Meta-analysis of working memory impairment in autism spectrum disorders

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Abstract

Autism spectrum disorders (ASD) are characterized by executive dysfunction, and working memory (WM) is one of the core components of executive function. Many studies have examined WM impairment in individuals with ASD, however, conclusive agreement has not yet been reached. The present study provided a meta-analytic review of WM impairment in individuals with ASD and explored potential moderating variables of this problem. A total of 29 studies were included in this study, and the participants comprised 862 individuals with ASD and 899 healthy controls. Significant WM impairment (Cohen's $d = -0.63$) was found in individuals with ASD, however the impairment was not found to be associated with age. A number of moderation analyses showed that: (a) spatial WM was more severely impaired than verbal WM; and (b) component of cognitive processing (maintenance vs. maintenance plus manipulation) did not affect WM impairment. These findings suggest that WM is impaired in individuals with ASD and may have implications for intervention of WM impairment in these individuals.

Keywords: working memory, autism spectrum disorders, meta-analysis, moderator

1. Introduction

Autism Spectrum Disorders (ASD), a spectrum of neurodevelopmental disorders, are characterized by persistent deficits in social interaction and communication, and restricted repetitive and stereotyped patterns of behavior (American Psychiatric Association, 1994). Many theories have been proposed to explain the prominent deficits of ASD, including the theory of mind deficit theory which states that individuals with ASD do not have the ability to mentalise or cannot infer others' mental states (Baron-Cohen, Leslie, & Frith, 1985); the weak central coherence theory which states that individuals with ASD tend to process parts or detail information of things rather than their global meaning (Frith, 1989); and executive dysfunction theory which states that most abnormalities of individuals with ASD are related to executive dysfunction (Hill, 2004). Among these theories, executive dysfunction theory can account for many of the non-social aspects of autism, and is the only theory that acknowledges both cognitive and motor aspects of ASD (Rajendran & Mitchell, 2007).

Executive function is a broad construct and there is not a unified definition. It is generally agreed that executive function is an umbrella term for abilities including planning, initiation, shifting, working memory (WM), problem solving, monitoring, self control, etc. (Chan, Shum, Touloupoulou, & Chen, 2008; Jurado & Rosselli, 2007). Studies have shown that executive functions are impaired at different age periods in individuals with ASD throughout development (from early childhood to adulthood) (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007). WM is an important component

of executive function and many researchers have studied WM impairment in individuals with ASD (Boucher, Mayes, & Bigham, 2012; Kercood, Grskovic, Banda, & Begeske, 2014). WM is important in daily functioning, for example, when we are having a conversation with a partner, we need to remember what was said by the partner and what we are going to say when the partner is speaking, these all involve WM. It has been shown that WM impairment is associated with learning disabilities (Alloway & Gathercole, 2006), and many problems associated with behavioural regulation and cognitive impairments such as sustaining attention, abstract thinking etc. (Kercood et al., 2014; Ozonoff & McEvoy, 1994). Also, WM impairment was reported to be related to communication and socialization deficits (Gilotty et al., 2002; Oliveras-Rentas et al., 2012) and restrictive and repetitive symptoms (Lopez et al., 2005; Sachse et al., 2013) in individuals with ASD. Thus, it is important to obtain a clearer and better understanding of WM impairment in individuals with ASD.

WM is the process by which information is maintained in an activated, on-line state to support a temporal continuity of behavior (Baddeley, 1986). Inconsistent findings have been reported regarding WM impairment in individuals with ASD. For example, some studies have shown that individuals with ASD were impaired on WM (Bennetto, Pennington, & Rogers, 1996; Bodner, Beversdorf, Saklayen, & Christ, 2012); however, other studies failed to find WM impairment in individuals with ASD compared to typically developed individuals (Morsanyi & Holyoak, 2010; Ozonoff & Strayer, 2001). One possible reason is that these studies did not differentiate verbal and spatial WM according to Baddeley's model (Baddeley, 1986). Baddeley et al.'s

(1986) model of WM suggests that WM is composed of a central executive component and two storage systems, namely the visuospatial sketchpad and the phonological loop. While the visuospatial sketchpad processes visual information, the phonological loop processes speech-based information. For studies that examined the two systems separately, differential impairment has been found, for example, intact verbal WM ability but defective spatial WM ability (Cui, Gao, Chen, Zou, & Wang, 2010; Williams, Goldstein, Carpenter, & Minshew, 2005).

In addition, different tasks which are considered to be measures of WM involved different components of cognitive processing, that is, maintenance and manipulation. While some of these tasks only involve maintenance, others involve both maintenance and manipulation. For example, while digit span forward and digit span backward are both considered measures of memory, the former assesses maintenance but the latter assesses both maintenance and manipulation (Redick & Lindsey, 2013). Studies have suggested that WM impairment in individuals with ASD may be related to component of cognitive processing or cognitive load (Goldberg et al., 2005; Williams, Goldstein, & Minshew, 2006). The present study aimed to systematically review and quantitatively analyze WM impairment in individuals with ASD, and further analyze whether there was differential impairment in verbal and spatial WM in these individuals. We were also interested in whether individuals with ASD would show different WM impairment with different components of cognitive processing. To understand whether individuals with ASD have WM impairment and which factors affect this problem is important for early intervention and cognitive training.

The nature and extent of WM impairment in individuals with ASD also depends on other factors such as age, IQ, and diagnostic criteria. Happé and colleagues found that young individuals with ASD made more errors on spatial WM tasks than typically developed controls while older individuals with ASD did not (Happé, Booth, Charlton, & Hughes, 2006). Most of the individuals with ASD showed intellectual disability, it may be related to WM impairment in these individuals. Moreover, Luna et al. (2007) found WM impairment in individuals with ASD but Edgin and Pennington (2005) did not find this kind of impairment in individuals with ASD. Luna et al. (2007) proposed that the discrepancy might be because they used the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) in addition to the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) which was used by Edgin and Pennington (2005). This might cause a more conservative diagnosis. As the ADI-R and the ADOS became the gold standard in diagnosing ASD (Filipek et al., 1999), we were also interested in whether there would be differential WM impairment between individuals with ASD diagnosed with only ADI/ADOS criteria, only Diagnostic and Statistical Manual of Mental Disorders (DSM)/International Classification of Disease (ICD), and both ADI/ADOS and DSM/ICD.

In sum, the current study aimed to provide a systematic review and meta-analysis on WM impairment in individuals with ASD. In addition, we aimed to examine the potential moderators on WM impairment in these individuals. Specifically, we would explore variables such as WM type (verbal vs. spatial), component of processing (maintenance vs. maintenance plus manipulation), diagnose criteria (ADI/ADOS,

DSM/ICD, both ADI/ADOS and DSM/ICD), age, and IQ.

2. Method

2.1 Literature search

A literature search was conducted to identify published studies that examined WM impairment in individuals with ASD. The databases searched included: Elsevier, PsychINFO, Springer, and ProQuest Psychology Journals. The key words used were "autism + working memory" and "Asperger + working memory" and the search period was from 1986 to June 1, 2014. We also searched for additional articles from the reference lists of the identified articles.

We found 499 potentially relevant articles from the literature search. A total of 29 studies were finally included in the current meta-analysis and all of them met the following criteria: a) Patients were diagnosed with DSM (American Psychiatric Association, 1987, 1994, 2000)¹, ADI/ADI-R (Le Couteur et al., 1989; Lord et al., 1994) or ADOS/ ADOS-Generic (Lord et al., 2000; Lord et al., 1989); b) Studies that included at least one WM task. WM tests measure maintenance or maintenance plus manipulation of information in the short term; c) Studies that reported sufficient data to enable the calculation of effect size. For those studies that met criteria a) and b) but not enough data to calculate effect size, we approached the authors of the articles to obtain the relevant data². The process of article selection is described in Figure 1. In total, we identified 499 papers. After removing duplications, 304

¹ DSM-III-R, DSM-IV, and DSM-IV-TR were used by reviewed studies.

² We sent two requests, and data was provided by author(s) of one article .

remained; after excluding papers which did not include a control group (as effect size could not be calculated) or did not include a WM task, 32 papers remained; after excluding one paper that studied siblings of ASD, one paper that did not have sufficient data to calculate effect size, one paper that WM performance was a matching variable (individuals with ASD and controls were matched on WM performance), 29 papers were included in the final analysis.

INSERT FIGURE 1 HERE

2.2 Data extraction

For each study, we recorded the following variables: (1) Name of the first author and year of publication; (2) Age, IQ and the number of participants in ASD and healthy control groups; (3) Name and type (verbal or spatial) of the WM tasks used; (4) Component of cognitive processing (maintenance vs. maintenance plus manipulation) included in the WM tasks; (5) Diagnostic criteria used: only ADI/ADOS, only DSM/ICD, or both ADI/ADOS and DSM/ICD; (6) Mean and *SD* of measures for each WM task for the two groups of participants (see Table 1).

INSERT TABLE 1 HERE

It should be noted that one study (Yi et al., 2014) included two control groups (age-matched and ability-matched), all the other studies used age-matched participants as healthy controls. Thus, we only coded age-matched control group for

all these studies in the current meta-analysis.

2.3 Data analysis

To quantify the magnitude of the difference between individuals with ASD and normal controls on each WM measure, we computed the effect size (*Cohen's d*) based on the means and *SDs* reported in each study using the Comprehensive Meta Analysis program (CMA Version 2.0) (<http://www.meta-analysis.com/index.php>). Most of the effect sizes were calculated based on accuracy but reaction time was used to calculate effect size in two studies (Cui et al., 2010; Koshino et al., 2008). A number of studies used several WM tasks, and therefore more than one effect size were calculated for these studies. According to the aims of each analysis, when several effect sizes were computed in one study, an unweighted average effect size was calculated and used. Then we conducted further analyses based on the sample sizes and averaged effect sizes with the CMA. When conducting the meta-analysis, the *Q* statistic was used to explore the homogeneity of studies. The publication bias was estimated by fail-safe *N*. The fail-safe *N* is the number of additional studies with a null effect (effect size =0) needed to increase the *p* value of the meta-analysis to larger than 0.05 (Rosenthal, 1979). If the fail-safe *N* is much larger than the number of studies included in the meta-analysis, it would be safe to say the difference tested does exist.

To summarise, we conducted the following analysis: 1) To examine the overall WM impairment of ASD, we analyzed the overall effect size of all studies (using a

mean effect size for studies that have more than one effect size). Two studies (Cui et al., 2010; Koshino et al., 2008) measured WM performance using both reaction time and accuracy. As individuals with ASD only showed impairment in reaction time, for these two studies we only used reaction time to calculate the effect size. For all effect size, we set the direction as negative effect size, that means better performances in healthy controls. 2) Moderator analyses were conducted on the following variables: diagnostic criteria (only ADI/ADOS, only DSM/ICD, both ADI/ADOS and DSM/ICD); WM type (verbal vs. spatial); component of cognitive processing (maintenance vs. maintenance plus manipulation); WM load (1-back vs. 2-back) as a form of cognitive load. In addition, meta-regression analyses were conducted on WM impairment using age, IQ of individuals with ASD as predictors.

3. Results

3.1. Overall WM impairment in individuals with ASD

A total of 29 studies that included 862 individuals with ASD and 899 healthy controls were identified to compare WM performance between the two groups. Since several studies had two or three experiments or two independent samples, a total of 33 contrasts were obtained for analysis. The Q value for heterogeneity analysis was significant ($Q = 77.05$, $p < 0.001$), which indicated that the results of these studies were heterogeneous. The pooled effect size (Cohen's d) for all WM tasks was -0.63 (95% confidence interval = $-0.79 \sim -0.47$; $Z = -7.95$, $p < 0.001$), which

indicated that individuals with ASD showed WM impairment to a medium to large degree. Results of publication bias analysis showed that 1289 studies with negative results were needed to reject this significant finding. This number is much larger than the number of studies included in the present analysis, thus it reduces the likelihood of publication bias (Borenstein, Hedges, Higgins, & Rothstein, 2009).

3.2. Moderator analysis

3.2.1 Effect of diagnostic criteria

Regarding diagnostic criteria, we excluded two studies in which individuals with ASD were not diagnosed with the same criteria (Poirier et al., 2011, exp1/2/3; Gabig, 2008) and one study did not specify diagnostic criteria (Geurt et al., 2012). As a result, 28 contrast remained in this analysis. Ten of the 28 contrasts used only ADOS/ADI criteria or both of them, 10 of the 28 contrasts used only DSM/ICD criteria and 8 contrasts used both ADI/ADOS and DSM/ICD. Results showed that individuals diagnosed with ASD with only ADOS/ADI criteria showed small to medium effect sized impairment ($d = -0.47$); individuals diagnosed with ASD with only DSM/ICD criteria showed small to medium effect sized impairment ($d = -0.47$); and individuals diagnosed with ASD with both criteria showed impairment with medium to large effect size ($d = -0.70$) (see Table 2 and Figure 2). Results of moderator analysis showed that the effect of diagnostic criteria was significant for WM impairment ($Q = 6.12, p = 0.047$). Further pairwise comparisons showed that studies that used both ADI/ADOS and DSM/ICD criteria showed larger WM impairment than studies that

used only ADI/ADOS criteria ($Q = 3.91, p = 0.048$) and studies used only DSM/ICD criteria ($Q = 4.93, p = 0.026$).

INSERT TABLE 2 HERE

INSERT FIGURE 2 HERE

3.2.2 Effect of WM type

To investigate whether individuals with ASD are differentially impaired on verbal and spatial WM tasks, we conducted a moderator analysis on WM type. In one study (viz., Crane et al., 2011), the authors did not report the scores for the Letter Number Sequencing and spatial span tasks separately, we have excluded this study in this moderator analysis. The statistics for verbal and spatial WM tasks are displayed in Table 3 and Figure 3. Individuals with ASD showed significant impairment in both spatial and verbal WM, with a medium to large effect size for spatial WM ($d = -0.72$) and a small to medium effect size for verbal WM ($d = -0.49$). Results of the moderator analysis showed a significant difference between spatial and verbal WM ($Q = 10.515, p = 0.001$), suggesting that individuals with ASD showed more severe impairment in spatial WM than verbal WM.

INSERT TABLE 3 HERE

INSERT FIGURE 3 HERE

3.2.3 Effect of component of cognitive processing in WM

To test whether individuals with ASD showed differential deficits for different components of cognitive processing (maintenance vs. maintenance plus manipulation), we conducted a moderator analysis. We excluded four contrasts (Crane et al., 2011; Nyden et al., 1999; Poirier et al., 2011,exp1; Williams et al., 2005a) and digit span test from Nakahachi et al. (2006) and Williams et al. (2006) and spatial span test from Williams et al. (2005b) from the moderator analysis. This is because authors of these studies only reported the total score of digit span task or spatial span task but not the forward and backward subtests scores separately. Results showed that patients did not show more severe impairment on WM tasks with a maintenance plus manipulation component than on tasks with only a maintenance component ($Q = 0.001$, $p = 0.970$) (see Table 4 and Figure 4).

INSERT TABLE 4 HERE

INSERT FIGURE 4 HERE

The effect of cognitive load analysis of n-back task

Since n-back task provided another method to examine the effect of cognitive load, we investigated whether WM load (1-back vs. 2-back) affect individuals with ASD's WM impairment. Results showed no significant difference between 1-back and 2-back ($Q = 0.029$, $p = 0.864$) (see Table 5 and Figure 5).

INSERT TABLE 5 HERE

INSERT FIGURE 5 HERE

3.2.4 Effects of age and IQ

We conducted a meta-regression analysis with age of individuals with ASD as the predictor and effect size of WM impairment as the dependent variable. Result showed that the effect of age was not significant, slope estimate $\beta = -0.001$, $Z = -0.21$, $p = 0.830$. A similar analysis using IQ as the predictor showed that the effect of IQ on WM impairment was not significant, slope estimate $\beta = -0.011$, $Z = -1.41$, $p = 0.161$.

4. Discussion

The main findings of the current meta-analysis are: overall, individuals with ASD were impaired in WM; individuals with ASD diagnosed using both ADI/ADOS and DSM/ICD criteria showed more severe WM impairment than those who were diagnosed using only ADI/ADOS or only DSM/ICD diagnostic criteria; spatial WM was more impaired than verbal WM in individuals with ASD; component of cognitive processing or cognitive load did not affect the extent of WM impairment in individuals with ASD; age and IQ were not associated with WM impairment in individuals with ASD.

4.1 Overall WM impairment in ASD

Individuals with ASD showed significant WM impairment, consistent with most

previous studies (Boucher et al., 2012; Kercood et al., 2014). This is likely to be due to brain abnormalities found in these individuals. For example, individuals with ASD have been found to have structural brain abnormalities, such as enlarged brain size and weight in childhood particularly in the frontal lobes (Courchesne & Pierce, 2005; Redcay & Courchesne, 2005). Moreover, studies showed brain hyperconnectivity at the whole-brain and subsystems levels, across long- and short-range connections (Lynch et al., 2013; Supekar et al., 2013; Uddin et al., 2013). Brain hyperconnectivity may result in isolation of neural systems involved in high-level cognitive processes, thus contributing to the core deficits of ASD including cognitive functions, social and emotional processing and communication, speech, etc. (Courchesne & Pierce, 2005; Courchesne et al., 2007; Lynch et al., 2013; Supekar et al., 2013; Uddin et al., 2013).

4.2 Effect of diagnostic criteria

The present results suggest that diagnostic criteria affected WM impairment in ASD. While there are no studies that examined whether there were differences in WM performance between individuals with ASD diagnosed using different criteria directly, the present result is consistent with a previous proposal. Luna et al. (2007) found WM impairment in individuals with ASD but Edgin and Pennington (2005) did not. Luna et al. (2007) suggested that the discrepancy could be because they used the ADOS in addition to the ADI used by Edgin and Pennington (2005). This might have resulted in a more conservative diagnosis of autism and the clinical participants were found to be more impaired in WM. Though ADI/ADOS are based on DSM-IV, the

studies with both ADI/ADOS and DSM-IV/ICD diagnostic criteria showed larger impairment than studies with only ADI/ADOS or DSM-IV/ICD, one confounding factor might be that the functions of participants might be different, i.e., there might be more high functioning individuals with ASD with only one of the criteria, but more low functioning individuals with ASD with both criteria. However, our results showed that IQ was not related to WM impairment excluded this possibility. We suppose that including both criteria might cause a more conservative diagnosis of autism and cause more severe impairment in WM.

4.3 Effect of WM type

Individuals with ASD generally showed impaired verbal ability and sometimes superior visual ability (e.g., as manifested in Block Design task, Children's Embedded Figures Task) (Jolliffe & Baron-Cohen, 1997; Morgan, Maybery, & Durkin, 2003). Some studies found individuals with ASD tend to process stimuli visually to compensate for their language deficits (Koshino et al., 2005; Koshino et al., 2008), thus one may propose that the visuospatial WM might be intact since their superior visuospatial ability might compensate for their central executive impairment. However, results of the current meta-analysis showed that visuospatial WM was more impaired than verbal WM. This is consistent with the recent review (Kercood et al., 2014) which suggested that individuals with ASD were impaired in WM tasks especially those that require spatial WM. It also showed a similar pattern as that reported by Williams and colleagues (Williams, Goldstein, Carpenter, et al., 2005; Williams, Goldstein, &

Minshew, 2005), that is, individuals with ASD were found to be intact in verbal WM but impaired in spatial WM.

We explain the results in the following ways: First, individuals with ASD may tend to process low-level visual features (details) but may not be able to integrate features into global structures reflecting the hierarchical nature of the environmental stimuli. This is also referred to as “local bias” (Plaisted, Swettenham, & Rees, 1999). Therefore, it is difficult for them to find the key meaning of the environmental stimuli (e.g., (Hill & Frith, 2003; Luna et al., 2002). Second, individuals with ASD may have reduced use of structure and enhanced retention of trivial details. The retained details may interfere with rather than enhance WM, thus showing spatial WM to be more impaired (Williams, Goldstein, & Minshew, 2005). Third, verbal information may provide a degree of scaffolding for memory, however, there is no analogue in spatial memory, thus the brain may have to use more computation to achieve the same degree of accuracy (Williams, Goldstein, Carpenter, et al., 2005). As a result visuospatial WM was in a sense more difficult than verbal WM. A fourth possibility is that the brain areas related to visuospatial WM were more impaired than those related to verbal WM. However, there is no direct evidence to support this possibility yet.

WM is generally considered to be associated with the dorsolateral prefrontal cortex and related areas. A meta-analysis (Owen, McMillan, Laird, & Bullmore, 2005) showed that dorsal cingulate, medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal poles, and medial and lateral posterior parital cortex were

activated during N-back tasks. Studies have shown that there were differences in the neural substrates associated with verbal and spatial WM. While verbal WM was mainly related to left hemisphere including prefrontal regions, posterior parietal cortex, Broca's area, the premotor and supplementary motor areas, spatial WM was predominantly related to right hemisphere including frontal cortex, posterior parietal, occipital regions etc. (Gruber & von Cramon, 2003; Smith & Jonides, 1998).

Several functional neuroimaging studies have been conducted studying WM in individuals with ASD. For example, Koshino et al. (2005) examined the neural mechanisms of WM using an n-back task with letters in individuals with ASD. Results found that these individuals showed similar activation in the right hemisphere as the control group but much less activation in the left hemisphere in the dorsolateral prefrontal cortex and the inferior frontal gyrus. Individuals with ASD also showed more lateralized right activation in the prefrontal and parietal regions. Furthermore, individuals with ASD showed more activation than healthy controls in posterior regions including temporal and occipital regions. Luna et al. (2002) examined the neural correlates of spatial WM in autism, and results showed that individuals with autism demonstrated less activation in dorsolateral prefrontal cortex and posterior cingulate cortex compared to controls. These results suggested that the functional disconnectivity of the dorsal lateral prefrontal cortex and posterior cingulate cortex circuitry was related to WM impairment. They also demonstrated that the spatial WM deficit was not caused by basic sensorimotor or attention processes. From these studies, it might be inferred that individuals with ASD processed verbal stimuli in a

nonverbal fashion, the verbal stimuli were processed as visual codes. However, due to the limited number of such studies, it is unclear why individuals with ASD showed more severe visuospatial than verbal WM impairment compared to controls. Future studies are needed to clarify this issue.

4.4 Effect of component of cognitive processing on WM

In this meta-analysis, component of cognitive processing or cognitive load was not found to affect WM impairment in individuals with ASD, reflected by the analysis on maintenance plus manipulation vs maintenance and n-back task. This is not consistent with the suggestion by Kercood et al. (2014) who found that individuals with ASD scored lower in WM measures with increasing task complexity. However, their study was a qualitative review, and the present study provided a meta-analysis and effect size showed that individuals with ASD showed similar impairment on tasks that included the processes of maintenance plus manipulation compared to maintenance only. Although individuals with ASD showed larger effect size impairment in tasks with maintenance plus manipulation than tasks with just maintenance, this did not reach significance. This suggested that individuals with ASD showed prominent WM impairment with low cognitive load, even the cognitive load increases, they did not show a greater impairment. These results are also consistent with previous findings that impairment in WM was present at all delay periods, suggesting an inherent impairment in the processes involved in maintaining and retrieving internal representations (Luna et al., 2007). The effect of cognitive load in

spatial WM task did not interact with group, indicating the WM impairment were not more impaired as load increased (Minshew, Luna, & Sweeney, 1999; Ozonoff & Strayer, 2001).

However, there were also studies that showed WM impairment was related to task demand. For example, Steele et al. (2007) demonstrated that the individuals with ASD became impaired as set size increased in spatial WM task. Some studies also suggested that as the complexity of stimuli increase, the WM performance in ASD decreased more rapidly than controls. For example, individuals with ASD did not differ from controls on letter span performance, but were worse on word span and sentences (Minshew & Goldstein, 2001); individuals with ASD were found to be intact in memory for location, but impaired in complex visual spatial WM (Williams et al., 2006). However, the number of these studies is too small to allow us to conduct a meta-analysis and to examine whether different form of cognitive load would make a difference on WM impairment.

4.5 Effect of age

While WM abilities develop with age (Thomason et al., 2009), whether WM impairment in ASD also develop with age remained debated. While Happe et al. (2006) found young children with ASD showed impairment in spatial WM, old children with ASD were not found to be impaired. Nevertheless, most other studies showed that WM impairment persist in individuals with ASD. For example, Ozonoff and McEvoy (1994) conducted a 3-year follow up study on children with ASD and

found no improvement in WM performance. Luna et al. (2007) revealed that individuals with ASD showed a persistent spatial WM impairment through development. While the Control group showed improvements in WM from adolescence to adulthood, the ASD group only showed improvements from childhood to adolescence. They suggested that spatial WM is a core deficit that appeared in childhood. Although this ability develops with age for individuals with ASD, the development is delayed and reduced, resulting a persisting impairment in spatial WM. Furthermore, Geuts et al. (2012) found older adults with ASD still showed WM impairment.

The present results showed that WM impairment did not correlate with age, thus also supporting persistent WM impairment across age in individuals with ASD. Redcay and Courchesne (2005) suggested that individuals with ASD showed greatest deviation from normal in brain size during 2-5 years of age may suggest they should be most impaired in this age period. However, almost all individuals with ASD included in this meta-analysis were beyond this age range. It can be suggested that although WM performance did developed in individuals with ASD, these individuals might still show stable impairment compared to controls. Furthermore, it should be noted that most of the studies are conducted in childhood and adolescence, and only a few studies were conducted in adults and even less in old people. Further studies are needed using participants in all these age periods to clarify this issue.

4.6 Limitations

There are several limitations in the present study. First, some studies found significant relationships between WM performance and clinical symptoms such as restricted, repetitive symptoms and the social domain on the ADOS (Landa & Goldberg, 2005; Lopez, Lincoln, Ozonoff, & Lai, 2005; Sachse et al., 2013), but some did not (Steele et al., 2007). The small number of studies reporting this relationship has prevented us from examining this issue in our meta-analysis. Second, the number of studies examining the relationships between WM and other cognitive functions (Sachse et al., 2013) and daily functioning (Williams, Goldstein, & Minshew, 2005) are also limited and therefore prevented us from examining them in our current meta-analysis. Third, most of the studies included in the current meta-analysis were conducted using children and adolescents as participants, the relationship between age and WM impairment in individuals with ASD over a large age range could not be clarified. Fourth, sometimes individuals with ASD have some comorbid diagnoses such as language impairment, learning disabilities and attention deficit and hyperactivity disorder (ADHD), and many individuals with ASD also take medications. These are the factors that were not considered in this meta-analysis.

4.7 Conclusion

The present meta-analysis showed that individuals with ASD showed general impairment in WM. Specifically, their spatial WM was more impaired than verbal WM. Component of cognitive processing or cognitive load, age and IQ were not found to have any effect on WM impairment in these individuals. These results have

implications for early intervention for individuals with ASD. For example, as mentioned in Kercood et al.'s (2014) review, a few intervention studies have been conducted for individuals with ASD by reinforcing correct responses during WM tasks performance. Results showed improved performance in WM tasks such as counting span, complex span and digit span backwards (Baltruschat et al., 2011a, 2011b). McGovern and Sigman (2005) suggested that interventions may improve cognitive abilities as well as social interaction skills. Early intervention that has an impact on cognitive abilities in young children with ASD is likely to have influence on their social skills as they grow into adolescence and early adulthood. Thus early intervention on WM are necessary for individuals with ASD as suggested by Ansari (2015) and WM is a potential therapeutic target for treating this clinical group.

Conflict of interest

None.

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Table 1 Descriptions of studies included in the meta-analysis

Study Name	Patient Group				Control Group			WM Measurement	WM Type	Cognitive Process	Basic Findings	Notes
	N	Diagnostic Criteria	Mean Age (SD)	IQ	N	Mean Age (SD)	IQ					
Crane et al.,2011	28	DSM-IV/ICD-10	41.57 (16.49)	117.18 (13.47)	28	40.53 (17.20)	115.11 (11.67)	Letter-Number Sequencing [#] , Spatial Span task [#]			ASD group showed a reduction in working memory abilities.	Typical adults matched for age, gender and IQ with ASD group.
Cui et al., 2010	12	DSM-IV	7.46 (0.84)	100.03 (17.13)	29	7.37 (0.48)	108.31 (14.08)	Digit recall task, Word list recall, Backward digit recall, Counting recall, Block recall, Variant-visual-pattern test, Digit n-back task, Figure n-back task, Location n-back task	verbal verbal verbal verbal spatial spatial verbal spatial spatial	maintenance maintenance manipulation manipulation maintenance maintenance manipulation manipulation manipulation	ASD children had advantage in the phonological loop storing, but disadvantage in the visuospatial sketchpad storing.	Healthy children were matched on age and IQ with children with ASD.
Eack et al.,2013	43	ADOS	24.86 (5.75)	113.05 (15.28)	24	26.25 (5.52)	106.75 (6.78)	Letter number span	verbal	manipulation	ASD showed significant deficits in working memory	Healthy control individuals were matched on age and IQ.

											than healthy control.	
Gabig 2008	15	at least one of ADI-R,ADOS, DSM-IV	6.5 (0.70)	None	10	6.70 (0.89)	None	Nonword repetition, Digits span, Sentence imitation	verbal verbal verbal	maintenance maintenance maintenance	A profile of verbal working memory deficits was seen in children with autism, with poorer performance on more complex verbal memory tasks.	Typical developing children were chronological age-matched with autism children.
Garcia- Villamisar et al.,2002	16	DSM-IV	23.5 (4.31)	None	16	21.19 (2.51)	None	Forward digit recall task	verbal	maintenance	The difference of mean digit span for the autistic and the control group was not statistically significant.	The two groups did not differ in chronological age and educational level.
Geurts et al.,2004	41	ADI-R	9.4 (1.8)	98.3 (18.4)	41	9.1 (1.7)	111.5 (18.0)	Self-ordered pointing task, Benton visual retention test, Corsi block tapping test	spatial spatial spatial	manipulation maintenance maintenance	Children with ASD demonstrated no deficits in working memory, but poorer short-term memory than the normal control group.	Study investigated age-matched children groups: HFA and normal controls.
Geurts et al.,2012	23	SRS, clinical diagnosis	63.6 (7.5)	109.5 (10.3)	23	63.7 (8.1)	109.8 (7.9)	Forward Spatial Span task	spatial	maintenance	Elderly with autism showed visual working memory problems comparing with the control group.	The control group were matched on age and gender with autism group.
Goldberg et al.,2005	17	ADI-R,ADOS/AD OS-G	10.3 (1.8)	96.5 (15.9)	32	10.4 (1.5)	112.6 (12.1)	CANTAB Spatial working memory task	spatial	manipulation	Spatial working memory is severely impaired in ASD than healthy control.	Healthy control were chronological age matched with ASD.
Gonzalez- Gadea et	23	DSM-IV	33.0 (9.8)	None	21	38.2 (14.4)	None	Backward digit span,	verbal	manipulation	ASD group showed no significant difference with	Typically developing controls were matched with the ASD

al.,2013								Letters and numbers	verbal	manipulation	typical developing control group in working memory.	group for sex, age, handedness, years of education and intellectual level.
Ham et al.,2011	19	DSM-IV,ADOS	12.1 (2.4)	106.0 (21.0)	23	12.0 (2.1)	111.4 (16.5)	Digit recall task, Word list matching, Listening recall task	verbal verbal verbal	maintenance maintenance manipulation	Participants with ASD did not differ from the typical developing control group on the test of digit recall, but they did perform significantly more poorly on the tests of word list matching and listening recall.	Typically developing children were matched to ASD group for age, gender and Full Scale Intelligence.
Happe et al.,2006	32	DSM-IV	10.9 (2.4)	99.7 (18.7)	32	11.2 (2.0)	106.8 (13.4)	CANTAB spatial working memory	spatial	manipulation	ASD children performed poorly in spatial working memory than the typical developing children.	The typically developing children were age- and IQ-matched with ASD.
Joseph et al.,2005a	24	ADI-R,ADOS,DS M-IV	8.9(2.3)	96(18)	24	8.9(2.2)	92(13)	Verbal span test, Self-ordered pointing test, Non-verbal self-ordered pointing test	verbal spatial spatial	maintenance manipulation manipulation	The autism group performed significantly less well in the former, but not the latter self-ordered pointing test.	The comparison group was matched to the autism group on age and on verbal and non-verbal IQ.
Joseph et al.,2005b	37	ADI-R,ADOS,DS M-IV	7.9(1.8)		31	8.3(2.1)		Forward Word span task,	verbal	maintenance	Children with autism performed significantly less	The nonautistic comparison participants were matched on

								Backward word span task,	verbal	manipulation	well on Block Span Backward.	age and on verbal and nonverbal IQ but not on language ability.
								Forward Block span task,	spatial	maintenance		
								Backward block span task	spatial	manipulation		
Koshino et al.,2008	11	ADI, ADOS	24.5 (10.2)	104.5 (13.1)	11	28.7 (10.9)	108.6 (9.1)	Face N-back task	spatial	manipulation	The autism and control groups showed similar n-back working memory task performance.	The control group were matched on age, Full Scale IQ, gender, race, and socioeconomic status.
Landa et al.,2005	19	ADI-R, ADOS/ADOS-G	11.01 (2.89)	109.7 (15.80)	19	11.00 (2.85)	113.4 (14.34)	CANTAB spatial working memory	spatial	manipulation	Compared to controls, participants with ASD more frequently made between-search errors and poorly used search strategies.	Controls were individually matched to the participants with ASD based on chronological age, gender, and full scale IQ.
Lopez et al.,2005	17	ADI-R, ADOS-G	29.1 (8.0)	77 (15)	17	29.4 (11.4)	89 (13)	Letter-Number Sequencing	verbal	manipulation	The two groups did not differ on a measure of working memory.	The control group were matched on age, gender and Performance IQ with autism group.
Nakahachi et al.,2006	16	DSM-IV	28	101	28	28.3	103	WM ratio in Advanced Trail Making Test, Digit span test [*] , Digit symbol task	spatial	maintenance	ASD subjects have intact in working memory.	The control subjects were IQ-, age- and sex-matched with ASD subjects.
									verbal	maintenance		

Nydén et al.,1999	10	DSM-IV,Gillberg and Gillberg (1989) criteria	10.1 (0.9)	100.7 (16.3)	10	10.0 (0.9)	None	Digit span task from WISC-III*	verbal			ASD group showed deficits in working memory than the population norm.	The normal children group were matched on age with children with ASD.
Poirier et al.,2011exp1	16	DSM-IV, part of participants with ADOS	31.6 (11.4)	100.3 (16.2)	16	34.8 (10.8)	102.4 (11.9)	Digit recall task*	verbal			The ASD group showed poorer working memory than the comparison participants through all three experiments.	The typical individuals were matched on age and IQ with individual with ASD.
Poirier et al.,2011exp2	22	DSM-IV, part of participants with ADOS	37.6 (13.3)	106.9 (18.8)	22	37.3 (11.3)	110.7 (12.6)	Immediate serial recall task	verbal	maintenance			
Poirier et al.,2011exp3	18	DSM-IV, part of participants with ADOS	40.3 (13.6)	107.8 (12.9)	18	41.0 (11.1)	107.2 (14.4)	Order recognition test	verbal	maintenance			
Russell et al.,1996exp1	33	DSM III-R	12.38 (2.95)	none	33	6.28 (1.19)	none	Word recall task, Non-verbal word recall task	verbal	maintenance		Children with autism were at least as likely as normal group to employ articulatory rehearsal.	The normal group were chronological age-appropriate.
Russell et al.,1996exp2	22	DSM III-R	12.47 (2.82)	none	22	6.85 (0.5)	none	Counting task, Odd-man-out task, Sums task	spatial	Manipulation	spatial	The working memory performance of the children with autism was inferior to that of the normally developing group.	Normally developing children were matched individually for verbal mental age with children with autism.
Sachse et al.,2013	30	DSM-IV-TR, ADOS, ADI-R	19.2 (5.1)	105.3 (12.3)	28	19.9 (3.6)	109.3 (11.5)	CANTAB spatial working memory task	spatial	manipulation		ASD individuals showed impaired spatial working memory.	The comparison group was matched to the ASD group on age, gender and non-verbal IQ.

Steele et al.,2007	29	ADI-R, ADOS, DSM-IV	14.83 (5.47)	107.76 (10.99)	29	16.93 (5.40)	110.79 (9.91)	CANTAB spatial working memory task	spatial	manipulation	Autism showed reduced spatial working memory abilities.	Typically developing individuals matched in Verbal IQ, Performance IQ, age and the socioeconomic status of their parents with individuals with ASD.
Verte et al.,2005	61	DSM-IV, ADI-R	9.1 (1.9)	99.2 (17.1)	47	9.4 (1.6)	112.1 (9.7)	Self-ordered pointing task, Benton Visual Retention Test	spatial	manipulation	The ASD group showed significantly poorer in spatial working memory task than the control group.	The normal control group were matched on age with ASD group.
								Corsi block task	spatial	maintenance		
Verte et al.,2006	66	DSM-IV, ADI-R	8.7 (2.0)	101.5 (18.2)	82	9.2 (1.7)	112.2 (16.0)	Self-ordered pointing task	spatial	manipulation	More symptoms of autism are related to a poorer working memory process.	The normal control children were matched on age with ASD group.
Williams et al.,2005a	29	ADOS,ADI/ADI-R , DSM-IV	28.72 (10.44)	105.86 (14.19)	34	26.53 (10.22)	109.65 (11.39)	Letter-Number Sequencing, Spatial span*	verbal	manipulation	The individuals with autism performed as well as the controls on verbal working memory, but had impaired spatial working memory.	The two groups did not differ significantly with respect to age, Verbal and Full Scale IQ score gender, race and socioeconomic status.
									spatial			
Williams et al.,2005b	31	ADOS,ADI-R	26.58 (8.68)	108.65 (16.75)	25	26.76 (9.08)	109.76 (11.63)	N-back letter task,	Verbal	manipulation	Individuals with autism, regardless of age, showed intact verbal working memory and impaired spatial working memory through two experiments.	The control group were matched on age and cognition.
S1								Letter-Number Sequencing,	verbal	manipulation		
								Spatial span subtest*	spatial			
Williams et	24	ADOS,ADI-R	11.75	109.67	44	12.39	109.95	N-back letter	verbal	manipulation		

al.,2005b S2			(2.36)	(16.07)		(2.16)	(10.66)	task, Number/Letter memory subtest, Finger windows subtest	verbal spatial	maintenance maintenance		
Williams et al., 2006	38	ADI,ADOS	11.68 (2.46)	103.82 (14.29)	38	12.16 (2.19)	107.18 (9.37)	Digit span *, Number/Letter memory subtest, Finger windows subtest	verbal verbal spatial	 maintenance maintenance	Children with autism was characterized by relatively intact verbal working memory and poor spatial working memory.	The two participant groups did not differ significantly with regard to age, Full Scale IQ, race, or socioeconomic status.
Yi et al.,2014	25	DSM-IV	7.66 (1.56)	None	25	7.68 (1.72)	91.12 (14.04)	Block recall task	spatial	maintenance	Children with ASD performed significantly poorer on the Block Recall Task than participants in both the age-matched typically developing group and the ability-matched typically developing group.	The typically control group were matched with ASD group on chronological age.
Zinke et al.,2010	15	ICD-10, ADI-R, ADOS	9.0 (1.5)	96.4 (14.5)	17	9.8 (1.7)	none	digit span forward task, Corsi-Block- Tapping forward task	verbal spatial	maintenance maintenance	The autism group showed intact verbal short-term memory (digit span), but poorer performance of visuospatial short-term memory.	The two groups were matched on chronological age.

Notes: # the author only reported the total score of the two tasks between the two groups.

* the digit span test comprises two subtests, digits forward and digits backward, but only total score were mentioned in the paper.

Manipulation means maintenance plus manipulation.

CANTAB is the abbreviation for Cambridge Neuropsychological Test Automatic Battery.

Exp1, exp2 and exp3 means there were three experiments in one study.

S1 and S2 means that two independent samples (children & adults) were included in one study.

Table 2

Effect of diagnostic criteria on WM impairment in individuals with ASD.

	<i>K</i>	<i>N</i> patient group	<i>N</i> control group	<i>d</i>	<i>Z</i>	<i>P</i>	95% <i>CI</i>	<i>Q</i>	<i>p</i>
ADI/ADOS	10	256	268	-0.47	-3.26	0.001	(-0.75, -0.19)	21.15	0.012
ADI/ADOS, DSM/ICD	8	295	298	-0.70	-8.25	<0.001	(-0.87, -0.54)	10.50	0.162
DSM/ICD	10	217	244	-0.47	-2.41	0.016	(-0.86, -0.09)	35.43	<0.001

Note: K = number of studies; N = number of participants; CI = confidence interval.

Table 3

Effect of WM type on WM impairment in individuals with ASD.

	<i>K</i>	<i>N</i> patient group	<i>N</i> control group	<i>d</i>	<i>Z</i>	<i>P</i>	95% <i>CI</i>	<i>Q</i>	<i>p</i>
Spatial WM	20	633	720	-0.72	-7.55	< 0.001	(-0.91, -0.54)	49.06	< 0.001
Verbal WM	20	480	502	-0.49	-4.62	0.001	(-0.69, -0.28)	44.31	0.001

Note: K = number of studies; N = number of participants; CI = confidence interval.

Table 4

Effect of component of cognitive processing on WM impairment in individuals with ASD.

	<i>K</i>	<i>N</i> patient group	<i>N</i> control group	<i>d</i>	<i>Z</i>	<i>p</i>	95% <i>CI</i>	<i>Q</i>	<i>p</i>
Manipulation	19	556	580	-0.56	-5.65	<0.001	(-0.76, -0.37)	44.66	<0.001
Maintenance	17	439	469	-0.62	-4.89	<0.001	(-0.87, -0.37)	51.27	<0.001

Note: K = number of studies; N = number of participants; CI = confidence interval.

Table 5

Effect of cognitive load on WM impairment in individuals with ASD.

	<i>K</i>	N patient group	N control group	<i>d</i>	<i>Z</i>	<i>P</i>	95% <i>CI</i>	<i>Q</i>	<i>p</i>
1-back	4	78	109	-0.84	-1.90	0.057	(-1.71,-0.03)	20.73	<0.001
2-back	4	78	109	-0.83	-2.24	0.025	(-1.55, -0.11)	14.63	0.002

Note: K = number of studies; N = number of participants; CI = confidence interval.

Fig. 1. Flow diagram of selection process of the articles included in the meta-analysis.

Figure 2. Forest plot for the results of diagnostic criteria on WM impairment in individuals with ASD. The plot displays effect size (standard difference) with associated 95% confidence intervals. The overall effect size is calculated using a random effects model.

Figure 3. Forest plot for the results of WM types on WM impairment in individuals with ASD. The plot displays effect size (standard difference) with associated 95% confidence intervals. The overall effect size is calculated using a random effects model.

Figure 4. Forest plot for the results of component of cognitive processing on WM impairment in individuals with ASD. The plot displays effect size (standard difference) with associated 95% confidence intervals. The overall effect size is calculated using a random effects model.

Figure 5. Forest plot for the results of n-back task in individuals with ASD. The plot displays effect size (standard difference) with associated 95% confidence intervals. The overall effect size is calculated using a random effects model.