Short title: Cognitive endophenotypes for ASD

Executive functioning and local-global visual processing: Candidate endophenotypes for autism spectrum disorder?

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Abstract

Background: Heterogeneity within autism spectrum disorder (ASD) hampers insight in the etiology and stimulated the search for endophenotypes. Endophenotypes should meet several criteria, the most important being the association with ASD and the higher occurrence rate in unaffected ASD relatives than in the general population. We evaluated these criteria for executive functioning (EF) and local-global (L-G) visual processing.

Methods: By administering an extensive cognitive battery which increases the validity of the measures, we examined which of the cognitive anomalies shown by ASD probands also occur in their unaffected relatives (*n* = 113) compared to typically developing (TD) controls (*n* = 100). Microarrays were performed, so we could exclude relatives from probands with a *de novo* mutation in a known ASD susceptibility copy number variant, thus increasing the probability that genetic risk variants are shared by the ASD relatives. An overview of studies investigating EF and L-G processing in ASD relatives was also provided.

Results: For EF, ASD relatives - like ASD probands - showed impairments in response inhibition, cognitive flexibility and generativity (specifically, ideational fluency), and EF impairments in daily life. For L-G visual processing, the ASD relatives showed no anomalies on the tasks, but they reported more attention to detail in daily life. Group differences were similar for siblings and for parents of ASD probands, and yielded larger effect sizes in a multiplex subsample. The group effect sizes for the comparison between ASD probands and TD individuals were generally larger than those of the ASD relatives compared to TD individuals.

Conclusions: Impaired cognitive flexibility, ideational fluency and response inhibition are strong candidate endophenotypes for ASD. They could help to delineate etiologically more homogeneous subgroups, which is clinically important to allow assigning ASD probands to different, more targeted, interventions.

Keywords: autism spectrum disorder, relatives, endophenotype, executive functioning, local-global visual processing

Autism spectrum disorder (ASD) is an early onset neurodevelopmental disorders characterized by impairments in social reciprocity and communication, and rigid, repetitive patterns of behavior, interests or activities (American Psychiatric Association [APA], 2013). Although genetic factors are known to contribute substantially, the etiology remains largely unknown (Geschwind & State, 2015; Persico & Napolioni, 2013). This is due to the complexity and heterogeneity within ASD, both at the phenotypic and genetic level. At the phenotypic level, each core impairment has a wide range of manifestations (APA, 2013), often accompanied by other features (e.g., language difficulties, intellectual disability) and psychiatric comorbidities (Gillberg & Fernell, 2014; Lai, Lombardo, & Baron-Cohen, 2014). Regarding the genotype, risk conferring variants in many different genes can contribute through different genetic mechanisms. Most of the genetic variants are neither necessary nor sufficient by themselves to cause ASD and a combination of different genetic and environmental factors determines the phenotype (Geschwind & State, 2015; Persico & Napolioni, 2013). This heterogeneity underscores the limitations of the behaviorally defined categorical diagnosis for understanding the etiology of ASD and has stimulated the search for endophenotypes[1] (Lenzenweger, 2013; Szatmari et al., 2007).

An endophenotype for ASD, is a quantitative trait that lies along the genotype-phenotype pathway and meets the following criteria: 1) it is associated and co-occurs with ASD; 2) it co-segregates in families and is thus expressed at a higher rate in unaffected relatives of ASD probands than in the general population; 3) it is heritable; 4) it is measured in a psychometrically reliable and valid manner; and 5) it is (ideally) state independent, implying that it should precede the onset of ASD symptoms (Gottesman & Gould, 2003; Lenzenweger, 2013). Endophenotypes may contribute to unraveling the etiology and

[1] In line with the recommendations of Lenzenweger (2013), the term 'endophenotype' is used. This concept corresponds to how Szatmari and colleagues (2007) define an 'intermediate phenotype'.

pathophysiology of ASD, e.g. by enabling the delineation of etiologically more homogeneous subgroups (Geschwind & State, 2015; Glahn et al., 2014; Szatmari et al., 2007).

Neurocognitive characteristics are valuable candidate endophenotypes, as they mediate the relationship between brain and behavior (Hill & Frith, 2003). Various cognitive deficits (and strengths) have been identified in individuals with ASD that might underlie their behavioral symptoms (Brunsdon & Happé, 2014). Here, we focus on executive functioning (EF) and local-global (L-G) visual processing. EF is an umbrella term covering several interrelated but distinct higher-order cognitive functions, serving goal-oriented planning and regulation of thoughts and actions (Denckla, 1996; Goldstein, Naglieri, Princiotta, & Otero, 2014). We distinguish the following EF domains: inhibition, cognitive flexibility, generativity, working memory, and planning (Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015a). Local visual processing refers to the processing of parts or details of visual information, while global processing requires the integration of pieces of information into coherent wholes (Frith, 2003; Happé & Booth, 2008). A distinction can be made between processing ability (or performance) and processing style (i.e., the natural tendency to process information in a particular way) (Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015b).

To assess which aspects of EF and L-G visual processing are candidate endophenotypes for ASD, we evaluated several endophenotype criteria. Firstly, in line with the fourth criterion, and given the problematic construct validity of many EF and L-G measures, we developed a cognitive battery aimed at increasing their validity (see Appendix B). With this battery each of the cognitive characteristics could be measured separately, while controlling for possible confounding variables. Secondly, we evaluated the first endophenotype criterion by administering this cognitive battery to children with non-syndromic ASD and matched typically developing (TD) children. The ASD group showed impairments in all EF domains, with the largest effect sizes for cognitive flexibility and generativity (Van Eylen et al., 2015a). Furthermore, individuals with ASD displayed a more locally oriented processing style, intact local processing abilities and selective global processing impairments, particularly when global processes were highly taxed[2] (Van Eylen et al., 2015b). Thirdly, in the present study we will address the second endophenotype criterion by evaluating which of these cognitive anomalies also occur in the unaffected first-degree relatives of these ASD probands (further referred to as ASD relatives).

Several studies have already examined EF and/or L-G processing in ASD relatives. Although some studies have provided evidence for cognitive atypicalities, others found no differences between ASD relatives and various control groups (for an overview, see Appendix A). These inconsistencies might be due to differences in the applied measures, the included ASD relatives (parents and/or siblings), the comparison group (TD individuals or relatives of individuals with another disorder), matching criteria, sample size, etc. (see Appendix A). Compared to previous studies, we examined both EF and L-G visual processing in a large sample of unaffected ASD relatives compared to TD individuals, matched for age, gender and IQ, with a cognitive battery designed to increase the validity of the measures. Given the first endophenotype criterion, we focused on those measures for which we previously found group differences between the ASD probands and TD individuals (Van Eylen et al., 2015a, 2015b).

We also investigated whether the atypicalities of ASD relatives differed for ASD siblings compared to ASD parents. Although siblings and parents on average share 50% of their DNA with the ASD proband, there is more variation in the degree of genetic overlap

[2] When the signal needed to be segregated from noise and when the task required a complex interplay between bottom-up and top-down processes.

for siblings. Previous studies obtained similar results for ASD siblings and parents, or found more cognitive anomalies in parents (see Appendix A).

Our group of ASD relatives comprises individuals from simplex families (with only one ASD proband) and individuals from multiplex families (with more than one ASD proband). There is evidence that the genetic mechanisms for ASD may differ for both family types, with an increased prevalence of *de novo* mutations in probands from simplex families (Marshall et al., 2008; Pinto et al., 2010; Sebat et al., 2007). Accordingly, the genetic liability for ASD, is higher in multiplex compared to simplex families. We could therefore expect a higher occurrence of ASD-like cognitive characteristics in multiplex compared to simplex ASD relatives (Oerlemans, Hartman, Franke, Buitelaar, & Rommelse, 2016). However, while it is straightforward to determine multiplex families, reliably determining 'true' simplex families is equivocal, especially if there is only one child in the family (De la Marche et al., 2012). Given this uncertainty, we did not directly compare simplex and multiplex family members. Yet, as we aim to trace endophenotypes, we performed microarrays so we could exclude the relatives from probands with a *de novo* mutation in a causal or known ASD susceptibility copy number variant (CNV). This increases the probability that genetic risk variants and the associated endophenotypes are shared by the ASD relatives. Furthermore, we separately compared multiplex ASD relatives to TD individuals to examine whether this comparison yields additional group differences (and thus additional endophenotype candidates) and/or larger effect sizes.

If EF impairments and/or altered L-G visual processing are good ASD endophenotypes, we expect unaffected ASD relatives to differ from TD individuals and to perform more similarly to ASD probands (although maybe less pronounced). Thus, based on our findings in the ASD probands (Van Eylen et al., 2015a, 2015b), we expect that ASD relatives may show EF impairments, a more locally oriented processing style, and reduced global processing abilities. However, Johnson (2012) has argued that good EF skills may enable ASD relatives to compensate for their anomalies and may therefore constitute a protective factor against the development of ASD. According to this alternative view, unaffected ASD relatives who share some ASD risk genes are expected to show better EF performance compared to a TD group. Both views will be evaluated.

Methods

Participants

Unaffected first degree relatives of ASD probands (*ASD relatives*) were recruited through the Leuven Autism Research (LAuRes) database. All probands have non-syndromic ASD. The ASD diagnosis was made by a multidisciplinary team according to DSM-IV-TR criteria (APA, 2000) and validated with the Developmental, Dimensional and Diagnostic Interview (3di) (Skuse et al., 2004). Probands and relatives were screened with microarrays to detect causal or known ASD susceptibility CNVs. One proband carried a causal *de novo* 9MB duplication (46,XY.arr 7q22.3q31.2 (107.379.895-116.395.422)x3 (Human genome build 19)), hence his family members were excluded from the analyses. This resulted in 113 ASD relatives (35 siblings and 78 parents) from 45 families (containing 69 probands). No pathogenic or known ASD susceptibility CNVs were detected in any of them. None of the relatives had a clinical diagnosis of ASD but seven of them were diagnosed with another psychiatric disorder: two had ADHD, three had dyslexia, one had an anxiety disorder, and one had obsessive compulsive disorder combined with panic disorder. Two relatives took psychoactive medication for these problems. The subsample of *multiplex ASD relatives* comprised 37 parents from 20 families (containing 44 probands). Only 8 siblings were part of an ASD multiplex family. Since they covered a large age range and given the large effects of age on our cognitive measures (Van Eylen et al., 2015a, 2015b), we only included parents in this subsample. None of them were diagnosed with a psychiatric disorder.

The *TD group* (*n* = 100) was recruited through schools, personal contacts and advertisements and consisted of 42 children and 58 adults (from 60 families). According to parental or self-report, none of the TD individuals nor any of their first-degree relatives presented with ASD or another psychiatric or neurological disorder. Furthermore, all TD individuals scored below 2 *SD* above the mean on the Social Responsiveness Scale (Noens, De la Marche, & Scholte, 2012; Roeyers, Thys, Druart, De Schryver, & Schittekatte, 2011) and none of them showed repetitive or stereotyped patterns of behavior as measured with the Repetitive Behavior Scale – Revised (Bodfish, Symons, Parker, & Lewis, 2000).

All participants had a verbal (VIQ), performance (PIQ), and full-scale IQ (FSIQ) above 70, as measured with an abbreviated version of the Wechsler Intelligence Scale (see Appendix B). Children were aged between 8 and 18 years, while adults were between 30 and 60 years old. The ASD relatives and TD individuals were group-wised matched for gender-ratio, age and IQ (Table 1).

(INSERT TABLE 1)

Informed consent was obtained from the participants' parents and from participants aged 16 years or older. The study protocol was approved by the Medical Ethical Committee of the University Hospitals Leuven and the Ethical Committee of the Faculty of Psychology and Educational Sciences of the KU Leuven.

Measures

An overview of all EF, L-G and control measures is provided in Table 2 (for a more elaborate description, see Van Eylen et al., 2015a, 2015b)[3]. For this study, we focused on the main outcome measures for which we previously observed differences between the ASD and TD group and on the control measures.

(INSERT TABLE 2)

Procedure

The same procedure was followed as described by Van Eylen and colleagues (2015a, 2015b), with addition of self-report forms of the questionnaires for adults.

Results

Mixed models were fitted with a random statement indicating that the participants are nested within families, to account for their kinship. When assumptions were violated Mann-Whitney *U* tests were used to investigate the effect of group ($\alpha < 0.05$, two-sided). To control for multiple comparisons, a False Discovery Rate (FDR) correction was applied (Benjamini & Hochberg, 1995).

For the full sample, we examined effects of group (ASD relatives vs. TD), age (children/siblings vs. adults/parents) and the group by age interaction, for all main EF and L-G measures (Table 3). Regarding the effect of group for EF measures, ASD relatives displayed a higher percentage No-Go errors on the Go/No-Go task, made more perseverative errors on the Wisconsin Card Soring Task – With Controlled Task Switching (WCST-WCTS), generated fewer correct answers on the Uses of Objects task and scored higher than the TD group on the EF questionnaires (i.e., on the Planning subscale of the Behavior Rating Inventory of EF [BRIEF] and the Cognitive Rigidity scale of the Detail and Flexibility

[3] References to all tasks and questionnaires are mentioned in Van Eylen et al. (2015a, 2015b), except for the Dutch adult version of the BRIEF (Scholte & Noens, 2011), which was not included in our previous studies. More information concerning the Detail and Flexibility questionnaire is provided in Appendix B.

questionnaire [DFlex]). On the L-G tasks, no significant group differences were found. Yet, ASD relatives scored higher on the Attention to Detail scale of the DFlex. Concerning the effect of age, children (or siblings) showed reduced EF compared to adults (or parents) on all EF measures, except for the switch cost RT measure of the WCST-WCTS and the Switch task, and for the Cognitive Rigidity scale of the DFlex. Furthermore, children had a higher fragmentation score on the Rey-Osterrieth Complex Figure (ROCF) and a higher Coherent Motion threshold. Finally, given the non-significant group by age interaction for all measures, the effect of group was similar for children (siblings) and adults (parents). Descriptive statistics for the age effects and the group by age interactions are provided in Appendix C.

For the multiplex subsample we examined the effect of group (see Table 3, the effects of age were not investigated because the multiplex sample only comprised adults). As for the full sample, we found that ASD parents of the multiplex sample made more perseverative errors on the WCST-WCTS and produced fewer correct answers on the Uses of Objects task compared to the TD group. They also showed a trend towards a higher percentage No-Go errors and more cognitive rigidity on the DFlex.

Figure 1 displays group effect sizes (Cohen's *d*) of the full and multiplex samples and of the ASD probands compared to TD individuals. Effect sizes of the ASD probands are larger or equally large as those of the relative samples (except for the switch cost RT of the Switch task), and effect sizes of the multiplex sample are larger than those of the full sample (except for the Planning scale of the BRIEF and the Attention to Detail scale of the DFlex).

(INSERT TABLE 3, FIGURE 1 AND TABLE 4 ABOUT HERE)

For the control measures (Table 4), ASD relatives performed equally (and even slightly better on the Motor Screening test) than the TD group. Furthermore, group differences on the main EF measures remained significant after controlling for possible EF confounds (see Appendix B). Finally, repeating the analyses while excluding the seven ASD relatives with a psychiatric diagnosis from the sample, yielded the same findings.

Additional details concerning the analyses and the results of all other measures are presented in Appendices B and D, respectively.

Discussion

We investigated which measures of EF and L-G visual processing are candidate endophenotypes for ASD, by comparing the performance of ASD relatives and TD individuals on those measures on which we previously found differences between ASD probands and TD controls (Van Eylen et al., 2015a, 2015b).

For the EF tasks, we found that ASD relatives showed significantly impaired response inhibition, cognitive flexibility and generativity, with the largest effect size for the generativity deficits. These impairments probably reflect genuine deficits in these EF domains, since groups were matched for several confounding variables (gender, age and IQ), no deficits were found on any of the control measures, and group differences remained after controlling for possible confounding EF deficiencies. Our findings largely correspond with those of Wong, Maybery, Bishop, Maley, and Hallmayer (2006), who investigated cognitive flexibility, generativity, planning and inhibition in ASD relatives compared to TD controls, and also found the most pronounced group differences on generativity tasks. Furthermore, they observed deficits in cognitive flexibility in the ASD parents and suggested that the rather structured nature of their flexibility task may have masked subtle impairments in the siblings (Wong et al., 2006). Our findings indeed indicate that open-ended compared to more structured tasks are more sensitive to reveal group differences in cognitive flexibility (i.e., the WCST-WCTS versus the Switch task), but also in generativity (the Uses of Objects task versus the Design Fluency task). This might explain why several other studies failed to find group differences in these EF domains (Appendix A). However, even when more open-ended tasks were used, ASD relatives did not always perform differently from controls (Bölte & Poustka, 2006; Delorme et al., 2007; Gokcen, Bora, Erermis, Kesikci, & Aydin, 2009; Hughes, Plumet, & Leboyer, 1999; Schmidt et al., 2008; Sumiyoshi, Kawakubo, Suga, Sumiyoshi, & Kasai, 2011; Szatmari et al., 1993). For cognitive flexibility, this could be due to the use of a non-TD control group and/or too small sample sizes to reveal group differences with a medium effect size (see Appendix A). Concerning generativity, the pattern of findings suggests that impairments depend on the type of generativity (or fluency). Turner (1999) distinguished three subtypes: word fluency, design fluency and ideational fluency. Overall, ASD relatives showed intact word and design fluency (for an exception, see Hughes et al., 1999 and Wong et al., 2006, respectively), but impaired ideational fluency (see Appendix A). This may signify an important new lead, especially given the large effect size for our measure of ideational fluency (i.e., Uses of Objects task). However, since there is only one other study that investigated ideational fluency (Wong et al., 2006), this hypothesis requires further investigation.

Similar to Wong and colleagues (2006) we found no impairments in interference control (one type of inhibition that we measured with the Flanker task), working memory and planning, while some other studies did (see Appendix A). All these studies included relatives of an ASD proband with low IQ (< 70) (Delorme et al., 2007; Gokcen et al., 2009; Hughes et al., 1999; Hughes, Leboyer, & Bouvard, 1997; Piven & Palmer, 1997), or did not provide information about the probands' IQ (Koczat, Rogers, Pennington, & Ross, 2002; Mosconi et al., 2010). Other authors already referred to the possible importance of the proband's IQ for finding impairments in ASD relatives (McLean, Johnson Harrison, Zimak, Joseph, & Morrow, 2014; Pilowsky, Yirmiya, Gross-Tsur, & Shalev, 2007; but see Szatmari et al., 1993). The "proband's level of functioning constitutes an important characteristic reflecting the severity of their phenotype, possibly leading to differences in genetic liability as well as presenting different stresses to the family" (Pilowsky et al., 2007, p. 539).

On the EF questionnaires, ASD relatives showed EF impairments in daily life. However, the specific results for both questionnaires were inconsistent and they also differed from the findings based on the EF tasks. On the BRIEF, ASD relatives revealed reduced planning (only for the full sample), with intact inhibition, working memory and shifting abilities, whereas with the DFlex questionnaire, cognitive flexibility impairments were found[4]. These inconsistencies correspond with the notion that questionnaires have a limited construct validity (e.g., it is hard to specify in which specific domain impairments occur, because multiple EF abilities jointly play a role in daily life situations).

Since group differences on the EF tasks were more pronounced on open-ended compared to more structured tasks, we expected even larger effect sizes for the questionnaires, which are the most open-ended and ecologically valid EF measures. However, this was not the case. This could be due to the 'informant contrast effect', where parents tend to underestimate the sibling's atypical behavior because he/she is implicitly compared to the more severely affected proband (De la Marche et al., 2015). Likewise, parents had to report about their own abilities and there are indications that adult ASD relatives tend to underestimate their own anomalies (De la Marche et al., 2015; Möricke, Buitelaar, & Rommelse, 2016). Both reporting biases may have induced an underestimation of the cognitive atypicalities of the ASD relatives.

[4] Cognitive flexibility is the only EF that is measured with the DFlex. Generativity is not measured with any of the questionnaires.

Regarding the L-G measures, we found no group differences on any of the laboratory tasks and effect sizes were small. To our knowledge, our study is the first to examine the performance of ASD relatives with measures aimed at distinguishing local and global processing abilities as well as processing style (Van Eylen et al., 2015b). Most of our measures were not used in previous studies with ASD relatives, except for the Coherent Motion task for which one previous study also reported intact performance of ASD relatives (de Jonge et al., 2007, see Appendix A). All other preceding studies have used more general 'central coherence' measures and only four out of 14 studies found differences between ASD relatives and TD controls on some of these measures (Appendix A)[5].

Despite a lack of group differences on our L-G tasks, the full sample of ASD relatives did score significantly higher on the Attention to Detail scale of the DFlex questionnaire. By administering a different questionnaire, Briskman, Happé, and Frith (2001) also reported enhanced detail focus for ASD parents (but not for ASD siblings). Unfortunately, these questionnaires have a limited construct validity, making it unclear what they actually measure.

For all measures we also found that the effect of group (ASD relatives vs. TD controls) did not differ for ASD siblings compared to ASD parents, indicating that they display a similar degree of ASD-like cognitive characteristics.

Concerning the multiplex ASD relatives, we replicated the impaired cognitive flexibility and generativity that was observed for the full sample and found a trend towards impaired response inhibition. The larger *p*-values for the multiplex sample are not surprising, given the smaller sample size. However, the group effect sizes were generally larger for the multiplex compared to the full sample. Since the full sample comprises both multiplex and simplex families, the larger effect sizes for the multiplex sample are in line

[5] Note that in some studies the Block Design subtest of the Wechsler intelligence scale was used as a measure of L-G processing (or central coherence), while in most studies it was included to determine PIQ.

with an increased genetic liability of ASD relatives in multiplex compared to simplex families (Pinto et al., 2010; Sebat et al., 2007). Yet, the smaller sample size of the multiplex versus the full sample may have yielded insufficient statistical power to detect additional group differences.

Did we find cognitive endophenotypes for ASD? Since ASD relatives showed impaired EF, this refutes the suggestion that EF is a protective factor that prevents them from developing ASD (Johnson, 2012). On the contrary, our findings support some of the endophenotype criteria. By administering a cognitive battery that enhances the validity of the measures (criterion 4), we demonstrated that some EF impairments (namely impairments in cognitive flexibility, generativity and response inhibition) that occurred in ASD probands (criterion 1) were also present in unaffected ASD relatives (criterion 2). Additionally, the effect sizes of the deficits in the ASD relatives were generally smaller than those of the corresponding impairments in ASD probands. This accords with the expectation for an endophenotype: not all relatives will share ASD risk genes with the proband, so at a group level cognitive impairments will generally be less pronounced. Previous studies have also demonstrated that EF is heritable, providing evidence for the third endophenotype criterion (Friedman et al., 2008; Rommelse, 2011). Yet, further research is needed to determine heritability estimates for each specific EF domain, especially as heritability estimates for generativity are lacking. For L-G characteristics no strong and valid evidence was found for impairments in ASD relatives (criterion 2). Furthermore, to our knowledge, no study has provided heritability estimates of L-G processing.

Since an endophenotype mediates the genotype-phenotype relationship of a disorder, additional requirements may be stipulated. Firstly, (partially) the same genes should underlie endophenotypic and phenotypic traits of ASD. As an indication of the degree of genetic overlap, the bivariate heritability could be calculated (Doyle et al., 2005). Secondly, an endophenotype should precede and not result from the phenotype (in line with endophenotype criterion 5). Since cognitive impairments also occur in unaffected ASD relatives, this suggests they are not a consequence of the disorder. However, the impairment could still result from a symptom that is part of the broader autism phenotype that is also present in ASD relatives. Interestingly, some intervention studies suggested that improved EF skills reduce phenotypic ASD traits (Kenworthy et al., 2014; de Vries, Prins, Schmand, & Geurts, 2015). Additional intervention and longitudinal studies should provide further evidence. However, proving that cognitive impairments precede ASD symptoms is extremely challenging, given the early onset of ASD (APA, 2013) and the methodological challenges associated with measuring cognitive impairments early in life (Epsy, Bull, Kaiser, Martin, & Banet, 2008). Moreover, no one-to-one relation between endophenotype and phenotype is to be expected, as a specific endophenotype might neither be necessary nor sufficient to induce the phenotype (Szatmari et al., 2007; Walters & Owen, 2007). Yet, the phenotype often results from a combination of endophenotypes and different combinations could induce the same phenotype. Therefore, an endophenotype does not have to be universal nor specific for ASD (Bearden & Freimer, 2006; Viding & Blakemore, 2007), corresponding with the large cognitive heterogeneity in ASD (Brunsdon et al., 2015; Geurts, Sinzig, Booth, & Happé, 2014).

The heterogeneity of cognitive characteristics that are associated with the genetic liability for ASD, is expected to be even larger in unaffected ASD relatives than in probands. This heterogeneity may explain why only small to medium effect sizes were found in this study and why inconsistent findings were found between studies that focus on a (small) subsample. To gain an overview of all candidate endophenotypes, future studies are needed comprising ASD probands and their relatives across the whole age, IQ and ASD spectrum. These studies need to be sufficiently large to have enough power to detect group differences and possible interactions with the type of relative (sibling vs. parent). To further increase the power, we advise to only include multiplex families.

Given the large heterogeneity, future studies should focus more on inter-individual differences and possibly underlying factors. Endophenotypes may help to delineate etiologically more homogeneous subgroups (Szatmari et al., 2007). More specifically, the heterogeneity at the cognitive level is thought to (partially) reflect the underlying biological (including genetic) heterogeneity and to (partially) explain the phenotypic heterogeneity. Accordingly, delineating different homogeneous subgroups based on cognitive performance could help to unravel biological pathways of the disorder, by investigating the associated behavioral and (neuro)biological characteristics of each subgroup (Lenroot & Yeung, 2013).

Conclusion

Impaired cognitive flexibility, generativity and response inhibition are valuable candidate endophenotypes, as they fulfil the classic endophenotype criteria. Yet, further research is needed to validate whether they lie on the genotype-phentoype pathway of ASD.

The initial purpose of endophenotypes was to aid in the discovery of ASD genes. However, this appeared to be more complex than originally thought. Additionally, detecting specific genetic mutations has become much easier due to great advances in genomic technologies. Both aspects have led to resistance to endophenotypic approaches in psychiatry (Glahn et al., 2014). Nevertheless, endophenotypes remain important to fill-in the missing links of the cascade from genes to behavior (Glahn et al., 2014; Jeste & Geschwind, 2014; State & Levitt, 2011). They could also help to delineate etiologically more homogeneous subgroups, which is clinically relevant as it allows assigning ASD probands to different and more targeted interventions.

Key points

- Heterogeneity within ASD stimulated the search for endophenotypes.
- We evaluated endophenotype criteria for executive functioning and local-global visual processing, by assessing these functions in ASD probands, their relatives and controls, with an extended cognitive battery. Furthermore, we provided a literature overview.
- Microarrays were performed so we could exclude relatives from a proband with a *de novo* mutation in a known ASD susceptibility CNV. This increases the probability that genetic risk variants are shared by the ASD relatives.
- Results indicated that impaired cognitive flexibility, ideational fluency and response inhibition are strong candidate endophenotypes.
- Endophenotypes allow the delineation of etiologically more homogeneous subgroups, which is clinically important to allow assigning ASD probands to different, more targeted, interventions.

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Table 1

Sample characteristics concerning gender ratio, age (in years), verbal, performance and full-scale IQ for the matched ASD relatives and TD groups. Characteristics of the full samples are presented, characteristics separated-out for children and adults, and characteristics of the multiplex ASD parents matched with TD adults

ASD relatives vs. TD groups	Gender ratio (M:F)	Age (years)	VIQ	PIQ	FSIQ
		Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Full sample					
ASD relatives (*n* = 113)	0.8 (51:62)	34.39 (15.05)	112.49 (15.35)	105.66 (15.90)	109.08 (13.10)
TD (*n* = 100)	0.9 (47:53)	31.75 (16.82)	116.06 (14.33)	105.10 (14.34)	110.58 (10.75)
Group effect: test statistic (*p*)	χ^2 = 0.02 (0.89)	*F* = 1.47 (0.23)	*F* = 3.06 (0.08)	*F* = 0.07 (0.79)	*F* = 0.83 (0.36)
Children					
ASD siblings (*n* = 35)	0.7 (14:21)	12.90 (2.98)	107.77 (14.91)	103.97 (13.13)	105.87 (11.76)
TD (*n* = 42)	0.9 (20:22)	12.86 (2.89)	112.76 (12.03)	103.64 (13.92)	108.20 (9.60)
Group effect: test statistic (*p*)	χ^2 = 0.19 (0.66)	*F* = 0.01 (0.96)	*F* = 2.64 (0.11)	*F* = 0.01 (0.92)	*F* = 0.92 (0.34)
Adults					
ASD parents (*n* = 78)	0.9 (37:41)	44.04 (4.60)	114.60 (15.17)	106.42 (17.02)	110.51 (13.48)
TD (*n* = 58)	0.9 (27:31)	45.43 (5.66)	118.45 (15.45)	106.16 (14.67)	112.30 (11.28)
Group effect: test statistic (*p*)	χ^2 = 0.01 (0.92)	*F* = 2.49 (0.12)	*F* = 2.10 (0.15)	*F* = 0.01 (0.92)	*F* = 0.67 (0.41)
Multiplex sample					
ASD parents (*n* = 37)	0.9 (18:19)	43.46 (5.26)	112.27 (15.46)	106.30 (17.93)	109.28 (13.59)
TD adults (*n* = 58)	0.9 (27:31)	45.43 (5.66)	118.45 (15.45)	106.16 (14.67)	112.3 (11.28)
Group effect: test statistic (*p*)	χ^2 = 0.04 (0.84)	*F* = 2.88 (0.09)	*F* = 3.61 (0.06)	*F* = 0.00 (0.97)	*F* = 1.38 (0.24)

Table 2

An overview of all administered EF, L-G and control measures. In black, the tasks and questionnaires that were the focus of the present study, since significant differences between ASD probands and TD individuals were observed on the main outcome measure (Van Eylen et al., 2015a, 2015b) or because they provided an additional control measure (i.e. the additional control tasks). In grey, the other tasks and measures that were part of the neurocognitive battery

Tasks/questionnaires per cognitive domain	Main outcome measures	Additional EF or control measures
EF tasks:		
Inhibition:		
Go/No-Go task	% No-Go errors	% errors on infrequent Go trials
		RT on infrequent Go trials
Flanker task	Inhibition cost RT	RT on compatible trials [a]
	Inhibition cost % errors	
Cognitive flexibility:		
WCST-WCTS	Switch cost RT	RT on maintain trials [a]
	Perseverative errors	
Switch task	Switch cost RT	RT on maintain trials [a]
	Switch cost % errors	
Generativity:		
Uses of Objects task	Correct responses	Number of responses
		% incorrect responses
		% redundant responses
		% repetitions
Design Fluency test (D-KEFS)	Correct responses	-
Spatial working memory:		
Spatial Working Memory test (CANTAB)	Total errors on 4, 6 and 8 box trials	Search strategy
Spatial Span test (WNV-NL)	Correct trials	-
Planning:		
Tower test (D-KEFS)	Move accuracy ratio	Time per step
		First step latency
EF questionnaires:		
BRIEF	Inhibition scale	-
	Shifting scale	
	Working memory scale	
	Planning scale	
DFlex	Cognitive rigidity	-
L-G tasks:		
Processing style:		

ROCF	Fragmentation score	-
Global processing abilities:		
Coherent Motion task	Coherent motion threshold	-
Fragmented Object Outlines task	Correct identification frame Correct identification latency	Proportion of unrecognized objects
Local processing abilities:		
Visual Search task	Target detection latency	-
	Similarity cost	
L-G questionnaire:		
DFlex	Attention to Detail	-
Additional control tasks		
Motor screening		
Motor Screening test (CANTAB)	Response latency	-
Simple Reaction Time task	Response latency	-

EF: Executive Functioning; L-G: Local-Global processing; RT: Reaction Time; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task switching; D-KEFS: Delis–Kaplan Executive Function System; CANTAB: Cambridge Neuropsychological Test Automated Battery; WNV-NL: Wechsler Nonverbal Scale of Ability – Dutch Version; BRIEF: Behavior Rating Inventory of Executive Function; DFlex: Detail and Flexibility questionnaire; ROCF: Rey-Osterrieth Complex Figure

[a] Baseline control measure reflecting processing speed

Table 3

Performance of ASD relatives compared to TD individuals on the main EF and L-G measures. The effect of group (ASD relatives vs. TD individuals), age (children vs. adults), and the group by age interaction are reported for the full sample. For the multiplex sample the effect of group is shown.

Cognitive measures	ASD relatives	TD	Effect of group		Effect of age		Group x Age effect	
	Mean (*SD*)	Mean (*SD*)	Test-statistic	*p*	*F* -value	*p*	*F*-value	*p*
Full sample								
EF tasks:								
Inhibition:								
Go/No-Go task: % No-Go errors	13.16 (11.31)	11.71 (10.95)	*F* = 5.85	**0.01**	57.32	**< 0.001**	1.67	0.20
Cognitive flexibility:								
WCST-WCTS: Switch cost RT	515.27 (299.16)	472.27 (341.51)	*F* = 1.82	0.18	0.66	0.42	0.12	0.73
WCST-WCTS: Perseverative errors	0.84 (1.53)	0.43 (0.42)	*F* = 7.98	**0.006**	20.38	**< 0.001**	0.26	0.61
Switch task: Switch cost RT	336.20 (112.45)	339.98 (97.65)	*F* = 0.17	0.68	0.01	0.96	0.41	0.52
Switch task: Switch cost % errors	0.74 (2.17)	0.77 (2.64)	*U* = 10563	0.74	[a]	[a]	[a]	[a]
Generativity:								
Uses of Objects task: Correct responses[b]	10.02 (3.81)	11.33 (4.07)	*F* = 10.64	**0.002**	71.17	**< 0.001**	0.16	0.69
Spatial working memory:								
Spatial Working Memory Test: Total errors[c]	7.77 (5.25)	8.48 (6.48)	*F* = 0.14	0.71	15.93	**< 0.001**	0.02	0.90
EF questionnaires:								
BRIEF: Inhibition	11.71 (2.95)	11.77 (2.83)	*F* = 0.19	0.66	57.53	**< 0.001**	0.28	0.60
Shifting	9.34 (2.74)	9.40 (2.50)	*F* = 0.05	0.83	31.45	**< 0.001**	0.24	0.62
Working memory	12.92 (3.83)	12.51 (3.66)	*F* = 3.62	0.06	77.20	**< 0.001**	0.14	0.71
Planning	16.22 (5.12)	15.52 (3.83)	*F* = 5.05	**0.02**	80.80	**< 0.001**	3.38	0.07
DFlex: Cognitive rigidity	31.67 (11.22)	25.79 (9.31)	*F* = 6.90	**0.01**	11.68	**< 0.001**	0.00	0.95

L-G tasks:								
Processing style:								
ROCF: Fragmentation score	2.39 (2.63)	2.65 (2.63)	*F* = 0.10	0.75	45.94	**< 0.001**	0.00	0.96
Global processing abilities:								
Coherent motion threshold	18.77 (10.20)	20.66 (9.37)	*F* = 1.65	0.20	35.18	**< 0.001**	0.51	0.48
L-G questionnaire:								
DFlex: Attention to Detail	27.97 (9.80)	21.83 (8.59)	*F* = 13.19	**< 0.001**	1.73	0.19	0.51	0.48
Multiplex sample								
EF tasks:								
Inhibition:								
Go/No-Go task: % No-Go errors	10.47 (7.89)	7.90 (7.14)	*F* = 3.88	0.05				
Cognitive flexibility:								
WCST-WCTS: Switch cost RT	618.21 (515.96)	618.29 (1169.71)	*F* = 1.87	0.17				
WCST-WCTS: Perseverative errors	1.41 (2.73)	0.57 (1.26)	*F* = 6.92	**0.01**				
Switch task: Switch cost RT	351.74 (115.64)	336.59 (88.11)	*F* = 0.53	0.47				
Switch task: Switch cost % errors	0.58 (1.37)	0.22 (1.34)	*F* = 1.58	0.21				
Generativity:								
Uses of Objects task: Correct responses	10.86 (3.43)	13.08 (3.33)	*F* = 9.97	**0.002**				
Spatial working memory:								
Spatial Working Memory Test: Total errors[b]	6.72 (4.53)	7.20 (6.12)	*F* = 0.38	0.54				
EF questionnaires:								
BRIEF: Inhibition	11.38 (2.68)	10.55 (1.96)	*F* = 2.67	0.11				
Shifting	8.92 (2.62)	8.50 (1.98)	*F* = 0.49	0.49				
Working memory	11.97 (3.05)	10.95 (2.38)	*F* = 3.07	0.08				
Planning	15.03 (4.38)	13.95 (2.69)	*F* = 1.22	0.27				
DFlex: Cognitive rigidity	34.75 (12.51)	28.99 (9.02)	*F* = 3.87	0.05				
L-G tasks:								
Processing style:								
ROCF: Fragmentation score	1.65 (2.37)	1.66 (2.06)	*F* = 0.11	0.74				

Global processing abilities:				
Coherent motion threshold	16.21 (5.95)	17.78 (5.98)	*F* = 1.96	0.16
L-G questionnaire:				
DFlex: Attention to Detail	28.47 (11.41)	23.63 (9.30)	*F* = 2.91	0.09

[a] The effect of ASD relatives vs. TD was tested non-parametrically (Mann-Whitney *U* test) so without including age and the interaction with age in the model.

[b] Including the within-subject factor 'item type' (conventional or non-conventional): Full sample: $F(1,213)=329.70$, $p < 0.001$; Multiplex sample: $F(1,95)=143.44$, $p < 0.001$

[c] Including the within-subject factor 'number of boxes' (4, 6 or 8): Full sample: $F_{(2,428)} = 557.05$, $p < 0.001$; Multiplex sample: $F_{(2,188)} = 220.43$, $p < 0.001$, for the full and the multiplex sample respectively.

Values in bold indicate significant differences that survived FDR correction.

EF: Executive Functioning; L-G: Local-Global processing; ASD: Autism Spectrum Disorder; TD: Typically Developing; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task switching; RT: Reaction Time; BRIEF: Behavior Rating Inventory of Executive Function; DFlex: Detail and Flexibility questionnaire; ROCF: Rey-Osterrieth Complex Figure

Table 4

Performance of the ASD relatives and the TD individuals on the control measures. The effect of group (ASD relatives vs. TD individuals) is reported for the full and the multiplex sample

Measures per task	ASD relatives		TD		Effect of group	
	Mean	*SD*	Mean	*SD*	Test-statistic	*p*
Full sample						
Go/No-Go task: Infrequent Go-trials:						
% errors[a]	0.18	0.83	0.16	0.79	*U* = 10676	0.88
RT	380.36	46.87	391.77	45.15	*F* = 2.88	0.09
WCST-WCTS:						
RT maintain trials	923.97	970.31	871.99	513.89	*F* = 0.11	0.74
Switch task:						
RT maintain trials	492.58	88.60	506.39	84.62	*F* = 1.40	0.24
Spatial Working Memory test:						
Search strategy	31.32	5.71	32.04	6.44	*F* = 0.76	0.38
Motor Screening test:						
Response latency	764.95	175.32	815.80	203.64	*F* = 4.44	0.04
Simple reaction time task:						
Response latency	288.31	49.15	292.02	44.53	*F* = 0.18	0.67
Multiplex sample						
Go/No-Go task: Infrequent Go-trials:						
% errors	0.00	0.00	0.00	0.00	-	-
RT	371.52	39.92	375.33	42.31	*F* = 0.16	0.69
WCST-WCTS:						
Maintain trials	484.26	68.42	481.10	73.24	*F* = 1.64	0.21
Switch task:						
Maintain trials	1145.43	1631.17	841.48	634.21	*F* = 0.07	0.79
Spatial working memory test:						
Search strategy	30.28	5.63	30.93	6.61	*F* = 0.24	0.63
Motor Screening test:						
Response latency	787.28	131.93	776.01	124.66	*F* = 0.18	0.67
Simple reaction time task:						
Response latency	287.10	41.84	296.82	52.85	*F* = 1.00	0.32

[a] A Mann-Whitney *U* test was performed

None of the group differences survived FDR correction.

ASD: Autism Spectrum Disorder; TD: Typically Developing; RT: Reaction Time; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task Switching.

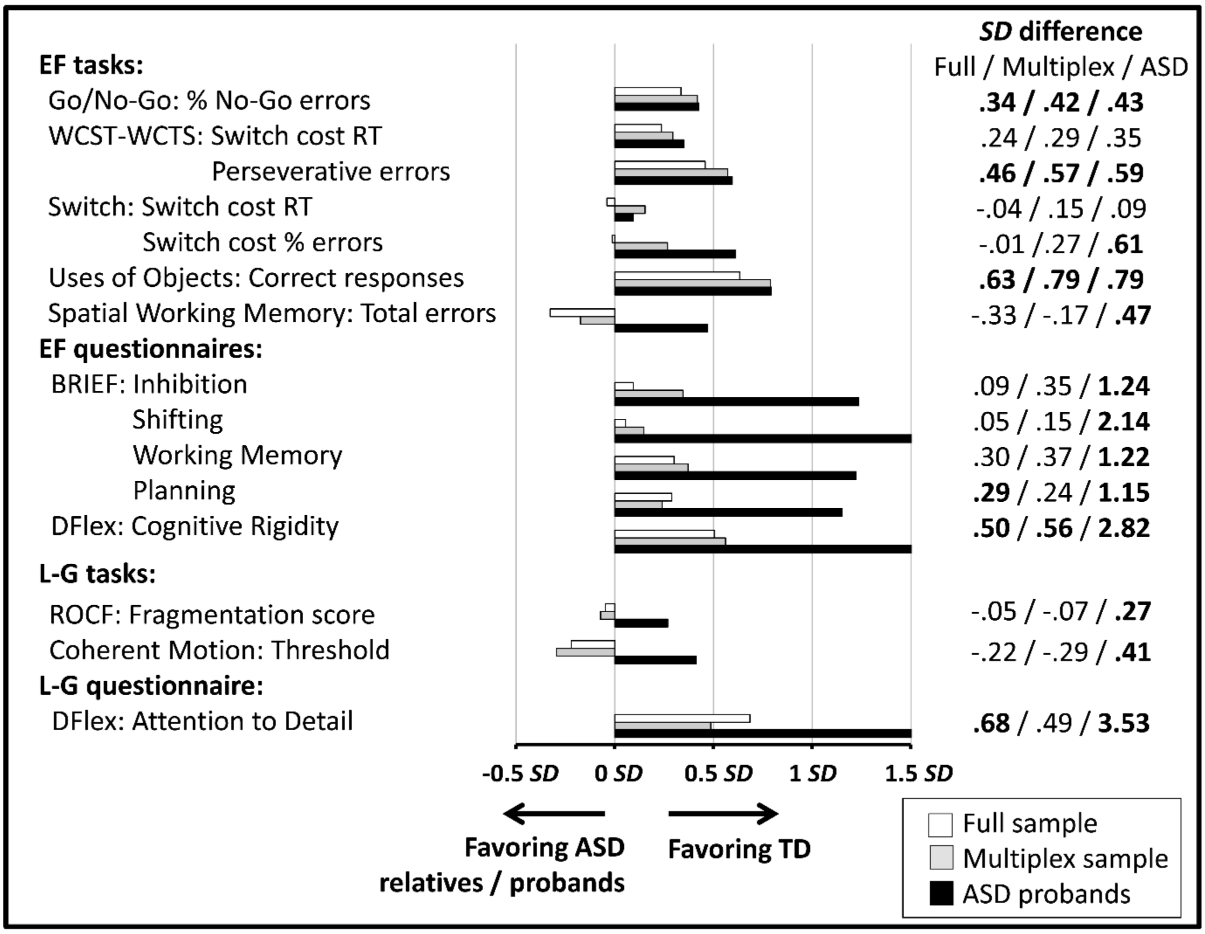

Figure 1. Cohen's *d* effect sizes comparing ASD relatives and ASD probands with TD individuals on the main measures of the EF and L-G tasks that yielded group differences between the probands with ASD and TD individuals (Van Eylen et al., 2015a, 2015b). Values in bold indicate significant group differences. The white bars display the results of the full sample, the grey bars represent the results of the multiplex sample and the black bars show the results of the ASD probands. Positive scores indicate better performance (for EF measures) or lower scores (for L-G processing measures) for TD individuals versus ASD relatives. EF: Executive Functioning; L-G: Local-Global processing; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task Switching; BRIEF: Behavior Rating Inventory of Executive Functioning; DFlex: Detail and Flexibility questionnaire; ROCF: Rey-Osterrieth Complex Figure.

Appendix A

Table A1

An overview of studies on executive functioning (EF) and local-global processing (L-G) in relatives of individuals with ASD, ordered chronologically

Study	Measures per cognitive domain	ASD relatives	Control group: relatives of	Group differences	Matched for
Szatmari et al. (1993)	EF:				?
	Cognitive flexibility: WCST	S (*n* = 72)	DS/LBW (*n* = 46)[c]	n.s.	
	'Working memory': Digit Span [a]	P (*n* = 97)	DS/LBW (*n* = 54)	n.s.	
	L-G: Block Design [b]	P (*n* = 97)	DS/LBW (*n* = 54)	n.s.	
Baron-Cohen & Hammer (1997)	L-G: EFT	P (*n* = 30)	TD (*n* = 30)	ASD-P > TD-P	age, gender, IQ and SES
Fombonne et al. (1997)	EF: 'Working memory': Digit Span [a]	P, S (*n* = 92)	DS (*n* = 26)	ASD-P/S > DS-P/S	maternal age of probands, SES
	L-G: Block Design [b]	P, S (*n* = 92)	DS (*n* = 26)	n.s.	
Piven & Palmer (1997)	EF: Planning: Tower of Hanoi	P (*n* = 48)	DS (*n* = 60)	ASD-P < TD-P	age, level of education
	L-G: Block Design [b]	P (*n* = 48)	DS (*n* = 60)	n.s.	
Hughes et al. (1997)	EF (CANTAB taken):				age; ASD and LD probands were matched for: IQ, age, sex ratio, parental age, parental education, parental occupational level and maternal age at birth
	Cognitive flexibility: ID/ED test	P (*n* = 40)	TD (*n* = 36), LD (*n* = 36)	ASD-P < TD-P = LD-P	
	Working memory:				
	Spatial Working Memory task	P (*n* = 40)	TD (*n* = 36), LD (*n* = 36)	ASD-P < TD-P	
	Spatial Span task [a]	P (*n* = 40)	TD (*n* = 36), LD (*n* = 36)	LD-P < TD-P	
	Planning: Tower of London	P (*n* = 40)	TD (*n* = 36), LD (*n* = 36)	ASD-P = LD-P < TD-P	
Hughes et al. (1999)	EF (CANTAB tasks):				age, parental occupation
	Cognitive flexibility: ID/ED test	S (*n* = 31)	TD (*n* = 32), DD (*n* = 32)	ASD-S < TD-S = DD-S	
	Working memory:				

	Spatial Working Memory task	S (*n* = 31)	TD (*n* = 32), DD (*n* = 32)	ASD-G = DD-G < TD-G	
	Spatial Span task [a]	S (*n* = 31)	TD (*n* = 32), DD (*n* = 32)	ASD-S > TD-S = DD-S	
	Planning: Tower of London	S (*n* = 31)	TD (*n* = 32), DD (*n* = 32)	ASD-S < TD-S	
	Non-computerized EF tasks:				
	Generativity: Verbal Fluency task	S (*n* = 31)	DD (*n* = 32)	ASD-S < DD-S	
Happé et al. (2001)	L-G:				age, IQ, SES and educational level
	Block Design (whole vs. segmented)	P, S (*n* = 62)	TD (*n* = 37), D (*n* = 44)	ASD-F > TD-F = D-F	
	EFT	P, S (*n* = 62)	TD (*n* = 37), D (*n* = 44)	ASD-F > TD-F = D-F	
	Visual Illusions	P, S (*n* = 62)	TD (*n* = 37), D (*n* = 44)	ASD-F > D-F	
	Sentence Completion task	P, S (*n* = 62)	TD (*n* = 37), D (*n* = 44)	ASD-P < TD-P = D-P	
Briskman et al. (2001)	L-G: Real-life Styles and Preferences questionnaire	P, S (*n* = 62)	TD (*n* = 48), D (*n* = 40)	ASD-F > TD-F	age, IQ, SES and educational level
Koczat et al. (2002)	EF: Spatial working memory:				age and gender
	Delayed Oculomotor Response task	P (*n* = 11)	TD (*n* = 17)	ASD-P < TD-P	
Bölte & Poustka (2006)	EF:				age, gender, SES and mean years of education
	Cognitive flexibility				
	WCST	P (*n* = 62)	EOS (*n* = 36), ID (*n* = 30)	n.s.	
	Trail Making test	P (*n* = 62)	EOS (*n* = 36), ID (*n* = 30)	n.s.	
	Planning: Tower of Hanoi	P (*n* = 62)	EOS (*n* = 36), ID (*n* = 30)	n.s.	
	L-G:				
	EFT	P (*n* = 62)	EOS (*n* = 36), ID (*n* = 30)	ASD-P > ID-P > EOS-P	
	Block Design	P (*n* = 62)	EOS (*n* = 36), ID (*n* = 30)	n.s.	
de Jonge et al. (2006)	L-G: EFT	P (*n* = 51)	DS (*n* = 54)	ASD-P > TD-P	age, gender and IQ
Wong et al. (2006)	EF:				age, PIQ, VIQ (gender was included as a covariate)
	Inhibition/Working memory: Response Inhibition and Load task	P, S (*n* = 211)	TD (*n* = 146)	n.s.	
	Cognitive flexibility: ID/ED test	P, S (*n* = 211)	TD (*n* = 146)	ASD-F < TD-F	
	Generativity				
	Pattern Meanings	P, S (*n* = 211)	TD (*n* = 146)	ASD-P/S < TD-P/S	

	Stamps task	S (*n* = 66)	TD (*n* = 50)	ASD-S < TD-S	
	Planning: Tower of London	P, S (*n* = 211)	TD (*n* = 146)	n.s.	
de Jonge et al. (2007)	L-G: Coherent Motion task	P (*n* = 52)	TD (*n* = 52)	n.s.	gender, age and IQ
Delorme et al. (2007)	EF:				gender, age and educational level
	Cognitive flexibility: Trail Making test	P, S (*n* = 58)	TD (*n* = 47), OCD (*n* = 64)	n.s.	
	Generativity:				
	Design Fluency task	P, S (*n* = 58)	TD (*n* = 47), OCD (*n* = 64)	n.s.	
	Verbal Fluency task	P, S (*n* = 58)	TD (*n* = 47), OCD (*n* = 64)	n.s.	
	Association Fluency task	P, S (*n* = 58)	TD (*n* = 47), OCD (*n* = 64)	n.s.	
	Planning: Tower of London	P, S (*n* = 58)	TD (*n* = 47), OCD (*n* = 64)	ASD-P/S = OCD-P/S < TD-P/S	
Pilowsky et al. (2007)	Mean number of EF tasks completed successfully:	S (*n* = 30)	ID (*n* = 28), DLD (*n* = 30)	n.s.	age, gender, birth-order; probands' gender, family size and family income
	Tower of Hanoi				
	Word Associations test				
	Rapid Automatic Naming test				
Scheeren & Stauder (2008)	L-G: Block Design	P (*n* = 25)	TD (*n* = 25)	n.s.	gender, age and educational level
Schmidt et al. (2008)	EF:				age, handedness, IQ and SES
	Generativity: Verbal Fluency (D-KEFS)	P (*n* = 22)	TD (*n* = 22)	n.s.	
	L-G: Block Design [b]	P (*n* = 22)	TD (*n* = 22)	n.s.	
de Jonge et al. (2009)	L-G: Block Design (whole vs. segmented)	P (*n* = 51)	DS (*n* = 57)	n.s.	age, gender and IQ
Gokcen et al. (2009)	EF:				age, gender and IQ
	Inhibition: Stroop test	P (*n* = 76)	TD (*n* = 41)	n.s.	
	Working memory: Auditory Consonant Trigrams	P (*n* = 76)	TD (*n* = 41)	ASD-P < TD-P	
	Generativity: Verbal Fluency task	P (*n* = 76)	TD (*n* = 41)	n.s.	
Losh (2009)	EF:				age, IQ, education level
	Cognitive flexibility: Trail Making test	P (*n* = 83)	TD (*n* = 32)	n.s.	

	Planning: Tower of Hanoi	P (*n* = 83)	TD (*n* = 32)	n.s.	
	L-G:				
	EFT	P (*n* = 83)	TD (*n* = 32)	n.s.	
	Sentence Completion task	P (*n* = 83)	TD (*n* = 32)	n.s.[d]	
	Block Design (whole vs. segmented)	P (*n* = 83)	TD (*n* = 32)	n.s.	
Mosconi et al. (2010)	EF:				age, gender and IQ
	Inhibition: Antisaccade task	P, S (*n* = 57)	TD (*n* = 40)	ASD-P/S < TD-P/S	
	Cognitive flexibility: Trail Making test	P, S (*n* = 57)	TD (*n* = 40)	n.s.	
	Working memory:				
	Spatial Span [a]	P, S (*n* = 57)	TD (*n* = 40)	ASD-P/S < TD-P/S	
	Digit Span [a]	P, S (*n* = 57)	TD (*n* = 40)	n.s.	
	Letter Number Sequence	P, S (*n* = 57)	TD (*n* = 40)	n.s.	
Nyden et al. (2011)	EF:				?
	Cognitive flexibility: Trail Making test	P, S (*n* = 49)	normative data	n.s.	
	Planning: Tower of London	P, S (*n* = 49)	normative data	ASD-P/S < norm	
	L-G: EFT	P, S (*n* = 49)	normative data	n.s.	
Sumiyoshi et al. (2011)	EF:				age, gender ratio, IQ
	Cognitive flexibility: WCST	S (*n* = 14)	TD (*n* = 15)	n.s.	
	Organization/memory: Verbal Learning task	S (*n* = 14)	TD (*n* = 15)	n.s.	
Warren et al. (2012)	EF (NEPSY-II):				gender, age and SES
	Generativity: Design Fluency test	S (*n* = 39)	TD (*n* = 22)	n.s.	
	Auditory Attention test [e]	S (*n* = 39)	TD (*n* = 22)	ASD-S < TD-S	
	Inhibition:				
	Inhibition test	S (*n* = 39)	TD (*n* = 22)	ASD-S < TD-S	
	Statue test	S (*n* = 39)	TD (*n* = 22)	ASD-S < TD-S	
	Composite of last 3 tests	S (*n* = 39)	TD (*n* = 22)	ASD-S < TD-S	
McLean et al. (2014)	EF composite variables:				?
	D-KEFS				
	Conceptual Flexibility factor [f]	P, S (*n* = 392)	normative data	ASD-P > norm	

	Monitoring factor [g]	P, S (*n* = 392)	normative data	ASD-P/S > norm	
	Inhibition factor [h]	P, S (*n* = 392)	normative data	ASD-P > norm	
	BRIEF				
	Behavior Regulation index [i]	S (*n* = 76)	normative data	n.s.	
	Metacognition index [j]	S (*n* = 76)	normative data	n.s.	
Brunsdon et al. (2015)	EF:				IQ and SES
	Inhibition: Luria Hand Game	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Cognitive flexibility: ID/ED test	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Generativity: Letter Fluency task	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Planning: Planning Drawing task, part B	S (*n* = 73)	TD (*n* = 160)	n.s.	
	L-G:				
	EFT	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Block Design	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Homographs Reading test	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Planning Drawing task, part A	S (*n* = 73)	TD (*n* = 160)	n.s.	
	Sentence Completion task	S (*n* = 73)	TD (*n* = 160)	n.s.	
Oerlemans et al. (2016)	EF:				Statistical control for age and gender
	Inhibition: Go/No-Go task	S: SPX (*n* = 77), MPX (*n* = 46)	TD (*n* = 124)	n.s.	
	Working Memory:				
	Digit span backwards	S: SPX (*n* = 77), MPX (*n* = 46)	TD (*n* = 124)	n.s.	
	Spatial temporal span backwards	S: SPX (*n* = 77), MPX (*n* = 46)	TD (*n* = 124)	n.s.	
	Cognitive flexibility:				
	Response organization objects	S: SPX (*n* = 77), MPX (*n* = 46)	TD (*n* = 124)	n.s.	

Note. The lay-out of this table is based on Table 1 in Bölte and Poustka (2006). We included all papers published since 1993 that were full-text available online, written in English and did not include infant siblings at risk for ASD.
[a] In some studies a Span task is used to assess working memory, while in other studies such a task is used as a control task measuring short-term memory capacity; [b] The subtest of the Wechsler intelligence test was included to determine PIQ, not L-G; [c] One control group consisting of relatives of probands with DS and relatives of probands with LBW; [d] ASD parents did respond faster than TD controls; [e] Measures selective attention, attention maintenance and cognitive flexibility; [f] The Conceptual Flexibility

factor consists of 3 scores from the Sorting test: Free Sort, Free Sort Description and Sort Recognition; [g] The Monitoring factor consists of the Verbal Fluency and Category Switching measures; [h] The Inhibition factor reflects scores on the Trail Making test, Color-Word Inhibition, and Color Word Inhibition/Switching.; [i] The Behavioral Regulation index contains the scales Inhibition, Shifting and Emotional Control; [j] The Metacognition index contains the scales Initiation, Working Memory, Planning/Organization, Organization of Materials, and Monitoring of Behavior.

n.s. = no significant group differences, > significantly ($p < .05$) better performance (or higher values: Real-life styles and preferences questionnaire), < significantly worse performance.
P = Parents, S = Siblings, F = Fathers, G = Girls, SPX = simplex, MPX = multiplex.
EF = Executive Functioning, L-G = Local-Global processing, WCST = Wisconsin Card Sorting Task, EFT = Embedded Figures Test, ID/ED = IntraDimensional/ExtraDimensional set-shifting, D-KEFS = Delis – Kaplan Executive Functions System, NEPSY = Neuropsychological assessment system, CANTAB = Cambridge Neuropsychological Test Automated Battery, BRIEF = Behavior Rating Inventory of Executive Function.
ASD = Autism Spectrum Disorders, TD = Typically Developing, D = Dyslexia, DD = Developmental Delay, DS = Down Syndrome, EOS = Early Onset Schizophrenia, LBW = Low Birth Weight, LD = Learning Disability, ID = Intellectual Disability, OCD = Obsessive Compulsive Disorder.
SES = Socioeconomic Status.

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Appendix B

Battery of EF and L-G processing tasks

Since many cognitive tasks conflate different cognitive processes, we took several measures to control for the contribution of possible confounding variables. Firstly, we selected tasks with a within-subject design where we compared performance on two task conditions that share some requirements, but differ in the particular cognitive process of interest. Calculating the difference score between both conditions then yields a more valid measure of that particular cognitive ability (i.e., for the following EF tasks: Flanker task, WCST-WCTS, and Switch task; and the following L-G processing tasks: Fragmented Object Outlines task and Visual Search task). Secondly, when a particular cognitive deficit was found, we sought to dissociate it from any confounding variable. Concerning EF tasks, confounding variables comprise various EF and non-EF abilities. Accordingly, we included several non-EF measures that are involved in the EF tasks (like motor or processing speed). To determine the potential EF confounds for all main laboratory EF measures, we calculated the correlations between them (Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015a). Also for the L-G processing tasks, control measures were included. Moreover, since many L-G processing tasks conflate local and global processing, we reduced the trade-off between both by selecting tasks such that reduced performance on the global processing tasks is not simply due to increased local processing abilities, and increased or faster performance on the local processing tasks is not simply due to reduced global processing abilities (Booth & Happé, 2016; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015b). If no group differences were found on any of the possibly confounding variables, this provides evidence that the group difference on the cognitive task is more likely due to differences in a specific cognitive function. However, if group differences were also found on possible confounds, we investigated whether EF impairments remained while statistically controlling for these confounds (by including them as a covariate in the analyses). Finally, for most of the cognitive domains several instruments were included to examine whether group differences emerged for all measures of that domain, or whether impairments depended on characteristics of the instruments or were restricted to specific cognitive subdomains. Regarding instruments' characteristics, for the EF domains cognitive flexibility, working memory and generativity we included one highly structured task (Switch task, Spatial Span task and Design Fluency task respectively) and one more open-ended task (WCST-WCTS, Spatial Working Memory task and Uses of Objects task). To measure global processing abilities we selected a more low-level (Coherent Motion task) and a higher level task (Fragmented Object Outlines task, requiring top-down feedback). Moreover, laboratory tasks were supplemented with questionnaires, providing an indication of daily life functioning (which can be regarded as the most open-ended measure). Concerning cognitive subdomains, for inhibition and generativity (or fluency) a distinction was made between tasks measuring response inhibition (Go/No-Go task) versus interference control (Flanker task) and between design fluency (Design Fluency task) versus ideational fluency (Uses of Objects task), respectively. A more detailed description of the EF measures is provided by Van Eylen and colleagues (2015a). For the L-G processing measures the distinction between cognitive subdomains is inherently linked with task open-endedness. More specifically, to measure the processing style open-ended measures are required, while processing abilities are measured with more structured tasks.

Measure of intelligence

Intelligence was estimated with an abbreviated version of the Dutch Wechsler Intelligence Scale for Children (Wechsler et al., 2005) or Wechsler Adult Intelligence Scale (Wechsler, 2005) containing two verbal subtests (Vocabulary and Similarities) and two performance subtests (Picture Completion and Block Design) providing an estimate of VIQ and PIQ, respectively (Sattler, 2001). Averaging the estimated VIQ and PIQ score resulted in an estimate of FSIQ.

Detail and Flexibility (DFlex) questionnaire

The Detail and Flexibility questionnaire (DFlex) contains 2 subscales: one measuring attention to detail and the other measuring cognitive rigidity (Roberts, Barthel, Lopez, Tchanturia, & Treasure, 2011).The questionnaire was translated into Dutch using the back-translation procedure. We previously administered this questionnaire from individuals with ASD and TD individuals and found large group differences for both subscales (Cognitive Rigidity scale: $F_{(1,63)} = 130.33$, $p < 0.001$ (not previously reported); Attention to Detail scale: $F_{(1,63)} = 198.97$, $p < 0.001$, Van Eylen et al., 2015b). For the sample of the current study, the internal consistency of both subscales was high (Cronbach's alpha for the Cognitive Rigidity scale = 0.89, and for the Attention to Detail scale = 0.90). As an indication of the validity of the Cognitive Rigidity scale, we calculated the correlation with the Shifting scale of the BRIEF. This yielded a highly significant ($p < 0.0001$), yet moderate ($r = 0.47$) correlation. A similar validating correlation could not be calculated for the Attention to Detail scale, since we had no additional measure of this construct in daily life.

Additional details of analyses and results

Mixed models were fitted in which a combination of fixed and random factors were included. The fixed factors were: group (ASD relatives versus TD), age (children versus adults) and Group x Age. The random factor was 'family ID'. This factor specified to which family each individual belongs. This factor was added to the model by a random statement in which we indicated that participants were nested within families (according to their family ID). As such, a multilevel model with two levels was defined, with level-1 reflecting the variance within families and level-2 dealing with the variance between families.

Prior to analyses, appropriate transformations (square root or logarithm base 10) were applied if necessary to obtain normally distributed variables. Yet, descriptive characteristics in the tables (mean and SD) were based on the raw, non-transformed variables. For RT data, only the correct trials were used and within-subject outliers (> 2.5 SD of the participant's own mean) were excluded. Analyses were performed with and without exclusion of group outliers (> 2.5 SD of the group mean). Since both analyses yielded essentially the same results, only analyses including group outliers are reported, except for two variables that only showed a normal distribution after outlier exclusion (i.e., for the full sample: the switch cost RT and the perseverative errors of the WCST-WCTS). When the normality assumption remained violated after transformation or when excluding outliers, a non-parametric Mann-Whitney *U* test was applied, as indicated in the Tables. For all analyses, a significance level of 0.05 (two-sided) was adopted. To control for multiple comparisons, a False Discovery Rate (FDR) correction was applied (Benjamini & Hochberg, 1995). All analyses were performed with SAS 9.4 or SAS Enterprise Guide 7.1.

The effect of gender and the group by gender interaction were also investigated, but only if these effects were significant in the previous ASD versus TD comparisons (i.e., the switch cost RT of the Switch task and the fragmentation score of the Rey-Osterrieth Complex Figure task) (Van Eylen et al., 2015a, 2015b). However, for the current samples these effects were not significant and were therefore not retained in the model, nor reported.

For several tasks, we also examined the main effect of the within-subject factor(s) (i.e. for the Uses of Objects task, the Spatial Working Memory task, the Fragmented Object Outlines task and the Visual Search task) and the interaction with group. We therefore added an additional random statement to the model. In this statement we specified that observations were nested within participants and that participants were nested within families. By doing so, a three-level model was specified, with level-1 reflecting the variance in the observations within a participant, level-2 dealing with the variance between participants within families, and level-3 being the level of the variance between families.

For the full sample we also examined the three-way interaction with Group x Age. Although we found main effects for several within-subject factors (as mentioned in the tables), the interactions (with age and group by age) were not significant and thus not retained in the model, nor reported.

Cohen's *d* effect sizes for the effect of group were calculated for all main EF and local-global processing measures. Since we wanted to compare these values for the full ASD sample, the multiplex ASD sample and the ASD probands (Van Eylen et al., 2015a, 2015b), they were calculated based on the following models: 1) for the full sample of ASD relatives versus TD individuals we included the effect of group and the effect of age (i.e., children versus adults), to account for differences between children and adults. 2) for the comparison between the multiplex ASD relatives and TD controls, and the ASD versus TD comparison, we only included the effect of group, since these samples contained either children or adults, respectively. Then Cohen's *d* was calculated for each of these comparisons by dividing the estimated group difference based on that model by the pooled within-group standard deviation. For the ASD versus TD comparison, this standard deviation equals $\surd[(\sigma^2_{ASD} + \sigma^2_{TD})/2]$, while for the comparison between the ASD relatives (full and multiplex) and the TD controls this corresponds to the square root of the sum of the variance between families and the variance within families (being the variance between the participants nested within a family) (Hedges, 2009). For non-parametrically tested measures, the estimated group difference was calculated as the difference between the group means and the standard deviation was calculated as follows: $\surd[(\sigma^2_{ASD\ relatives} + \sigma^2_{TD})/2]$. An effect size ranging from 0.2 to 0.3 is considered small, values around 0.5 are medium and values of 0.8 or above are considered large effects (Cohen, 1988).

Furthermore, we investigated whether the group differences on the EF tasks remained significant after statistically controlling for possible EF confounds (by including them as a covariate in the analyses). In the current study, group differences were found on two correlated EF measures, namely the perseverative errors of the WCST-WCTS and the percentage of No-Go errors. This could suggest that one of the EF impairments could underlie the reduced performance on the other EF task and thus function as a confounding factor. However, when including the percentage of No-Go errors as a covariate, we found that ASD relatives still showed significantly more perseverative errors on the WCST-WCTS compared to the TD group (for the full sample: $F(1,95.9) = 5.23$, $p = 0.024$; for the multiplex sample: $F(1,52.3) = 5.97$, $p = 0.018$). For the Uses of Objects task we also found group differences. However, the main measure of this task did not correlate with any other EF task, indicating that none of the other EF impairments are potential confounds that should be controlled for.

The results of the measures that were not the focus of this study are presented in Appendix D. Table D1 shows the results of the main EF and local-global processing measures, and Table D2 displays the values for the additional EF and control measures. The additional EF measures of the Uses of Objects task suggest that the fewer correct responses on the Uses of Objects tasks for the ASD relatives were not due to a difference in the number of total responses. However, the full sample of ASD relatives displayed a higher percentage of redundant responses and the multiplex sample showed a higher percentage of incorrect answers. Nevertheless, these differences did not survive the false discovery rate correction. For all other measures, no group differences were observed between ASD relatives and TD controls as expected, since ASD probands also performed similar to TD controls.

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Appendix C

Table C1

Descriptive statistics (mean and standard deviations) comparing children and adults on all main EF and L-G measures for the full sample.

Cognitive measures	Children		Adults	
	Mean	*SD*	Mean	*SD*
EF tasks:				
Inhibition:				
Go/No-Go task:				
% No-Go errors	19.16	13.42	8.70	7.32
Flanker task:				
Inhibition cost RT	47.43	27.67	48.38	25.23
Inhibition cost % errors	2.97	3.76	1.47	2.01
Cognitive flexibility:				
WCST-WCTS:				
Switch cost RT	462.55	278.85	522.61	342.98
Perseverative errors	0.81	0.88	0.60	1.32
Switch task:				
Switch cost RT	337.46	113.49	338.27	101.18
Switch cost % errors	1.14	3.07	0.54	1.90
Generativity:				
Uses of Objects task:				
Correct responses	8.23	3.49	12.00	3.58
Design Fluency test:				
Correct responses	8.38	2.77	10.79	3.21
Spatial working memory:				
Spatial Working Memory test:				
Total errors	10.10	6.10	6.98	5.43
Spatial Span test:				
Correct trials	16.16	3.32	17.10	2.84
Planning:				
Tower test:				
Move accuracy ratio	1.85	0.47	1.65	0.42
EF questionnaires:				
BRIEF:				
Inhibition	13.49	3.13	10.79	2.24
Shifting	10.61	2.64	8.69	2.36
Working memory	15.20	4.15	11.38	2.69
Planning	18.90	4.88	14.25	3.40
DFlex:				
Cognitive rigidity	25.12	10.30	31.45	10.32
L-G tasks:				
Processing style:				
ROCF:				

Fragmentation score	3.97	2.65	1.68	2.22
Global processing abilities:				
Coherent Motion task:				
Coherent motion threshold	24.66	12.72	16.82	6.21
Fragmented Object Outlines task:				
Correct identification frame	4.84	1.10	4.30	0.77
Correct identification latency	4344.55	1103.76	3809.96	754.88
Local processing abilities:				
Visual Search task:				
Target detection latency	1981.86	457.41	1656.48	263.07
Similarity cost	304.84	299.23	416.41	230.12
L-G questionnaire:				
DFlex:				
Attention to Detail	23.24	9.37	26.31	9.80

EF: Executive Functioning; L-G: Local-Global processing; RT: reaction time; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task switching; BRIEF: Behavior Rating Inventory of Executive Function; DFlex: Detail and Flexibility questionnaire; ROCF: Rey-Osterrieth Complex Figure

Table C2

Descriptive statistics for all main EF and L-G measures comparing ASD relatives with TD individuals, separately for children (ASD siblings) and adults (ASD parents) for the full sample.

Cognitive measures	Child		Adult	
	ASD siblings	TD	ASD parents	TD
	Mean (*SD*)	Mean (*SD*)	Mean (*SD)*	Mean (*SD)*
EF tasks:				
Inhibition:				
Go/No-Go task:				
% No-Go errors	21.79 (13.60)	16.96 (13.03)	9.30 (7.44)	7.90 (7.14)
Flanker task:				
Inhibition cost RT	47.39 (29.06)	47.46 (26.79)	46.97 (23.18)	48.04 (23.49)
Inhibition cost % errors	3.43 (4.04)	2.58 (3.52)	1.54 (2.21)	1.38 (1.71)
Cognitive flexibility:				
WCST-WCTS:				
Switch cost RT	458.97 (222.37)	465.33 (318.61)	539.51 (325.12)	477.42 (360.40)
Perseverative errors	1.08 (1.18)	0.59 (0.43)	0.74 (1.66)	0.31 (0.37)
Switch task:				
Switch cost RT	328.84 (118.10)	344.65 (110.43)	339.51 (110.45)	336.59 (88.11)
Switch cost % errors	0.95 (2.69)	1.29 (3.38)	0.64 (1.91)	0.40 (1.89)
Generativity:				
Uses of Objects task:				
Correct responses	7.40 (2.96)	8.92 (3.78)	11.19 (3.57)	13.08 (3.33)
Design Fluency test :				

Correct responses	8.54 (2.95)	8.24 (2.63)	10.71 (3.21)	10.91 (3.24)
Spatial working memory:				
Spatial Working Memory test:				
Total errors	9.92 (5.47)	10.25 (6.63)	6.81 (4.89)	7.20 (6.12)
Spatial Span test:				
Correct trials	16.31 (3.88)	16.02 (2.82)	16.82 (2.90)	17.47 (2.74)
Planning:				
Tower test:				
Move accuracy ratio	1.96 (0.52)	1.75 (0.42)	1.66 (0.43)	1.63 (0.41)
EF questionnaires:				
BRIEF:				
Inhibition	13.52 (3.35)	13.48 (2.99)	10.96 (2.42)	10.55 (1.96)
Shifting	10.55 (2.71)	10.65 (2.63)	8.84 (2.62)	8.50 (1.98)
Working memory	15.84 (4.31)	14.70 (4.01)	11.71 (2.87)	10.95 (2.38)
Planning	20.42 (5.41)	17.73 (4.13)	14.48 (3.85)	13.95 (2.69)
DFlex:				
Cognitive rigidity	27.81 (11.31)	23.00 (9.05)	33.64 (10.75)	28.35 (8.92)
L-G tasks:				
Processing style:				
ROCF:				
Fragmentation score	3.91 (2.59)	4.02 (2.73)	1.71 (2.35)	1.66 (2.06)
Global processing abilities:				
Coherent Motion task:				
Coherent motion threshold	24.69 (14.13)	24.63 (11.60)	16.11 (6.33)	17.78 (5.98)
Fragmented Object Outlines task:				
Correct identification frame	4.77 (1.01)	4.90 (1.18)	4.29 (0.83)	4.32 (0.68)
Correct identification latency	4274.57 (1002.76)	4402.87 (1190.29)	3790.60 (813.13)	3836.00 (674.74)
Local processing abilities:				
Visual Search task:				
Target detection latency	1970.37 (487.93)	1991.16 (436.93)	1679.34 (293.70)	1625.86 (214.14)
Similarity cost	288.09 (272.74)	318.80 (322.26)	421.80 (224.78)	409.04 (239.04)
L-G questionnaire:				
DFlex:				
Attention to Detail	27.12 (9.57)	20.18 (8.11)	28.41 (9.98)	23.33 (8.84)

ASD: Autism Spectrum Disorder; TD: Typically Developing; EF: Executive Functioning; L-G: Local-Global processing; RT: Reaction Time; WCST-WCTS: Wisconsin Card Sorting Task With Controlled Task Switching; BRIEF: Behavior Rating Inventory of Executive Function; DFlex: Detail and Flexibility questionnaire; ROCF: Rey-Osterrieth Complex Figure

Appendix D

Table D1

Performance of ASD relatives compared to TD individuals on the main EF and L-G measures for which no group differences were found between the ASD proband and the TD group. The effect of group (ASD relatives vs. TD individuals), age (children vs. adults), and the group by age interaction are reported for the full sample. For the multiplex sample the effect of group is shown.

Cognitive measures	ASD relatives		TD		Effect of group		Effect of age		Group x Age effect	
	Mean	*SD*	Mean	*SD*	Test-statistics	*p*-value	*F*-value	*p*-value	*F*-value	*p*-value
Full sample										
EF measures:										
Inhibition:										
Flanker task:										
Inhibition cost RT	47.10	25.01	47.80	24.77	*F* = 0.13	0.72	0.53	0.47	0.01	0.99
Inhibition cost % errors	2.12	3.01	1.88	2.68	*U* = 10492	0.63	[a]	[a]	[a]	[a]
Generativity:										
Design Fluency test:										
Correct responses	10.04	3.28	9.78	3.27	*F* = 0.01	0.91	30.56	**< 0.001**	0.34	0.56
Spatial working memory:										
Spatial Span test:										
Correct trials	16.66	3.23	16.86	2.85	*F* = 0.31	0.58	6.60	**0.01**	0.83	0.36
Planning:										
Tower test:										
Move accuracy ratio	1.75	0.47	1.68	0.41	*F* = 3.58	0.06	11.64	**< 0.001**	1.64	0.20
L-G measures:										
Global processing abilities:										
Fragmented Object Outlines task:										
Correct identification frame [b]	4.44	0.91	4.56	0.96	*F* = 0.39	0.53	12.19	**< 0.001**	0.06	0.81
Correct identification latency [b]	3940.50	900.18	4074.08	963.30	*F* = 0.49	0.49	11.75	**< 0.001**	0.03	0.85

Local processing abilities:										
Visual Search task:										
Target detection latency [c]	1770.12	387.55	1782.42	373.78	*F* = 0.17	0.68	45.96	**< 0.001**	0.41	0.53
Similarity cost	380.39	247.34	370.76	279.48	*F* = 0.05	0.82	8.97	**0.003**	0.34	0.56
Multiplex sample										
EF measures:										
Inhibition:										
Flanker task:										
Inhibition cost RT	52.08	28.73	47.43	23.76	*F* = 0.23	0.63				
Inhibition cost % errors	1.40	1.90	1.38	1.71	*F* = 0.00	0.99				
Generativity:										
Design Fluency test:										
Correct responses	10.30	3.28	10.91	3.24	*F* = 0.82	0.37				
Spatial working memory:										
Spatial Span test:										
Correct trials	16.54	2.75	17.47	2.74	*F* = 2.60	0.11				
Planning:										
Tower test:										
Move accuracy ratio	1.58	0.38	1.63	0.41	*F* = 0.30	0.58				
L-G measures:										
Global processing abilities:										
Fragmented Object Outlines task:										
Correct identification frame [d]	4.42	0.94	4.32	0.68	*F* = 0.08	0.78				
Correct identification latency [d]	3918.87	922.94	3836.00	674.74	*F* = 0.03	0.87				
Local processing abilities:										
Visual Search task:										
Target detection latency [c]	1737.85	348.69	1625.86	214.14	*F* = 3.16	0.08				
Similarity cost	400.05	219.56	409.04	239.04	*F* = 0.03	0.87				

ASD: Autism Spectrum Disorder; TD: Typically Developing; EF: Executive Functioning; L-G: Local-Global processing; RT: Reaction Time

Values in bold indicate significant differences that survived False Discovery Rate correction.

[a] The effect of ASD relatives vs. TD was tested non-parametrically, so without including age and the interaction with age in the model.

[b] Repeated-measures mixed model with additional effects of within-subject factors: Type, Symmetry, Homogeneity

[c] Repeated-measures mixed model with additional effects of within-subject factors: Similarity and 'number of distractors'

[d] Repeated-measures mixed model with additional effects of within-subject factors: Type, Homogeneity

Table D2

Performance of the ASD relatives and the TD individuals on the additional EF and control measures, not reported in Table 4. The effect of group (ASD relatives vs. TD individuals) is reported for the full and the multiplex sample.

Additional EF and control measures	ASD relatives		TD			
	Mean	*SD*	Mean	*SD*	Test-statistics	*p*
Full sample						
Flanker task:						
RT compatible trials	441.41	67.90	451.89	58.35	*F* = 1.93	0.17
Uses of Objects task:						
Number of responses	41.26	15.04	42.51	15.83	*F* = 0.40	0.53
% incorrect responses	34.58	14.31	31.25	15.98	*F* = 2.11	0.15
% repetitions	5.76	5.37	5.50	5.04	*F* = 0.10	0.75
% redundant responses[a]	13.24	8.14	10.69	6.97	*U* = 9684	0.02
Tower test:						
Time per step (sec)	3.30	1.43	3.52	1.78	*F* = 1.15	0.28
First step latency (sec)	5.09	2.55	4.88	2.39	*F* = 0.25	0.62
Multiplex sample						
Flanker task:						
RT compatible trials	450.33	61.93	434.67	53.71	*F* = 1.90	0.17
Uses of Objects task:						
Number of responses	43.03	12.15	46.14	14.25	*F* = 1.15	0.29
% incorrect responses	33.68	13.62	27.73	12.99	*F* = 4.28	0.04
% repetitions[a]	5.31	4.11	5.23	4.36	*U* = 1811	0.79
% redundant responses	12.15	6.59	10.31	6.84	*F* = 1.70	0.19
Tower test:						
Time per step (sec)	3.25	1.23	3.50	1.56	*F* = 0.60	0.44
First step latency (sec)	5.91	2.77	5.69	2.51	*F* = 0.02	0.89

[a] A Mann-Whitney *U* test was performed

None of the group contrasts survived FDR correction

ASD: Autism Spectrum Disorder; TD: Typically Developing; EF: Executive Functioning; RT: Reaction Time