

Not applicable.

## Competing interests

None.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81171293) and the Natural Science Foundation of Guangdong Province (Grant No. 2018A030310336, 2020A1515010942).

## Contributions

ZW designed the study. QC (Qi Chen) and QC (Qingxin Chen) collected the data. QC (Qi Chen) analyzed the data and wrote the manuscript. ZW modified and revised the manuscript. BW provided a critical review and gave some valuable suggestions for improving the manuscript. YJ provided support and guidance to complete the study. All authors read and approved the final manuscript.

## Acknowledgements

The authors thank all of the children and parents who took part in the study and acknowledged all other participants involved in this research endeavor. The authors also thank the State Key Laboratory of Cognitive Neuroscience and Learning to provide the Chinese Facial Affective Pictures System for the stimuli of face encoding and retrieving task.

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## Figures

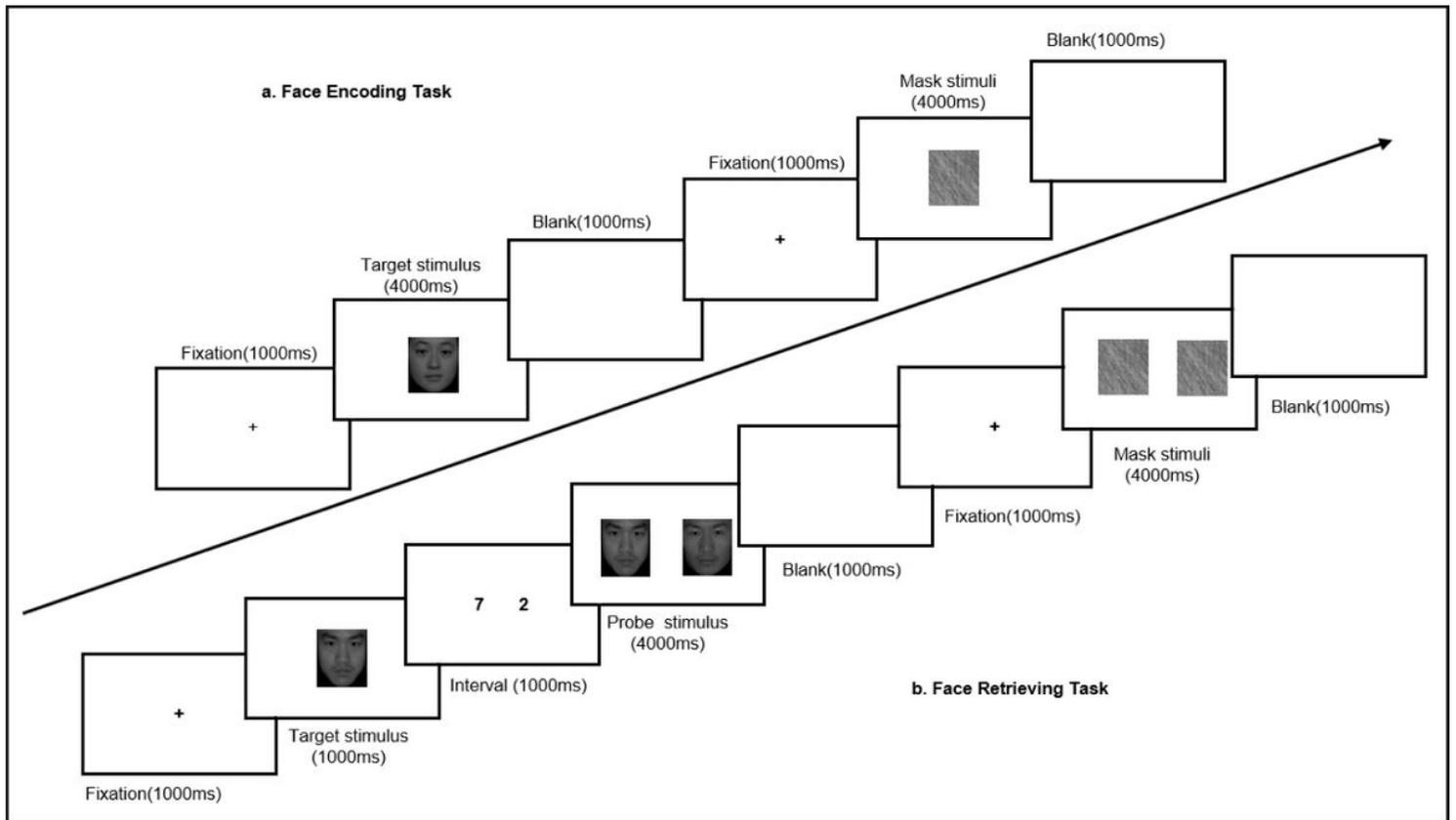
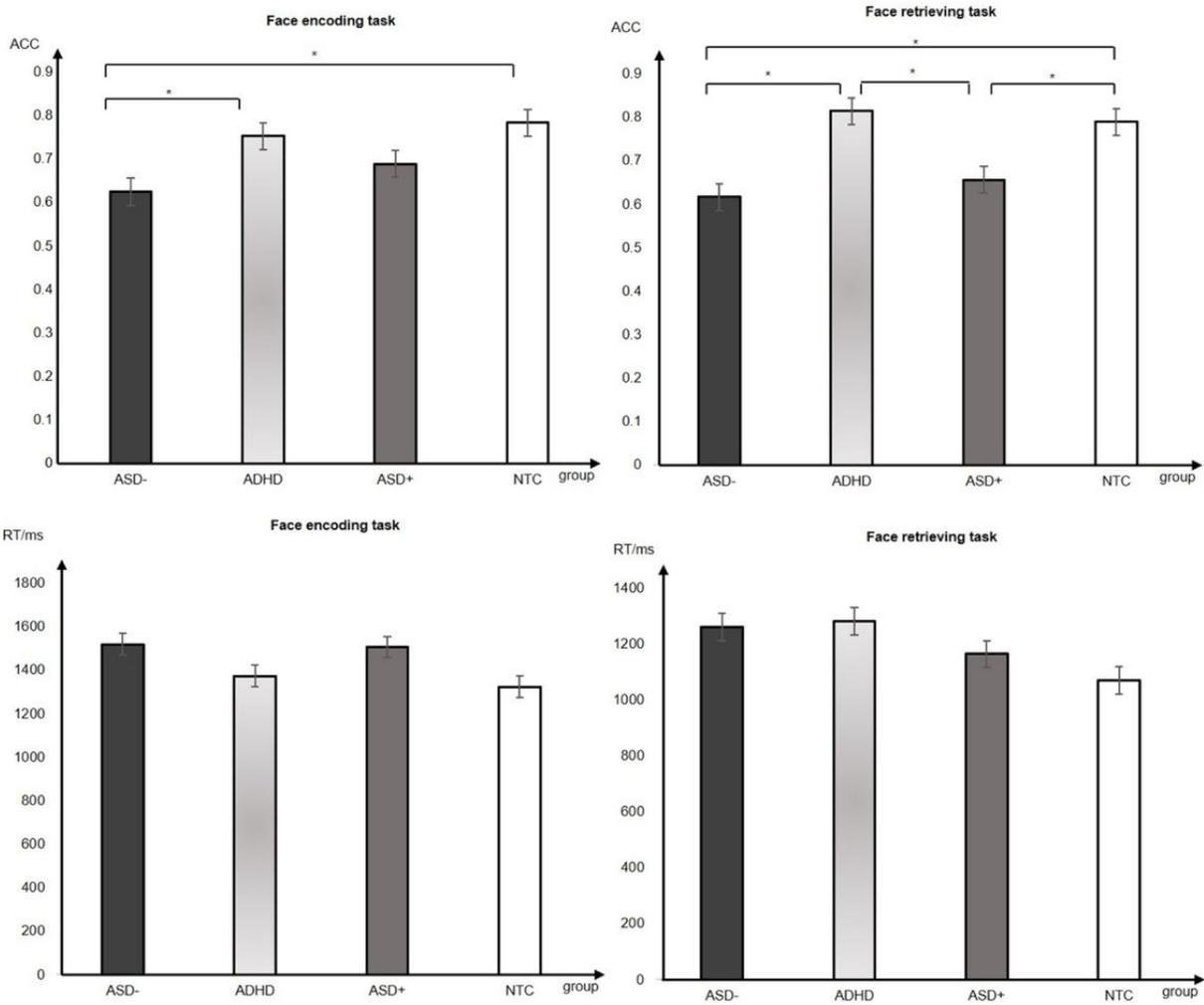


Figure 1

A demonstration of face encoding and retrieving paradigm



**Figure 2**  
 Group differences of performance on face encoding and retrieving task Note: \* $P < 0.05$ ; ACC, accuracy; RT, response time; ASD-, autism spectrum disorder (without ADHD symptoms); ADHD, attention-deficit/hyperactivity disorder; ASD+, ASD children with ADHD symptoms; NTC, neurotypical controls

### Supplementary Files

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