The Neuroanatomy of Pictorial Reasoning in Autism

by

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Abstract

Individuals with autism present with a constellation of social, behavioral, and cognitive symptoms. A striking characteristic is the contrast between their language and visual processing abilities. The work in this thesis combines behavioral, functional MRI, and diffusion tensor imaging methods to examine the neurobiological basis of the discrepancy between linguistic and visuospatial skills in autistic cognition.

A pictorial reasoning task, designed to manipulate the degree to which language vs. visuospatial abilities may be differentially engaged in solving picture puzzles, was administered under three conditions: visuospatial, semantic and a hybrid visuospatial-cum-semantic condition. Whereas participants with Asperger's syndrome and typically developing controls (CTRL) were found to exhibit similar performance profiles, high-functioning individuals with autism (HFA) differed from these two groups: they were least efficient on the semantic condition and appeared to benefit from and favor the use of visuospatial mediation in problem solving. Results from functional MRI revealed a pattern of decreased activation in fronto-temporal language areas, and an increased reliance on posterior brain regions in the parietal and ventral temporal lobes in HFA, supporting the earlier behavioral findings. Specifically, the inferior frontal gyrus appeared to play an important role in verbal mediation and semantic integration in CTRL, whereas HFA relied more extensively on inferior and ventral regions of the temporal lobe, in keeping with a cognitive preference for visual strategies. An examination of white matter integrity yielded a similar finding in the relationship between structural neuroanatomy and cognitive profile, such that connectivity patterns were related to the semantic mediation difficulties and visual processing preference in the HFA group: tracts relevant for semantic processing in CTRL were disrupted in HFA along the superior longitudinal fasciculus and in the frontal lobe, whereas parietal and inferior temporal white matter supporting visuospatial processing were intact in HFA

The results suggest that performance in high functioning autism may be related to deficits in frontal cortex connectivity, in favor of visualization strategies in higher-level cognition. The findings appear to support the use of visuospatial vs. linguistic tasks to differentiate between potential subtypes on the autism spectrum.

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Chapter 1: Thesis Overview

1.1. Introduction

Children with autism struggle with social, communicative, and behavioral abilities, and consequently fail to thrive in a society that extensively relies on these skills. Difficulties in characterizing the autistic cognitive profile stem from the wide heterogeneity of the disorder, and from the absence of a neurobiological explanation for both peaks and valleys of abilities. Of particular interest in this thesis is the neurobiological origin of the difference between often markedly impaired linguistic abilities and strong visuospatial skills. Interestingly however, semantic access via pictures has been argued to be intact in autism, and many remediation programs rely on pictorial aids. It is therefore necessary to examine the cognitive profile of autism spectrum disorders (ASD) in a well-defined population, using an experimental task that manipulates visuospatial vs. linguistic demands. In addition, relating performance on such a task with functional and anatomical processing networks in the brain is essential to developing behavioral or pharmacological interventions that may address difficulties without adversely affecting strengths.

The work presented in this thesis combined a novel task design with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to build upon our understanding of the dichotomy between visuospatial and linguistic abilities in autism. Specifically, we designed a pictorial problem-solving task varying in the extent to which visuospatial and linguistic mediation strategies were available or necessary for successful solving, and introduced an experimental condition amenable to strategy preferences and cognitive styles. Using these methods, we aimed to examine cognitive biases and their neurobiological underpinnings in individuals with autism but without intellectual deficiency. This thesis provides insight into compensatory mechanisms in autism, by increased reliance on visualization strategies in light of lower efficiency in linguistic processing.

1.2. Thesis Layout

In chapter 2, we first discuss the current competing theories of autism, highlighting potential neural mechanisms suggested by proponents of the different models. We then discuss the differences in cognitive profiles observed along the spectrum, focusing on differences between high-functioning autism and Asperger syndrome. We also describe neuroanatomical findings in autism, both at the cellular and macroscopic levels, and address potential relationships between structure and behavioral symptoms. We argue that a global, connections-oriented approach may provide a necessary framework for understanding autistic cognition. We then describe the nature and development of visuospatial and linguistic reasoning skills in typical development, highlighting the underlying functional neuroanatomy, and describe how disorders of cognition may affect each ability independently. Finally, we discuss behavioral and neuroimaging findings of visuospatial and linguistic processes in autism, and conclude that children with autism appear to approach high-order cognitive tasks visuospatially, in possible relation to a local overconnectivity model with long-distance disturbance in fronto-parietal and fronto-temporal networks.

In chapter 3, we describe a behavioral study of children and adults with high-functioning autism (HFA), Asperger syndrome (ASP), and typically developing controls (CTRL), using our designed task. Despite no significant differences between groups in any condition, whereas ASP showed a similar cognitive profile to CTRL, HFA participants appeared to benefit from the availability of visuospatial mediation, and showed a cognitive preference for visuospatial strategies in reasoning.

In chapter 4, we extend these results with an experiment comparing HFA to CTRL using functional MRI and diffusion tractography. We observed that whereas CTRL relied on an extended fronto-temporal language network in reasoning, HFA showed decreased activation in frontal language regions, in favor of increased processing within posterior brain regions in parietal and ventral temporal areas. In fact the structural integrity of tracts connecting ventral temporal pictorial processing areas to frontal language processing regions was lower in HFA compared to the CTRL group.

In chapter 5, we compared the HFA and CTRL groups' white matter integrity (fractional anisotropy, FA) throughout the brain, and found increased FA in CTRL in long-distance tracts, but increased FA in HFA in radiate white matter, consistent with connectivity models of autism. We also correlated response times on the three pictorial reasoning conditions with FA, and found that higher-level visuospatial cognition appears to be supported by white matter within the parietal and ventral temporal lobes in autism, whereas CTRL showed more efficient use of fronto-temporal language pathways in semantic reasoning. Finally, a correlation of FA with age suggested an atypical white matter maturation trajectory in HFA, in the form of delayed growth during adolescence.

Chapter 6 combines our results in chapters 3 to 5, to discuss similarities and differences between autism and typical development. We argue that disrupted white matter maturation results in decreased connectivity between frontal and posterior brain areas in autism, thus explaining decreased use of language processing regions and increased reliance on ventral temporal and occipito-parietal networks in service of visualization strategies in autistic cognition.

Finally, chapter 7 summarizes our work and suggests future studies. This thesis emphasizes the usefulness in employing multiple methodologies in cognitive neuroscience in order to establish structure-function relationships in complex disorders such as autism. The series of experiments presented here contributes to our insight of the neurobiological bases for the dichotomy between visuospatial and linguistic abilities in high-functioning autism.

Chapter 2: Cognitive Profiles in Autistic Spectrum Disorders

2.1. Theories and Neuroanatomy of Autism

2.1.1 General Definition

When it was first observed independently by Leo Kanner (1944) and Hans Asperger (1944), autism was construed as a psychiatric disorder and patients were generally qualified as mentally retarded, whereas those on the higher end of the spectrum were likely not diagnosed and simply considered socially awkward. Better characterization of behavioral traits has led to filling this dichotomy with a set of phenotypes forming what is today known as Autistic Spectrum Disorders (ASD). Whereas the cardinal symptoms of autism are impaired social interactions and communication, delayed language, and restricted interests and stereotyped activities, both the severity and quality of these symptoms are variable (see for ex. Table 2.1 for typical differences between Asperger syndrome and autism, after Volkmar & Pauls, 2003).

Clinical characteristic	**Autism**	**Asperger syndrome**
Age of presentation	0-36 months	Usually > 36 months
Gender differences	Male predominance	Male predominance
Communication	poor	fair
Social ability	very poor	poor
stereotyped behavior and restricted interests	variable (mechanical focus)	severe (facts focus)
IQ range	severe MR to normal	mild MR to normal

Table 2.1. Typical presentation characteristics of autism and Asperger syndrome. MR: mental retardation.

Diagnosis, Epidemiology, and Prognosis:

Children typically come to attention when they fail to meet language development milestones. Diagnosis of autism is typically based on DSM-IV (or equivalent) criteria, using several screening, parent interview and interaction assessment tools. Standardized tools, such as the Diagnostic Interview-Revised (ADI-R, Lord et al., 1994), Autism Diagnosis Observation Schedule (ADOS, Lord et al., 2000), and Childhood Autism Rating Scale (CARS, Schopler et al., 1980) are considered gold standards for research purposes, but are not commonly used clinically as they are time-consuming.

The prevalence of ASD is currently accepted to be about 1 in 166, with a significant male predominance (4:1), particularly in Asperger Syndrome (9:1). Autism has a high heritability of 0.7, with an expected concordance of 70-90% in monozygotic twins vs. 10-25% in dizygotic twins. Findings of genetic abnormalities have recently burgeoned, consistent with the distribution of autistic characteristics along a spectrum and with a multigenic model whereby multiple risk alleles interact to cause disease susceptibility. Recently, cytogenetic work has shown that certain copy number variations (CNVs) on chromosome 16p, 15q, 22q, 2q, 5p or 17p may account for 6-7% of cases. These cytogenetic studies identify large amounts of DNA, such that CNVs may include a large number of candidate genes for further investigation. However more than 20 genes related to nervous system development have already been identified, and include neuroligins, SHANK3, MET, neurexin1, PTEN, CNTNAP2 and reelin. These hold great promise for constructing a genetic model that will account for phenotypic heterogeneity and offer intervention opportunities (for a full review, see Abrahams & Geshwind, 2008).

Prognosis for patients with ASD is correlated with age of diagnosis, age of starting intervention, language use by five years of age, as well as with the severity and number of symptoms. Intervention has been shown to be most effective when tailored to each child, yielding positive outcomes in social interaction, language skills, frustration, and aggression events (Eigsti & Shapiro, 2003).

2.1.2. Weak Central Coherence

One of the most influential theories of autism is that of Weak Central Coherence. Frith and Happe (1994) suggested that autistics suffered first and foremost of an inability to integrate parts of information into meaningful wholes. According to this model, ASD will have difficulties in tasks requiring a global view and meaning extraction using context cues, whereas they will perform well on localized processes. The WCC theory was recently revisited from a "core deficit in central processing" to a "secondary outcome" of a "possible superiority in local or detail-focused processing" (Happe and Frith, 2006). This shift in position was motivated by evidence for biased cognition instead of deficit, as coherence may be achieved under certain conditions, and by evidence for astute or enhanced low-level sensory perception, which may explain difficulties in interpolating occurrences into categories, as small deviations from prototypes are then construed as entirely new items or events.

Neurobiologically, the WCC theory supports a top-down cognitive deficit hypothesis. Possible neuronal explanations include deficient magnocellular pathways (Milne et al., 2002), right hemisphere impairments, dorsal visual pathway deficits (Pellicano et al., 2005), or the increasingly widely adopted reduced connectivity model (Just et al., 2004). In line with the latter, Brock et al. (2002) have proposed that reduced connectivity would result in deficits in synchronization between areas, necessary for extracting coherence from information. Similarly, Frith and Happe (Frith, 2003; Happe & Frith, 2006) have claimed that "failure of early neural pruning [could result in] lack of modulation by higher-level meaning".

2.1.3. Executive Function Deficits

Executive functions (EF) encompass goal-directed abilities such as planning, monitoring, inhibition, and set shifting, as well as working memory. The executive function model of autism states that behavioral symptoms in ASD are a consequence of impairments in frontal executive processes (Ozonoff et al., 1991). This deficit in cognitive control would then "cause individuals to perseverate in over-learned behaviors" (Solomon et al., 2008).

Deficits in executive functions have been found in autism and in family relatives (Hughes et al., 1997), but have lacked reproducibility, possibly because uneven ability profiles in autism interact with the wide range of EF tests (Russo et al., 2007). Among the tasks that revealed an impairment in ASD were the Wisconsin Card Sorting task, the Tower of Hanoi, and working memory tests (Joseph et al., 2005b; Kleinhans et al., 2005; Luna et al., 2007; Verte et al., 2006). The latter are, however, often complex and have yielded conflicting findings, some arguing for impaired memory span (Williams et al., 2005), while others suggested no impairments (Ozonoff et al., 2001), or a more subtle difficulty with maintaining and updating verbal rules (Joseph et al., 2005b). Conversely, no differences were found in autism in inhibitory control tasks such as the Stroop test (Eskes et al., 1990; Ozonoff et al., 1999), or go/no-go tasks, which however suggested possible difficulties with set shifting. It therefore appears that executive function deficits, if existent in autism, are process or task specific, with relatively intact inhibition, but possible problems with cognitive flexibility and disengagement, as well as with the maintenance of cognitive rules (Hill, 2004; Russo et al., 2007).

Anatomically, executive control relies on the frontal lobe (medial and prefrontal cortices) for maintenance and conflict monitoring, but also on the parietal lobe for set shifting (Solomon et al., 2008). Using fMRI to investigate the different aspects of EF, Schmitz et al. (2006) found increased activation in autism within the left inferior/orbitofrontal gyrus during go/no-go, within the left insula during inhibition, and within the parietal lobes during set-shifting tasks, colocalized with increased gray matter density in this group. Some researchers have argued that executive deficits may derive from difficulties when neuronal complexity is increased (Kleinhans et al., 2005; Silk et al., 2006).

The heterogeneity of EF abilities in ASD makes generalizable claims about executive dysfunction in autism difficult. EF deficits also do not explain social difficulties (Volkmar & Pauls, 2003), and therefore cannot be an exclusive theory of autism neurobiology.

2.1.4. Theories of Social Cognition

Theories of social cognition rely on three main categories of functions: interpersonal relatedness (awareness of others' affective points of view), joint attention, and imitation.

Theory of Mind:

The theory of mind (ToM) model of autism was proposed by Baron-Cohen in 1985, and poses that autism is characterized by a deficit in the frontal lobe ability to "read minds", or attribute beliefs and feelings to others based on external signs. This model carried great success in light of the failure of autistics in many variants of false belief tasks. An example (the "Sally-Ann" test) of such task is as follows: The participant is told a story whereby character A puts an object in a box in front of character B, character B leaves the room and character A moves the object to another location. When character B returns, the participants is asked where the character will look for the object. Individuals with autism will tend to answer the true location, based on their own knowledge, rather than the box, based on what the character is supposed to know. Whereas a variable proportion of ASD patients do succeed at simple false belief tasks, "no child with autism has yet been documented to demonstrate normal attribution of mental states at the appropriate age/mental age" (Happe and Frith, 1996). ToM, or "mentalizing" is also an important requirement for pretend play and imagination, which children with ASD rarely exhibit. While it explains many social deficits in autism, this theory does not account for non-social characteristics of ASD, such as repetitive behaviors or early language deficits (Williams et al., 2001).

Neurobiologically, the ToM network is believed to involve the anterior cingulate cortex, superior temporal sulcus, and temporal pole, bilaterally, and these regions have been shown to exhibit reduced activation in Asperger syndrome in a mentalizing task (Happe & Frith, 1996).

The Mirror Neuron System Hypothesis:

The Mirror Neuron System (MNS), which is typically activated during the observation and imitation of others' actions, has been suggested to serve the function of creating internal representations of the cognitive and emotional state of others. As such, the MNS would serve not only in understanding actions but would also play a role in empathy, theory of mind, and social cognition. The MNS was thus hypothesized as a deficient network in ASD (Williams et al., 2001; 2006; Minshew et al., 2007). Beyond the intuitive necessity of imitation in forming an understanding of the world and others, studies have identified deficits in motor imitation in autism (Hamilton, 2008). Whereas it may appear contradictory that an imitation deficit could result in such symptoms as echolalia or stereotyped behaviors, a disordered mirror system could conceivably yield both reduced and increased imitation behaviors.

The MNS is well characterized, based on macaque studies, which led to specific hypotheses of focal disturbances of the inferior parietal and inferior frontal regions, as well as the middle temporal gyrus in autism (Hamilton, 2008). In a brain morphometry study, cortical thinning was found in ASD in the inferior frontal gyrus, inferior parietal lobe, and superior temporal regions (Hadjikhani et al., 2006), and was correlated with a measure of symptom severity (ADI-R social+communication score). Other functional MRI studies have identified differences during motor imitation between participants with autism and typically developing controls in the temporoparietal junction (Williams et al., 2006). While these findings implicate the network of areas encompassing the MNS in autism, MNS dysfunction or underdevelopment may be consecutive to a lack of interest in social interactions, or simply part of a more complex set of neurological manifestations of the disorder.

2.1.5. Enhanced Perceptual Processing and the Complexity Models

Individuals with autism typically present an uneven IQ profile, marked by significant peaks (most evident on the bloc design test), contrasting clear deficits (most evident on the comprehension test of Wechsler's IQ) (Happe & Frith, 1996). Special abilities in autism have also been long documented (calendar calculations, graphical reproductions, superior performance on the embedded figure test, perfect pitch, etc.). What were originally considered as abnormal "islets of abilities", or at best positive side-effects of more fundamental impairments, are now considered true skills, and much research has recently aimed at explaining their underlying neurobiology and cognitive mechanisms. Lately, interest was given to identifying potential inherent abilities (Mottron & Belleville, 1993), which were shown to be present in a larger population than so-called "savant autistics" (Plaisted et al., 1998). The enhanced perceptual functioning theory (EPF) states that low-level perception may be enhanced in autism and could serve as a basis for the development of certain superior abilities (Mottron et al., 2003; 2006). A local bias in processing would then subserve exquisite detection and reproduction of surface or structural properties of stimuli, as well as underlie the development of restricted and repetitive behaviors, while simultaneously result in the cognitive neglect of global features.

Anatomically, local patterns of brain overconnectivity could give rise to low-level superiority, whereas impaired long-range, fronto-temporal connections would affect the integration of information (Just et al., 2004, Koshino et al., 2005, Courchesne et al., 2005). Another, related theory states that the level of task complexity modulates neural processing in autism such that performance decreases with higher levels of complexity (as these imply increased cross-talk between distant cortical regions) (Minshew et al. 1997; 2007). While EPF and the complexity hypotheses share similarities and may be explained by underconnectivity patterns, the former better accounts for the positive symptoms found in autism.

It is worth noting that no theory so far has been able to fully reconcile social, behavioral, linguistic, and cognitive symptoms of autism.

2.1.6. Cognitive Profiles Along the Autistic Spectrum

Pervasive developmental disorders encompass autism, Asperger's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS), as well as Rett's syndrome and childhood disintegrative disorder. These disorders are segregated by the quality and severity of social, communicative, and behavioral symptoms, as well as genetic factors, epidemiology, comorbidity, and neuroanatomical and cognitive characteristics (see Volkmar et al., 2004, for a review). We are particularly interested here in higher-level processes in autism in order to gain understanding of ecologically valid cognitive profiles of the disorder. Differences in verbal and non-verbal IQ scores have consistently been associated with ASD (Koyama et al., 2007; Mayes & Calhoun, 2003), and the extent of these differences has been associated with different phenotypes along the spectrum (Tager-Flusberg & Joseph, 2003), such that certain children would present a superiority of visual perception over linguistic information processing (Kamio & Toichi, 2000) and may benefit from visually cued instruction (Quill, 1997). In order to examine higher-level visuospatial and linguistic processes, we will concentrate our efforts on ASD without intellectual deficiency, and specifically on high-functioning individuals with autism and Asperger's syndrome.

Both Asperger syndrome (ASP) and autism are pervasive developmental disorders, characterized by severe and chronic deficits in social interactions, difficulties in language pragmatics and non-verbal communication, as well as restrictive and repetitive behaviors and interests. Whereas diagnosis reliability depends on the tools and criteria used (Klin et al., 2005), there is general clinical agreement that individuals with autism exhibit specific communication impairments before age 3, in the form of delayed or lack of expressive language, whereas individuals with ASP appear to reach developmental language milestones normally (e.g. first word by 24 months, first two-word phrases by 36 months). While not a DSM-IV diagnosis, high-functioning autism (HFA) is accepted as a subset of autism in which no overall cognitive impairment is present (i.e. IQ >= 75). To the extent that epidemiological, psychological, genetic, motor, and neurobehavioral differences between HFA and ASP have been documented and support a distinction between these two groups (Rinehart et al., 2002; Tager-Flusberg & Joseph, 2003; Thede & Coolidge, 2007; Volkmar, 2004), we will focus primarily on cognitive disparities.

Part of the difficulty in comparing individuals with high-functioning autism and Asperger's syndrome stems from differences in the operationalization of the diagnoses, which has contributed to inconsistencies in research results (Volkmar et al., 2004). For example, a strict use of DSM-IV guidelines almost always results in a diagnosis of autism, as a "priority rule" states that a diagnosis of Asperger's syndrome can only be applied if autism has been excluded (i.e. when NO communication deficit signs are seen, which is extremely rare if behavioral and especially social criteria are met). This has, in practice, led to either the elimination of Asperger's syndrome as a diagnosis, or to a further subdivision of communication criteria in order to make a distinction. One such operationalization states that the absence of delayed language for one- and two-word phrases, echolalia, stereotyped language, and idiosyncratic language use, can be used to diagnose a patient as having Asperger's syndrome (for a full discussion, see Mottron, 2006), raising questions about any atypical early language (albeit not delayed) observed in Asperger's syndrome. Despite these diagnostic difficulties, certain differences between the two clinical subgroups have emerged: participants with autism, but not ASP, have shown difficulties with executive functions such as attention shifting or inhibition. Similarly, Rinehart et al. (2002) have suggested that despite intact performance on certain perceptual tasks in both Asperger's syndrome and autism, decreased global processing may follow only in autism, while staying relatively unaffected in ASP. Conversely, some studies have argued that motor difficulties, most often seen in atypical gait and clumsiness, may be more specific to Asperger's syndrome than to autism. Clearly however, some of the most striking differences between individuals on the autism spectrum are related to IQ (low- vs. high-functioning) and language vs. visuospatial skills. In fact, there is growing interest in examining the potential correspondence between genetic/biological findings and endophenotypes along the spectrum (Belmonte et al., 2004; Abrahams & Geshwind, 2008). For example, Alarcon et al. (2008) have examined a potential association between language development (age at first word) in autism and the Contactin Associated Protein-like 2 (CNTNAP2) gene.

ASP individuals appear to show superior theory of mind, and a more pedantic language than HFA patients, although these findings are contested (Kasari & Rotheram-Fuller, 2005; Rinehart et al., 2002; Seung, 2007; Verte et al., 2006; Volkmar et al., 2004). Age and full-scale IQ (FSIQ) matched ASP subjects scored higher than HFA participants on verbal IQ (VIQ), vocabulary, and comprehension subtests of the Wechsler Intelligence Scale (WISC) (Koyama et al., 2007; Ghaziuddin & Mountain-Kimchi, 2004). Conversely, the HFA group presents superior visuospatial processing / performance IQ (NVIQ) relative to ASP participants, as evidenced in the Block Design and Embedded Figures Tests of visuospatial function (Verte et al., 2006). Proposed models of autism have, therefore, suggested that these patterns may reflect autism vs. Asperger's syndrome phenotypes, in relation to the extent of an imbalance between local and global processing functions (Happe & Frith, 2006; Mottron et al., 2006). Whereas no single theory of autism accounts for all signs and symptoms observed within or along the spectrum, Belmonte et al. (2004) have proposed that low-level salience of information may overload higher cognitive functions, and therefore result in inefficient global processing (e.g. increased processing of local facial features with reduced recognition of a face as a whole), which is necessary for the development of social, communicative, and flexible behavior (e.g. using facial cues in context to infer communicative intent of a speaker). We will discuss our results in light of this view in section 6.4.

Little research has attempted to examine cognitive differences between high-functioning autism and Asperger's syndrome at the neurobiological level, but existing findings suggest that there are structural differences between autism and ASP, with enlarged gray matter volume in autism but not ASP compared to controls. Interestingly, performance IQ was found to correlate positively with white matter volume in ASP but with gray matter volume in HFA (Lotspeich et al., 2004).

2.1.7. Neuroanatomy of Autism

Neurodevelopmental disorders such as autism often result in systemic reorganization of the brain, such that a focus on localized abnormalities may be insufficient to reflect their cognitive manifestations. Instead, a focus on network alterations and modulation of functions is necessary (Muller, 2007). Although clinical signs of autism can typically be detected by 18 months, it is suspected that brain growth dynamics are abnormal in autism from the first year of life. Mechanistically, early overgrowth (by neuronal differentiation, synaptogenesis, myelination) followed by decreased growth rate may result in overconnectivity within primary areas, whereas tracts involving regions of slow maturation such as the frontal lobe will be underdeveloped (Courchesne et al., 2005, 2007). While both white and gray matter abnormalities have been found in autism (for reviews see Amaral et al., 2008; Brambilla et al., 2003; Eigsti & Shapiro, 2003; Tager-Flusberg, Lindgren & Mody, 2008), the heterogeneity of structural findings likely reflects differences along the spectrum, and emphasizes the widespread nature of the neurobiological bases of the disorder.

Microscopic/histological neuroanatomy in ASD:

Neuropathology findings have pointed to neuroinflammatory changes and morphological changes in both neurons and glia during development in autism (Picket & London, 2005). It has been suggested that astro- and microglia, which play an important role in neuroinflammatory and immune responses, may be overactivated and contribute to autistic neuropathology (Pardo et al., 2005; 2007; Vargas et al., 2005). Another, intriguing theory states that cortical minicolumns, most notably within prefrontal, temporal, and cingulate cortices, may present altered morphology: the human cortex is organized in layers (laminae I-VI), themselves composed of radial minicolumns containing around 80 neurons sharing similar receptive fields. Minicolumns in Layer III (containing predominantly association and commissural fibers) were suggested to be narrower and more numerous in autism than in controls, with smaller neuronal bodies and neuropil space (Crossman & Neary, 2000; Casanova et al., 2006). This would geometrically favor the proliferation of short-range fibers, thus causing functional specialization at the expense of transcortical connections (Casanova, 2007). Other pathology findings include a decrease in the number of cerebellar Purkinje cells (Bailey et al., 1998), densely packed small neurons within the forebrain (Bauman & Kemper, 2003), and alterations in grey matter density in ASD (Kwon et al., 2004). Whereas some studies have attempted to relate histology to brain morphometry (Hutsler et al., 2007), methodological issues have made sound conclusions elusive. Investigation of the neuropathology of autism, albeit embryonic, holds great promise in linking genetic expression to the structural and functional brain underpinnings of autism spectrum disorders.

Morphometry:

The first relationship between autism and brain structure dates to the observation that group mean head circumference was at the 60-70th percentile compared to controls, and that 15-20% had frank macrocephaly (Minshew & Williams; 2007). However, in light of contradicting reports, Hobbs and colleagues used retrospective ultrasound records to compare fetal brain size, and found no enlargement in autism before birth (Hobbs et al., 2007), suggesting post-natal onset. Nevertheless, imaging data suggests an increase in total brain volume among 2-4 year-old children with autism, specifically with enlargement of dorsolateral and medial frontal areas (Brambilla et al., 2003; Carper and Courchesne, 2005; Hardan et al., 2006a), which does not persist into adolescence (Courchesne et al., 2001). The most consistent findings were increased total brain, cerebellar, and basal ganglia volumes, and reduced corpus callosum and medial temporal lobe volumes (Eigsti & Shapiro, 2003; Palmen & Engeland, 2004). A rightward hemispheric asymmetry bias in autism was also shown using morphometric measures, most notably in higher order association areas and language association areas (De Fosse et al., 2004; Herbert et al., 2003, 2004, 2005). However, it is unclear if these results were due to right hemisphere enlargement or left hemisphere volume decrease. Among other relevant findings were volume increases in autistic adolescents in the right fusiform, right temporo-occipital, left frontal pole, and medial frontal regions (Haznedar et al., 2006; Hollander et al., 2005; Howard et al., 2000; Langen et al., 2007; Muller, 2007; Waiter et al., 2004). In addition, the middle and inferior temporal gyri were also larger in autism whereas the left inferior frontal gyrus showed decreased volume (Abell et al., 1999). Conversely, Rojas et al. (2005) found that the planum temporale volume was decreased in autistic children, and McAlonan et al. (2004) found fronto-striatal and temporal gray matter reductions in ASD.

Relationship between brain structure and behavior in autism:

Although informative, absolute differences in morphometry between autistic and typically developing subjects do not alone provide a neurobiological explanation for cognitive characteristics. It is therefore necessary to attempt to relate performance measures and/or activation patterns during specific tasks of interest to brain structure in order to infer a direct relationship. Recently, Schmitz et al. (2007) found that performance on a reaction time task was correlated with frontal lobe morphometry (volume and gray matter density) in autism. This suggests that some of the cognitive deficits in autism may be related to altered localized structural maturation dynamics in the brain. Using the superior temporal gyrus (STG) as a window into language function, Bigler et al. (2007) found a positive correlation between STG volume and receptive language (assessed with CELF-3) in controls, but not in ASD. Similarly, although focusing more on social cognition, correlations were found in ASD between amygdala volume and social competence (Dziobek et al., 2006), and between ADI-R scores and cortical thinning in the mirror neurons system (Hadjikhani et al., 2006). Interestingly, despite conflicting results, morphometric measures in ASP and autism seem to be related to performance and verbal IQ differences that define their respective clinical diagnoses (Kwon et al., 2004; Lotspeich et al., 2004). These results clearly point to an neuroanatomical basis for cognitive traits in ASD.

White matter abnormalities and the Connectivity Model of ASD:

In order to examine connectivity in ASD, increasing interest has been given to white matter changes in autism (Courchesne, 2004; Hendry et al., 2006; Petropoulos et al., 2006; Waiter et al., 2005). The earliest and most common white matter abnormality found in autism was a decrease in callosal volume, specifically in the body and posterior parts (Piven et al., 1997; Vidal et al., 2006; Waiter et al., 2005). Herbert et al. (2004) found that in 6-7 year-old children, white matter in an inner area comprising the corpus callosum and internal capsule did not show differences to controls, whereas the outer, radiate white matter contributed to the increased brain volume in autism. These results suggest an overgrowth of cortico-cortical short tracts, which tend to develop earlier that longer association fibers. Recent findings of gyral window (the space through which fibers enter and exit the cortex) reduction may provide a key mechanism for local overconnectivity in autism, as fibers would then be locally constrained (Casanova, 2007). Hardan et al. (2006b) attempted to directly investigate short vs. long cortical connections by relating them to cortical thickness in sulci vs. gyri, respectively. They found an increase in sulcal cortical thickness in compared to gyral thickness in children with autism, pointing to a relative increase in short transverse over longer radial tracts.

Further aiming at characterizing white matter connectivity in autism, recent studies have attempted to use new diffusion tensor imaging techniques. Water diffusion is highly anisotropic around white matter tracts, as diffusion along axons is much faster than perpendicular diffusion. This forms the basis for diffusion tensor imaging (DTI), which has been used to calculate fractional anisotropy (FA), a measure of directional cohesiveness of white matter tracts. FA thus provides information about white matter integrity in the brain (cf. Appendix B). DTI studies have shown that, compared with full-scale IQ-matched controls, children with autism presented with lower FA in the anterior cingulate, ventromedial and subgenual prefrontal areas, temporoparietal junction, and in the corpus callosum (Alexander et al., 2007; Barnea-Goraly et al., 2004). While promising, DTI results are still sparse in autism, and need to be related to function and behavior for interpretation.

2.2. Thinking and Reasoning

2.2.1. The Nature of Thought

Reasoning is the process of "drawing inferences (conclusions) from some initial information (premises)" (Holyoak & Morrison, 2005a). It typically requires the manipulation of mental representations of external stimuli or internal knowledge. These representations may be perceptual (i.e. transposed from sensory information, e.g. a sound or picture) or conceptual (i.e. meaningful/semantic). This thesis will focus on visuospatial and semantic reasoning based on pictorial input only. In this context, visuospatial reasoning is the manipulation of static (shape, size, etc.) and dynamic (rotation, direction, etc.) properties of pictures. Conversely semantic reasoning comprises the manipulation of concepts extracted from pictorial input.

The processes responsible for reasoning, regardless of the nature of the mental representations manipulated, rely on so-called “working” memory (WM) (Gilhooly et al., 1999;

Kyllonen & Christal, 1990; Morrison, 2005). Working memory was defined by Baddeley as "a system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks such as comprehension, learning, and reasoning" (Baddeley, 1986). The working memory model relies on "slave" systems, the phonological loop and visuospatial sketchpad, which are modality-specific, and can be construed as low-level temporary storage space for verbal or visual data, respectively. These are attended to and manipulated by the "central executive", via the "episodic buffer", where modality-specific information can be combined, and where temporary representations are formed.

While clearly sharing neuronal resources, there is significant debate over the intrinsic verbal or visuospatial nature of thought processes. As Gleitman and Papafragou wrote, "there are no ideologues ready to man the barricades at the absolute extremes of the debate", and research tends to establish the conditions in which reasoning and thought are linguistically or visuospatially biased (Gleitman & Papafragou, 2005; Holyoak & Morrison, 2005b).

2.2.2. Visuospatial and Linguistic Reasoning

Language and reasoning have been intuitively linked since Aristotle operationalized the rules of logical thought and defined syllogistic reasoning more than 2300 years ago in ancient Greece. In fact, "logic" is derived from the word *logos*, which means reason, thought, and... language.

The involvement of language in reasoning, while intuitive, is however unclear and subject to conflicting evidence. Young children initially process analogies based on object similarity (i.e nonlinguistically), but later develop to use relational (i.e conceptual) information

(Holyoak et al., 1984; Ratterman & Gentner, 1998). This ability has been shown to develop with domain knowledge (Goswami et al., 1990a; 1990b; 1991), working memory capacity (Waltz et al., 2000), inhibitory control, and the relational complexity of the task (Goswami et al., 1998; Richland et al., 2006). Cognitive styles and individual preferences may also influence the processing of reasoning tasks (Newstead et al., 2004; Reichle et al., 2000). As such, the internal representation of a problem to be solved can take different forms (verbal/declarative or pictorial/ diagrammatic) based on problem context, solver's knowledge expertise, and cognitive preferences or impairments (Bransford & Brown, 1999; Novick & Bassok, 2005). It is possible, for example, to access concepts from pictures without verbalization, in the presence of impaired language or despite deficits in semantic access via oral or written words (McCarthy & Warrington, 1988). In addition, much of the discrepancies in reasoning studies are due to the use of tasks that do not control for the linguistic content of stimuli (Houde, 2002).

Reasoning tasks using pictures (as opposed to written or spoken words) negates any intrinsic verbal bias in evaluating the role of language in reasoning. According to Schwartz et al. (1995), pictures can be interpreted and manipulated "as a referent", or as a representation of a referent. In other words, either visual features are manipulated (attention to details), or the picture is a mere window to the concept it illustrates, regardless of visual details. Visuospatial reasoning is therefore based on internal representations of visual input in the form of images similar to their external perceptual features, and mental manipulations on these images match externally observable 3-dimensional transformations and motor processes. This was first demonstrated by Shepard and Metzler (1971), who dramatically found that the time to perform mental rotation of an object was linearly related to the rotation angle. Conversely, semantic reasoning merely uses the visual stimuli as a way to "activate" conceptual representations, at the expense of visual accuracy (Brandimonte et al., 1992, 1993), and verbal reasoning involves discursive (i.e. internal speech) strategies, such that the picture labels are used to mediate reasoning. Thus, the intended use of pictures and the extent to which verbal coding/semantic knowledge may facilitates task performance determine the cognitive processes involved (Casasanto, 2003).

The extent to which verbal vs. visuospatial processes are engaged in higher cognition is therefore dependent both on stimulus bias and on the amenability of a given task to verbal mediation, as well as on task difficulty, resource allocation, and cognitive style. Pictorial reasoning tasks provide the opportunity to manipulate these factors to examine individual visuospatial and linguistic biases and abilities.

2.2.3. The Neurobiology of Reasoning

Studies of reasoning processes have established overlapping functional networks for linguistic and visuospatial reasoning (Luo et al., 2003). Visuospatial tasks are typically associated with a more right-lateralized activation pattern, while verbal tasks are more left lateralized, as shown by a study using an assessment task of line orientation or verbal analogies, respectively (Gur et al., 2000). Semantic reasoning with pictures, compared with perceptual matching, has been found to recruit the occipital, middle and inferior temporal, ventral temporal and inferior frontal areas (Ricci et al., 1999; Simons et al., 2003; Vandenberghe et al., 1996;). Conversely, visuospatial working memory appears to engage parietal, occipital, posterior temporal, as well as premotor and prefrontal regions (Brambilla et al., 2004; Ecker et al., 2008;

Fangmeier et al., 2006; Goel, 2007; Klingberg et al., 2002; Zacks et al., 2008). A diagram of the main processing centers involved in pictorial reasoning is shown in Figure 2.1.

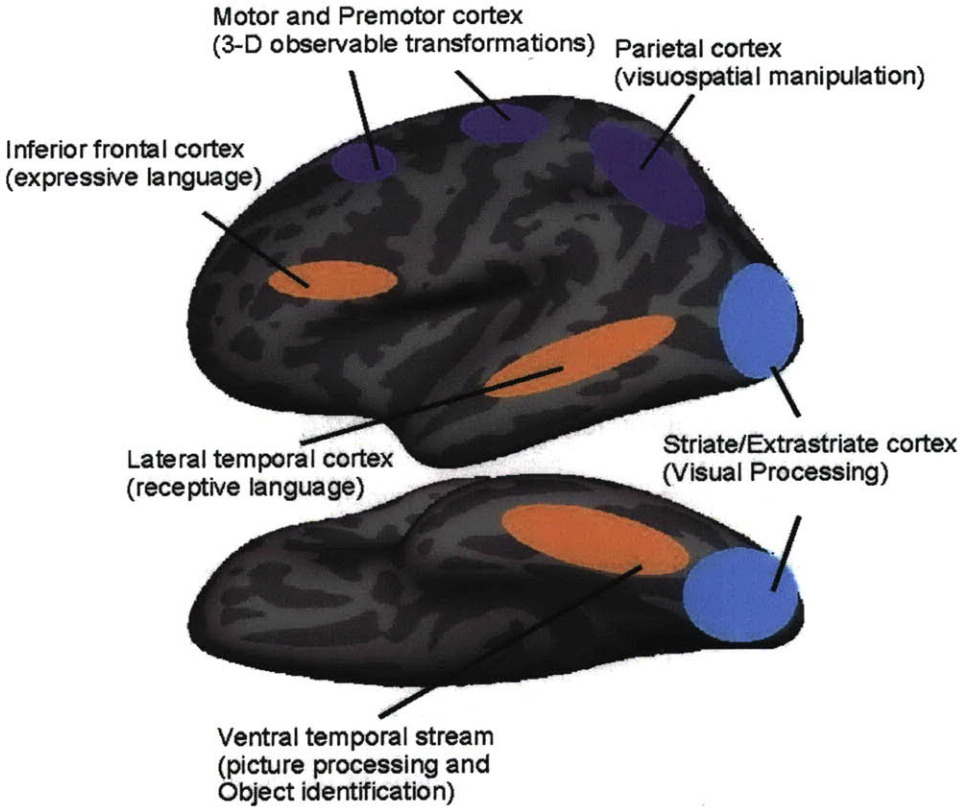


Figure 2.1. Pictorial reasoning areas involved in linguistic (orange) and visuospatial (purple) processing (striate/extrastriate cortex (blue) is not exclusively associated with either), shown on inflated lateral (top) and ventral (bottom) views of the left hemisphere. Dark grey regions represent sulci and light grey regions represent gyri.

These findings seem to point to distinct visuospatial and verbal processing networks, however, certain theories advocate that thought is intrinsically based on language and syntax ("mental proof" model, Goel et al., 1998) or on graphical representations ("mental model/imagery" model, Knauff et al., 2002). In fact, there is evidence for the use of language areas in certain visuospatial tasks, and for visuospatial areas involvement in linguistic tasks: Even within a visually presented nonverbal task such as Raven's matrices, Prabhakaran et al.

(1997) found that certain problems elicited regions involved in verbal working memory, possibly reflecting verbal strategies with increased problems difficulty. Conversely, Knauff et al. (2002) found that with auditory presentation of logical inferences, an occipitoparietal-frontal networked was recruited. The same group further dissected the involvement of visuospatial brain areas by using four types of verbal relations: visuospatial relations easy to envision both visually and spatially (above, below...), visual relations easy to envision visually but not spatially (cleaner...), spatial relations easy to envision spatially but not visually (further north...), and control relations difficult to envision visually and spatially (better...) (Knauff et al., 2003). They found that all conditions recruited left middle temporal gyrus, right superior parietal, and bilateral precuneus, as well as middle and inferior frontal areas, but that only visual relations elicited activation in the visual association cortex. This implies that the nature of the visuospatial relations used determines the extent of visuospatial processing in verbally presented tasks. In contrast, Goel et al. (1998) found, using verbally presented syllogisms, that spatial relations did not result in the recruitment of VS integration regions in the occipito-parietal cortex but were confined to the left hemisphere. This result could, however, be explained by the "imposed" linguistic mediation of an inherently verbal task presented using sentences.

Reasoning networks may therefore be influenced by task demands as well as cognitive preferences and strategies. In fact, Reichle et al. (2000) found that in a sentence-verification task, verbal and visuospatial mediation elicited different cortical regions, and that activation within each network was correlated with linguistic vs. visuospatial abilities. This strongly suggests a role for individual skill differences (either preferential or pathological) in the neurobiology of reasoning.

2.2.4. Disorders of Visuospatial and Linguistic Reasoning

Certain neurological disorders have been shown to selectively impair visuospatial or linguistic abilities. This was first evidenced in case studies of patients with selectively impaired verbal (Shallice & Warrington, 1970) or visual (De Renzi & Nichelli, 1975) working memory spans. Other examples of selective impairements include Klinefelter syndrome, showing impaired conceptual reasoning with relatively intact nonverbal skills (Fales et al., 2002), or semantic dementia, in which picture recognition is intact but naming is impaired (interestingly coincident with temporal pole atrophy) (Gold et al., 2005). Conversely, Turner syndrome is characterized by relatively intact verbal skills with deficits in visuospatial cognition (Holzapfel et al., 2006). Finally, frontal lobe injury impairs relational mapping in favor of similarity-based mapping, as do increased working memory load or stress (Holyoak & Morrison, 2005).

Of particular interest in the pathological dissociation of visuospatial and semantic skills is Williams Syndrome (WS), which has been often considered diametrically opposed to autism spectrum disorders in its clinical presentation. The cognitive profile of WS is characterized by impaired VS abilities (most markedly for spatial cognition, global visual organization, block design tasks and orientation transformations), whereas expressive language, face processing and picture naming are relatively unaffected (Bellugi et al., 2000; Meyer-Lindenberg et al. 2006; Vicari et al., 2004, 2006). Anatomically, patients with WS present functional abnormalities, reduced gray matter density, and decreased sulcal depth in visuospatial processing areas (parietal lobule, occipital cortex), whereas their face and emotion processing areas seem to show an increase in cortical volume, consistent with hypersociability in WS (Eckert et al., 2005; Grodofsky et al., 2006; Meyer-Lindenberg et al., 2004, 2006; Reiss et al., 2004). In addition, gross anatomy and cytoarchitectural studies also point to dorsal and occipital abnormalities (Galaburda & Bellugi, 2000). Recent DTI tractography studies showed a relative increase in number of fibers in the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, temporal portion of the cingulum and superior longitudinal fasciculus in WS (Grodofsky et al. 2006; Hoeft et al., 2007).

2.3. Reasoning and Language in Autism

2.3.1. Visuospatial and Linguistic Processing in Autism

Individuals on the autism spectrum have been found to vary in their linguistic vs. perceptual abilities, as well as in their relative use of linguistic vs. visuospatial information in cognitive tasks (Behrmann et al., 2006; Tager-Flusberg & Joseph, 2003).

Research studies point to impaired or delayed language abilities in autism from a very early age (Luyster et al., 2008), evident in a variety of domains, including lexical and semantic processing (Harris et al., 2006; Kamio et al., 2007; Perkins et al., 2006; Rapin & Dunn, 2003). Phenotypes range from entirely non-verbal children to accomplished verbal abilities in Asperger's syndrome, but are confounded by communication difficulties, as the "absence of communicative intent" may supplant language difficulties (Happe & Frith, 1996). For example, it is easy to conceive that a reduced social drive to talk may manifest as impaired language development. Indeed, social deficits and communication difficulties may be mutually reinforcing in autism. Individuals with autism typically appear to have difficulties taking advantage of semantic context cues and with language pragmatics, while semantic knowledge and comprehension (as well as phonological processing, evident from echolalic behavior) are relatively spared (Harris et al., 2006; Tager-Flusberg et al., 1985a,b; Toichi and Kamio, 2001). Many factors typically used in speech to enhance communication are often abnormal in autism, resulting in monotonous speech, with little or no eye contact, and lack of production or comprehension of body language cues (Tager-Flusberg et al., 2007). Also notable is a tendency for literal comprehension and production of language, with diminished understanding of figurative expressions, regardless of the clinical phenotype considered. This has led to the comparison between autistic individuals and patients with right hemisphere damage, who show similar difficulties with language comprehension, with a focus on literal meaning (Martin & McDonald, 2003). This observation has yielded a growing interest in right hemisphere function in autism (Herbert et al., 2002; McKelvey et al., 1995; Ozonoff & Miller, 1996). Studies have attempted to determine the reliability of semantic access in autism in different modalities. Kamio and Toichi (2000) have used a word-word and picture-word semantic priming paradigm with five conditions: categorical (car-bus), noncategorical (gasoline-engine), emotional (tears-sad), somatosensory (ice-cold) and unrelated (clock-soup). The authors found that whereas all participants showed a main effect of semantic relatedness, children with autism performed better than controls matched on chronological/mental age and verbal/performance IQ in picture-word than word-word conditions. This was interpreted as evidence for superior pictorial access to semantics in autism, consistent with a recent report suggesting that picture naming is also intact in autism (Walenski et al., 2008). The implication of these studies was that semantic information processing *per se* may not be impaired, but rather some of the language deficits observed in participants with autism could be modality-dependent, with a visual advantage in autism spectrum disorders (ASD). In a study of verbal recall using visually-presented pictures and words, it was found that individuals with autism demonstrated reduced use of inner speech strategies, as they were unaffected by articulatory suppression, and showed a reduced word-length effect, which may point to dysfunction of language production centers of the frontal lobe (Whitehouse et al., 2006, but see also Williams et al., 2008). In these studies, no significant main effects of group were found, suggesting that the reduced verbal coding of information occurred at no cost to overall performance, and reflects a strategic focus on structural coding of stimuli in autism. A preference for pictorial access to information is indeed the empirical basis for much intervention and remediation materials, and has been a focus of introspective writings of individuals with autism (Grandin, 2007).

Individuals with autism have been found to show normal to superior visuospatial abilities on specific tasks such as the Block Design subtest of non-verbal IQ, low-level visual discrimination, figure disembedding, or mental rotation (Caron et al., 2006; Dakin & Frith, 2005; de Jonge et al., 2007; Edgin & Pennington, 2005; Falter et al., 2007; Kuschner et al., 2007; Mottron et al., 2006). The pattern of performance on other tasks of higher cognition is however less clear, in part because of confounding influences of working memory and executive functions capacities, and in part because of the intrinsic linguistic load of most higher cognition tests, which may affect individuals along the spectrum to different extents. In fact, recent studies using Raven's Progressive Matrices have shown that, in a language-free measure of intelligence, participants with autism performed as well or better than control participants (Dawson et al., 2007). Controlling for the above potential confounds, cognitive difficulties in autism may therefore only arise when the use of verbal strategies is required: Joseph et al. (2005), using a self-ordered pointing task with pictures varying in the extent to which they were amenable to verbalization, showed that whereas the phonological loop and VS sketchpad of WM were intact in autism, verbalization was facilitative for controls and not in autism. The authors argued that deficits arise when self generation of verbal mediation strategies are involved, resulting in a failure to inhibit prepotent responses, which may point to impaired executive functions (Joseph et al., 2005a,b; Luna et al., 2007). However, these results could be explained by more specific problems, such as the inability to convert between visual and verbal modalities, or simply by a prepotent low-level perceptual bias, leading to visuospatial strategies, even when verbal mediation could provide task facilitation. In addition, participants with autism showed similar performances on non-verbal and verbal self-ordered pointing, suggesting they were tackling both tasks with a similar strategy. Working memory task performance was therefore consistent with a cognitive preference for visuospatial codes over linguistic mediation. Thus, when available, individuals with autism appear to rely on visual rather than linguistic codes and favor visuospatial strategies in reasoning (Koshino et al., 2005). As a possible etiology for these patterns in autistic cognition, it has been argued that auditory-visual integration may be impaired in autism; however recent evidence suggests that low-level sensory integration is intact, such that difficulties only arise at higher stages of processing (Van der Smagt et al., 2007; Magnee et al., 2008; Grossman et al., 2009).

As discussed in section 2.1.6, differences in visuospatial vs. linguistic skills may reflects phenotypes along the autism spectrum, and as such provide a useful framework in understanding autistic subtypes. The difference between individuals with autism, who show early language difficulties, and Asperger's syndrome, who do not, readily suggest, for example, differences in the lateralization of information processing. Indeed, autism appears to be associated with a compromised left hemisphere, whereas Asperger's syndrome show intact left hemisphere processing (Rinehart et al., 2002). Difficulties with language appear to persist later in life in autism: they are most evident in individuals with low-functioning autism in all aspects of language, although these observations are confounded by overall cognitive difficulties and lower IQ in this group. Linguistic/semantic ability differences between ASP and HFA appear to rely mostly on expressive language tasks, and semantic impairments are milder in ASP (difficulties with non-literal meaning) than in autism (more severe difficulties with abstract and deictic terms) (Boucher, 2003). Semantic access, as we mentioned, appears to be relatively intact in individuals with autism spectrum disorders (ASD), who show similar performance to CTRL in word fluency, free/cued recall, and semantic priming tasks; however the use of semantic context in free recall appears reduced. In fact, it appears that it is the spontaneous utilization of linguistic strategies, in the form of inner speech and verbal rules maintenance, that is most reliably compromised. In addition, verbal fluency (both phonemic and semantic) was found to be inferior in HFA compared with ASP or CTRL, and was found to be related to processing speed, which suggests an inefficiency in verbal mediation in HFA (Spek et al., 2009). Whereas cluster analyses of similarities and differences between HFA and ASP are numerous using standardized tests (Ghaziuddin & Mountain-Kimchi, 2004; Koyama et al., 2007; Macintosh & Dissanayake, 2004; Thede & Coolidge, 2006), few studies have directly examined the differences in visuospatial vs. linguistic processing between autistic subtypes using experimental paradigms. In light of the results above, we note that a decreased ability to verbally express lexical entries, in keeping with decreased verbal mediation and a preference for visuospatial strategies, may be more specific to autism than Asperger's syndrome.

2.3.2. Neurobiology of Autistic Cognition

From a behavioral neurology perspective, many signs and symptoms of autism point to the association cortex, while sparing primary sensory and motor regions (Minshew & Williams, 2006). If proven to be true, this would suggest that low-level perception may be relatively spared and that advanced processing or input combinations could result in autistic traits. With the advent of neuroimaging technologies, the task-specific functional integrity of brain areas is currently under active investigation (see Brambilla et al., 2004; Cody et al., 2002, for reviews).

Research on social deficits in autism, specifically on face processing, has led to investigating ventral stream functions (Cody et al., 2002). In studies of face processing, individuals with autism failed to recruit the fusiform face area (FFA), middle temporal gyri, and amygdala (Baron-Cohen et al., 1999; Critchley et al., 2000; Schultz et al., 2000). A post-mortem study also found morphological changes (decreased size and number) in fusiform gyrus neurons in autism (Van Kooten et al., 2008), and reduced FFA-amygdala functional connectivity has been recently reported (Kleinhans et al., 2008a). However, participants with autism showed increased activity during face processing in the inferior temporal and extrastriate areas, which are typically associated with visual object processing (Brambilla et al., 2004). This may imply a role for ventral stream regions in visual mediation of higher cognitive functions, at the expense of social cognition processes. In addition, whereas typical visuospatial processing involves the DLPFC, parietal cortex, middle temporal and frontal gyri, as well as premotor regions (Brambilla et al., 2004), Belmonte and Yurgelun-Todd (2003) found a ventral occipital and striate network in autism. Similarly, using the Embedded Figures Test for visual search, Ring et al. (1999) found that participants with autism did not recruit prefrontal working memory regions, but instead a ventral occipito-temporal network, suggesting a greater reliance on visuospatial strategies in higher cognition (Boddaert & Zilbovicius, 2002; Manjaly et al., 2007; Soulieres et al., submitted). In fact, even when stimuli with low-imageability were presented verbally, autistic subjects were found to rely on visualization to support comprehension (Kana et al., 2006a).

Conversely, the language system appears to be affected in autism. Studies have reported bilateral hypoperfusion of the temporal lobe in autism, possibly related to the language deficits or avoidance of verbal mediation observed behaviorally (Boddaert & Zilbovicius, 2002). In addition, the inferior frontal gyrus appears to show reduced activation difference between semantic and perceptual (letter case judgment) processing of words in autism compared to controls (Harris et al., 2006). In a sentence comprehension task, participants with autism showed again decreased activation within the left inferior frontal gyrus, but and increased activation in the left superior caudal temporal region (Just et al., 2004). These results suggest decreased use of frontal areas and possibly increased reliance on posterior regions of the brain in language processing.

Children with autism, thus, would approach reasoning tasks visuospatially, and therefore show increased activation in extrastriate, parietal, and ventral stream activation compared with controls (Manjaly et al., 2007). Control subjects, in contrast, would show more activation within the temporal cortex and inferior frontal area to mediate higher-level cognition. These patterns of activation are consistent with the model of local overconnectivity and long-distance underconnectivity in autism, which is based on decreased synchronization of activation between frontal and posterior brain regions in a variety of linguistic, visuospatial, and working memory tasks (Just et al., 2004; Courchesne et al., 2005; Kana et al., 2006a,b; Kennedy & Courchesne, 2008; Just et al., 2007; Silk et al., 2006).

The functional neuroanatomy of visuospatial and linguistic tasks in autism therefore supports a processing bias towards visuospatial mediation in reasoning, based on ventro-occipital and parietal regions, consistent with a model of local brain overconnectivity with long distance underconnectivity.

Chapter 3: Cognitive Differences in Pictorial Reasoning Between High-Functioning Autism and Asperger's Syndrome

3.1. Abstract

We investigated linguistic and visuospatial processing during pictorial reasoning in high-functioning autism (HFA), Asperger's syndrome (ASP), and age and IQ-matched typically developing participants (CTRL), using three conditions designed to differentially engage linguistic mediation or visuospatial processing (Visuospatial, V; Semantic, S; Visuospatial+Semantic, V+S). The three groups did not differ in accuracy, but showed different response time profiles. ASP and CTRL participants were fastest on V+S, amenable to both linguistic and nonlinguistic mediation, whereas HFA participants were equally fast on V and V+S, where visuospatial strategies were available, and slowest on S. HFA participants appeared to favor visuospatial over linguistic mediation. The results support the use of linguistic vs. visuospatial tasks for characterizing subtypes on the autism spectrum.

3.2. Introduction

Reasoning skills entail encoding, relating, and transforming premise stimuli to produce a logical output (Holyoak & Morrison, 2005). This processing framework is essential to making sense of one's experiences as well as interactions with other individuals. Research in the typical development of reasoning skills has shown a transition from perceptually-based thought processes to concept-oriented reasoning (Holyoak, Junn, & Billman, 1984; Ratterman & Gentner, 1998). This ability to transition from a perceptual- to a conceptual-based approach to reasoning relies on a number of factors, including increased domain knowledge, working memory capacity, and inhibitory control, as well as on the nature of instructions and the relational complexity of the task (Goswami, Leevers, Pressley, & Wheelwright, 1998; Richland, Morrison, & Holyoak, 2006; Waltz, Lau, Grewal, & Holyoak, 2000). Additionally, the presentation modality and nature of the stimuli also influence one's use of conceptual vs. perceptual processes. While verbally presented stimuli, such as oral or written words, are likely to be processed linguistically, by default, (Houde, 2002), pictures may be processed and manipulated "as a referent" (i.e. visually) or as a representation of a referent (i.e. semantically) (Schwartz, 1995). Furthermore, the intended use of pictures and the extent to which linguistic coding (i.e. use of labels or semantic knowledge) may facilitate task execution can also impact the cognitive processing of pictures (Casasanto, 2003).

To the extent that individuals on the autism spectrum have been found to vary in their linguistic vs. perceptual abilities (Behrmann, Thomas, & Humphreys, 2006; Tager-Flusberg & Joseph, 2003), we proposed to investigate visual perception and conceptual processing in high-functioning autism (HFA) vs. Asperger syndrome (ASP). We designed a reasoning task involving a variety of pictorial puzzles that differed in the extent to which they necessitated the use of language or visuospatial processes to solve them. If effective, such a task could provide insight into the relative contributions of language and visuospatial skills to phenotypic differences that may be related to specific subtypes across the spectrum. In the following, we define linguistic strategy as one that makes use of verbal (i.e. pertaining to receptive or productive speech), or semantic (i.e. conceptual) processes.

Research studies point to impaired or delayed language abilities in autism from a very early age (Luyster, Kadlec, Carter, & Tager-Flusberg, 2008), evident in a variety of domains, including lexical and semantic processing (Harris et al., 2006; Kamio, Robins, Kelley, Swainson, & Fein, 2007; Perkins, Dobbinson, Boucher, Bol, & Bloom, 2006; Rapin & Dunn, 2003). Individuals with autism typically appear to have difficulties taking advantage of semantic context cues and with language pragmatics, though semantic comprehension is relatively spared (Harris et al., 2006; Toichi & Kamio, 2001). Studies have attempted to determine the reliability of semantic access in autism using different modalities. Kamio and Toichi (2000) used a word-word and picture-word semantic priming paradigm with five conditions: categorical (car-bus), noncategorical (gasoline-engine), emotional (tears-sad), somatosensory (ice-cold) and unrelated (clock-soup). The authors found that whereas all participants showed a main effect of semantic relatedness, children with autism performed better in picture-word than word-word conditions while typically developing participants (matched on chronological/mental age and verbal/performance IQ) did not. This was taken as evidence for superior pictorial access to semantics in autism. The implication of this study was that semantic information processing *per se* may not be impaired, but rather some of the language deficits observed in participants with autism could be modality-dependent, with a visual advantage in autism spectrum disorders (ASD). Superior performance with pictorial materials has indeed been the empirical basis for much of the intervention in autism.

Individuals with autism have also been found to show normal to superior visuospatial abilities on tasks such as the Block Design subtest of the Weschler scales of Intelligence or low-level visual discrimination (Caron, Mottron, Berthiaume, & Dawson , 2006; Dakin & Frith, 2005; Edgin & Pennington, 2005; de Jonge et al., 2007; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006). The pattern of performance on other high-level tasks is, however, less clear in part because of confounding influences of working memory and executive functions capacities, and in part because of the intrinsic linguistic load of most higher level tests, which may affect individuals along the spectrum to varying extents. Recent studies using Raven's Progressive Matrices have shown that, in a language-independent measure of fluid reasoning, participants with autism and Asperger syndrome performed as well as or better than a normally developing comparison group (Dawson, Soulieres, Gernsbacher, & Mottron, 2007; Hayashi, Kato, Igarashi, & Kashima, 2007). Despite controlling for some of the above mentioned confounds, cognitive difficulties in autism were most evident when the use of verbal strategies was required (Joseph, Steele, Meyer, & Tager-Flusberg, 2005). It appears then that some individuals with autism may rely on visual rather than verbal codes and favor visuospatial strategies in reasoning (Koshino et al., 2005). In fact, differences in verbal and non-verbal IQ scores have been frequently reported in ASD (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Koyama, Tachimori, Osada, Takeda, & Kurita, 2007; Mayes & Calhoun, 2003), and the direction and magnitude of these differences may be associated with autism subtypes (Tager-Flusberg & Joseph, 2003). Thus, a systematic investigation of reasoning skills in the conceptual/semantic and visuospatial domains appears warranted for an improved understanding of the varying profiles in autistic cognition.

Both, Asperger syndrome (ASP) and autism are pervasive developmental disorders, characterized by severe and chronic limitations in social interactions, difficulties in language pragmatics and non-verbal communication, as well as restrictive and repetitive behaviors and interests. While diagnosis reliability depends on the tools and criteria used (Klin, Pauls, Schultz, & Volkmar, 2005) individuals with autism exhibit specific communication impairments before age 3, in the form of delayed or lack of expressive language, whereas individuals with ASP appear to develop language normally in these early years (DSM-IV). Although not a DSM-IV diagnosis, high-functioning autism (HFA) is viewed as a subtype of autism with no overall cognitive impairment (i.e. IQ >= 70). Studies have documented epidemiologic, psychological, genetic, motor, and neurobehavioral differences between HFA and ASP (Rinehart, Bradshaw, Brereton, & Tonge, 2002; Tager-Flusberg & Joseph, 2003; Thede & Coolidge, 2007; Volkmar, Lord, Bailey, Schultz, & Klin, 2004); however, we focus here on cognitive disparities, and, more specifically, on visuospatial and linguistic processing in these two groups.

Individuals with autism have been found to present with superior visuospatial processing abilities compared to typically-developing participants, as evidenced in the Block Design and Embedded Figures Tests; in contrast, age and full-scale IQ (FSIQ) matched ASP participants score higher than HFA participants on verbal IQ (VIQ), vocabulary, and comprehension subtests of the Wechsler Intelligence Scale (WISC) (Ghaziuddin & Mountain-Kimchi, 2004; Koyama et al., 2007). Conversely, performance IQ (NVIQ) may be lower in ASP than in HFA (Klin et al., 1995). Macintosh and Dissanayake (2004) warn against the potential circularity in interpretation when selecting dependent variables that are co-dependent on diagnostic criteria. For instance, group differences on tasks that measure language ability should not be surprising when the groups are formed based on language development criteria. For this reason, the HFA and ASP groups where matched on Full Scale IQ, and the task we used was designed to reveal potential differences in processing strategies (i.e., visuospatial vs. linguistic) in reasoning by incorporating a "hybrid" condition, amenable to the use of both strategies in solving the pictorial problem. Any differences between the groups in their performance on this condition relative to the linguistic and/or visuospatial conditions could help improve our understanding of potentially different cognitive subtypes within autism spectrum disorders.

In the present study we manipulated both stimulus type (pictures that are easy to label, or geometric forms that are more difficult to label) and processing strategy (visuospatial or semantic/conceptual manipulation). Task difficulty was equated by matching the number of dimensions and operations required across three fill-in-the-blank pictorial problem solving conditions: SEMANTIC, where reasoning necessitated access to the conceptual referents of picture stimuli in order to draw associative relationships between them; VISUOSPATIAL, where the stimuli presented were meaningless black and white geometric forms, and therefore less amenable to linguistic mediation, and where reasoning required visuospatial manipulations; and VISUOSPATIAL+SEMANTIC, a hybrid condition involving visuospatial manipulations of picture stimuli similar to those used in the SEMANTIC condition, but where linguistic (i.e. semantic) codes, while available, were not required for solving the puzzle (see examples in Fig. 1). Happé and Frith (2006) have emphasized the superiority of open-ended tasks in investigating processing biases in autism. The VISUOSPATIAL+SEMANTIC condition was therefore critical, as it allowed the use of both linguistic and visuospatial strategies by providing an open-ended problem-solving paradigm to investigate any processing biases in autistic cognition.

It was hypothesized that given the apparent differences in their linguistic versus visuospatial processing abilities, performance of the ASP, HFA, and the typically developing (CTRL) groups would differ as a function of the degree to which these processes may be involved in the three pictorial reasoning conditions: we predicted that HFA participants would perform superiorly to typically developing children and ASP participants on the VISUOSPATIAL condition, but would perform more poorly than both these groups on the SEMANTIC condition, reflecting their relative superiority in visuospatial skills but poorer language skills. Thus, in the V+S condition, we predicted that the HFA group would favor visuospatial mediation, whereas the ASP group would, as predicted by their lack of language delay in development, resemble the typically developing comparison participants, using both visuospatial and linguistic processes.

3.3. Materials and Methods

3.3.1 Participants

Participants consisted of three groups of adolescents and adults, matched in age and FSIQ (N = 21/group): high-functioning autism (HFA, 3 females, mean age = 18.95, std dev. = 5.45, range 12-29); Asperger syndrome (ASP; no females, mean age = 19.33, std dev. = 4.92, range 12-30); and a typically developing comparison group (CTRL, 4 females, mean age = 18.43, std dev. = 4.75, range 12-30). Participants had no history of gross neurological or psychological damage, and scored in the normal range on FSIQ (75-126), as measured by the Wechsler

Intelligence Scales (WISC-III or WAIS-III, Wechsler 1991, 1997). None of the groups differed significantly from each other on age ($p > 0.55$) and IQ (Verbal IQ, $p > 0.07$; Performance IQ, $p > 0.15$ and full-scale IQ, $p > 0.32$). All participants had normal hearing and normal or corrected-to-normal vision, with no evidence of color blindness. Individuals on the autism spectrum were identified on the basis of the ADI-R (Lord, Rutter & Le Couteur, 1994) and ADOS-G (Lord et al., 2000), and met DSM-IV criteria for autism or Asperger syndrome. Specifically, whereas both these groups scored above the ADI cut-off for autism, participants with Asperger syndrome were without significant history of early language delay (e.g. absence of one-word at 24 months or two-word phrases at 36 months), echolalia, pronoun reversal, or stereotypical language (no occurrence of out-of-context repetitive sentences). In contrast, individuals with HFA manifested delayed and/or atypical spoken language development based on the above criteria. Participants were also screened for comorbid neurodevelopmental conditions based on their medical record. In addition the first-degree relatives of participants in the comparison group were without neurological or major psychiatric disorders as well, based on a screening questionnaire. Participants were also administered Raven's Progressive Matrices (RPM, Raven, Raven, & Court, 1998). Wechsler IQ scores were unavailable for one ASP participant, and RPM scores were unavailable for three comparison participants and one HFA (Table 3.1).

3.3.2. Stimuli

The experimental paradigm consisted of a pictorial problem solving task. Participants were presented plates in the form of a matrix of items (individual items ©2009 Jupiter Images Corporation) related by visuospatial or semantic relationships. Subjects were instructed to select the most appropriate item from among three choices to fill a blank in the matrix, as fast and accurately as possible. The layout of the problem "plates" was a grid of 2x2 to 3x3 images with an empty cell, to be filled using one of 3 choices given below the grid. The experiment consisted of 3 conditions, VISUOSPATIAL, SEMANTIC, and VISUOSPATIAL + SEMANTIC, differing in the involvement of linguistic skills needed to solve the plates. In the nonlinguistic, VISUOSPATIAL condition, reasoning was based on visuospatial transformations of geometric patterns similar to those in the standard Test of Nonverbal Intelligence (Brown, 1997). In the SEMANTIC condition, clipart drawings readily identifiable and easy to label were used in problems where selection of the correct answer necessitated the ability to draw thematic or associative relationships between the presented items. In this condition, a successful strategy would require linguistic mediation, that is, extracting meaning from individual clipart pictures, recognizing semantic relationships between them, and inferring a logical solution consistent with these relationships. In the VISUOSPATIAL + SEMANTIC condition, pictorial stimuli, similar to those in the semantic case, were to be manipulated visuospatially, with similar reasoning patterns to the visuospatial condition. In this case, the semantic information carried by the pictures was not needed, but their labels were accessible for linguistic mediation, and potentially served a facilitative role. Example plates from each condition are shown in Figure 3.1.

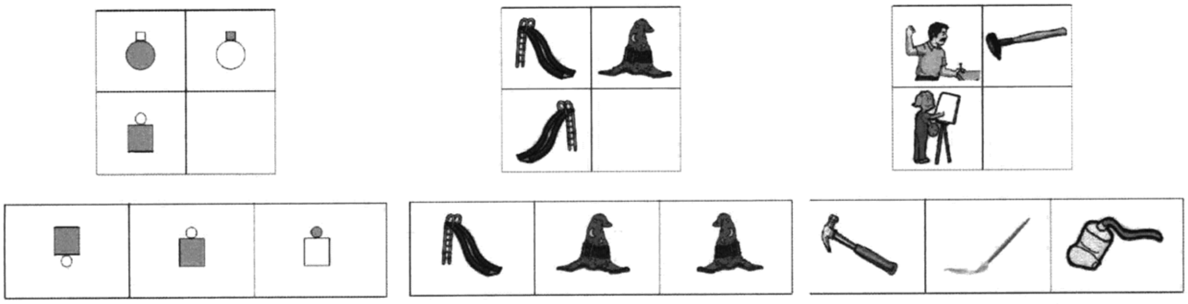


Figure 3.1. Examples of stimuli from the three pictorial reasoning conditions. left: VISUOSPATIAL, perceptual reasoning from nonlinguistic pictures; middle: VISUOSPATIAL+SEMANTIC, visuospatial reasoning using pictures with verbal labels; right: SEMANTIC, semantic reasoning from linguistic pictures

Plates were matched across the three conditions based on a framework inspired by Halford's theory of relational complexity (Halford, Wilson, & Phillips, 1998). According to this theory, the complexity of a relation depends on the number of arguments to be considered simultaneously (e.g. 2 arguments a and b in the relation "bigger-than (a,b)") as each argument provides a degree of freedom. In addition, arguments (dimensions to be considered) are used as instances of first order relations (transformations or relationships between arguments), which may be embedded in hierarchical structures (operations on relations). Cognitive complexity is therefore dependent on the number of elements (or arguments) to be processed in parallel for a given task, and on the number of structural links between these elements. This was implemented here in terms of three custom-made factors, based on relational databases of semantic taxonomy (Chaffin & Herrmann, 1984; Storey, 1993; Winston, Chaffin, & Herrmann, 1987) and visuospatial transformations (Brown, 1997; Tversky, 2005): 1) reasoning type or manipulation of interest (e.g. analogy, series completion, group formation, or addition/subtraction/intersection), 2) number of transformations or relationships (e.g. part-whole, sequential transformation, identity matching, spatial inclusion etc.), and 3) number of dimensions manipulated (e.g. shape, orientation, size, or semantic category (animals, foods, sports…). The first two factors were therefore representative of relational structure units, while the dimensions accounted for the number of elements to be considered. Conditions were equated in terms of structural units and elements required for each plate. This framework was thus operationalized in keeping with the relational complexity theory of reasoning, whereby task difficulty is gauged by the number of relations available and necessary for successful solving (Cho, Holyoak, & Cannon, 2007; Halford, 2005). Designing conditions that were thus matched for complexity was essential to avoid confounds in interpretation. The plate and paradigm were piloted on 20 adult comparison participants (not included in this study) to ensure difficulty matching across conditions.

3.3.3. Experimental Procedure

A total of 144 plates (3 conditions x 48 plates per condition) were presented in 6 self-paced consecutive runs on a PC desktop running the Presentation software (Neurobehavioral Systems, CA, USA, n.d.). Within each run, the plates were presented using a pseudo-randomized event-related paradigm, with equiprobable conditions (i.e. 8 plates/condition) and correct button assignments. Participants were instructed to respond as fast and accurately as possible, using pre-assigned keys on a keyboard. Each plate presentation lasted between 1 and 12s, as the plate disappeared upon subject response or timed out after 12 seconds. A fixation cross was shown between stimulus plates with a random ISI ranging from 1500 to 3500ms. The maximal duration of each run was 5 minutes, and short breaks were offered between runs for subject comfort.

3.3.4. Behavioral Measures and Analysis

Behavioral statistics on response times (RT) and accuracy (percent correct responses) measures were carried out in SPSS v.15.0 (SPSS Inc., IL, USA, n.d.). Response times were measured between the appearance of a problem plate and the button press ending that trial, and registered by the Presentation software. Incorrect responses and trial outliers were discarded from all analyses. Trial outliers were defined as any trial more than 2 standard deviations from the mean response time for that condition, and represented 5% of all trials in the comparison group, and 6% of all trials in both PDD groups. Repeated measures 3 x 3 ANOVAs were carried out for RT and accuracy separately, with condition as within-subject factor, group as between-subject factor, and using age as a covariate to control for developmental effects. Post-hoc t-tests were carried out appropriately with Bonferroni correction for multiple comparisons. Statistics were considered significant for $p < 0.05$.

In order to investigate potential differences in processing strategies, we conducted non-parametric correlation analyses (Spearman's rho) between accuracy scores on the VISUOSPATIAL+SEMANTIC condition and each group's performance on standardized tests of verbal ability (VIQ) and nonverbal ability (NVIQ), as well as general, language-independent fluid reasoning ability (RPM). The purpose was to delineate preferred strategies (visual or linguistic), if any, in the groups' performance on a dual-strategy condition (V+S).

3.4. Results

Participants in all three groups (HFA, ASP, CTRL) were able to perform the task, evident in their performance on the different conditions (Table 3.1).

		Age	FSIQ	NVIQ	VIQ	RPM	MEAN RT V	MEAN RT S	MEAN RT V+S	% CORRECT V	% CORRECT S	% CORRECT V+S
Control	**Mean**	18.43	103.7	100.6	106.4	108.36	4724.5	4800.1	4536.4	87.5	86.5	88.4
	Std Dev.	4.75	8.3	11.2	9.2	11.70	844.7	761.9	773.8	3.7	6.2	4.4
Asperger Syndrome	**Mean**	19.33	102.0	96.1	108.0	113.39	4930.5	5039.9	4569.8	85.7	84.5	85.8
	Std Dev.	4.92	10.4	12.7	10.3	10.22	865.1	904.1	776.4	9.6	6.5	9.1
High-functioning autism	**Mean**	18.95	100.4	101.2	99.6	113.86	4502.6	5088.8	4396.5	87.4	83.3	87.6
	Std Dev.	5.45	12.6	9.6	16.9	17.65	932.3	1084.7	884.4	9.2	10.9	7.5

Table 3.1. Group performance and standardized test scores. (FSIQ: Wechsler full-scale IQ; NVIQ: Wechsler nonverbal IQ; VIQ: Wechsler verbal IQ; RPM: Raven's Progressive Matrices; RT: response time, V: visuospatial condition; S: semantic condition; V+S: visuospatial+semantic condition)

Accuracy: Group (HFA, ASP, CTRL) x Condition (V, S, V+S) ANOVA with accuracy, using age as a covariate, did not yield any significant main effects or interactions.

Response times: Group (HFA, ASP, CTRL) x Condition (V, S, V+S) ANOVA with response times, using age as a covariate, showed a significant Group x Condition interaction ($F = 4.338$, $p < 0.005$). Post-hoc paired comparisons did not yield any significant differences between the groups on any condition, but revealed significant within-group contrasts: in the ASP group: V > V+S ($p < 0.0001$) and S > V+S ($p < 0.0001$); similarly, in the CTRL group V > V+S ($p < 0.035$) and a trend for S > V+S ($p < 0.057$); in contrast, for the HFA group S > V+S ($p < 0.0001$) and S > V ($p < 0.0001$). Thus, the ASP and CTRL participants were fastest on the V+S condition, whereas the high-functioning autism group was slowest on the SEMANTIC condition (Figure 3.2).

We performed condition-wise correlations between speed and accuracy for each group to examine potential speed-accuracy trade-offs. There was a trend for a significant correlation between RT and accuracy on the V+S condition in the ASP group only (rho = .41, $p = .063$), whereas all other correlations were non-significant ($p > 0.149$). This may indicate that in the V+S condition, the ASP group's performance showed some degree of speed-accuracy trade-off.

In order to exclude overall speed differences as confounds to the RT differences between V and S, we performed additional t-tests between groups, using the difference between response times on V and S, adjusted for individual speed by dividing it by RT on the V condition, as our variable of interest. This analysis yielded no differences between ASP and CTRL, but there were significant differences between HFA and both ASP and CTRL ($p < 0.006$). The results confirmed that the RT difference between V and S was significantly greater in HFA than in CTRL or ASP, while accounting for potential overall speed differences.

Using the speed-adjusted RT difference between V and S as a dependent variable, we also conducted a complementary stepwise multiple regression analysis to examine the extent to which group membership predicted the discrepancy between the SEMANTIC and VISUOSPATIAL response times above and beyond IQ measures or gender. This analysis used PIQ, VIQ, the difference between PIQ and VIQ, gender, and group membership as predictor variables. Of these, only group membership significantly contributed to the model (R squared = .117, F=8.073, $p < 0.006$), while other variables were not found to be significant predictors ($p > .619$).

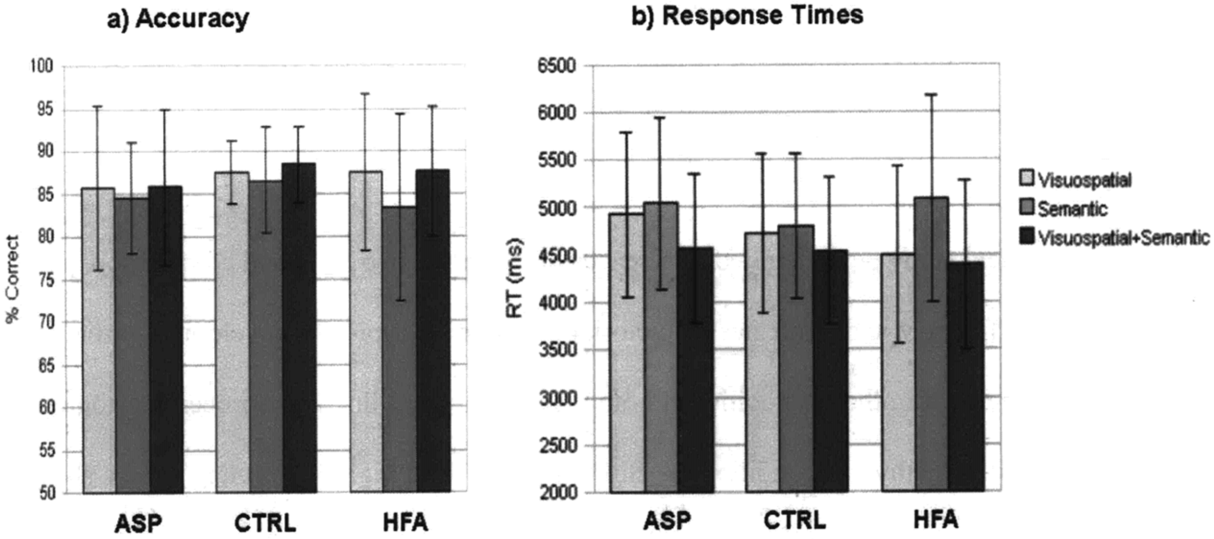


Figure 3.2. a) Accuracy on each condition for each group. b) Response times on each condition for each group. (ASP: Asperger Syndrome group; CTRL: comparison group; HFA: High-functioning Autism group; error bars represent standard deviations of the mean)

Correlation Analysis: The comparison group (CTRL) showed no significant correlations between accuracy on the V+S condition and both verbal (rho=.12; p=0.61), and nonverbal IQ (rho=-.21; p=0.35) scores. There was a trend for a correlation between accuracy on V+S and RPM score (rho=.42; p=0.07). However, typically developing participants appeared not to show a strong bias for either in their use of linguistic or visuospatial processing when both strategies were available.

The ASP group showed significant correlations between accuracy on the V+S condition and both VIQ (rho=.482, $p < 0.031$) and RPM (rho=.493, $p < 0.023$), but not with NVIQ (rho=.37; p=0.11). The ASP group thus showed a significant relationship between their performance in the V+S condition and their verbal skills as well as more general, language-independent fluid reasoning ability.

In contrast, we found that the HFA group had significant correlations between accuracy on the V+S condition and NVIQ (rho=.501, $p < 0.021$), but not with VIQ (rho=.19; p=0.41) or

RPM (rho=.36; p=0.12). Therefore, in the HFA group, only the relationship between the dual-strategy condition V+S and nonverbal ability was significant.

3.5. Discussion

The present study demonstrated differences between the two ASD and comparison groups in processing efficiency and strategies in pictorial reasoning. Typically developing participants appeared to benefit from the availability of both visuospatial and linguistic processing routes, as they were fastest in the hybrid condition, V+S. Participants with high-functioning autism showed an increased processing efficiency in favor of visuospatial mediation when this strategy was available: they were faster on the V and V+S conditions than on the S condition. Asperger syndrome participants, while sharing a similar RT profile with the comparison group, appeared to have used verbal mediation in conjunction with a more general, language-independent fluid reasoning ability, at no cost to performance. Taken together, these results point to the existence of different cognitive profiles across the autistic spectrum.

The task used in this study was carefully designed to equate the three conditions on multiple dimensions, using a simplified relational complexity metric. The relatively high performance and absence of group difference in accuracy on these three conditions attest to their comparability. Difference in response times on these conditions, thus, provides insight into the relative processing efficiency of visuospatial or linguistic mediation in the three groups of participants. The VISUOSPATIAL+SEMANTIC condition, which allows the use of both verbal and visuospatial strategies, served as a reference within each group, and offered the opportunity to examine strategy preferences in problem solving, as a function of clinical diagnosis. The comparison group's performance on this task (lack of correlation between performance on the dual-strategy condition and measures of verbal and nonverbal IQ, with faster solving of the V+S condition) reflects the absence of any strong strategy preference, and may suggest that the availability of both visuospatial and linguistic routes facilitates processing efficiency in this group. However, the trend for a correlation between accuracy on the V+S condition and score on the RPM, a measure of fluid reasoning ability, may in turn point to a relationship between performance and general cognitive ability in the CTRL group. Deviations from this pattern of efficiency may therefore be reflective of PDD diagnosis (Lincoln, Allen, Hanson, & Kilman, 1995). The V+S condition was hence critical as it went beyond the assessment of linguistic or visuospatial abilities provided by the other conditions, to reveal potential cognitive preferences in processing strategies.

Whereas there was no significant difference between the groups on accuracy, the group x condition interaction was significant for reaction times. The SEMANTIC condition took significantly longer to solve than the VISUOSPATIAL or VISUOSPATIAL+SEMANTIC conditions in the HFA group but not in the ASP, or CTRL groups (though, note minor trend for S > V+S in the CTRL group). This suggests that linguistic processing may be less efficient than visuospatial processing of pictorial stimuli in HFA. A diagnosis of autism requires early language delay, and despite inconsistent prognoses of linguistic development, language difficulties may persist later in life. The most common difficulties pertain to the pragmatics of language, but lexical and semantic problems have also been documented (Harris et al., 2006; Kamio et al., 2007; Perkins et al., 2006; Rapin & Dunn, 2003). Semantic access through pictorial stimuli has been found to be preserved in autism, as also evident in the lack of difference in accuracy between the ASD groups compared to the non-ASD group in the SEMANTIC condition in the present study (see also Kamio & Toichi, 2000); however, the efficiency of the ability to use this information, as required in the S condition, was clearly more limited in the HFA group (Joseph et al., 2005).

This suggests that the effects of early language delays in HFA may persist in later years, in the form of increased reliance on a visuospatial mediation strategy. While oral language deficits in autism have been reliably demonstrated, recent studies of intelligence in autism have shown spared or superior intelligence in tests devoid of language requirements (Dawson, 2007; Mottron et al., 2006; Plaisted, O'Riordan, & Baron-Cohen, 1998). It is likely that deficits in language and good visuospatial abilities interact to provide a picture whereby the processing efficiency of HFA is increased by the availability of visuospatial mediation (V and V+S conditions), but reduced where conceptual/linguistic processing is necessary. Thus, when presented with a task where both visuospatial and verbal mediations were possible, the HFA group appeared to favor the use of visuospatial strategies. This was confirmed by the correlation between NVIQ and accuracy on the VISUOSPATIAL+SEMANTIC condition in HFA but not CTRL participants, suggesting that nonverbal processes were primarily recruited for solving the V+S condition in autism. This clearly points to a strategy preference for visuospatial processing in HFA, while the lack of correlation in CTRL suggests an absence of bias in their approach of the hybrid condition.

Our finding is consistent with an elegant study by Joseph et al. (2005), who examined differences in verbal and non-verbal working memory skills in autism. Using a self-ordered pointing task with pictures varying in the extent to which they were amenable to verbalization, they showed that the phonological loop and visuospatial sketchpad of working memory were intact in autism; however, the availability of verbalization improved performance for the comparison group but not in participants with autism. The authors argued that individuals with autism were unable to spontaneously generate strategies based on verbal mediation when these could help task performance. However, these results may result from a difficulty in converting visual and verbal modalities, or an effect of a prepotent perceptual preference, leading to the use of visuospatial strategies, even when verbal mediation could facilitate task performance. In the same study, individuals with autism showed improved performance relative to a typically developing comparison group on a non-verbal self-ordered pointing condition. The autism group also showed no difference in performance between verbal and non-verbal conditions, indicative of the use of similar strategies in both tasks. These results suggest that individuals with autism favor the use of visuospatial strategies.

The Asperger syndrome group performed similarly to typically developing participants. Both ASP and CTRL solved V+S more rapidly than V or S. Insofar as the V+S condition was designed to be solved visuospatially but with the possibility of verbal mediation, having both processing routes available therefore appeared to be facilitative for both ASP and CTRL groups. In addition, we found no significant difference between V and S in both ASP and CTRL groups, suggesting that both tasks were performed similarly. Thus, the ASP and typically developing comparison groups shared similar accuracy and response time profiles across the three conditions. Interestingly, the ASP group took slightly longer to solve the problem plates overall, though this difference between the groups was not significant. Their accuracy on the V+S condition was correlated with both RPM, a language-independent measure of fluid reasoning ability (also seen in the CTRL group as a trend, further supporting processing similarities between these two groups), as well as verbal ability (VIQ). Somewhat difficult to interpret, this result clearly warrants further investigation of the use of both linguistic mediation and general fluid reasoning abilities in ASP, especially as this seems to occur at no cost to performance (Ozonoff, Rogers & Pennington, 1991).

In contrast to results in HFA, research with adults with ASP has shown that while not typical, their linguistic abilities are relatively spared (Koyama et al., 2007; Volkmar, 2004). The ASP group did not show a significant difference between V and S, suggesting that conceptual processing was not less efficient than visuospatial processing. There have been questions raised about the validity of ASP as a mutually exclusive diagnosis from HFA, and about the criteria for adequately differentiating between the two phenotypes (Baron-Cohen, 2006; Volkmar, 2004). Although the ASP group did not differ in accuracy from the HFA group, the two groups presented different RT profiles: the HFA group took longest to solve the S problems, whereas the ASP group resembled the typically developing participants, without marked differences between visuospatial and conceptual processing. The relationship between visuospatial and linguistic abilities may therefore be a more powerful metric for differentiating between high-functioning autism and Asperger syndrome than an absolute measure of language abilities alone.

The present experiment suggests a difference in relative processing efficiency of visuospatial vs. linguistic processes between the HFA and ASP groups. High functioning autism participants appear to favor a visuospatial strategy in pictorial reasoning, whereas Asperger Syndrome individuals may recruit both verbal mediation and fluid reasoning resources. This difference in processing patterns found in the performance of the ASP and HFA are in keeping with studies characterizing cognitive profiles in ASD. Koyama et al. (2007) found that whereas both groups (HFA and ASP) present similar patterns of relatively superior visuospatial ability vs. lower social intelligence and language scores, this profile was less marked in ASP, who also showed superiority to HFA in Wechsler VIQ (esp. in Vocabulary and Comprehension subtests) and in communication scores using the Japanese CARS-TV autism rating scale. In the present study, no superiority in visuospatial skills was found in ASP over the typically developing comparison group. Instead, individuals with Asperger syndrome and the comparison group presented similar performance profiles, but the HFA group appeared to favor visuospatial processing in the face of linguistic processing difficulties. A potential limitation of the study is the possibility that early language difficulties, used here as a selection criterion, may have persisted in later years in HFA, thereby leading to a decreased development and use of verbal strategies and/or a preference for visuospatial strategies in this group, as found here. Whereas our groups were matched on FSIQ, there was a trend for a significant difference in verbal IQ between the HFA and ASP groups ($p = 0.07$) which may account for some of the differences between them. A multiple regression analysis, however, showed that verbal IQ was not a significant predictor for the difference between response times on the V and S conditions.

3.6. Conclusion

The protocol developed in this study may be a powerful paradigm for differentiating cognitive profiles characteristic of autistic phenotypes. Our findings suggest that high-functioning autism participants have more difficulties in pictorial reasoning involving semantic manipulations, and appear to rely in a larger extent on visuospatial strategies. This is in contrast with Asperger syndrome individuals who resembled the non-ASD comparison group in their performance profiles and were not significantly slower in conceptual-based pictorial reasoning. The current task may prove useful in studying the neurobiological bases of ASD in current efforts to establish genotypes and phenotypes along the spectrum. The dichotomy between visuospatial and linguistic profiles along the autism spectrum provides opportunities for using functional brain imaging to elucidate the neurobiological correlates of the different patterns of cognitive efficiency found in this study, along with structural imaging to help differentiate between possible phenotypes of the disorder.

Chapter 4: Neuroimaging of the Functional and Structural Networks Underlying Pictorial Reasoning in High-Functioning Autism

4.1. Abstract

Individuals with high-functioning autism have been found to favor visuospatial processing in the face of typically poor language abilities. We aimed to examine the neurobiological basis of this difference using functional magnetic resonance imaging and diffusion tensor imaging. We compared 12 children with high functioning autism (HFA) to 12 age- and IQ-matched typically developing controls (CTRL) on a pictorial reasoning paradigm under three conditions: V, requiring visuospatial processing, S, requiring language (i.e. semantic) processing, and V+S, a hybrid condition in which language use could facilitate visuospatial transformations. Activated areas in the brain were chosen as endpoints for probabilistic diffusion tractography to examine tract integrity (FA) within the structural network underlying the activation patterns. The two groups showed similar reasoning networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporo-parietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. However, HFA appeared to activate occipito-parietal and ventral temporal areas, whereas CTRL relied more on frontal and temporal language regions. The increased reliance on visuospatial abilities in HFA was supported by intact connections between the inferior parietal and the ventral temporal ROIs. In contrast, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in this group, reflecting impaired activation of frontal language areas in autism. The HFA group's engagement of posterior brain regions along with its weak connections to frontal language areas suggest support for a preferred use of visual mediation in autism, even in tasks of higher cognition.

4.2. Introduction

Individuals with autism spectrum disorders (ASD) are known to have difficulties with certain aspects of language, most evident in pragmatics, verbal memory, and in taking advantage of semantic context cues (Harris et al., 2006; Kamio, Robins, Kelley, Swainson, & Fein, 2007; Perkins, Dobbinson, Boucher, Bol, & Bloom, 2006; Rapin & Dunn, 2003; Tager-Flusberg, Lindgren, & Mody, 2008). However, access to semantics via pictures, as well as picture naming, appear relatively spared in autism (Kamio & Toichi, 2000; Walenski, Mostofsky, Gidley-Larson, & Ullman, 2008), such that non-social cognitive difficulties in autism may arise primarily when the use of verbal strategies is required (Joseph, Steele, Meyer, & Tager-Flusberg, 2005; Whitehouse, Maybery, & Derkin, 2006). In contrast to linguistic difficulties, visuospatial abilities have been reported as intact or superior in autism, in tasks such as the Block Design subtest of the Wechsler Intelligence Scale, low-level visual discrimination, or Raven's Progressive Matrices (Caron, Mottron, Berthiaume, & Dawson , 2006; Dakin & Frith, 2005; Dawson, Soulieres, Gernsbacher, & Mottron, 2007; de Jonge et al., 2007; Edgin & Pennington, 2005). To the extent that high-functioning autism (HFA) has been associated with a cognitive bias towards visuospatial mediation (Sahyoun, Soulières, Belliveau, Mottron, & Mody, in press; Toichi & Kamio, 2001), there appears to be a dichotomy between visuospatial and linguistic abilities in autism (Behrmann, Thomas, & Humphreys, 2006; Tager-Flusberg & Joseph, 2003). We propose to examine the neurobiological basis of this difference using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI).

Verbal stimuli are likely to bias brain activation toward language centers; pictures, on the other hand, may be processed and manipulated "as a referent" (i.e. visually) or as a representation of a referent (i.e. semantically) (Schwartz, 1995). Pictorial tasks, thus, provide opportunities to study both visuospatial and linguistic abilities, which have been shown to rely on different but overlapping functional networks (Luo et al., 2003). Visual tasks that entail structural coding and perceptual matching of stimuli have been found to activate bilateral parietal, occipital, posterior temporal, as well as premotor and prefrontal regions (Brambilla et al., 2004; Ecker, Brammer, & Williams, 2008; Fangmeier, Knauff, Ruff, & Sloutsky, 2006; Goel, 2007; Zacks, 2008). In comparison, picture-based semantic coding and conceptual reasoning processes appear to be associated with increased activation within left inferior frontal as well as inferior/ventral temporal and occipital cortices (Ricci et al., 1999; Rossion et al. 2000; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Interestingly, visuospatial tasks where verbal strategies are facilitative have been shown to activate language areas (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997); conversely, visuospatial activation has been found in verbal tasks involving visual/spatial relations (Goel, Gold, Kapur, & Houle, 1998; Knauff, Fangmeier, Ruff, & Johnson-Laird, 2003). As such, reasoning networks may be influenced by task demands, as well as by working memory capacity and differences in individual cognitive profiles (Casasanto, 2003; Goswami, Leevers, Pressley, & Wheelwright, 1998; Richland, Morrison, & Holyoak, 2006; Waltz, Lau, Grewal, & Holyoak, 2000). In a sentence-verification task, Reichle et al. (Reichle, Carpenter, & Just, 2000) found that verbal and visuospatial mediation recruited different cortical regions, such that activation within each network was correlated with the linguistic vs. visuospatial abilities of their typically developing participants. Taken together, the results from these studies point to a functional network of overlapping areas involved in pictorial reasoning, which may be differentially modulated depending on visuospatial vs. linguistic demands of the task or individual cognitive processing differences.

Functional imaging findings in autism have been consistent with a preference for visuospatial coding strategies, evident in increased reliance on extrastriate and parietal regions (Koshino et al., 2005; Manjaly et al., 2007). This has been argued to reflect a disruption in fronto-striatal and fronto-parietal functional connectivity (Just, Cherkassky, Keller, Kana, & Minshew, 2007), such that activation in prefrontal but not parieto-striatal regions is decreased in autism (Silk et al., 2006), even when using low-imageability verbal stimuli (Kana, Keller, Cherkassky, Minshew, & Just, 2006). In yet other studies, increased functional synchronization within posterior regions but decreased synchronization within frontal regions has been observed compared with controls (Koshino et al., 2005). Individuals with autism also show atypical processing along the ventral visual stream. In visuospatial tasks such as the Embedded Figures Test, or Raven's Progressive Matrices, these individuals showed increased activation compared with neurotypical control subjects in a ventral occipital and striate network (Belmonte & Yurgelun-Todd, 2003; Soulieres et al., submitted), whereas frontal activation was larger in controls (Ring et al., 1999). Stronger reliance on a ventral occipito-temporal network and a functional imbalance between frontal and posterior regions have, in fact, been argued to play a role in the strong visuospatial abilities of individuals with autism (Boddaert & Zilbovicius, 2002); in turn, abnormal activation within frontal and temporal regions has been related to the linguistic difficulties in this population (Groen, Zwiers, van der Gaag, & Buitelaar, 2008).

In a sentence comprehension task, participants with autism showed decreased activation within the left inferior frontal gyrus but increased activation in the left superior caudal temporal region (Just, Cherkassky, Keller, & Minshew, 2004; Muller et al., 1998), whereas other studies have suggested bilateral hypoperfusion or underconnectivity of the temporal lobe in autism (Boddaert & Zilbovicius, 2002; Castelli, Frith, Happe, & Frith, 2002). In a separate study, the inferior frontal gyrus showed reduced activation differences between semantic and perceptual (letter case judgment) processing of words in autism compared with controls (Harris et al., 2006). In summary, individuals with autism present a neurocognitive profile of increased reliance on visuospatial skills and ventral stream processing, and decreased use of language functions within frontal areas. In fact, these patterns of activation are consistent with a recent model of altered brain growth dynamics in autism (Courchesne et al., 2007; Just et al., 2004; Kana et al., 2006; Kennedy and Courchesne, 2008; Schmitz, Daly, & Murphy, 2007).

Mechanistically, early brain overgrowth followed by decreased growth rate in autism is thought to result in overconnectivity within primary areas, whereas white matter tracts involving regions of slow maturation, such as the frontal lobe, would be underdeveloped (Courchesne & Pierce, 2005). In keeping with this general picture of reduced long-distance connections and local overconnectivity, morphometric MRI studies have found relative increases in gray matter and decreases in white matter volume in autism compared with control participants (Bonilha et al., 2008; Brambilla et al., 2003; Eigsti & Shapiro, 2003; Herbert et al., 2004), particularly evident in the corpus callosum (Alexander et al., 2007; Egaas, Courchesne, & Saitoh, 1995; Vidal et al., 2006; Waiter et al., 2005). Other autism studies have used functional connectivity measures to infer anterior-posterior underconnectivity between the occipital or parietal cortices and frontal regions, and not between occipital and parietal areas (Just et al., 2004, 2007; Kana et al., 2006; Villalobos, Mizuno, Dahl, Kemmotsu, & Muller, 2005). Diffusion tensor imaging

(DTI), which allows one to assess white matter integrity *in vivo*, has helped provide additional insight into structural connectivity patterns in autism. These studies have found lower fractional anisotropy (FA) in individuals with autism, compared with controls, in the anterior cingulate, ventromedial and subgenual prefrontal areas, temporoparietal junction, corpus callosum, and in the STG white matter and temporal stem (Barnea-Goraly et al., 2004; Lee et al., 2007). Contrary to expectations, Sundaram and colleagues (2008) found decreased tract integrity in both long-range fibers of the frontal lobe and in short-range fibers throughout the autistic brain. The mixed results reflect the need for carefully designed structure-function relationship studies to better understand the role of connectivity in autism.

In the present study, we used a combination of fMRI and DTI to examine the neurobiology of reasoning in autism. We used a pictorial problem-solving paradigm involving three conditions designed to vary in the extent to which linguistic vs. visuospatial mediation may be necessary to solve each problem. This task, used previously in a behavioral study, established that individuals with HFA were less efficient in a reasoning condition that involved linguistic (i.e. semantic) rather than visuospatial abilities, whereas control and Asperger syndrome participants showed similar cognitive profiles and benefited from the availability of both visuospatial and linguistic processing routes (Sahyoun et al., in press). Here we used fMRI to investigate the neurocognitive signature of this difference between the groups in reasoning strategies. We used DTI to examine the white matter integrity of a priori pathways of interest connecting functionally implicated nodes to understand the structural basis of potentially impaired brain mechanisms. Based on our previous findings, we hypothesized that a visuospatial processing preference in children with high-functioning autism would be evident in increased activation of posterior occipito-parietal and ventral temporal regions, supported by greater fractional anisotropy in the white matter connections between these regions. Conversely, we predicted that the typically developing group would rely more on frontal language nodes in reasoning, supported by greater FA, compared with HFA, in pathways involving these regions.

4.3. Materials and Methods

4.3.1. Participants

Participants consisted of 12 typically developing children (CTRL; 3 females; 10-17 years old; mean = 13.3, std dev = 2.45), and 12 children with high-functioning autism (HFA; 2 females; 11-18 years old; mean = 13.3, std dev = 2.07). Participants had no history of frank neurological or psychological damage, and scored in the normal range (80-125) on FSIQ, as measured by the Wechsler Intelligence Scales (WISC-III or WASI, Wechsler, 1991, 1999). The two groups did not differ on age ($p = 0.94$) or IQ (Verbal IQ, $p > .08$, Performance IQ, $p > .48$, Full-Scale IQ, $p > .24$) (Table 4.1) and were matched for handedness (Annett, 1970). All subjects had normal hearing and normal or corrected-to-normal vision, with no evidence of color blindness. Children with autism were diagnosed by experienced clinicians and met DSM-IV criteria, based on standardized test instruments (ADI-R, Lord, Rutter & Le Couteur, 1994; CARS, Schopler, Reichler & Renner, 1988). They also had delayed and/or atypical spoken language development, evident in histories of speech delay, echolalia and pronoun reversals. None of the children had previously participated in our earlier behavioral study using the same task (Sahyoun et al., in press). Subjects were also screened for comorbid neurodevelopmental conditions and medication history based on their medical record. In addition, first-degree relatives of participants in the CTRL group were without neurological or major psychiatric disorders, based on a screening questionnaire.

	CTRL (N = 12, 3F)		HFA (N = 12, 2F)	
	Mean	**StDev**	**Mean**	**StDev**
AGE	13.3	2.5	13.3	2.1
VIQ	108.4	9.3	98.9	15.4
PIQ	104.9	10.1	101.8	10.9
FSIQ	106.1	8.6	100.8	12.3

Table 4.1: High-functioning autism (HFA) and typically developing (CTRL) group descriptions. VIQ: Verbal IQ; PIQ: Performance IQ; FSIQ: Full-scale IQ; F: female participants.

4.3.2. Stimuli

The experimental paradigm consisted of a pictorial problem solving task (Sahyoun et al., in press). Participants were presented plates in the form of a matrix of items (individual items ©2009 Jupiter Images Corporation) related by visuospatial or semantic relationships. Subjects were instructed to select the most appropriate item from among three choices to fill a blank in the matrix, as fast and accurately as possible. The layout of the problem "plates" was a grid of 2x2 to 3x3 images with an empty cell, to be filled using one of 3 choices given below the grid. The experiment consisted of 3 conditions, VISUOSPATIAL (V), SEMANTIC (S), and VISUOSPATIAL + SEMANTIC (V+S), varying in the extent to which linguistic skills were needed to solve the plates. In the nonlinguistic, V condition, reasoning was based on visuospatial transformations of geometric patterns similar to those in the standard Test of Nonverbal Intelligence (Brown, 1997). In the S condition, clipart drawings readily identifiable and easy to label were used in problems where selection of the correct answer necessitated the ability to draw thematic or associative relationships between the presented items. In this condition, a successful strategy would require linguistic mediation, that is, extracting meaning from individual clipart pictures, recognizing semantic relationships between them, and inferring a logical solution consistent with these relationships. In the V+S condition, pictorial stimuli, similar to those in the semantic case, were to be manipulated visuospatially, with similar reasoning operations to those in the visuospatial condition. In this case, the semantic information carried by the pictures was not needed, but their labels were accessible for linguistic mediation, and potentially served a facilitative role. As such, the V+S condition provided an opportunity to examine cognitive strategy preferences for the use of verbal mediation to assist in a visuospatial task. Example plates from each condition are shown in Figure 3.1.

Plates were matched across the three conditions in terms of manipulations of interest (e.g. analogy, series completion, group formation, or addition/subtraction/intersection), number of transformations or relationships (e.g. part-whole, sequential transformation, identity matching, spatial inclusion etc.), and number of dimensions manipulated (e.g. shape, orientation, size, semantic category [animals, foods, sports...]). This matching was operationalized in keeping with the relational complexity theory of reasoning, whereby task difficulty is measured by the number of relations available and necessary for successful solving (Cho, Holyoak, & Cannon, 2007; Halford, 2005). For a more detailed description of the relational complexity framework used, see Sahyoun et al. (in press).

4.3.3. MRI Protocols

Data were acquired on a 3-tesla Siemens Trio scanner using a 12-channel standard head coil. High-resolution (sagittal) structural MRI scans were obtained using a T1-weighted MPRAGE protocol (176 slices, matrix = 256 x 256, voxel size = $1.3 \times 1 \times 1.3 mm^3$, TR = 2530 ms, TE = 3.48ms, Flip angle = 7°). Functional scans were divided into six runs of 5 minutes to allow for short in-scanner breaks (EPI sequence, matrix= 64X64, voxel size = $3.1 \times 3.1 \times 5 mm^3$, TR = 2760 ms, TE = 28 ms, Flip Angle = 90°, 150 volumes). Diffusion-weighted images were acquired with 60 gradient directions, with a *b*-value of $700 s/mm^2$, in addition to 10 non-weighted ($b = 0 s/mm^2$) volumes (64 slices, matrix = 256 x 256, voxel size = $2 \times 2 \times 2 mm^3$, TR = 7980ms, TE = 84ms).

4.3.4. Experimental Procedure

All participants were given supervised practice on the task outside of the MRI scanner, using 12-24 additional plates (not used during functional MRI scanning), to ensure adequate performance and understanding of the procedure. During scanner acquisition, stimuli were projected onto a screen at the back of the scanner bore, which participants could see using a mirror mounted on the head coil. A total of 144 plates (3 conditions x 48 plates/condition) were presented in six 5-minutes runs on a PC laptop running the Presentation software (Neurobehavioral Systems, Inc., CA, USA), synchronized to scanner acquisition. Within each run, the plates were presented using a pseudo-randomized event-related paradigm, with equiprobable conditions (i.e., 8 plates/condition) and correct button assignments (no more than three consecutive repetitions of the same correct button). The order of presentation of the plates was identical for each participant, and no more than three plates of the same condition were shown consecutively. The paradigm was self-paced, with each plate presentation lasting between 1 and 10s, as the plate disappeared upon subject response or timed out after 10 seconds. A fixation cross was shown between plates, with a randomly varied inter-stimulus interval ranging from 1500 to 3500ms. A longer rest period was inserted after every six plates in order to equate the length of each run. Participants were instructed to respond using a nonmagnetic button box as fast and accurately as possible, and to fixate on the cross that appeared in the middle of the screen between plates. Short in-scanner breaks were offered between each run for comfort, after which head position was measured again to ensure correct localization.

4.3.5. Behavioral Analysis

Accuracy and response times (RT) were computed by the Presentation software and submitted to statistical analysis in SPSS v.15.0 (SPSS Inc., IL, USA). Incorrect responses and trial outliers, including timed-out trials, were discarded from analysis. Trial outliers were defined as any trial more than 2 standard deviations from the mean response time for that condition, and represented 5.27% of all trials in the comparison group, and 5.73% of all trials in the HFA group (n.s. for group differences, $p = 0.27$). Repeated measures 2 (CTRL, HFA) x 3 (V, S, V+S) ANOVAs were carried out for accuracy and RT separately, with group as between-subject factor, condition as within-subject factor, and age as a covariate to control for developmental effects. Post-hoc t-tests included Bonferroni correction for multiple comparisons, and results were considered significant at $p < 0.05$.

4.3.6. Functional MRI processing

Functional BOLD analysis and structural processing were undertaken using FS-FAST and Freesurfer tools, respectively (https://surfer.nmr.mgh.harvard.edu). Structural processing, surface reconstruction, and cortical parcellation were carried out to generate inflated surface brain maps, registered to an average template via spherical morphing (Dale, Fischl, & Sereno, 1999, Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). Automated segmentation of structural scans generated surface-based labels, including cortical ribbons for each hemisphere (Fischl & Dale, 2000; Fischl et al., 2002, 2004).

EPI pre-processing involved motion correction (using AFNI, afni.nimh.nih.gov), smoothing with a 5mm FWHM Gaussian kernel, intensity normalization (to correct for intensity changes and temporal drifts across runs), and brain mask creation (using FSL's BET, www.fmrib.ox.ac.uk/fsl). Signal intensity was averaged for each condition across runs, excluding incorrect behavioral responses. A whitening filter was applied to account for autocorrelation in the data for each participant (Burock & Dale, 2000). Voxelwise general linear modeling was performed both assuming a hemodynamic response gamma function (onset time 2.25, dispersion 1.25) and using a finite impulse response model for region-of-interest timecourse analysis. Trials were modeled between stimulus onsets and correct button presses for each condition. Incorrect and missed trials were also modeled as a separate explanatory variable. Although no subject presented excessive motion during functional acquisition, motion correction parameters were used as external regressors to model out the effects of head motion.

The mean and variance volumes of each subject were resampled in surface space and group statistics were computed using a random effects model, correcting for multiple comparisons using simulation testing (10000 permutations). Both within-group contrasts between conditions and between-group contrasts for each condition were generated. Within-group contrasts were of particular interest as the task was specifically designed to capture response differences to the varying conditions as a function of the availability of linguistic and visuospatial mediation, especially in the V+S condition. In fact, our earlier behavioral study (Sahyoun et al., in press) revealed differences in cognitive profiles across conditions for the groups, whereas there were no between-group differences within each condition. In addition, within-group contrasts would help shed light on the loci of differences in activation between groups within each condition. Statistical results were displayed on the average inflated cortical surface ($p < 0.05$, corrected).

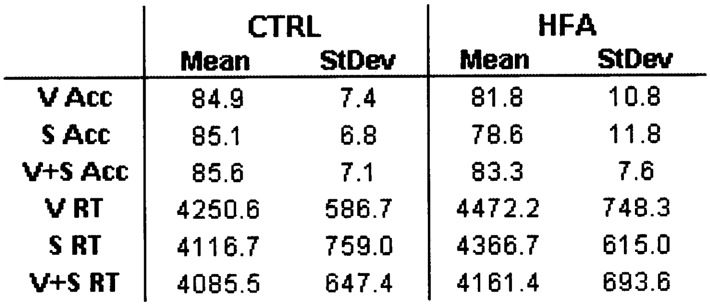
4.3.7. DTI Analysis

Diffusion data were processed using the FMRIB Diffusion Toolbox (FDT, http://www.fmrib.ox.ac.uk/fsl/fdt/index.html). Pre-processing involved correction for eddy current distortions by affine registration to a non-diffusion weighted volume, and brain masking using the same volume. Diffusion tensors were fitted at each voxel (Basser, Mattiello, & LeBihan, 1994) and fractional anisotropy (FA) and mean diffusivity (MD) maps were created. A probability distribution function was calculated using Markov Chain Monte-Carlo sampling, to support probabilistic tractography (Behrens et al., 2003a; 2003b, Smith et al., 2004). In order to directly examine structure-function relationships in our subjects, regions of interest (ROI) based on functional activation in our reasoning task were used in the tractography algorithm as endpoints of pathways potentially implicated in autism. Findings of reduced activation in the inferior frontal language region (Harris et al., 2006), decreased fronto-parietal functional connectivity (Just et al., 2007; Kana et al., 2006; Koshino et al., 2006), and lower FA in the temporal stem in autism (Lee et al., 2007), motivated the investigation of specific pathways connecting the frontal (inferior frontal area, IF) to posterior (superior/middle temporal areas, STS/MTG, and inferior parietal sulcus, IPS), and ventral temporal (fusiform/lingual area, FG) regions of interest. These ROIs (IF, STS/MTG, IPS, and FG) were defined and manually drawn on an omnibus map of functional activation of all three condition contrasts across all subjects, on the template inflated surface (Kuperberg et al., 2000, 2003; Wehner, Ahlfors, & Mody, 2007) (see Figure 4.1a). They were then spherically morphed to each participant's structural scan, by aligning with individual cortical folding patterns (Fischl et al., 1999) and projected 2.5mm from the grey-white surface into the underlying white matter. This projection maximized our ability to perform tractography between endpoints that may otherwise lie in regions of high uncertainty within grey matter. Finally, the ROIs were resampled to native DTI space by linear registration (FLIRT) to serve as seed and target masks for tractography. Given the impaired function of frontal language regions in autism (Groen et al., 2008), we hypothesized lower FA in the pathways between frontal and posterior brain areas. However, in light of evidence for intact access to pictorial semantics (Kamio & Toichi, 2000) and increased reliance on the ventral temporal and parietal cortices in higher cognition in autism (Belmonte & Yurgelun-Todd, 2003; Boddaert & Zilbovicius, 2002; Just et al., 2007; Manjaly et al., 2007), we hypothesized that FG-STS/MTG and FG-IPS pathways would be intact in the HFA group. The tractography algorithm used drew 5000 samples from each seed voxel on the principal diffusion directions, which stopped upon encountering a target voxel, and progressed with a step length of 0.5mm, a curvature threshold of 0.01, and a maximum of 2000 steps. Only samples reaching the target region without looping on themselves were kept in the corresponding pathway map. For each pair of ROIs used, tracking was performed in both directions, and the probabilistic union of the pathways was calculated. The values at each voxel, representing the number of samples passing through it, were converted to percentages of the maximum number of samples passing through any voxel, and thresholded at 0.2, to exclude voxels with low probability of lying on the pathway of interest (Ciccarelli et al., 2006). These thresholded pathways were binarized and used as masks to extract mean FA along the path for each subject. Independent samples t-tests ($p < 0.05$) were conducted between groups using these extracted values, to evaluate differences in white matter integrity along the hypothesized pathways involved in pictorial reasoning.

4.4. Results

4.4.1. Behavioral:

All participants were able to perform the task as shown by their performance on the three conditions (see Table 4.2). Group (HFA, CTRL) x Condition (V, S, V+S) ANOVA with both accuracy and response times, using age as a covariate, did not yield any main effects (Accuracy: group $F = 1.7, p = .205$, condition $F = .7, p = .5$; RT: group $F = .855, p = .366$, condition $F = .11$, $p = .89$), or significant interactions (Accuracy: $F = .72, p = .49$; RT: $F = .346, p = .7$).



	CTRL		HFA	
	Mean	**StDev**	**Mean**	**StDev**
V Acc	84.9	7.4	81.8	10.8
S Acc	85.1	6.8	78.6	11.8
V+S Acc	85.6	7.1	83.3	7.6
V RT	4250.6	586.7	4472.2	748.3
S RT	4116.7	759.0	4366.7	615.0
V+S RT	4085.5	647.4	4161.4	693.6

Table 4.2: Behavioral performance (means and standard deviations) of CTRL and HFA on V, S, and V+S conditions. Acc: Accuracy (percent correct); RT: Response time (ms).

4.4.2. Functional MRI:

Both groups activated a similar network of bilateral cortical areas during pictorial reasoning (Figure 4.1b).

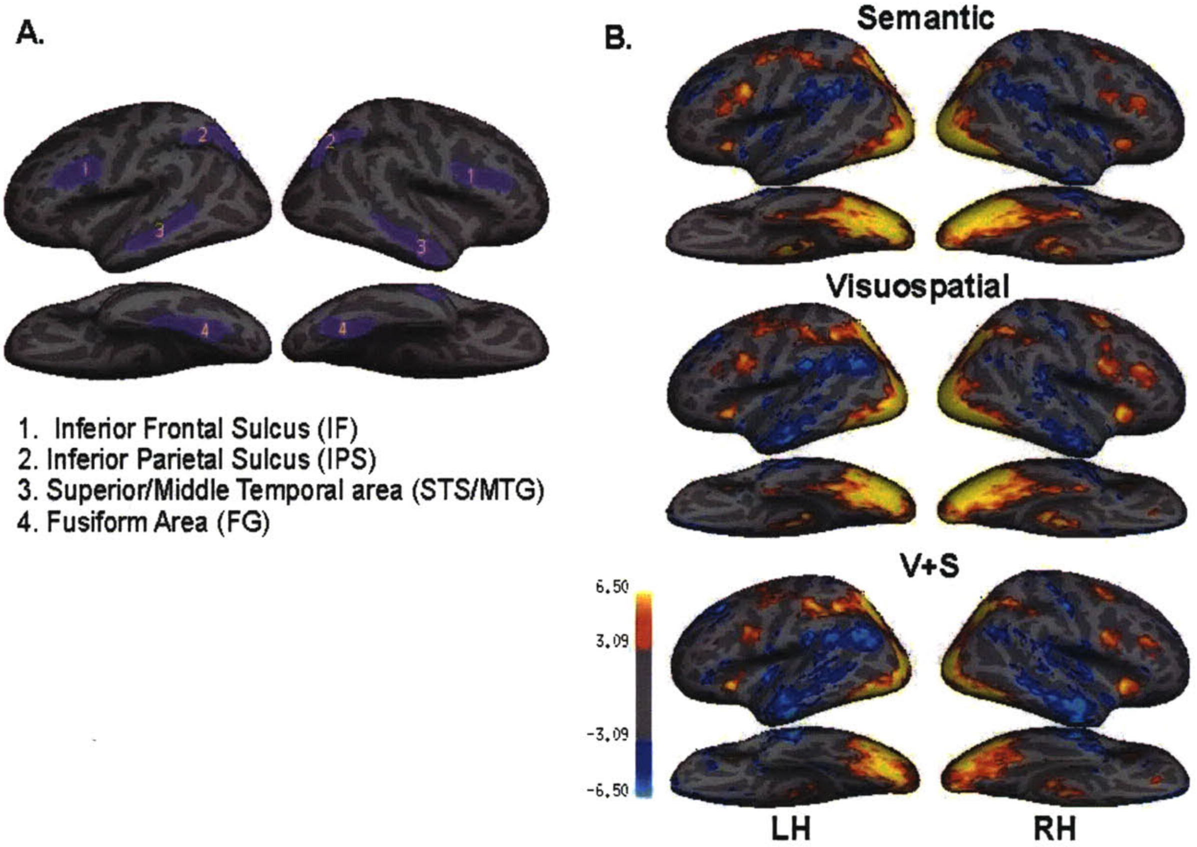


Figure 4.1: A. Regions of interest obtained from omnibus activation maps, used in tractography analysis. LH: left hemisphere; RH: right hemisphere. B. Statistical z-maps of fMRI activation for each condition vs. fixation (shown here for the CTRL group). Lateral (top) and ventral (bottom) views are shown for each condition. The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively.

The network comprised the extrastriate cortex, intraparietal sulcus (IPS), ventral temporal cortex (including the fusiform and lingual cortices, FG), superior precentral and inferior frontal (IF) areas, as well as the insula and postcentral gyrus. In addition, there were areas of decreased activation compared to the fixation condition within the temporo-parietal junction (TPJ), supramarginal gyrus, cingulate cortex, superior frontal sulcus, and medial frontal cortex, as well as in the left hemisphere superior temporal sulcus (STS) and right hemisphere middle temporal gyrus (MTG) in both groups. It is likely that task-related deactivation in these regions may be inversely related to their recruitment (Raichle, 1998), and may therefore be reflective of differential involvement of the regions in the three task conditions.

Within-group comparisons yielded a number of differences between the three conditions based on the manipulation of visuospatial and linguistic demands. These may be seen in Figure 4.2 and are summarized in Table 4.3.

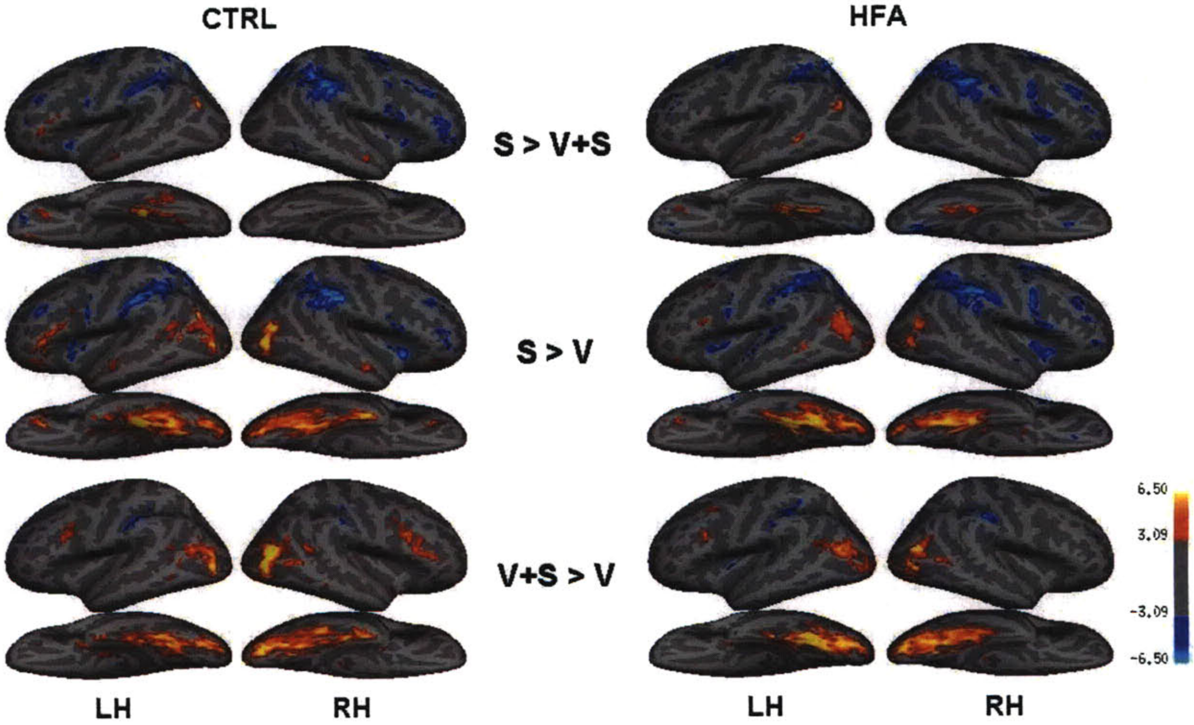


Figure 4.2: Within-group subtraction z-maps of fMRI activation (S vs. V+S, S vs. V, V vs. V+S) between condition pairs in CTRL (left) and HFA (right) groups. The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively. The direction of subtractions was chosen such that increased language demands are shown in red/yellow, vs. blue/light blue for visuospatial demands. LH: left hemisphere; RH: right hemisphere

	CTRL	HFA		CTRL > HFA	HFA > CTRL
S > V	Bil.: Ventral stream, Occipito-temporal cortex LH: STS (ant.), IF RH: STS (ant.)	Bil.: Ventral stream, Occipito-temporal cortex LH: STS	**S**	LH: MTG, lingual gyrus, superior precentral sulcus RH: supramarginal gyrus, occipito-temporal cortex	LH: lateral occipito-temporal sulcus, posterior lateral fissure, RH: insula, MTG (ant.), ITS, IF (ant.)
S > V+S	LH: STS (ant.), IF RH: STS (ant.)	LH: STS			
V > S	Bil.: IPS, insula, superior precentral sulcus	Bil.: IPS, insula, superior precentral sulcus RH: IF (post.)	**V+S**	LH: MTG, lingual gyrus, superior precentral sulcus RH: angular gyrus, IF, STS	Bil.: MTG (ant), ITS LH: lateral occipito-temporal sulcus, posterior lateral fissure, IPS, occipital cortex RH: postcentral gyrus
V > V+S	Bil.: IPS	Bil.: IPS			
V+S > V	Bil.: Ventral stream, Occipito-temporal cortex LH: IF RH: IF (ant.)	Bil.: Ventral stream, Occipito-temporal cortex	**V**	LH: MTG, lingual gyrus, superior precentral sulcus RH: angular gyrus	Bil.: MTG (ant.) ITS LH: lateral occipito-temporal sulcus, pre/post-central sulcus, posterior lateral fissure RH: IF (ant.), postcentral gyrus
V+S > S	Bil.: IPS, insula, superior precentral sulcus	Bil.: IPS, insula, superior precentral sulcus RH: IF (post.)			

Table 4.3: Summary of results for each within-group contrast (left) and between-group contrast (right). S; Semantic; V+S: Visuospatial+Semantic; V: Visuospatial; LH: left hemisphere; RH: right hemisphere; Bil. Bilateral; STS: Superior Temporal Sulcus; IF: Inferior Frontal area; IPS: Inferior Parietal Sulcus; MTG: Middle Temporal Gyrus; TPJ: Temporo-Parietal Junction; ant.: anterior; post.: posterior

A few of these differences were particularly worth noting: there was significantly greater activation in S and V+S than in V in both groups in ventral temporal areas, bilaterally. Additionally, in both groups, activation in S and V+S was greater than in V in the left hemisphere (LH) occipito-temporal area, whereas this difference was much smaller in S vs. V+S. Although both groups showed greater activation in S compared to either V or V+S within the LH STS, the location of this activation appeared to extend more anteriorly (close to the temporal pole) in CTRL than HFA. In addition, the right anterior STS showed greater activation in S compared to V or V+S in CTRL but not in HFA. In the typically developing group, the left inferior frontal area was more strongly activated for S and V+S compared to the V condition. These differences were noticeably reduced in the HFA group. Similarly, the right hemisphere IF area was also activated in the CTRL group, but absent in HFA in V+S compared to V. Both groups, however, showed greater activation in bilateral IPS in V and V+S compared to S.

Direct group contrasts for individual conditions while confirming similarities between the groups across conditions, also showed activation differences (Figure 4.3). CTRL relative to HFA showed increased activation in all three conditions within the left hemisphere in MTG, lingual gyrus and precentral sulcus; HFA, in contrast, showed increased activation in the lateral occipito-temporal sulcus, pre- and post-central sulcus, and in the posterior segment of the lateral fissure in the left hemisphere, regardless of condition. There were also a number of differences between the groups as a function of condition (Table 4.3). Of note, CTRL activated left STS/MTG and RH supramarginal gyrus, most noticeable in the S condition. They also showed greater activation than HFA in the angular gyrus, STS and IF in the right hemisphere for V+S. The HFA group, in comparison, showed greater activation than controls within the left hemisphere IPS and right hemisphere STS/MTG, most noticeably in the V+S condition.

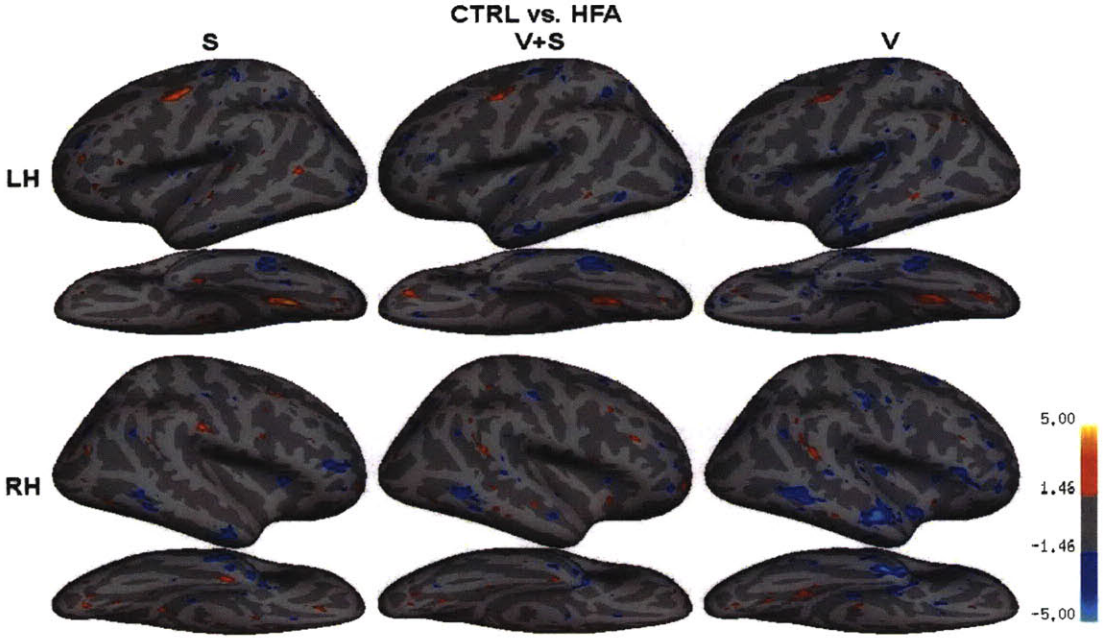


Figure 4.3: Group comparison of fMRI activation (z-map): CTRL > HFA (red/yellow) and HFA > CTRL (blue/light blue) for each condition (S, left; V+S, middle; C, right). The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively. The top and bottom rows represent left (LH) and right (RH) hemisphere differences between the two groups, respectively.

4.4.3. Diffusion tractography

We examined mean fractional anisotropy (FA) in probabilistic pathways defined a priori, between functionally defined ROIs (Figure 4.1a). Three HFA participants were excluded from the analysis due to excessive motion during DTI acquisition. In order to illustrate the tractography results, the pathway distributions between the left IPS and left IF of all subjects were resampled to a common template, binarized, and added for each group. The resulting group maps therefore represented the overlap in location of the IPS-IF pathway for each group, confirming the consistency of the tracking algorithm across subjects (Rilling et al., 2008). Group maps were thresholded to only keep voxels through which at least three subjects had pathways to confirm that all subjects produced similar pathway distributions (Figure 4.4b).

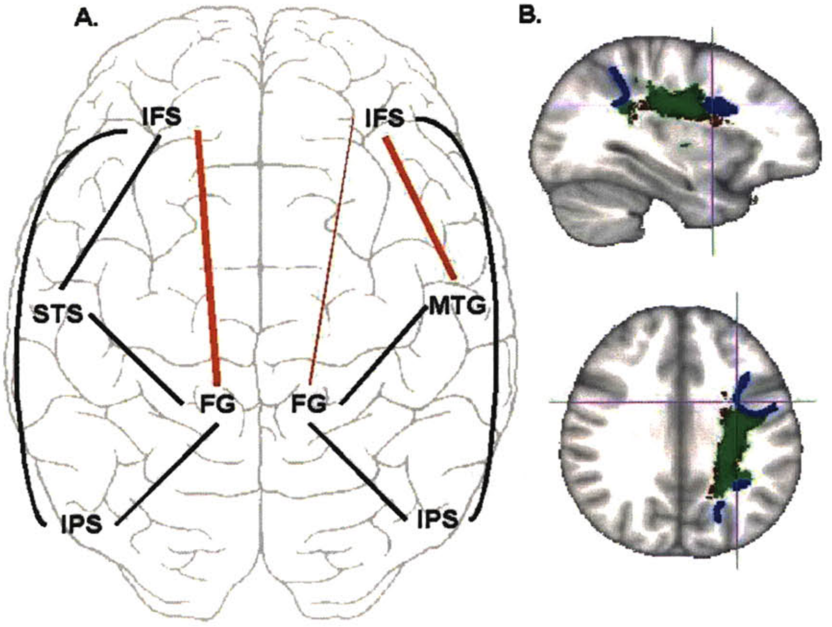


Figure 4.4: A. Summary schematic of FA differences: Black lines represent pathways investigated where no differences in FA were fond between HFA and CTRL. Red Lines represent pathways showing significantly decreased FA in HFA compared with CTRL; thinner red lines represent pathways showing a trend for decreased FA in HFA compared with CTRL. IPS: Inferior parietal sulcus; FG: Fusiform gyrus; STS: Superior temporal sulcus; MTG: Middle temporal gyrus; IF: Inferior frontal area. B. example output of tractography, overlayed on MNI template; Blue: endpoints of tractography (left hemisphere IPS and IF), Green: CTRL group pathway, Red: HFA group pathway. As shown in this example, pathways generally overlap almost perfectly in HFA and CTRL.

	CTRL	HFA			CTRL	HFA	
LH	Mean FA		p	RH	Mean FA		p
IPS-IF	0.44	0.44	1	**IPS-IF**	0.44	0.43	0.2
FG-IF	0.46	0.42	***0.02***	**FG-IF**	0.47	0.38	***0.07***
IPS-FG	0.49	0.48	0.6	**IPS-FG**	0.5	0.47	0.14
FG-STS	0.53	0.52	0.75	**FG-MTG**	0.5	0.48	0.19
STS-IF	0.49	0.48	0.43	**MTG-IF**	0.48	0.45	***0.02***

Table 4.4: Mean FA within probabilistic pathways between ROIs involved in pictorial reasoning. Significant differences in FA between HFA and CTRL are highlighted. IPS: Inferior parietal sulcus; FG: Fusiform gyrus; STS: Superior temporal sulcus; MTG: Middle temporal gyrus; IF: Inferior frontal area.

The pathways investigated and their mean FA, calculated after thresholding out low probability voxels, are listed in Table 4.4. The results revealed pathways where the HFA group showed lower FA compared with the CTRL group, whereas no pathway showed greater FA in HFA (Figure 4.4a). The HFA group had lower FA in pathways between the IF and FG in the left hemisphere ($p < 0.02$), as well as in the right hemisphere (trend, $p = 0.07$). In the right hemisphere, the pathway between the IF and MTG also showed reduced FA in HFA ($p < 0.02$), but not the pathway between IF and STS in the left hemisphere. We also found no differences between the groups in pathways connecting the IF and IPS regions in either hemisphere. Finally, there were no group differences in FA between FG and either IPS or STS/MTG, in both left and right hemispheres..

4.5. Discussion

The current study aimed at examining neurocognitive differences in the pictorial naming network in children with and without high functioning autism. Our findings revealed that despite similar behavioral performances of the two groups, the underlying structural and functional neuroanatomy showed significant differences between HFA and CTRL.

The two groups did not differ in accuracy or response times on the task, supporting the view that HFA have intact visuospatial processing skills (Dakin & Frith, 2005; Edgin & Pennington, 2005), and intact pictorial access to semantics (Kamio & Toichi, 2000). That the HFA performance was less accurate on S than on V or V+S, though not significant, may reflect subtle effects of this group's early language difficulties and is consistent with the trend for a difference in verbal IQ between the groups that we observed. Thus, as children with autism do worse under language processing conditions (Rapin & Dunn, 2005; Sahyoun et al, in press; Tager- Flusberg, Lindgren & Mody, 2008), this may explain some of the differences in brain activation of our HFA participants.

We found that regardless of the differing linguistic versus visuospatial demands of the task, pictorial reasoning engaged a similar, largely overlapping network of cortical regions in both groups. This core network comprised of areas related to language processing (TPJ, supramarginal gyrus, STS, MTG, IF), visuospatial manipulations (IPS, superior precentral sulcus), and visual processing and picture identification (occipital cortex, ventral temporal stream). Regions known to be involved in visuospatial processing were more active during V and V+S than in S (Ecker et al., 2008; Klingberg, 2006; Zacks, 2008), and language-processing areas were more active and often, more anterior (suggesting more conceptual coding) (Gold & Buckner, 2002) in S and V+S than in V.

The two groups, however, clearly differed in their activation profiles. Whereas CTRL appeared to engage fronto-temporal areas when verbal mediation was available and/or necessary, as in the V+S and S conditions, HFA relied more on posterior, occipito-temporal and ventral temporal, brain areas, evident in the within-group fMRI comparisons. Compared to the control group, HFA's poorer frontal activation in S and V+S than in V (Fig. 4.2), and greater activation of IPS, especially in V+S (Fig 4.3), together with its reduced structural connectivity between frontal and ventral temporal areas (Fig 4.4), suggest an impaired frontal language system and greater reliance on visual mediation via inferior parietal and ventral temporal areas to do the task. This could account for the absence of significant difference between the groups in behavioral performance, reflecting an intact visually-mediated access to semantics in a pictorial reasoning task like the one used in the present study.

That both CTRL and HFA participants showed greater activation of the occipito-temporal and ventral temporal areas in the S and V+S conditions than in V, implies more of a conceptual than structural coding of pictorial stimuli by both groups; however, the CTRL group also showed greater activation in language areas, STS and IF, for S and V+S than V. A direct contrast between CTRL and HFA in the S condition revealed greater activation in CTRL in the left STS/MTG and right supramarginal gyrus, as well as in right angular gyrus in the V+S condition in keeping with their tendency to use semantic and visuospatial information, when both processing routes are available (Sahyoun et al., in press). These results also suggest that control subjects may engage an extended network of language areas, including right hemisphere homologues, during tasks that involve linguistic mediation (Harris et al., 2006).

In striking contrast to the increased activation in the CTRL group within the language network in S and V+S, the HFA group showed increased activation in these conditions in left IPS and occipital cortex. This pattern of increased reliance on posterior processing areas has been associated with "structural" coding of information (Kellenbach, Hovius, & Patterson, 2005) and with a cognitive preference for visual strategies in problem-solving in autism (Manjaly et al., 2007; Soulieres et al., submitted). The HFA group also showed increased activation in all three conditions in the left hemisphere lateral occipito-temporal sulcus, and pre- and post-central sulci, which have been implicated in visuospatial transformations (Ecker et al., 2008); in contrast, the CTRL group showed greater activation in all conditions in left hemisphere MTG and lingual gyrus which may reflect greater processing of semantic attributes of the stimuli in CTRL. The superior precentral sulcus was also consistently activated in this group. Given its location in what might be functionally defined as the frontal eye field, the activation in the superior precentral sulcus warrants a closer investigation of eye movements and potential differences in visual search strategies between HFA and CTRL.

The results of our tractography analysis provide a window into the structural basis for the activation differences in pictorial reasoning between HFA and CTRL. Connections between the FG and IPS and FG and STS/MTG were intact in both hemispheres in the HFA group (Figure 4.4, Table 4.4), consistent with accounts of a reliance on visuospatial processing abilities and intact pictorial access to language in autism. These results also highlight an important mediating role for the FG in higher-level cognition in autism. The HFA group, however, showed reduced FA compared to CTRL in the IF-FG pathways in both hemispheres (Koshino et al., 2008; Lee et al., 2007), consistent with lower functional activation of the IF in semantic processing observed in this group, relative to CTRL, and in keeping with accounts of decreased use of covert speech strategies in autism (Kana et al., 2006). In addition, HFA participants showed lower FA compared to CTRL in the right hemisphere IF-MTG pathway, consistent with our finding that CTRL but not HFA may engage the right frontal areas as part on an extended language network. Surprisingly, we did not find reduced fronto-parietal connectivity, or left hemisphere IF-STS underconnectivity, seen in some studies (Just et al., 2004; Kennedy & Courchesne, 2008). These studies used functional correlations between activated areas, and assess connectivity using a different (i.e., indirect) approach (Hughes, 2007), making it difficult to compare results across the studies. Insofar as functional underconnectivity may be associated with altered grey matter, white matter, or both, with little information about potential cytoarchitectural underpinnings (Kleinhans et al., 2008), recent methods, including DTI, could allow one to examine the potential correspondence between functional and anatomical connectivity (Just et al., 2006). It is worth noting that the present tractography approach averages FA over large pathways, such that some localized differences in white matter integrity may not be detected, as these may lie primarily within the tails of the FA distributions (Ciccarelli et al., 2006). Further developments in quantitative tractography, such as point-by-point comparisons along pathways (Salat et al., 2008), may provide better sensitivity to localized differences and help reconcile differences between functional and structural connectivity findings.

In conclusion, the neuroimaging results from the present study on pictorial reasoning suggest that individuals with autism may favor the use of visual mediation strategies in tasks of higher cognition. The HFA recruited posterior brain regions particularly the occipital and ventral temporal areas and the intraparietal sulcus, related to visuospatial processing. The typically developing group, in contrast, relied more on a fronto-temporal language network for reasoning. This pattern was consistent with differences in white matter integrity: HFA showed intact connections between ventral temporal areas and posterior language and visuospatial processing regions, but reduced connectivity with inferior frontal areas.

Chapter 5: White Matter Integrity and Pictorial Reasoning in High-Functioning Children with Autism

5.1. Abstract

Individuals on the autistic spectrum are found to vary in their linguistic versus visuospatial abilities. However, little is known about the neurobiological basis of this difference. The current study examined differences in white matter integrity between high-functioning children with autism (HFA) and typically developing controls (CTRL), in relation to response times (RT) in a pictorial reasoning task under three conditions (visuospatial, semantic, and V+S, a hybrid condition allowing language use to facilitate visuospatial transformations).

Diffusion-weighted MR images were acquired from 12 HFA and 12 age- and IQ-matched CTRL, and significance maps were computed for group differences in fractional anisotropy (FA), age-FA correlation, and RT-FA correlations for each condition.

Typically developing children showed increased FA in frontal white matter and within the superior longitudinal fasciculus (SLF). The HFA showed increased FA within peripheral white matter, including the ventral temporal lobe. An increase in FA with age was evident primarily within the frontal lobe in CTRL, but was more dispersed in HFA. Correlations of RT with FA implicated white matter near the STG and in the SLF within the temporal and frontal lobes in the semantic condition to a greater extent in CTRL. Performance in visuospatial reasoning, however, was more correlated with peripheral parietal and superior precentral white matter in HFA, and with the SLF, callosal, and frontal white matter in CTRL. Our results suggest a widespread delay in white matter maturation in HFA, and point to efficient use of linguistic pathways in CTRL, but a reliance on visuospatial networks in autistic cognition.

5.2. Introduction

A characteristic feature of individuals with autism is their difficulty with certain aspects of language, most evident in pragmatics, verbal memory, and in taking advantage of semantic cues in context (Harris et al., 2006; Kamio et al., 2007; Perkins et al., 2006; Rapin and Dunn, 2003; Tager-Flusberg et al., 2008). However, access to semantic information via pictures, as well as picture naming, appear relatively spared in autism (Kamio and Toichi, 2000; Walenski et al., 2008), suggesting that non-social cognitive difficulties in autism may arise primarily when the use of verbal strategies is required (Joseph et al., 2005; Whitehouse et al., 2006). In contrast to linguistic difficulties, visuospatial abilities have been reported as intact or superior in autism, using tasks such as the Block Design subtest of the Wechsler Intelligence Scale, low-level visual discrimination, or Raven's Progressive Matrices (Caron et al., 2006; Dakin and Frith, 2005; Edgin and Pennington, 2005; de Jonge et al., 2007). Further support for these findings comes from our recent study involving pictorial reasoning under three conditions that varied in the extent to which verbal versus visuospatial mediation was involved (Sahyoun et al., 2009). We found that high-functioning individuals with autism (HFA) were slowest on the condition that required the use of semantic relationships, but were fastest when visuospatial strategies were available to solve the problem. The aim of the present study was to investigate the white matter basis of this difference in visuospatial versus linguistic processing efficiency to better understand the neurobiological basis of autism.

Despite evidence for atypical brain development in autism, there remains the lack of a clear neuropathological account of the disorder (Amaral et al., 2008; Schmitz and Rezaie, 2008). According to Courchesne et al. (2004, 2007), a lack of pruning in the first two years of life could well explain brain enlargement and increased short-distance connectivity, in keeping with a disproportionate increase in radiate white matter found in individuals with autism (Herbert et al., 2003, 2004). This accelerated neuronal growth subsequently appears to halt by two to four years of age, in turn leading to long-distance underconnectivity (Courchesne and Pierce, 2005). Cytoarchitecturally, this model is consistent with accounts of early glial activation and neuroinflammation leading to disrupted organization of cortical minicolumns (Casanova et al., 2002; Vargas et al., 2005).

Patterns of underconnectivity in autism, found in functional and structural neuroimaging studies, have taken the form of decreased coherence of EEG/MEG oscillations, reduced fMRI correlations across areas, and anatomical differences in brain volume, cortical folding, or white matter integrity (Hughes, 2007). In the present study, we focus on using diffusion tensor imaging (DTI) to examine white matter integrity in children with autism, and its relation to behavioral measures on a task of higher level cognition. Diffusion tensor imaging allows one to indirectly examine connections in the brain by measuring directional hindrance to water movement caused by white matter tracts. It has become a tool of choice for assessing disorders of connectivity such as multiple sclerosis and autism (Beaulieu, 2002; Ciccarelli et al., 2008; Jones, 2008). Of particular interest is fractional anisotropy (FA), which measures directional cohesiveness of water movement in the brain, such that increased FA is thought to reflect greater integrity of white matter tracts. DTI studies of autism have found increased fractional anisotropy before 3 years of age, mainly in the corpus callosum (CC) and left frontal cortex (Ben Bashat et al., 2007), whereas older children and adults present with increased white matter diffusion (Barnea-Goraly et al., 2004; Keller et al., 2007). As such, atypical correlations between age and FA have been found in autism, most evident in the corpus callosum (Alexander et al., 2007; Keller et al., 2007).

In general, individuals with autism show reduced fractional anisotropy in the body and genu of the corpus callosum, as well as in the white matter adjacent to the anterior cingulate and prefrontal cortices, temporo-parietal junction (TPJ), superior temporal sulcus, and optic radiations extending towards the amygdala and fusiform regions (Barnea-Goraly et al., 2004). FA was shown to also be significantly reduced in the temporal lobe and temporal stem (Lee et al., 2007). These patterns are thought to reflect the social, communicative, and behavioral deficits of the disorder. However, the relationship between white matter integrity and cognition in autism remains elusive.

Studies of functional connectivity, on the other hand, while not pointing to specific white matter tracts, allow one to identify connectivity patterns based on correlated activation between different brain areas under specific task conditions. These studies have often implicated frontal lobe underconnectivity in autism (Courchesne and Pierce, 2005; Horwitz et al., 1988; Kennedy and Courchesne, 2008; McAlonan et al., 2005; Muller et al., 1998). Specifically, reduced functional connectivity has been found in individuals with autism in fronto-temporal, fronto-parietal (Just et al., 2004, 2007) and fronto-striatal (Silk et al., 2006) networks, in tasks of executive function, working memory, as well as mental rotation and sentence comprehension (Kana et al., 2006). However, parieto-occipital connections appear to be intact (Villalobos et al., 2005), such that posterior brain areas, including occipital and ventral temporal regions, appear to play an important role in visuospatial cognition in autism (Ring et al., 1999; Soulières et al., submitted), in contrast to frontal lobe recruitment in typically developing individuals (Sahyoun et al., submitted). This pattern has been argued to reflect increased reliance on visual codes and pictorial processing along the ventral stream in autism (Kana et al., 2006), consistent with reports of reduced use of inner speech and verbal codes (Joseph et al., 2005; Koshino et al., 2005; Whitehouse et al., 2006).

It is important to note that a particular tract showing decreased white matter integrity may be involved in a number of functional networks or symptoms; similarly, functional neuroimaging may provide information about disrupted functional connections between specific cortical processing nodes, but no details about the white matter underlying these connections. Thus, there remains the question of the relationship between white matter structure and behavioral performance (Klingberg et al., 2000; Moseley et al., 2002).

Attempts to relate structural brain abnormalities to cognitive measures in autism have primarily focused on volumetric studies or region-of-interest (ROI) approaches. In one study, Hadjikhani et al. (2006) found scores on the Autism Diagnostic Interview –Revised (ADI-R) to correlate with cortical thinning in inferior frontal (IF), parietal, superior temporal, inferior occipital, and supramarginal cortices. In a volumetric study of the superior temporal gyrus (STG), Bigler et al. (2007) demonstrated that although there were no absolute differences between groups in gray, white, or total STG volume, performance on the Clinical Evaluation of Language Fundamentals-3 (CELF-3), a measure of language ability, was correlated with STG volume in typically developing children, but not in the autism group. Lee et al. (2007) found that FA in the superior temporal gyrus was correlated with age in typically developing but not in autistic participants between 7 and 33 years, suggestive of a relationship between language difficulties and reduced connectivity in autism. Alexander et al. (2007) found correlations between FA in the corpus callosum and a measure of performance IQ (PIQ) in autism but not in normal controls. In summary, few studies have attempted to relate specific cognitive behaviors in autism with measures of white matter diffusion.

In the current study, we explicitly tested for differences in white matter anisotropy between HFA and typically developing controls in relationship to the performance of the two groups on our pictorial reasoning task (Sahyoun et al, 2009). We used a tract-based statistical approach to relate the structural integrity of white matter tracts in the two groups, to their response times under three pictorial reasoning conditions (visuospatial (V), semantic (S), and a hybrid condition (V+S), which allows language use to facilitate visuospatial transformations). Our aim was to investigate the potential role of white matter in autistic cognition.

5.3. Materials and Methods

5.3.1. Participants

Participants consisted of 12 typically developing children (CTRL), and 12 high-functioning children with autism (HFA). However, data from from 3 HFA participants could not be used due to excessive motion during DTI acquisition, to avoid affecting the quality of inter-subject registration. Thus, data from 12 typically developing controls (3 females; 10-17 years old; mean = 13.3, s.d. 2.45), and 9 HFA participants (2 females; 11.8-15 years old; mean = 12.8, s.d. 1.5) were included in the analysis. Participants had no history of frank neurological or psychological damage, and scored in the normal range (80-125) on FSIQ, as measured by the Wechsler Intelligence Scales (WISC-III or WASI, Wechsler, 1991, 1999). The two groups did not differ on age (p = .6) or IQ (Verbal IQ, CTRL: 108.4 (s.d. 9.34), HFA: 100.3 (s.d. 14.36), p

= .13; Performance IQ, CTRL: 104.9 (s.d. 10.06), HFA: 102.4 (s.d. 12.49), $p = .62$; Full-Scale IQ, CTRL: 106.1 (s.d. 8.56), HFA: 101.4 (s.d. 12.48), $p = .32$) and were matched for handedness (Annett, 1970). All subjects had normal hearing and normal or corrected-to-normal vision, with no evidence of color blindness. Children with autism were diagnosed by experienced clinicians and met DSM-IV criteria, based on standardized test instruments (ADI-R, Lord et al., 1994; CARS, Schopler et al., 1988). They also had delayed and/or atypical spoken language development, evident in histories of speech delay, echolalia and pronoun reversals. None of the children participated in our earlier behavioral study using the same task (Sahyoun et al., 2009). Subjects were also screened for comorbid neurodevelopmental conditions and medication history based on their medical record. In addition, first-degree relatives of participants in the CTRL group were without neurological or major psychiatric disorders, based on a screening questionnaire.

5.3.2. Stimuli

The experimental paradigm consisted of a pictorial problem solving task (Sahyoun et al., 2009). Participants were presented plates in the form of a matrix of items (individual items ©2009 Jupiter Images Corporation) related by visuospatial or semantic relationships. Subjects were instructed to select the most appropriate item from among three choices to fill a blank in the matrix, as fast and accurately as possible. The layout of the problem plates was a grid of 2x2 to 3x3 images with an empty cell, to be filled using one of 3 choices given below the grid. The experiment consisted of 3 conditions, VISUOSPATIAL (V), SEMANTIC (S), and VISUOSPATIAL + SEMANTIC (V+S), varying in the extent to which linguistic skills were needed to solve the plates. In the nonlinguistic, V condition, reasoning was based on visuospatial transformations of geometric patterns similar to those in the standard Test of Nonverbal Intelligence (Brown, 1997). In the S condition, clipart drawings readily identifiable and easy to label were used in problems where selection of the correct answer necessitated the ability to draw thematic or associative relationships between the presented items. In this condition, a successful strategy would require linguistic mediation, that is, extracting meaning from individual clipart pictures, recognizing semantic relationships between them, and inferring a logical solution consistent with these relationships. In the V+S condition, pictorial stimuli, similar to those in the semantic case, were to be manipulated visuospatially, with similar reasoning operations to those in the visuospatial condition. In this case, the semantic information carried by the pictures was not needed, but their labels were accessible for linguistic mediation, and potentially served a facilitative role. As such, the V+S condition provided an opportunity to examine cognitive strategy preferences for the use of verbal mediation to assist in a visuospatial task. Example plates from each condition are shown in Figure 3.1.

Plates were matched across the three conditions in terms of manipulations of interest (e.g., analogy, series completion, group formation, or addition/subtraction/intersection), number of transformations or relationships (e.g., part-whole, sequential transformation, identity matching, spatial inclusion.), and number of dimensions manipulated (e.g., shape, orientation, size, semantic category [animals, foods, sports, etc]). This matching was operationalized in keeping with the relational complexity theory of reasoning, whereby task difficulty is measured by the number of relations available and necessary for successful solving (Cho et al., 2007; Halford, 2005). For a more detailed description of the relational complexity framework used, see

Sahyoun et al. (2009).

5.3.3. MRI Protocols

Data were collected on a 3-tesla Siemens Trio scanner using a 12-channel standard head coil, at the end of a one hour functional and structural imaging session (Sahyoun et al., submitted). Participants were given a choice to sleep/relax or watch a movie during the 10-minute DTI protocol. Diffusion-weighted images were acquired with 60 gradient directions, with a b-value of 700 s/mm^2, in addition to 10 non-weighted ($b = 0$ s/mm^2) volumes (64 slices, matrix = 256 x 256, voxel size = 2x2x2 mm^3, TR = 7980 msec, TE = 84 msec).

5.3.4. Experimental Procedure

The task was presented in the context of a functional MRI scanning session (reported separately in Sahyoun et al., submitted). A total of 144 plates (3 conditions X 48 plates/condition) were presented in six 5-minute runs on a PC laptop running the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA.). Within each run, the plates were presented using a pseudo-randomized event-related paradigm, with equiprobable conditions (i.e., 8 plates/condition) and correct button assignments (no more than three consecutive repetitions of the same correct button). The order of presentation of the plates was identical for each participant, with no more than three consecutive presentations of plates from the same condition. The paradigm was self-paced, with each plate presentation lasting between 1 and 10 s, as the plate disappeared upon subject response or timed out after 10 seconds. A fixation cross was shown between plates, with a randomly varied inter-stimulus interval ranging from 1500 to 3500 msec. A longer rest period was inserted after every six plates in order to equate the length of each run. Participants were instructed to respond using a nonmagnetic button box as fast and accurately as possible, and to fixate on the cross that appeared in the middle of the screen between plates. Short in-scanner breaks were offered between each run for comfort, after which head position was measured again to ensure correct localization.

5.3.5. Behavioral Analysis

Accuracy and response times (RT) were computed by the Presentation software and submitted to statistical analysis in SPSS v.15.0 (SPSS Inc., IL, USA). Incorrect responses and trial outliers, including timed-out trials, were discarded from the analysis. Trial outliers were defined as any trial more than 2 standard deviations from the mean response time for that condition, and represented 5.3% of all trials in the comparison group, and 5.7% of all trials in the HFA group (n.s. for group differences, $p = .27$). A 2 (CTRL, HFA) x 3 (V, S, V+S) repeated measures ANOVA was carried out for accuracy and response time separately, with group as a between-subject factor, condition as a within-subject factor, and age as a covariate to control for developmental effects. Post-hoc t-tests included Bonferroni correction for multiple comparisons, and results were considered significant at $p < .05$.

5.3.6. MRI processing

Diffusion data were processed using the FMRIB Diffusion Toolbox (FDT, http://www.fmrib.ox.ac.uk/fsl/fdt/index.html). Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, Smith et al., 2006), part of the FMRIB

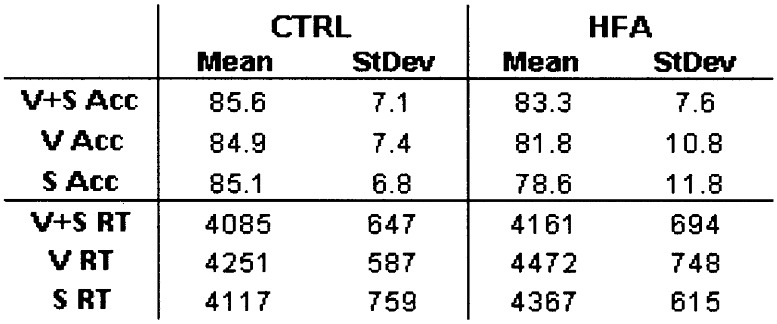
Software Library (FSL, Smith et al., 2004). Pre-processing involved correction for eddy current distortions by affine registration to a non-diffusion weighted volume, and brain masking using the same volume. Fractional Anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data (Basser et al., 1994) using FDT, and then brain-extracted using FSL's Brain Extraction Tool (BET, Smith, 2002). All subjects' FA data were then aligned to a common standard template for group comparison (MNI152, Montreal Neurological Institute, McGill, USA) using the nonlinear Image Registration Tool Kit (IRTK, Rueckert et al., 1999, www.doc.ic.ac.uk/~dr/software). Next, a mean FA image was created and thinned to create a mean FA skeleton which represented the centers of all tracts common to the group. Each subject's maximum local FA was then orthogonally projected onto this skeleton and the resulting data were used in voxelwise cross-subject statistics.

A general linear model was applied using explanatory variables for each group, demeaned ages for each group, as well as demeaned response times for each condition and each group. Correction for multiple comparisons was carried out using 5,000 permutations testing and effects were considered significant for corrected $p < .05$. Statistical maps were obtained for FA, FA correlation with age, and FA correlations with response times in each condition for each group, as well as for differences in these correlations between the groups. Regions of significant FA difference within the skeleton frame were thickened for visualization purposes and identified with reference to tracts from the Johns Hopkins University probabilistic white matter atlas (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). Mean FA values within significant clusters were extracted for each subject to test for the magnitude of group differences and for plotting representative correlations between FA and age/response time.

5.4. Results

5.4.1. Behavioral

All participants were able to perform the task, as shown by their performance on the three conditions (see Table 5.1). Group (HFA, CTRL) x Condition (V, S, V+S) ANOVA, with age as a covariate, did not yield any main effects or significant interactions for accuracy or reaction times.



	CTRL		HFA	
	Mean	**StDev**	**Mean**	**StDev**
V+S Acc	85.6	7.1	83.3	7.6
V Acc	84.9	7.4	81.8	10.8
S Acc	85.1	6.8	78.6	11.8
V+S RT	4085	647	4161	694
V RT	4251	587	4472	748
S RT	4117	759	4367	615

Table 5.1: Behavioral performance (means and standard deviations) of CTRL and HFA on V, S, and V+S conditions. Acc: Accuracy (percent correct); RT: Response time (msec).

5.4.2. DTI

Significant FA findings were localized relative to major pathways identified using the Johns Hopkins University probabilistic atlas of white matter, and further refined by citing adjacent gray matter structures (in parentheses in Tables 5.2 and 5.3, as well as in Figures 5.3, and 5.5). The various pathways implicated in our findings (see following sections) are shown in a schematic (Figure 5.1) modeled after Mori et al. (2005), and all significant group-, age-, and condition-related FA findings summarized in Tables 5.2 and 5.3.

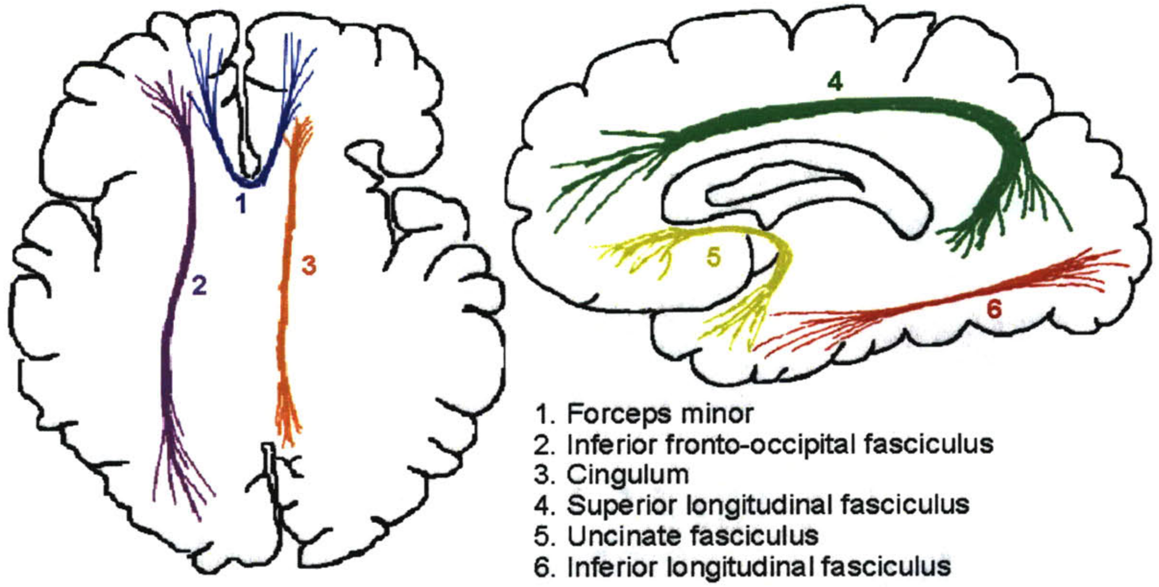


Figure 5.1: Summary schematic of major white matter pathways found to be differentially implicated in HFA versus CTRL. Pathways were traced to reflect known anatomy in order to serve as a reference in interpreting results.

Group differences: Differences in FA between the groups were found in a number of areas on the skeletonized tracts (shown in Figure 5.2). The typically developing group showed increased FA, compared to HFA, within white matter tracts connecting with the frontal lobe: bilaterally within the forceps minor, in the left inferior fronto-occipital fasciculus (IFOF) adjacent to the middle and inferior frontal gyri, the left superior longitudinal fasciculus (SLF), and the right posterior IFOF. In contrast, the HFA group had increased FA, relative to CTRL, bilaterally within the uncinate fasciculus in the temporal lobe, as well as in the right SLF peripherally near the middle frontal gyrus (MFG). Mean FA for each group within significant clusters are shown in Table 5.2.

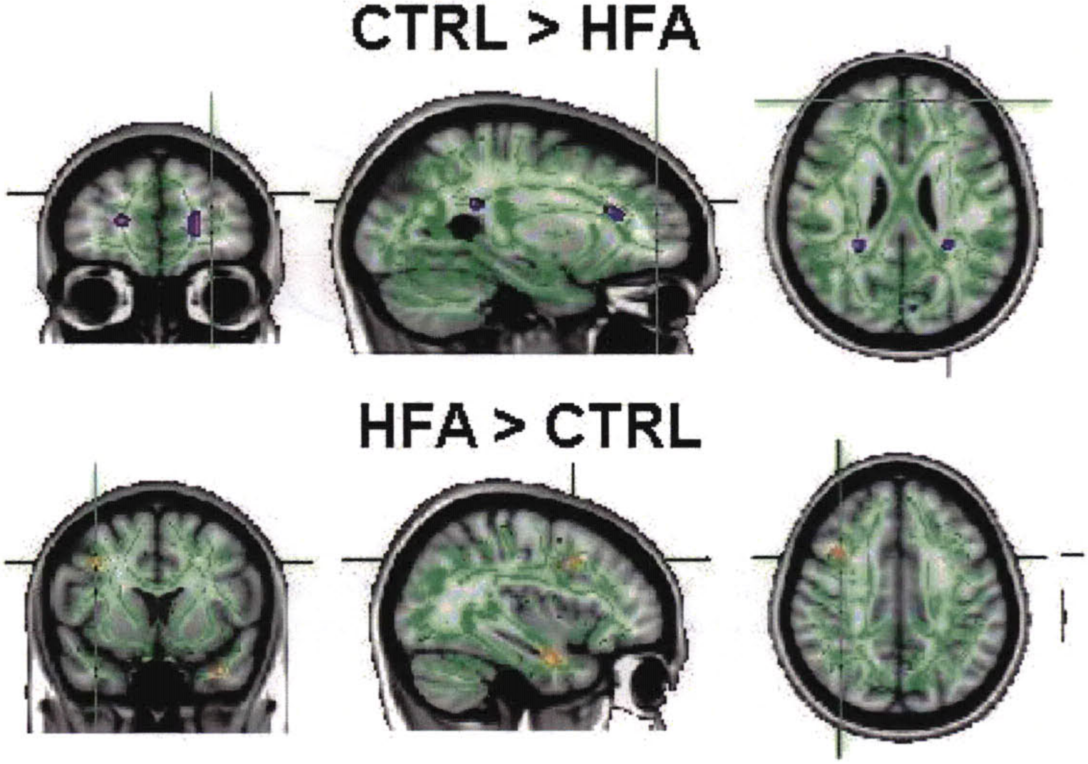


Figure 5.2: Group differences in fractional anisotropy (FA), overlaid on white matter skeletonized template (green). Regions of significance were thickened for visualization. The top panel shows regions where typically developing children presented increased FA compared to HFA participants (Purple). The bottom panel shows the opposite contrast, where FA was higher in HFA than in the CTRL group (Orange). Crosshairs indicate the orthogonal slices, in radiological view, chosen to capture a maximum number of regions of significant difference.

	CTRL		HFA		
CTRL>HFA	**Mean**	**StDev**	**Mean**	**StDev**	***p***
LH forceps minor (frontal pole)	0.53	0.03	0.45	0.03	*0.0000*
LH forceps minor (frontal pole)	0.41	0.06	0.34	0.03	*0.0027*
LH forceps minor (frontal pole)	0.6	0.07	0.51	0.03	*0.0020*
LH SLF (parietal opercumum / splenium of CC)	0.57	0.05	0.48	0.03	*0.0001*
LH SLF (supramarginal gyrus)	0.61	0.05	0.52	0.05	*0.0011*
LH anterior IFOF (IFG/MFG)	0.53	0.03	0.45	0.03	*0.0000*
RH forceps minor (frontal pole)	0.61	0.06	0.5	0.06	*0.0004*
RH posterior IFOF	0.41	0.02	0.35	0.02	*0.0000*
RH SLF (precentral gyrus)	0.45	0.15	0.27	0.06	*0.0022*
RH IFOF (superior occipital cortex)	0.55	0.04	0.48	0.05	*0.0008*
RH cerebellar WM	0.6	0.05	0.49	0.05	*0.0001*
HFA > CTRL					
RH uncinate fasciculus (temporal pole)	0.25	0.06	0.42	0.12	*0.00066*
LH uncinate fasciculus (temporal pole)	0.32	0.05	0.42	0.08	*0.00240*
RH SLF (MFG)	0.41	0.02	0.49	0.04	*0.00001*

Table 5.2: Regions of significant difference in fractional anisotropy (FA) between HFA and CTRL. Closest gray matter structures are indicated in parentheses. LH: left hemisphere, RH: right hemisphere, CC: corpus callosum, SLF: superior longitudinal fasciculus, IFOF: inferior fronto-occipital fasciculus, WM: white matter, MFG: middle frontal gyrus.

Age: The relationship between age and FA was clearly different for the two groups (Fig. 5.3a, Table 5.3). Typically developing participants showed increased FA with age mostly within the frontal lobe: in the right IFOF near the frontal orbital cortex, middle frontal and precentral gyri white matter, as well as in the left superior frontal gyrus white matter. In comparison, the HFA group showed a widespread (i.e. diffuse) pattern of correlations between age and FA in a number of areas, including the body of the CC, and in the left hemisphere the SLF near the planum temporale, STG and supramarginal gyrus, the inferior longitudinal fasciculus (ILF) near the STG, and the IFOF between the frontal operculum and IFG, as well as the right hemisphere forceps minor. A direct contrast between the age-FA correlations of the groups yielded notable differences in white matter near the fusiform cortex and superior parietal lobule in the left hemisphere (Figure 5.3b). Plotting participants' mean FA against age within these two clusters revealed a sharp decrease in FA with age in HFA but an increase in CTRL in the superior parietal lobule. In the left fusiform region, however, HFA showed an increase in FA with age which was not evident in the CTRL group.

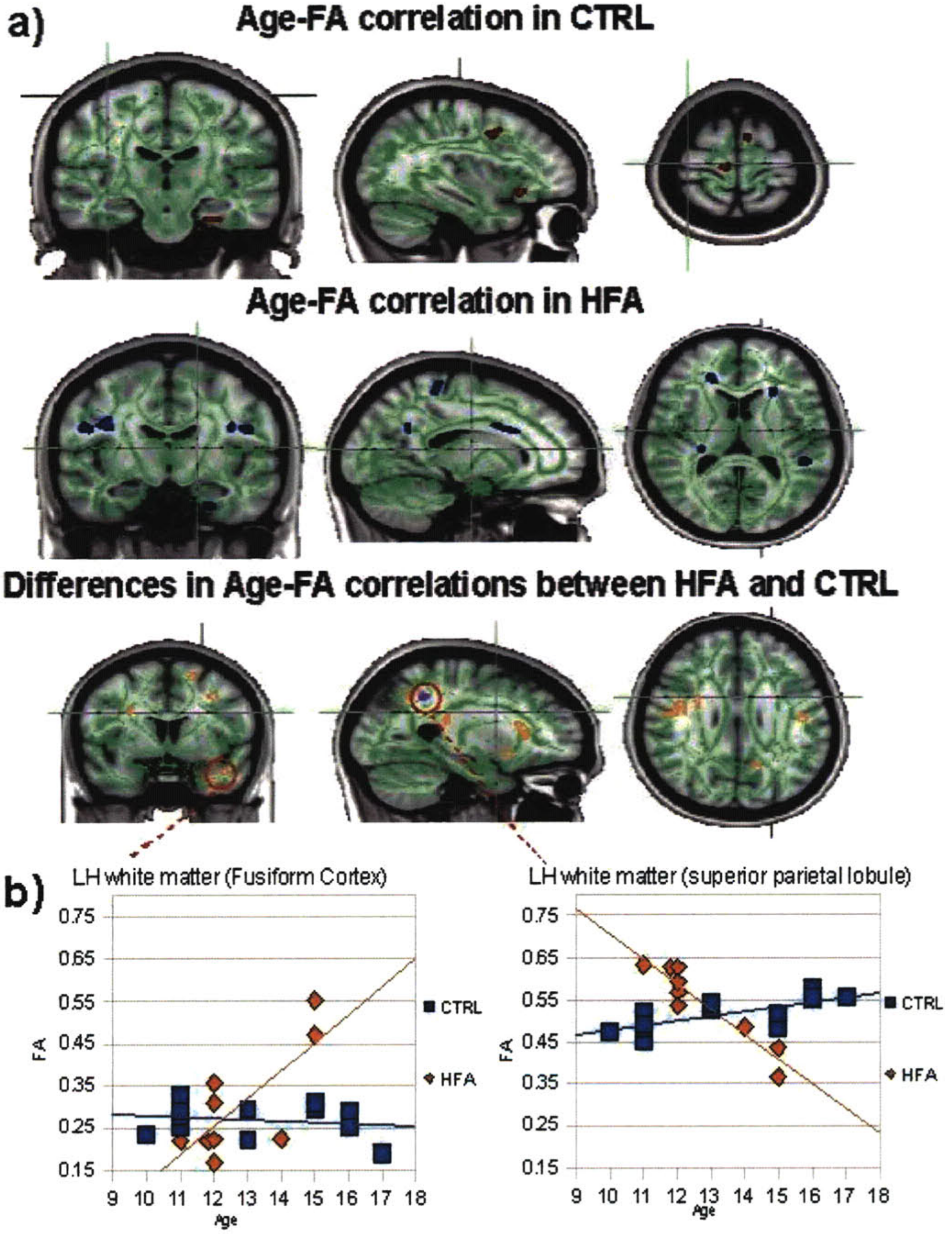


Figure 5.3: Correlation between age and fractional anisotropy (FA). a) Areas of significant correlation, overlaid on white matter skeletonized template (green), and thickened for visualization. Red: correlation between age and FA in CTRL; Blue: correlation between age and FA in HFA; Orange: increased age-FA correlation in HFA compared to CTRL; Purple: increased age-FA correlation in CTRL compared to HFA.. b) Representative plots of FA versus Age in each group, within regions of significant difference.

	CTRL	**HFA**	**CTRL>HFA**	**HFA>CTRL**
Age	LH SFG WM LH cingulum (parahippocampus) RH IFOF (frontal orbital cortex) RH MFG WM RH precentral G WM	CC (body) LH cingulum (precuneus) LH SLF (STG, suprmarginal G, planum temporale) LH ILF (STG) LH UF (insula) LH IFOF (frontal operculum/IFG) LH MFG WM LH postcentral G WM RH forceps minor RH internal capsule Bil. UF (temporal pole, postcentral G)	LH superior parietal lobule WM	LH fusiform G WM LH cingulum LH SLF LH ILF LH UF LH IFOF LH MFG WM LH postcentral G WM RH forceps minor RH SLF RH ILF (fusiform) LH SFG WM
Visuospatial +Semantic RT	LH cingulum (parahippocampus) LH anterior thalamic radiation LH UF (frontal pole, IFG) LH cerebellar WM RH SLF (precentral G)	CC (genu) LH ILF (superior lateral occipital cortex) LH UF (frontal orbital cortex) LH fusiform WM LH insula WM RH SLF (MTG, precentral G) RH planum temporale WM		CC (genu) LH superior parietal lobule WM LH ILF (ITG/MTG)
Visuospatial RT	CC (body) anterior corona radiata	LH cingulum (parahippocampus) LH SLF (superior parietal lobule) LH IFOF (operculum/IFG)	CC (body) LH forceps minor	RH SFG WM RH cingulum (precuneus)
Semantic RT	LH SLF (SFG) Bil. SFG WM Bil. CST		CC (genu) LH ILF (STG) RH SLF (MTG, precentral G) Bil. SLF (postcentral G)	

Table 5.3: Summary of the location of significant fractional anisotropy (FA) correlations with age and response time for each condition (V+S, V, S) in each group, as well as differences in these correlations between the two groups. Localization was based on a white matter probabilistic atlas of main pathways, and further defined by proximity to gray matter cortical regions, shown here in parentheses. LH: left hemisphere; RH: right hemisphere; Bil.: bilateral; WM: white matter; G: gyrus; CC: corpus callosum; IFOF: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; ILF: inferior longitudinal fasciculus; UF: uncinate fasciculus; CST: cortico-spinal tract; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus

FA and reaction times: The correlations between tract anisotropy and reaction times for each experimental condition revealed distinct white matter networks in HFA and CTRL (Table

5.3). A comparison of these correlations between the groups yielded differences in the white matter regions implicated in each condition, highlighted in Figure 5.4, along with representative plots to illustrate the direction of the correlation difference in these regions.

The V+S condition showed a different pattern of correlations between RT and FA in the two groups. Of note, in the CTRL group, response time decreased with increasing FA in the left hemisphere uncinate fasciculus near the frontal pole and IFG. The HFA participants also presented significant negative correlations between response time and FA, but in the left hemisphere ILF near the superior division of the lateral occipital cortex, and in white matter near the fusiform cortex. A comparison between the groups revealed that the negative correlation between response time and FA in the left ILF (near the inferior and middle temporal gyri), as well as in the superior parietal lobule, was greater in HFA than in CTRL (Figure 5.4a, Table 5.3). The CTRL group, however, did not show significantly greater correlation than HFA in this condition in any region.

The visuospatial condition, similarly, yielded a number of negative correlations between FA and response time, most notably within the body of the corpus callosum in CTRL, but within the left hemisphere SLF near the superior parietal lobule in HFA (Table 5.3). A comparison between the groups revealed a significantly greater negative correlation between FA and response time in CTRL, compared to HFA, in the body of the corpus callosum and left forceps minor for the V condition. In the right hemisphere cingulum (near the precuneus), however, HFA showed a significantly greater negative correlation between FA and response time than CTRL in this condition (Figure 5.4b).

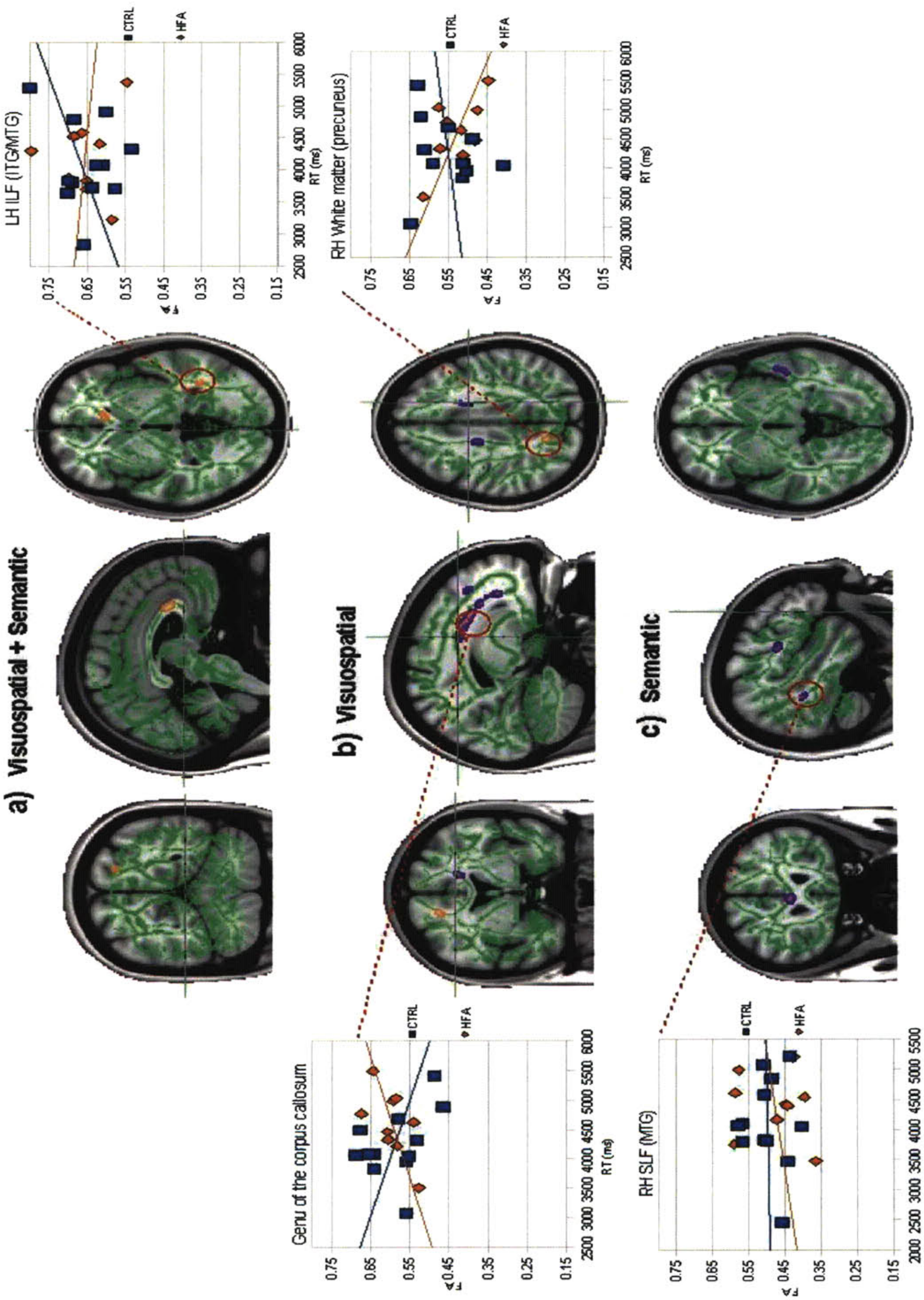


Figure 5.4: Group differences in correlation between fractional anisotropy (FA) and response time on the V+S (a) , V (b) and S (c) conditions, overlayed on white matter skeletonized template (green), and thickened for visualization. Purple: increased RT-FA correlation in CTRL compared to HFA; Orange: increased RT-FA correlation in HFA compared to CTRL. Inserts show representative plot of FA versus response time within areas of interest in each group, to illustrate the direction of the effect.

In the Semantic condition, the HFA group did not show any significant correlation between reaction time and FA (Table 5.3). A comparison of the two groups yielded a negative correlation between FA and response time, significantly greater in CTRL than HFA, within the genu of the corpus callosum, the left hemisphere ILF near the STG, and along the SLF in the right hemisphere near the middle temporal gyrus (Figure 5.4c).

5.5. Discussion

The current study examined differences in white matter integrity between high-functioning children with autism and a typically developing group in relation to their performance on a pictorial reasoning task.. We found differences in the maturation of white matter with age, as well as in the relationship of tract integrity (FA) to reaction times in the different conditions (V, S, V+S) between the groups.

In our earlier behavioral study, we found that both groups could do the task, suggestive of intact pictorial reasoning in autism (Dakin and Frith, 2005; Edgin and Pennington, 2005; Kamio and Toichi, 2000). However, compared to the CTRL group, the HFA participants were slowest in the S condition, and appeared to benefit from the availability of visuospatial strategies in the V and V+S conditions (Sahyoun et al., 2009). The findings support the existence of a language deficit and an apparent reliance on visual strategies in autism, frequently reported in the literature. In the present neuroimaging study, however, HFA and CTRL groups did not differ in accuracy or reaction times in any of the three conditions (V, S, V+S). The lack of difference between the groups, compared to our earlier findings, may have been due to increased variance associated with the performance of younger participants, like those in the present study, as well as to the smaller number of subjects (data from a three HFA subjects had to be discarded due to excessive motion during scanning).

We used a skeletonized template to compare the core of white matter bundles across participants, thereby minimizing partial voluming effects seen with voxel-based methods (Smith et al., 2006). To interpret the results, differences in radiate white matter regions were associated with short-distance U-fibers (Herbert et al., 2004), and hence, taken to reflect the function of nearby gray matter, whereas findings within large tracts (i.e., “deeper” within white matter) were assumed to be functionally related to known anatomical end-points of the corresponding major pathways. Thus, a significant correlation between FA and response time was interpreted in terms of the relevance of the specific pathways involved in solving each type of reasoning problem, such that a higher negative RT-FA correlations in a group would reflect increased reliance on the white matter tract implicated for the given condition in that group.

White Matter Integrity in HFA versus CTRL

The between-group FA contrasts revealed differences in white matter cohesiveness, which were consistent with models of long-distance disconnection to the frontal lobe and increased local peripheral connectivity in autism. The HFA group showed decreased FA compared to controls in the left SLF. As the SLF forms the main connection between frontal and parietal regions, we may infer decreased fronto-parietal connectivity in HFA. This is consistent with previous reports of decreased functional correlation in ASD in fronto-parietal networks (Just et al., 2007; Kana et al., 2006; Keller et al., 2007). Similarly, the IFOF showed reduced FA in HFA bilaterally (though anteriorly in the left hemisphere and posteriorly in the right hemisphere), consistent with reports of decreased fronto-occipital and fronto-striatal connectivity in autism (Silk et al., 2006; Villalobos et al., 2005). In addition, there was a decrease in FA bilaterally within the forceps minor near the frontal pole in HFA compared to CTRL. The forceps minor radiates from the genu of the corpus callosum towards the frontal pole, and the anterior part of the corpus callosum has consistently been implicated in autism (Keller et al., 2007, Muller, 2007). Together, these differences suggest that connectivity to, and within, the frontal cortex is affected in autism, consistent with long-distance underconnectivity models and with decreased use of frontal brain areas in higher cognition (Kana et al., 2006; Sahyoun et al., submitted; Soulières et al., submitted).

Compared to CTRL, the HFA group showed increased FA in anterior temporal white matter ventrally, supporting an increased reliance on visualization strategies within ventral temporal regions in HFA (Manjaly et al., 2007; Sahyoun et al., submitted), and consistent with reports of increased radiate white matter volume reflecting U-fiber overconnectivity (Bonilha et al., 2008; Herbert et al., 2004). The HFA group also showed increased FA peripherally close to the middle frontal gyrus in the right hemisphere, in keeping with local overconnectivity within frontal regions that has also been reported in functional connectivity studies of autism (Koshino et al., 2008). The apparent bias towards short fibers in autism is consistent with theories of reduced complex information processing (Minshew et al., 2007), as well as with models of visually-driven cognition (Kana et al., 2006; Mottron et al., 2006).

Maturation of White Matter Tracts in HFA versus CTRL

The analysis of age-FA correlations revealed abnormal trajectories of white matter development in high-functioning autism. Increases in FA with age in the CTRL group were mostly confined to the frontal lobe, in keeping with typical development trajectories (Giorgio et al., 2008; Qiu et al., 2008). In comparison, the HFA group showed a distributed pattern of age-related increases in FA. Interestingly, a number of the regions involved were adjacent to temporal and frontal language processing areas, suggesting delayed maturation of linguistic pathways. Current models of brain development in autism support accelerated growth in early years (<3 years old) followed by a halt in growth (Ben Bashat et al., 2007; Courchesne et al., 2004). However, little is known about the maturation of brain networks in autism in adolescent years, as studies have typically involved younger children, or spanned a large age range (Courchesne et al., 2005). Insofar as numerous regions showed significantly greater correlation between FA and age in HFA compared to controls (Figure 5.3a), development appears to resume in HFA in teenage years, with pronounced differences in regional growth of white matter integrity compared to CTRL. The functional implications of such late maturation need to be investigated to determine whether it is due to consolidation of existing pathways, or to adaptive plastic reorganization. The HFA group also showed a steep decrease in FA with age within parietal white matter. As children with autism have been argued to rely on parietal visuospatial processes in cognition, this decrease warrants further investigation.

White Matter Tracts Underlying Visuospatial and Linguistic Processes in HFA versus CTRL

Negative correlations between FA and response times on the V+S condition reflected white matter tracts relevant to processing strategy preference.

In the HFA group, FA was negatively correlated with reaction times on the V+S condition within the ILF posteriorly near the lateral occipital cortex, as well as in white matter near the fusiform area. The HFA group showed a similar pattern within the left ILF near the ITG/MTG, and within white matter near the left superior parietal lobule, consistent with the group's negative correlation between FA and response times on the V condition in the SLF posteriorly within the parietal lobe. Both the V and V+S conditions, therefore, appear to rely on parietal visuospatial and ventral visual pathways, in support of a preference for visual strategies in posterior brain regions in autism (Sahyoun et al. 2009; Sahyoun et al., submitted). It has been proposed that parieto-occipital and ventral visual stream networks are preserved in autism, possibly providing an advantage in visuospatial tasks (Belmonte and Yurgelun-Todd, 2003; Boddaert and Zilbovicius, 2002; Koshino et al., 2008; Manjaly et al., 2007; Ring et al., 1999).

In the CTRL group, FA correlated with reaction times on the V+S condition within the uncinate fasciculus near the IFG, possibly reflecting the use of frontal linguistic processes. As we have shown previously , typically developing children appear to favor the use of semantic information in the V+S condition. In addition, the negative correlation between FA and response times on the V condition was greater in CTRL than in HFA within the anterior body of the corpus callosum and forceps minor, suggesting a an involvement of both hemispheres for solving the V condition in CTRL, especially in the frontal lobe. This is in keeping with reports of decreased FA within the CC in autism (Alexander et al., 2007; Keller et al., 2007), and with our earlier fMRI study where the CTRL group showed increased activation of frontal language areas, bilaterally (Sahyoun et al. submitted).

It therefore appears that visuospatial reasoning, in the presence of available verbal mediation, relies on intact frontal interhemispheric fibers in typically developing children, but on parietal and ventral temporal connections in HFA.

The CTRL group showed a negative correlation between FA and response time on the Semantic condition in the SLF within the frontal lobe; importantly, the HFA group did not show any significant correlation between white matter integrity and performance in this condition, possibly reflecting inadequately developed language pathways. Difficulties with semantic processing, though not evident in this study, for reasons explained earlier, are thought to stem from impaired activation of frontal areas Harris et al., 2006). Significant differences in RT-FA correlations between the groups in the S condition were also found in the corpus callosum, SLF near the middle temporal gyrus, and in the left ILF near the superior temporal gyrus, pointing to significantly increased use of pathways connecting the temporal and frontal language regions, as well as to increased reliance on bilateral processing networks, in typically developing children. Language pathways thus appear to be structurally more robust in CTRL than in HFA, in keeping with the lack of correlation between STG volume and language ability in autism (Bigler et al., 2007). Additionally, decreased FA has also been found in th temporal stem, STG and along the SLF in individuals with autism. (Lee et al., 2007; Barnea-Goraly et al., 2004; Keller et al, 2007), consistent with decreased functional connectivity between STG and IFG (Groen et al., 2008; Just et al., 2004; Muller et al., 1998). Finally, the difference in correlation within the ILF, showing increased relevance of the ILF to semantic reasoning in CTRL compared to HFA, may reflect a lack of connectivity between the fusiform and frontal regions, as predicted by Koshino et al. (2008).

The current study aimed at examining disruptions in white matter integrity in children with autism, in relationship to age as well as performance on visuospatial and linguistic processing tasks. In agreement with previous research, we found decreased FA in autism within long-reaching white matter tracts, especially to the frontal lobe, as well as within frontal callosal fibers. In contrast, children with HFA presented increased FA in radiate and ventral temporal white matter, consistent with models of local overconnectivity and ventral visual stream development in autism. We also found evidence for increasing FA with age in the HFA group, but not in typically developing controls, in a number or tracts throughout the brain, suggesting delayed white matter maturation during adolescence in autism. Correlating fractional anisotropy in the brain with processing efficiency in different pictorial reasoning conditions revealed that performance on visuospatial tasks may rely on peripheral U-fiber connectivity and on ventral temporal processing in autism, whereas typically developing children engage a bilateral frontal network. In semantic reasoning, there was a lack of correlation between FA and response times in HFA, possibly reflecting poorly a developed language network, whereas typically developing children revealed intact fronto-temporal language connections. Taken together, the white matter findings in this study provide neurobiological support for a discrepancy in visuospatial versus linguistic processing abilities frequently found in autism.

Chapter 6: General Discussion

The work presented in this thesis aimed at understanding the neurobiological underpinnings of the dichotomy between linguistic and visuospatial skills in higher-level cognition in autism. To this end, we designed a picture-based problem-solving task that equated cognitive complexity across conditions, while manipulating the availability of linguistic vs. visuospatial mediation for successful solving. The paradigm used consisted of three conditions: Semantic, requiring pictorial access to concepts illustrated by individual pictures (i.e. referents) and drawing relationships between these concepts; Visuospatial, requiring visuospatial manipulations of meaningless geometric forms, and Visuospatial+Semantic, a hybrid condition requiring visuospatial manipulations of items with the availability of verbal mediation. We used this task to examine behavioral differences in cognitive profiles, and to relate these to their functional and structural underpinnings, using neuroimaging, as seen in Chapters 3-5. We examined within- and between-group differences in cortical activation as a function of task condition, established diffusion tractography pathways between a subset of critical processing nodes, assessing the structural integrity of white matter along these pathways, and performed a whole-brain investigation of white matter tract differences between high-functioning autism and control subjects, as well as correlating tract integrity with age and with processing efficiency in each condition. This allowed for the emergence of a pattern underlying the structure-function relationship of the autistic cognitive profile. In this chapter, we first discuss similarities in autism and typically-developing participants in the three pictorial reasoning conditions, as well as their underlying neuroanatomical signatures. We then note how our behavioral, functional, and structural findings support a neurocognitive bias towards pictorial mediation of higher cognitive functions in autism. Finally, we discuss our structural findings in the context of developmental deficits in white matter integrity in autism, and their relationship to current theoretical models.

6.1. Similarities between ASD and CTRL

We found that children and adults with Asperger syndrome (ASP) and high-functioning autism (HFA) did not differ from age and IQ-matched typically developing participants (CTRL) in accuracy or speed in any of the conditions. These findings clearly indicate that individuals on the autism spectrum, but without intellectual deficiency as assessed by full-scale IQ, are able to perform higher-order cognitive tasks presented pictorially, regardless of visuospatial and semantic processing demands. In addition, the functional networks involved in solving pictorial reasoning problems, and the modulation of this network by the cognitive requirements of each condition were greatly similar in CTRL and HFA (see chapter 4): visuospatial reasoning showed increased activation compared to semantic reasoning within occipito-parietal and superior frontal regions, whereas the semantic condition elicited increased activation in the left hemisphere IFS and STS, as well as in the occipito-temporal and ventral fusiform regions bilaterally. The V+S condition, in turn, engaged more areas related to visuospatial processing than the S condition, yet more areas involved in language processing than the V condition.

We therefore established that individuals with high-functioning autism or Asperger syndrome share many processes in pictorial reasoning with their typically developing peers. In fact, aside from a qualitative increase in response times, the ASP group had the same cognitive profile as controls, and only differed in that they showed a correlation between accuracy on V+S and verbal IQ, whereas CTRL did not. This is in keeping with relatively spared language functions in Asperger syndrome (Volkmar, 2004). Our findings in high-functioning autism are in turn consistent with evidence that linguistic difficulties in autism are most evident in tasks requiring verbal mediation in the form of overt of inner speech strategies (Joseph et al., 2005). As such, the use of pictorial stimuli, unbiased towards verbal mediation, allows children with autism to reason similarly to controls, as suggested in previous studies (Dawson et al., 2007; Plaisted et al., 1998).

Within the pictorial domain, then, autism appears to be characterized by relatively intact access to semantics (Kamio & Toichi, 2000) as well as relatively intact ability to draw relationships between picture referents. This may suggest that in picture-based reasoning, the autistic profile of abilities is better characterized by patterns of cognitive preference or bias, as opposed to deficits.

6.2. Differences between ASD and CTRL

The existence of exclusive diagnoses between Asperger syndrome and high-functioning autism has been contested (Ghaziuddin et al., 2008; Klin et al., 1995; Koyama et al., 2007; Mayes et al., 2001; Miller & Ozonoff, 1997; Mottron, 2006; Witwer & Lecavalier, 2008), as the diagnosis of Asperger syndrome is one of exclusion and depends on testing tools and operationalization methods (Klin et al., 2005). Although we did not include Asperger syndrome participants in our imaging studies, our behavioral findings suggest important differences between ASP and HFA. Individuals scoring above the ADI threshold for autism and with normal-range IQ, but without significant early history of language delay (ASP), differed from their peers with early language difficulties (HFA) in their respective cognitive profiles: Whereas HFA showed a preference for visuospatial mediation strategies, ASP had a similar response time profile as typically developing participants, with lower RT for V+S than for V or S, attesting to the facilitative effect of having both visuospatial and linguistic mediation routes available in these two groups. It therefore appears that the relationship between visuospatial and linguistic abilities may be a more powerful metric for differentiating ASP from HFA than absolute differences in language abilities alone. We expect that the underlying functional neuroanatomy in our task would be similar in ASP and CTRL, in keeping with our behavioral results. However the interesting correlation between verbal IQ and the V+S condition accuracy in ASP, but not in CTRL, warrants closer examination and may suggest alterations in processing strategies in ASP.

Despite similar performance and functional brain networks in HFA and CTRL in pictorial reasoning, we established clear differences in their respective cognitive profiles and found biases in the underlying processing centers recruited, as a function of task condition. As seen in Chapter 3, HFA participants showed reduced processing efficiency when linguistic mediation was necessary. Conversely, they benefited from the availability of visuospatial mediation strategies. In fact, in the hybrid V+S condition, HFA showed a correlation between accuracy and performance IQ, confirming the utilization of nonverbal resources. These findings suggest that early language delays in HFA may persist in the form of increased reliance on pictorial and visuospatial strategies, at the expense of language mediation (Dakin & Frith, 2005). As seen in chapter 4, this view is consistent with intact posterior brain networks and decreased activation in frontal language regions in HFA compared with CTRL (Manjaly et al., 2007; Kana et al., 2006; Just et al., 2004). Lower white matter integrity between ventral temporal and inferior frontal regions, as found in our tractography analysis, may be related to the decreased frontal activation, and thus favor of an important role for the ventral temporal lobe in autistic cognition. In fact, the HFA group showed correlations between processing speed on the V and V+S conditions and white matter FA in the parietal and ventral temporal regions (Chapter 5), confirming increased reliance on posterior networks in pictorial reasoning. Conversely, the CTRL group showed increased reliance on fronto-temporal language networks in semantic reasoning, and were shown to recruit an extend language network including hemispheric homologues (Harris et al., 2006), in keeping with increased correlation between processing speed in the semantic condition and FA in the superior longitudinal fasciculus (connecting frontal and temporal regions) and corpus callosum.

6.3. Structural Anatomy of Pictorial Reasoning in Autism

In chapter 5, we presented evidence for overall differences in white matter integrity between the groups, such that long-ranging tracts to the frontal lobe showed lower FA in HFA, whereas peripheral white matter had higher FA, compared with CTRL, in U-fibers of the frontal lobe, as well as in the temporal pole. These results, again, may point to increase reliance on "local", peripheral networks, as well as on ventral temporal processing regions in HFA. We also found that white matter maturation dynamics may be different in autism during adolescence, in keeping with findings of abnormal brain growth early in life (Kennedy & Courchesne, 2008). Indeed, whereas the CTRL group showed increasing FA with age primarily within the frontal lobe, HFA participants had a widespread pattern of increasing FA between 9 and 18 years of age, possibly pointing to delayed growth of connections compared with typical development (Ben

Bashat et al., 2007). These alterations in connectivity patterns may be related to the formation of local networks and to increased reliance on posterior brain functions at the expense of language functions (Belmonte & Yurgelun-todd, 2003; Boddaert & Zilbovicius, 2002; Groen et al., 2008).

Taken together, these findings provide a picture of disrupted white matter growth, resulting in decreased connectivity between frontal and posterior brain regions in autism. Reduced activation of frontal language regions and increased reliance on ventral temporal and occipito-parietal networks in turn explain a cognitive bias towards visuospatial mediation and decreased efficiency in linguistic processing (Kana et al., 2005). It is worth noting, however, that our results are uninformative as to the causal effects between connectivity, language and visuospatial bias, such that the brain-behavior events leading to this pattern remain to be elucidated.

Our results are thus in keeping with recent models of underconnectivity in autism (Hughes, 2007; Kennedy & courchesne, 2008). We note that a view of autism as a disorder of connectivity may in fact reconcile apparent discrepancies between current theories of autism. Whereas it is tempting to approach autism though a theory or expertise-focused window of methods and interpretation, the models of autism are not mutually exclusive or contradictory. As such a "big picture" framework is necessary to assemble together the wealth of heterogeneous findings in autism (Belmonte 2009, personal communication). Atypical patterns of connectivity in the autistic brain, albeit vague, may provide such a framework. For example, decrased long-distance connectivity may explain local processing focus and expertise (Mottron et al., 2006), as well as difficulties with integration of information within the frontal lobe (Happe & Frith, 2006), reduced task switching and executive control in autism (Russo et al., 2007), or impaired ability to process complex tasks (Minshew et al., 2007). Our results support the notion that autism is a disorder of imbalance between cognitive processing abilities and styles, supported by alterations in frontal connectivity patterns.

6.4. A Comprehensive Model of Autistic Cognition?

Our results disambiguate the heterogeneous behavioral findings regarding semantic use in autism, and provide insight into neuroimaging findings of language use and reasoning in autism. Whereas some studies have highlighted intact semantic access via pictures, others have questioned the flexibility of semantic representations in working memory, as well as the verbal components of executive functioning. We have demonstrated that whereas encoding of semantic information is intact, verbally-mediated manipulation of concepts may be inefficient in autism. Instead, HFA show a cognitive profile in favor of pictorial/imagery mediation of thinking processes.

Separate studies have identified reduced activation in certain language areas, recruitment of non-language regions in verbal tasks, and evidence for more general connectivity abnormalities. We believe that the language-visuospatial dichotomy in autistic cognition is rooted in reduced frontal verbally-mediated support of semantic processing in the temporal lobe: the verbal-semantic "loop" between frontal and temporal regions may be weak or inefficient in autism, yielding inadequate sub-vocal verbalization of semantic concepts, supplanted by strong visuospatial and pictorial abilities, evident in the intact posterior connectivity between parieto-occipital and ventral temporal areas associated with visuospatial processing. Thus, the decreased use of verbal strategies in autism is reflected by decreased frontal activity and by patterns of brain connectivity showing underconnectivity to frontal language centers.

These results suggest a relationship between peaks and valleys of abilities in autism. Rather than imposing a causal linear model whereby all autistic symptoms can be traced back to an original insult, we believe that a brain-behavior reinforcement cycle provides a pattern of inefficient and preferred processing networks. As such, it may be useful to consider that autism does not result from a sequence of problems, but instead may emerge from the interactive evolution of brain regions under some developmental constraints. This approach would shed light onto our understanding of autistic disorders, and suggests that current, deficit-centered models, could be combined into a consistent, development-centered framework for characterizing autism.

The concept of a single, comprehensive model of autism, taking into account cognition, behavior, and biology, faces first and foremost the major obstacle of heterogeneity of signs, symptoms, and their severity (Happe et al., 2006; Geschwind, 2007; Waterhouse, 2008). In fact, Happe et al. (2006) argue that despite clustering of the three classes of symptoms of autism, it is unlikely that these stem from a single core cognitive, biological, or genetic influence. Cognitive models of autism can broadly be grouped as "social-first" models, which satisfactorily explain social and communicative traits (ToM, mirror-neuron etc), or general cognitive models, which pose high-level difficulties in mediating information (WCC, executive dysfunction etc.) or low-level salience of information (EPF). These may be seen as "social-last" accounts whereby atypical fundamental processes needed for social and communicative functions to develop are the primary deficit (Figure 6.1). A systematic review by Happe & Ronald (2008) showed that the three cardinal symptoms of autism (social, communication, behavior) can be fractionated cognitively, genetically, and neurobiologically. As such, no single theory of autism satisfactorily explains all signs and symptoms of the disorder. For example, Happe and Frith (2006) have argued that WCC could explain all non-social symptoms in autism, but is independent of social difficulties. As another, broader example, it is often assumed that rigid traits, perseveration, and repetitive and specialized behaviors, as well as social and linguistic difficulties, could be related to cognitive inflexibility. However a review of cognitive flexibility tests in autism has shown that this may not be the case, possibly reflecting the discrepancy between controlled cognitive experimental paradigms and ecological situations (Geurts et al., 2009).

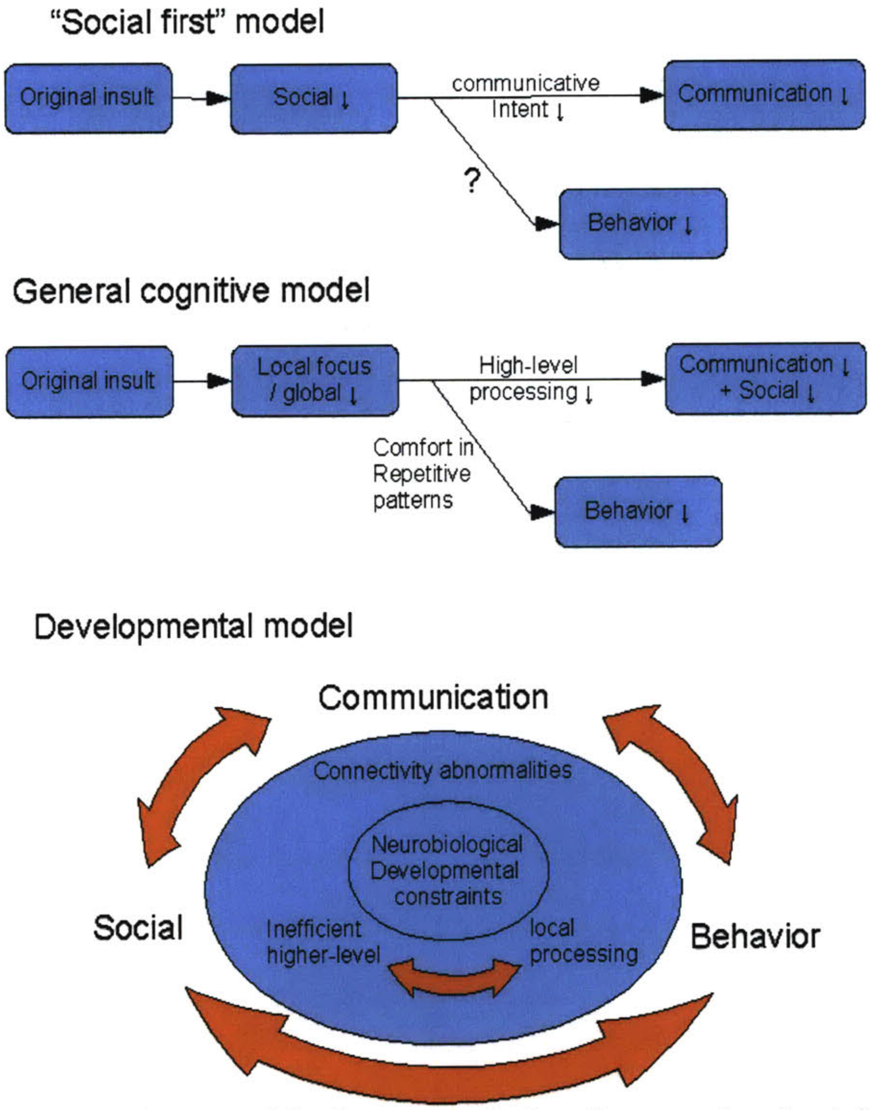


Figure 6.1. Current linear models of autism can be broadly grouped as "social first" and general cognitive models. Our results are consistent with a development-centered model whereby symptoms of autism result from interactions between cognitive traits under developmental constraints.

From a neuropsychology perspective, the diagnostic triad of autistic symptoms point more readily to a core abnormality in neural development rather than to a central cognitive deficit (Minshew & Williams, 2007). Generic theories such as the connectivity hypothesis (Just et al., 2004; Takarae et al., 2007) have been argued to explain most symptoms in autism, as association and integration circuitry are central to most autistic characteristics (excluding non-cognitive impairments such as motor or gastro-intestinal problems). It appears, however, that not all long-distance tracts are affected, as Muller (2007) reports that subcortico-cortical functional connectivity is intact in autism, which may suggest that underconnectivity patterns reported in the disorder may be specific to the frontal lobe. This raises the question of how far apart two areas need to be in the brain for a connecting tract to be compromised. It is also worth noting that this distance, or length of a connection, may not itself be the cause of a problem but rather a common characteristic of impaired tracts. There is little understanding about the factors affecting the spatial localization of connectivity abnormalities, despite promising genetic and neuropathological accounts (Abrahams & Geshwind, 2008; Casanova et al., 2009).

The difficulty in identifying a biological or cognitive etiology of autism stems from the developmental aspect of the disorder. As such, an early injury or abnormality would have a series of repercussions that could easily diverge into the characteristic triad of symptoms. However, cascading events and brain-behavior cycles then make it difficult to trace back to the original insult(s). Current mechanistic models describing abnormal distributions of connectivity patterns provide the most complete, albeit non-specific, account of autistic symptomatology, and may be consistent with evidence for glial inflammation or minicolumnopathy (Casanova et al., 2009), as altered minicolumns would affect the geometry of gyral windows, thereby favoring shorter connections. Cognitively, Belmonte et al. (2004) proposed an interesting view that underselective or over-salient low-level processing may overload higher-level regions, resulting in a cognitive emphasis on representations that are closer to the original perceptual inputs. This is consistent with high levels of accuracy often seen in autism in cognitive tasks, as overloaded processing circuits may become inefficient, without becoming entirely defective, which would result in different compensatory cognitive strategies. Our results are consistent with this view, whereby higher-level recoding (verbalization) of perceptual or lexical representations is inefficient, in relation with compromised frontal connectivity. Decreased reliance on higher level processes could also lead to decreased cognitive sensitivity to contextual cues, as described by WCC models, which in turn may yield deficits in theory of mind, social interactions, and language development. In addition, an "overload" of sensory input may easily explain the relatively calming and comforting effect of highly reproducible behaviors and routines that individuals on the spectrum engage (Figure 6.1). The brain-behavior cycle produced by this pattern may provide a target process for pharmacological or behavioral interventions, by favoring the use of inefficient higher-level networks, or by preventing the exclusive reliance on low-level features (Belmonte et al., 2004). This is similar in concept to current clinical interventions which, for example, reward echolalic utterances when these are used appropriately and discourage them otherwise. Whereas genetic influences are now beyond question, as we discussed in section 2.1.1, genetic effects may be multiplicative rather than additive, which makes the identification of individual mutations elusive. Therefore, although there has been growing interest in linking genotypic variations to brain correlates of cognitive traits, effects are small and riddled with confounds (Bishop, 2009). The inclusion of siblings and first degree relatives presenting sub-clinical autistic traits (a.k.a. the broader autism phenotype) in recent research may lead to better characterization of genetic susceptibility and risk factors for autism. Animal models also hold great promise in elucidating the mechanisms involved in the disorder, by allowing the manipulation of postulated biological influences (e.g. hyperserotonaemia, GABA expression, or the cholinergic system), or of autistic-like behaviors (Abrahams & Geshwind, 2008; Belmonte et al., 2004). Our results provide one such opportunity and suggest that inhibiting the development of frontal connections or training animals towards perceptually-oriented behavior may provide insight into the neurobiology of autism cognition (Mottron, 2006). In addition, an approach such as ours, able to examine both behaviorally and structurally inefficient networks and cognitive preferences, would consequently prove extremely valuable in monitoring remediation and intervention programs in autism.

Chapter 7: Final Remarks and Suggestions for Future Studies

7.1. Conclusions

In light of the dichotomy between linguistic and visuospatial skills in autism, we aimed to identify the neural correlates of each set of ability. In addition, in order to avoid confounds imposed by inherently verbal tasks, and as it has been shown that individuals with autism have intact semantic access via pictures, we elected to use a high-level, pictorial problem-solving task. The stimuli developed (Appendix C) successfully allowed to identify cognitive preferences and processing biases in ASP and HFA. We found that individuals with Asperger syndrome resembled the control group in their cognitive profile, whereas there was a cognitive bias in high-functioning autism towards visual processes in ventral temporal and parieto-occipital posterior brain regions, with decreased reliance on frontal language areas. This pattern was consistent with decreased white matter integrity between frontal and ventral temporal regions in HFA, as well as with increased reliance on posterior white matter tracts in relation to processing speed. In contrast, control participants engaged a fronto-temporal language network in reasoning, in keeping with increased reliance on long-distance connections to the frontal lobe.

We have demonstrated the usefulness of both innovative task design, and multidisciplinary imaging approaches in investigating cognitive profiles and their underlying neurobiology in autism. Autism Spectrum Disorders (ASD) are characterized by a variety of phenotypes and symptoms profiles. As such, understanding of the neurocognitive biology of autism requires 1) a well-defined study population and matched typically developing comparison participants; 2) a task design aimed at specific cognitive aspects of interest; 3) a neuroimaging approach that will integrate the functional and structural networks underlying behavioral performance. The value of this approach lies in its complementarity. Indeed, only by identifying specific behavioral atypicalities, the brain functional networks generating this behavior, and precise anatomical locations of white matter disruptions, can one obtain a systemic neurocognitive picture with enough information to suggest behavioral or pharmacological intervention targets. We have clearly identified a decrease in efficiency in semantic processing in autism, supported by increased reliance on posterior brain processing centers, in turn related to a disruption of frontal connections. This suggests remediation and education approaches that capitalize on pictorial mediation strengths in autism. In addition, although the aetiology of patterns of decreased connectivity lies in the investigation of early cellular and molecular pathology, possibly guided by breakthroughs in the identification of susceptibility genes, our findings point to potential pharmacological agents to prevent disconnections or promote structurally sound axonal growth.

It is worth noting that the current thesis addressed visuospatial and linguistic processes but that the integration of multiple approaches could equally provide better understanding of social and behavioral aspects of ASD.

7.2. Suggestions for Future Studies

In chapter 3, we observed differences in the cognitive profiles of individuals with and without autism. However, the wide age range of our participants, while providing statistical power, may have cost decreased sensitivity to age-specific deficits. In fact, we found that children showed more variance in both response time and accuracy than older individuals. The reproduction of our findings using smaller age ranges may, thus, give insight into developmental effects on the altered cognitive profile in autism. In addition, an adaptation of the task, aimed at even younger children, may allow one to monitor language development in relation to the cognitive profile of autism: whereas it is likely that the cognitive profiles observed result from a brain-behavior cycle reinforcing visual information processing in detriment of language skills, it is unclear whether perceptual biases or specific language difficulties (or even a prior origin, such as non-specific connectivity alterations) may have initiated this cycle.

Our tractography analysis yielded differences in ventral fronto-temporal structural integrity in autism. However, we averaged fractional anisotropy across the entire tract obtained, which may have "hidden" localized disruptions in white matter, as we did not reproduce earlier functional connectivity findings of fronto-parietal underconnectivity (Just et al., 2007). This may also explain the differences in findings between tractography and skeleton-based statistics (chapters 4 and 5). Future refinements of quantitative tractography (Salat et al., 2008), may give opportunities to examine the structure of functional pathways with increased spatial accuracy. In addition, integration of structural integrity findings with emerging methods of effective connectivity would allow one to accurately pinpoint the "breakdown" in structure related to the functional networks underlying autistic cognition. Finally, the advent of combined molecular and functional imaging methodologies will provide a critical missing piece by tying macroscopic to microscopic brain manifestations of the disorder.

The most challenging aspect of addressing the autism puzzle remains that the continuum fades into normal variance of cognitive characteristics. As such, neurobiological models will need to factor in the modulation of individual traits. Despite a prolific research community, it is still unclear how to reconcile the variety of phenotypes to any core biological trigger(s). Whereas the present thesis focused on a well-defined and characterized subtype of autism, the neuro-behavioral characterization of phenotypes will be paramount to understanding autism and helping children and their families.

APPENDIX A: PRINCIPLES OF MAGNETIC RESONANCE IMAGING

The basis of the MR signal

Atomic nuclei have a quantum property called spin, representing their momentum and direction of rotation. In natural conditions, nuclei have random spin orientations, but when a uniform magnetic field (MF) is applied, a portion of them will align with it, either in phase (low energy) or in antiphase (high energy). Protons precess around this MF with a frequency (the Larmor Frequency), proportional to the strength of the MF and to a fixed property of the nucleus, the gyromagnetic ratio. The aligned spins can then be excited into higher energy levels by the application of radio frequency (RF) pulses that match the Larmor frequency, and move their axis of rotation away from the static field direction. As nuclei "relax" (i.e. re-align with the uniform field), energy is released at the Larmor frequency, and detected by a receiving RF coil. Contrasts in MRI are generated by differences in nuclei relaxation times of hydrogen in water, and localisation is achieved by using small magnetic field gradients (25-40mT/m), added three-dimensionally to the large static field (1.5-7T). These gradients result in the emission of energy at a different resonant frequency, which is proportional to the total magnetic field at each point. Therefore a given frequency will correspond to a specific spatial location, dependent on the total applied field, and the timing of energy emission will reflect tissue properties.

Spin-lattice relaxation is induced by interactions between the nuclei and their surroundings, and is characterised by a rate constant T1. After T1, excited nuclei have regained 66% of their relaxed magnetisation, and after 3T1s, 95% of the original magnetisation has been recovered. If enough time is not allowed for relaxation, the signal from the tissue in question drops; hence reducing the inter-pulse delay (TR) will emphasise contrast between short T1 regions (tissue water, < 1sec.) with respect to the smaller signal generated by areas with longer T1 (CSF water, > 1sec.).

A single proton will relax in T1 milliseconds without interference, but if there are several nuclei interacting with one another, they will lose energy at each collision, and hence lose energy coherence in their emission pattern. As protons interact, energy is lost exponentially. This is called spin-spin relaxation time (T2). T1 and T2 are decay times in the longitudinal and transverse directions respectively. If the time between nuclei excitation and signal detection (TE) is increased, then long T2 brain matter (grey) will produce a relatively greater signal than slower T2 tissues (white matter). Altering the pulse sequence (excitation and recording) of MR scanning will therefore allow to selectively image different tissues and different tissue properties. The change in net magnetisation of spins over time is described by the Bloch equation, which is solved to obtain the magnetic signal and hence forms the basis of image reconstruction.

Due to the nature of the frequency-encoded signal resulting from the spatial magnetic field gradients, data is acquired in frequency space, and each line of this "k-space" is the frequency spectrum of a whole slice. Echo-Planar Imaging (EPI) uses rapid switches of the MF gradients to allow the whole k-space to be sampled after one RF pulse. EPI is a much faster scanning technique and is therefore preferred in fMRI studies. The raw data is then Fourrier transformed to obtain a brain image. The intensity at a particular voxel depends on the amount of signal recorded at the voxel's frequency and phase.

The source of the functional signal

The magnetic properties of blood change according to its oxygenation state:

oxyhaemoglobin (HbO2) is diamagnetic, and hence shows reduced magnetic flux compared to the more paramagnetic deoxyhaemoglobin (Hb), which produces steep local MF gradients. This difference in magnetic susceptibility produces field distortions, which reduce T2 to shorter, T2* relaxation times, therefore offering a contrast mechanism to localize regions of increased oxygen consumption, thought to reflect brain activity. As T2/T2* obeys an exponential relationship to the ratio of Hb/HbO2 (Thulborn et al., 1982), the rate of change of T2* is a *Blood Oxygenation Level Dependent* phenomenon (BOLD), which can be observed with fMRI.

Brain activity is known to be related to increased blood flow, blood volume, glucose utilization, and venous oxygen concentration. The latter is believed to form the basis of the BOLD signal. To compensate for the local oxygen consumption, arterial flow or vasodilatation occurs, resulting in a total net increase in oxygen level (because the loss of O2 is overcompensated), and therefore generate an increase in signal.

Neurotransmitter capture and transport back to the presynaptic button appear to be the most energetically demanding processes in signal transmission in the brain, and there is much debate regarding the relationship between oxygenation level and neuronal activity. In addition, oxidative metabolism and ensuing signal changes are highly dependent on local vascularization and haemodynamic properties of the blood. As such, changes in image intensity (1-10%) due to T2* signal loss are an **indirect** measure of brain activity.

Whereas the spatial resolution of fMRI is typically between 1-3mm, depending on voxel size, the haemodynamic response function typically reaches its peak in 6-10 seconds although this varies across regions, individuals, and disease. Practically, however, the temporal resolution depends on TR, the delay between consecutive acquisitions of data for a particular slice. There is a lower limit to TR, as sufficient T1 recovery time is necessary to obtain sufficient signal, around 1-1.5sec. It is worth noting that low TRs require fast gradient switching and hence hardware considerations play an important role in temporal resolution.

Diffusion tensor imaging

Diffusion is the thermodynamic movement of molecules through space. If a magnetic gradient is applied, diffusing water molecules would experience different total fields, hence causing an exponential drop in MRI signal. This drop is characterized by a *b* factor, describing the duration and strength of the applied gradient, and by the apparent diffusion coefficient, D. In a homogeneous medium (e.g. cerebro-spinal fluid), D is constant regardless of direction (isotropic diffusion), whereas structures in the brain yield directional constraints to water movement, and therefore different diffusion coefficients depending on the orientation of the applied field. Diffusion tensor imaging (DTI) applies successive diffusion-weighted gradients to characterize local tensors, which describe an ellipsoid whose principal axis is that of easiest diffusion. As water diffusion is highly anisotropic around white matter tracts, with faster diffusion along axonal fibers, DTI may provide information about brain connectivity. For example anisotropy increases with white matter maturation, as myelin sheaths are formed and hinder water movement. Quantitative measures of diffusion can be used to infer white matter defects. Fractional anisotropy (FA) is the most commonly used measure, and quantifies the amount of directional cohesiveness at a given voxel. FA varies between 0 (isotropic water movement, i.e. no hindrance) to 1 (water can only move in one direction). As such, differences in FA reflect white matter integrity, as changes in width or permeability of axons will yield changes in FA. Conversely, mean diffusivity (MD) is a measure of the absence of orientation preference in diffusion (i.e. how "free" to move water is). Finally, axial and radial diffusivities (Da, Dr) represent the freedom of water movement parallel or perpendicular to the principal orientation of a voxel, respectively. These are therefore reflective of the permeability of tracts to water, and it has been argued that Da is sensitive to axonal degeneration, whereas Dr may be sensitive to demyelination.

APPENDIX B: IMAGE PROCESSING

Functional image processing

After an image has been reconstructed, pre-processing steps are used to correct for motion artifacts, exclude non-brain tissue, correct for signal loss, and increase the signal to noise ratio of the data using a set of spatial and temporal filters.

The analysis of fMRI data is performed using a *General Linear Model* (GLM), and relies on fitting an expected response to the data at each voxel separately (univariate analysis). Good correlation means that the voxel in question does show activation in response to the modelled stimulation (i.e. the brain region is "active").

The GLM has the form:

$$Y(t)=a_i.x_i(t)+b+e(t)$$

Where $y(t)$ is the 1D vector of intensity values over time for a given voxel; $x_i(t)$ is the model, also a 1D vector to which a value was assigned at each time point according to the expected response to each of the i conditions or stimuli, and is referred to as an explanatory variables (or regressor); a_i is the parameter estimate (PE), a scaling factor by which $x_i(t)$ is multiplied to fit the data; b is a constant representing the baseline value of the data (i.e. rest activation); and $e(t)$ is the error estimate, which accounts for noise and mistakes in model design. Note that $x_i(t)$ reflects the time course of each condition, and is typically generated from subject behaviour on the task. Statistical maps are obtained from the PEs, by dividing them by the error in their estimation. A t-value is thus calculated, which reflects the goodness of fit between the data and the model at each voxel. The combination of all t-values forms a t-map, and is converted into a Z or P probabilistic map showing areas of significant correlation between the data and the EVs. A z statistic is a “Gaussianised t”. PEs therefore assess the amplitude of the physiological response to a particular condition. It is possible to compare, or contrast, conditions and tasks by subtracting the corresponding PEs from each other. For example, to identify areas of the brain where one explanatory variable EV1 generates a stronger response than EV2, their respective PE are subtracted and this new estimate is divided by the standard error. This will show relative increases in brain activity between the two conditions. As these statistics are performed over a very large number of voxels, statistical correction for multiple comparisons is necessary, and can take the different forms. In this thesis, we used a permutation testing simulation, which randomly reassigns data to assess whether the current results have occurred by chance.

In order to obtain results that can be generalized to a particular population of interest, group statistics are performed which account for both within- and between-subject variance in the data. This requires registration of low-resolution fMRI images to individual high-resolution structural scans, themselves aligned to a common template, ensuring the overlap of structures across subjects for comparison.

Structural image processing

Whereas functional imaging relies on T2*-weighting of the images, high-resolution structural acquisition is T1-weighted. The present work used cortical reconstruction in order to obtain inflated surfaces that optimize inter-subject registration. The T1 intensity gradients are used to automatically identify the surface boundary between white and grey matter, and the boundary between grey matter and cortico-spinal fluid. These surfaces are tessalated using a finite element model and inflated while preserving the identity of vertices. This effectively generates a representation of the brain where cortical sulci and gyri are unfolded (Fig. A.1). Further inflation yields a spherical representation that can be used to align folding patterns across subjects, hence providing accurate correspondence between structures. Automatic parcellation of structural scans is then achieved by alignment with a spherical template, and functional activation can be registered onto the inflated template for group statistics and visualization.

Figure A.1. Illustration of an image reconstruction sequence. From left to right: white (green) and gray (red) matter segmentation; Pial surface; inflated surface (red, sulci; green, gyri); spherical inflation. (images courtesy of Bruce Fischl and Douglas Greve)

Diffusion tensor imaging processing

Pre-processing in diffusion tensor imaging typically consists of eddy current correction and motion correction by affine registration to a reference scan. Diffusion tensors are then fitted to the data at each voxel. Fractional anisotropy is often calculated to investigate group differences reflecting white matter abnormalities in clinical populations. However, voxel-based whole brain or region-of-interest approaches raise significant issues because of image smoothing and registration limitations. Tract-based comparisons appear to be more robust, and rely on comparing FA values within individually defined pathways, either by specifying seed voxels and following a tractography algorithm, or by generating skeletonized networks of dominant white matter bundles:

1) Probabilistic Tractography:

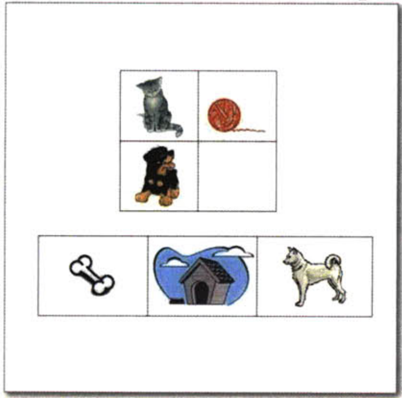
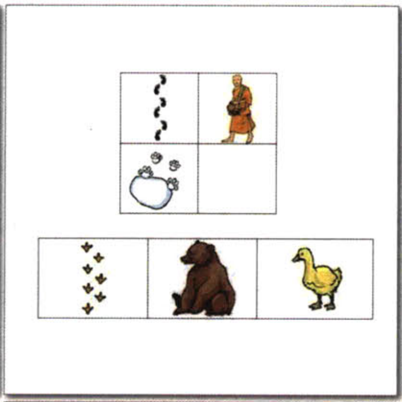
Tractography analyses follow the principal diffusion direction from voxel to voxel to obtain the path of minimum resistance to water movement, hence constructing pathways, typically restricted by maximum turn angle and step length. In probabilistic tractography, Markov Chain Monte Carlo sampling is used to build distributions on diffusion parameters at each voxel. Repetitive sampling from the computed distributions on principal diffusion directions generates a set of streamlines forming a connectivity distribution. When a region of increased path uncertainty (unclear principal direction) is reached, the streamlines thus "split apart", eventually resulting in a connectivity distribution map. This allows for the use of seed masks based on fMRI to establish probabilistic pathways of least resistance to water movement between activated areas. Mean FA within individually-tracked pathways may then be related to the integrity of functional networks.

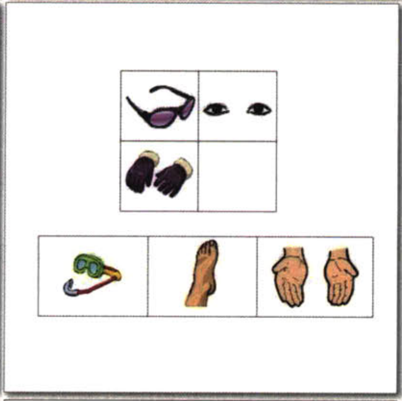
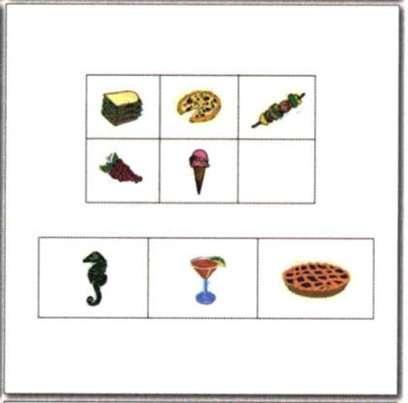
2) Tract-based statistical comparison of fractional anisotropy:

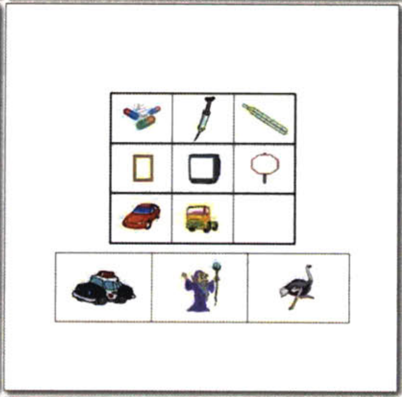
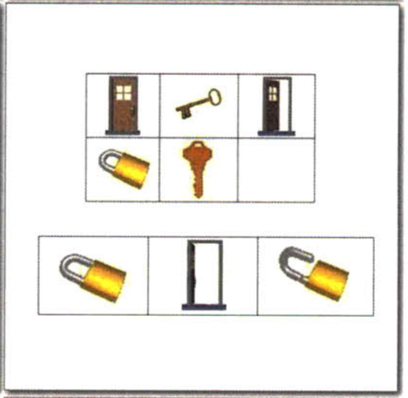
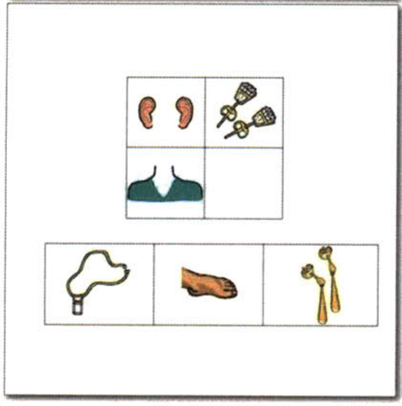
This method (used in Chapter 5) relies on nonlinear registration of FA maps, followed by the creation of a "core" skeleton obtained from local maxima of average FA. Each subject's maximum FA is orthogonally projected onto this skeleton, thus ensuring the comparison of the center of each tract, notwithstanding individual variability in path. Statistical analysis can then be performed using a GLM, similarly to fMRI analyses.

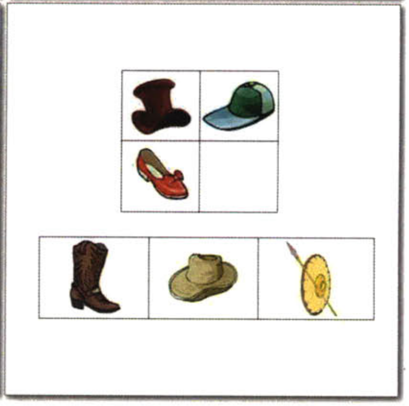
APPENDIX C - STIMULI

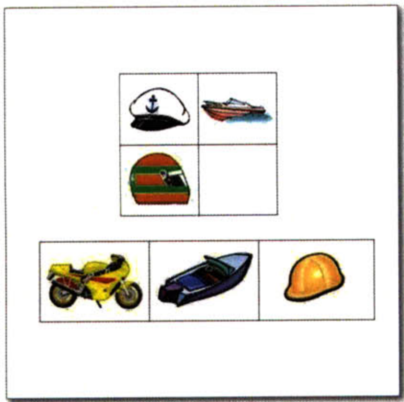
Semantic condition Problem plates:

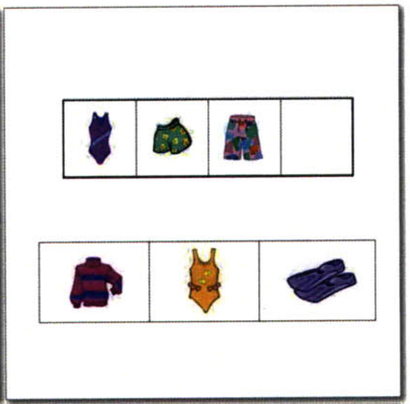
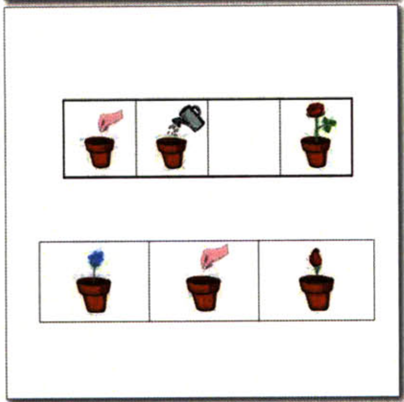
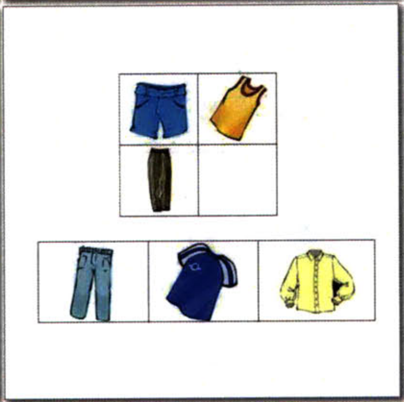



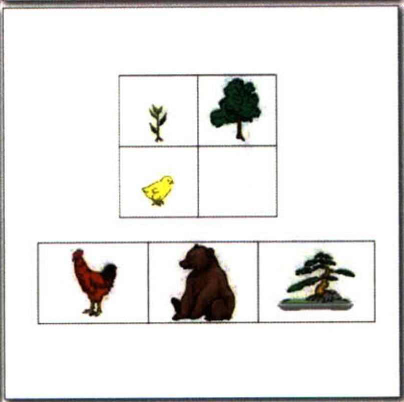
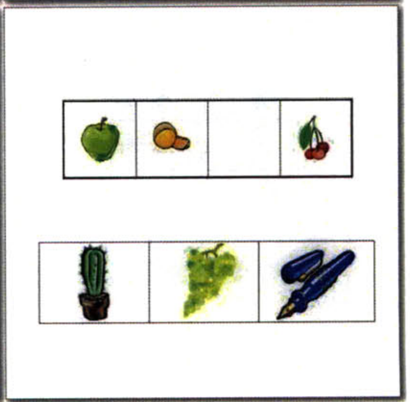
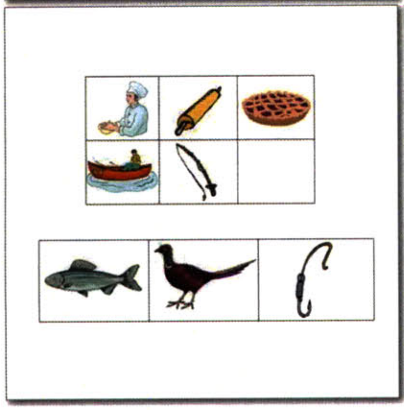




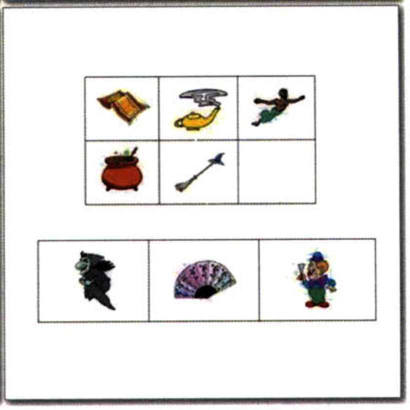




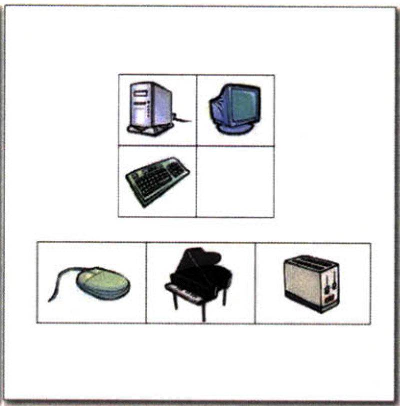
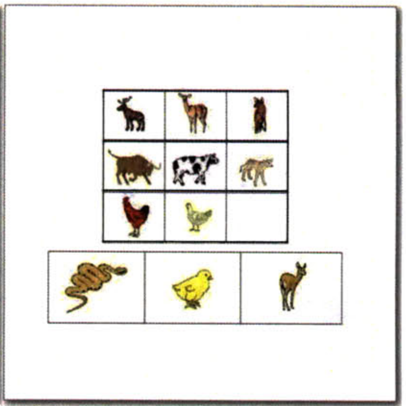
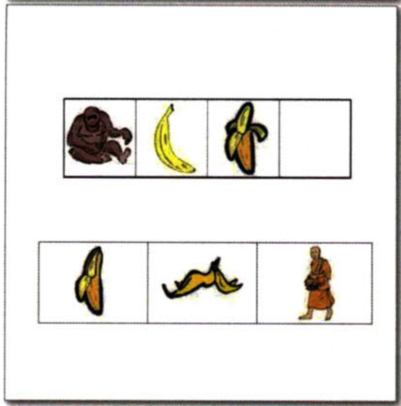
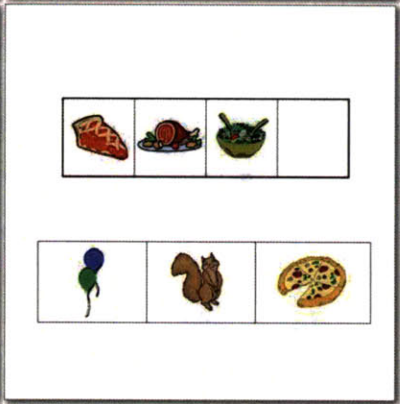


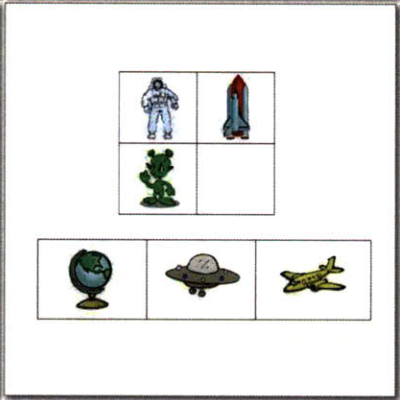
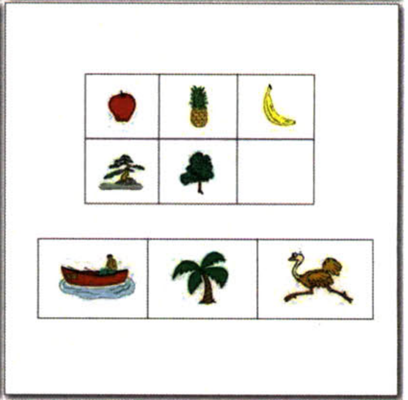
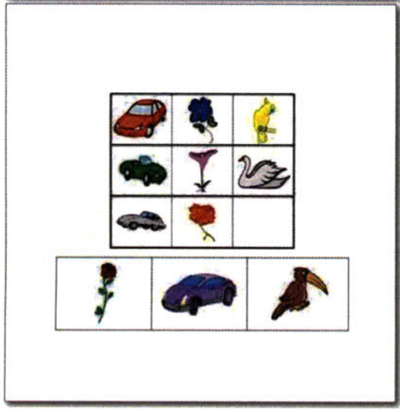
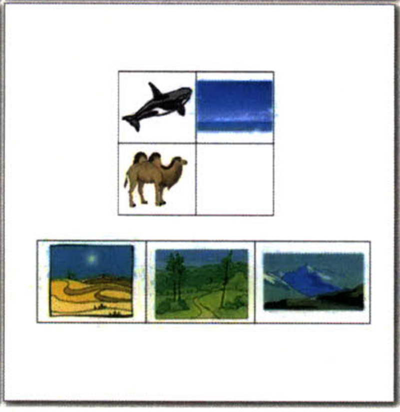


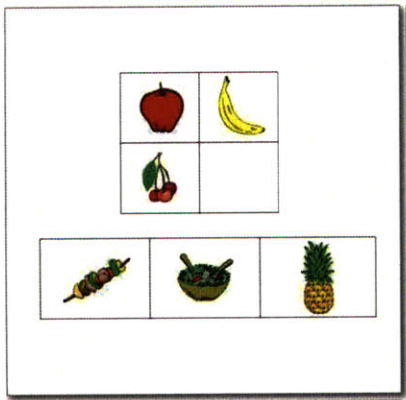




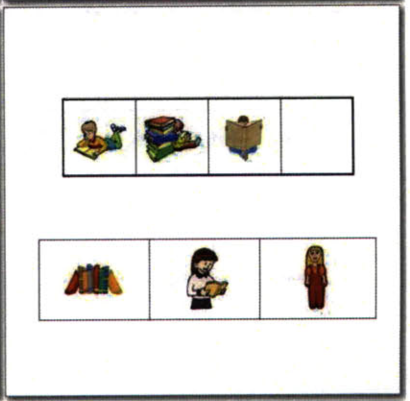


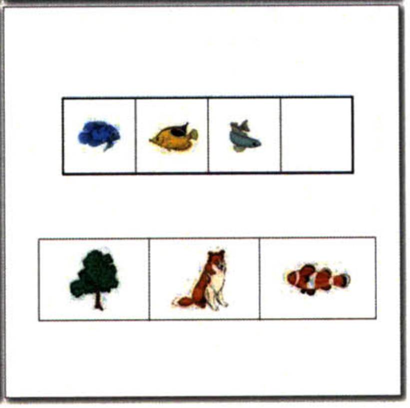





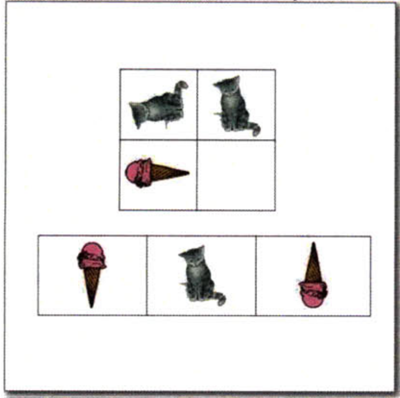



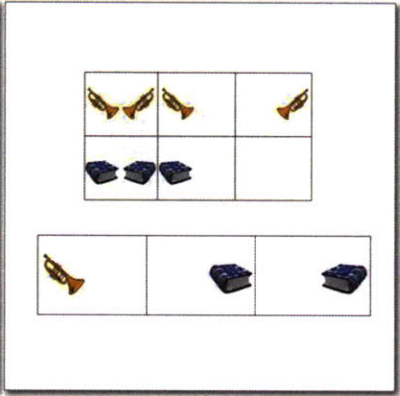


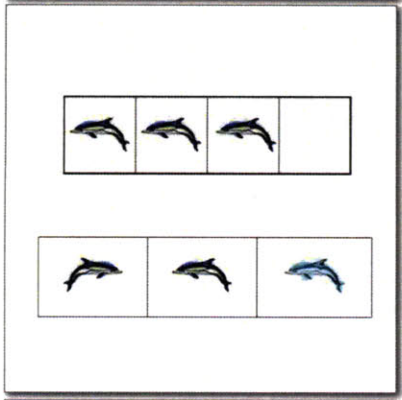


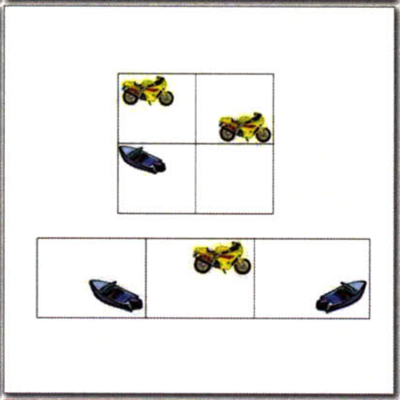


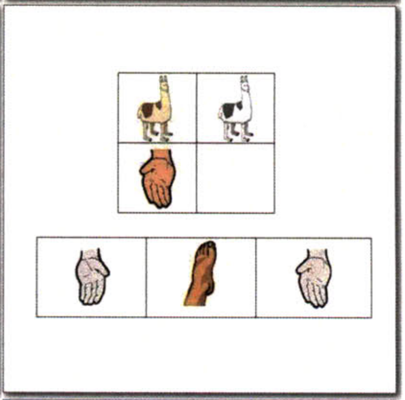
Visuospatial+Semantic problem plates:

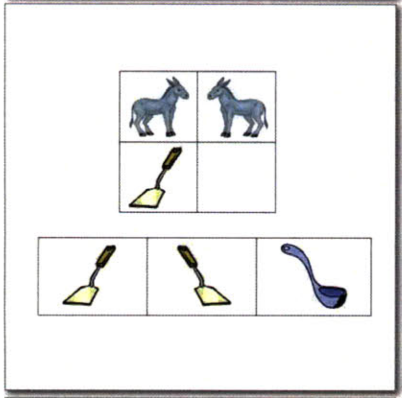


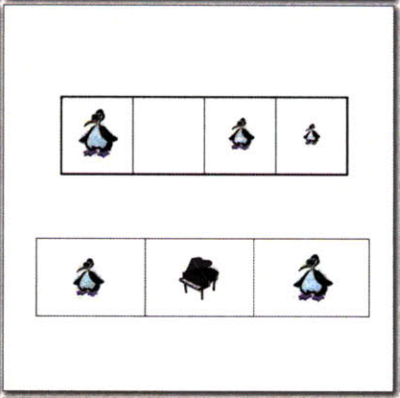


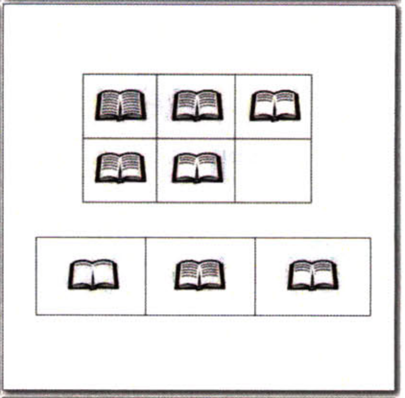


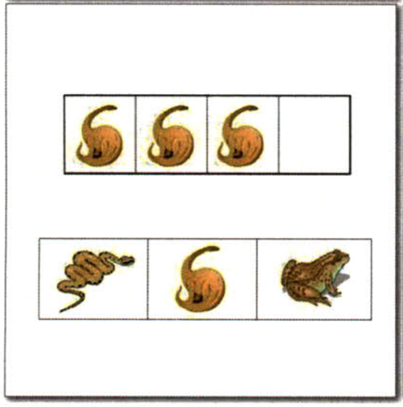


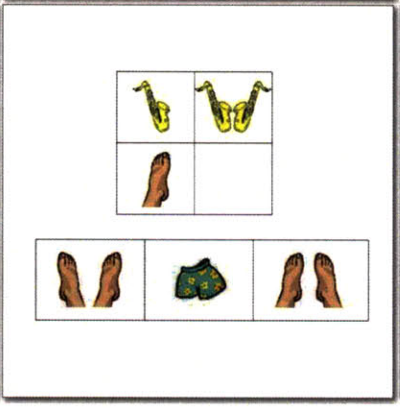


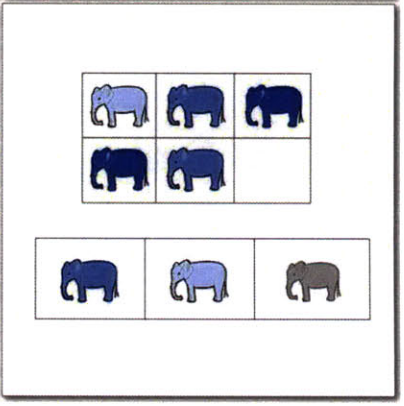


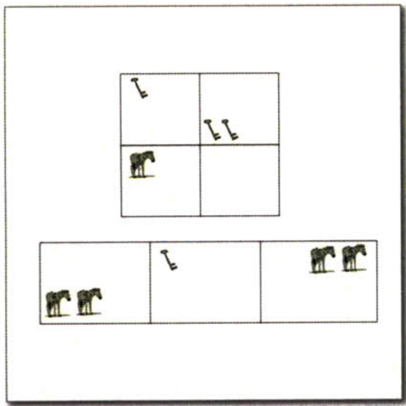
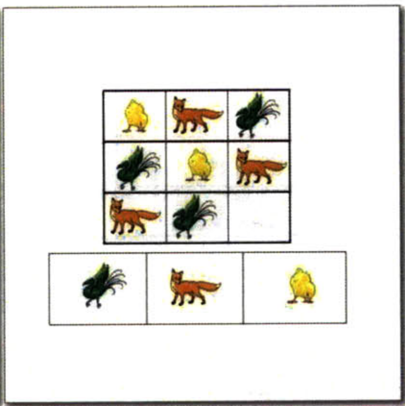
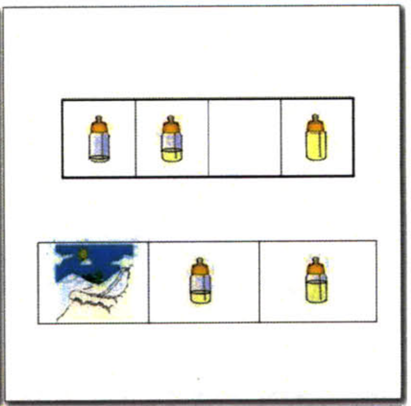
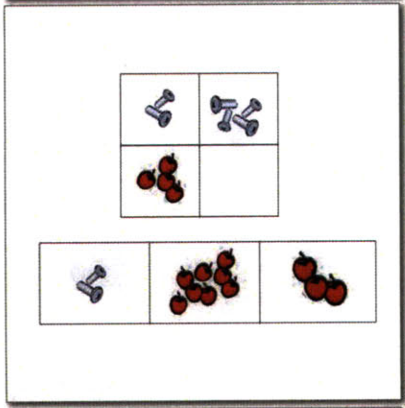


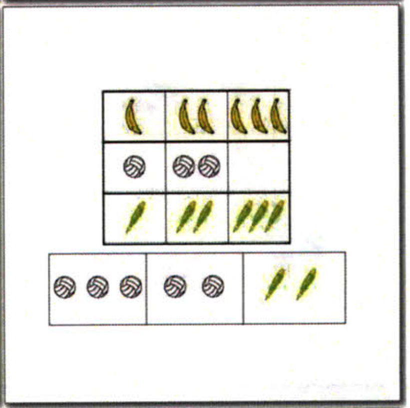


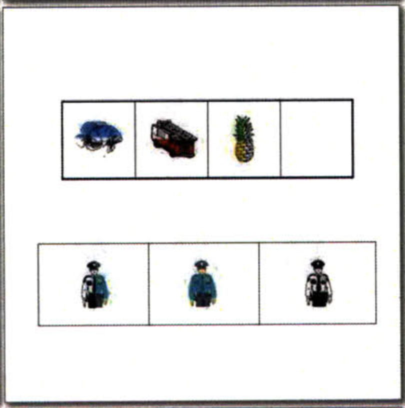
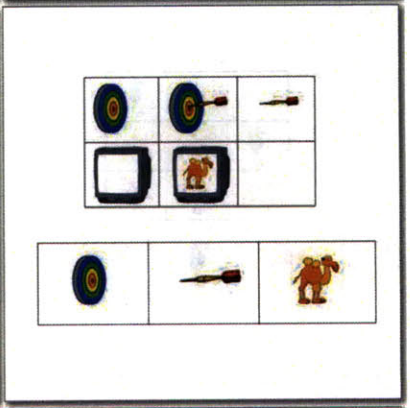
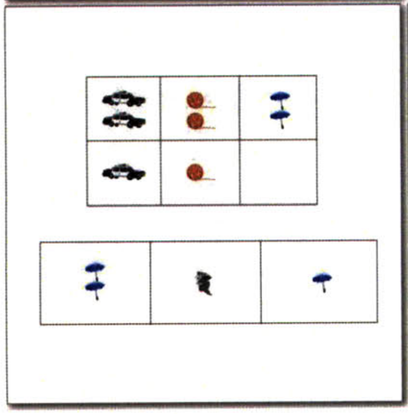


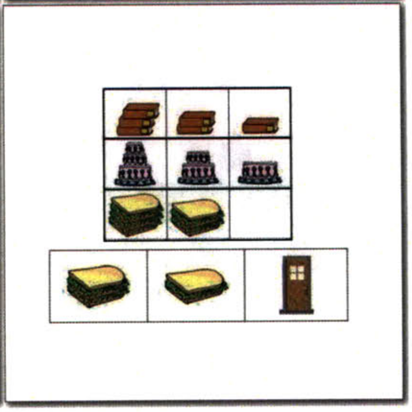


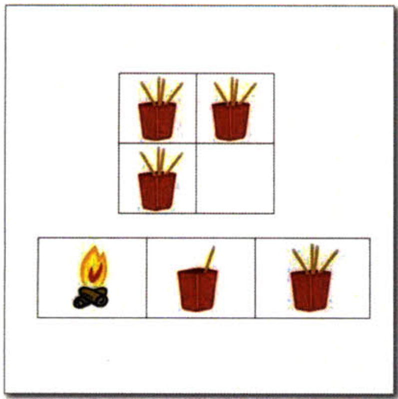


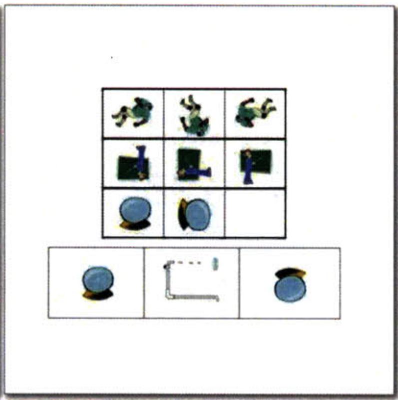





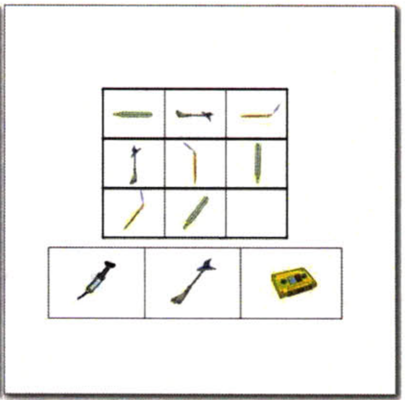


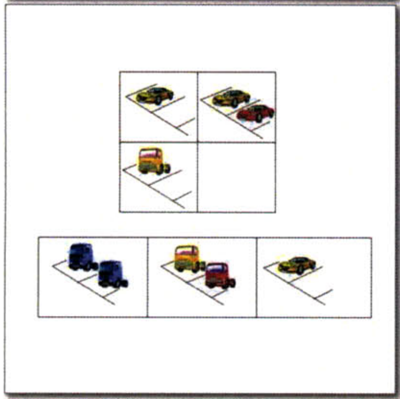




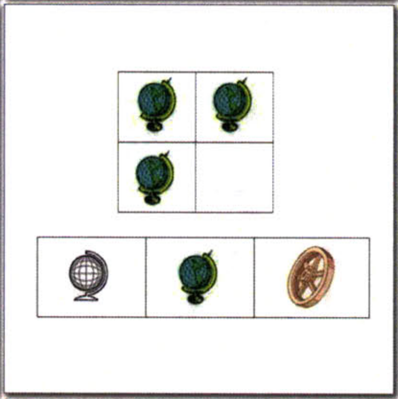


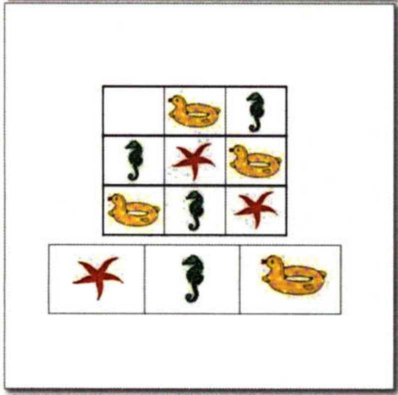


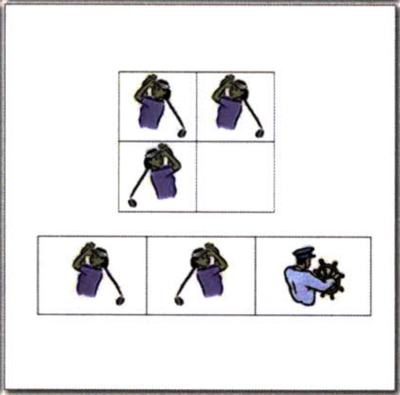


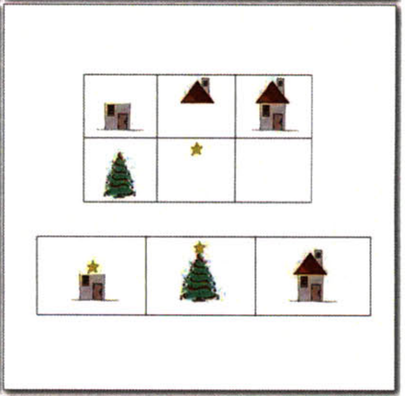


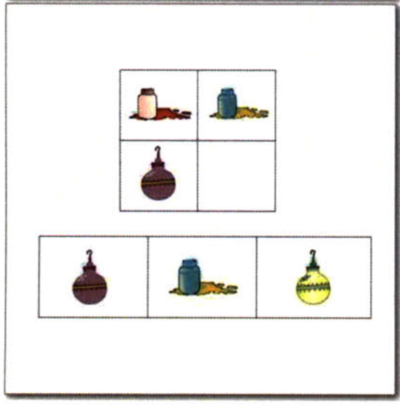


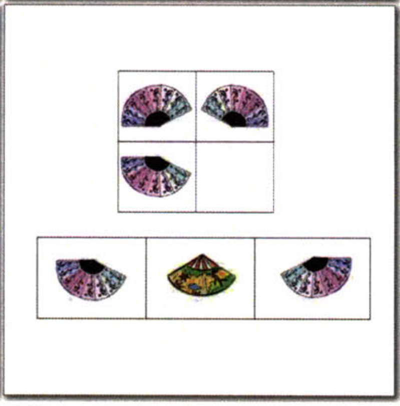


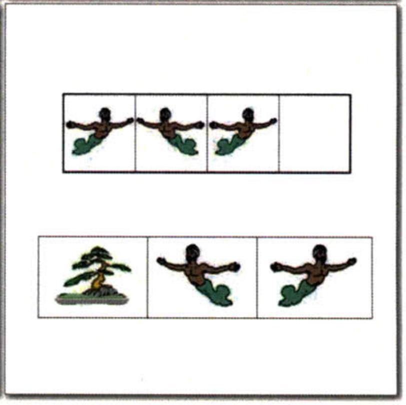


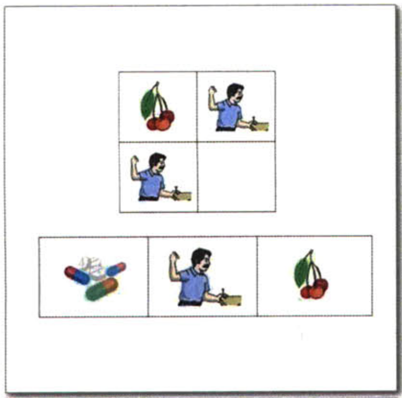
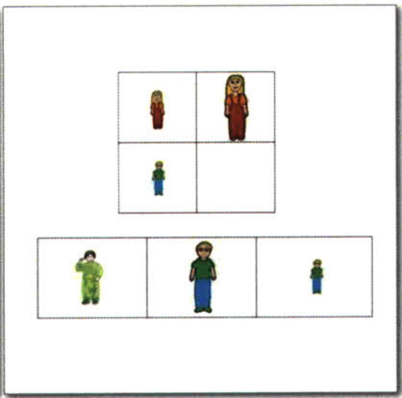
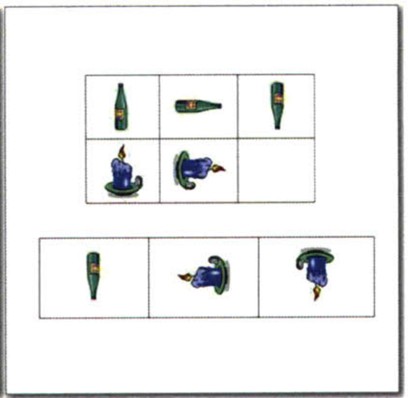
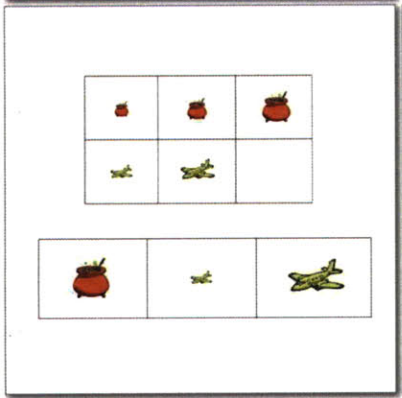
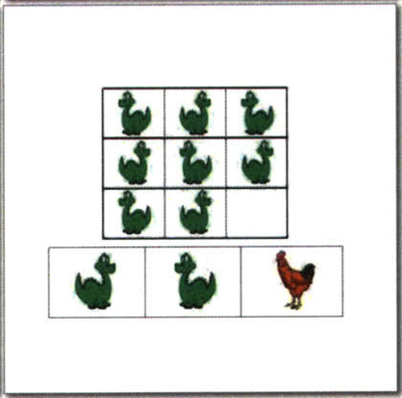
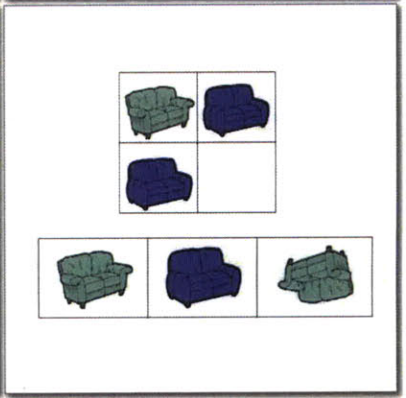
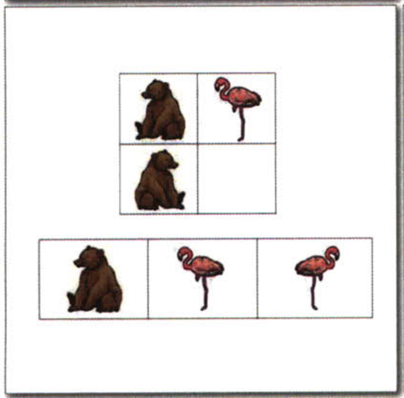
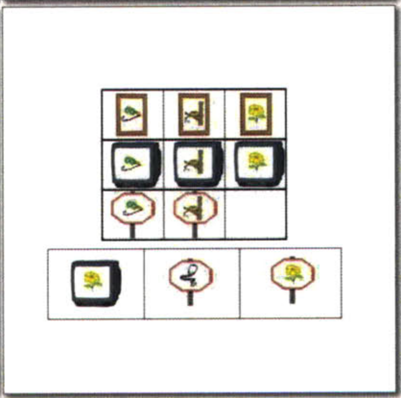
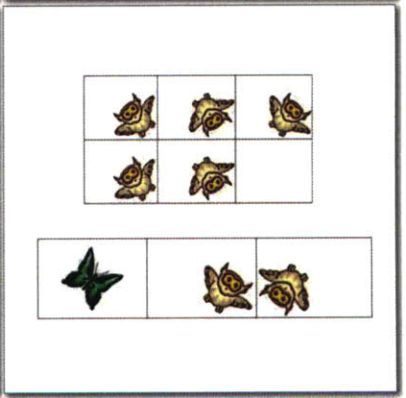
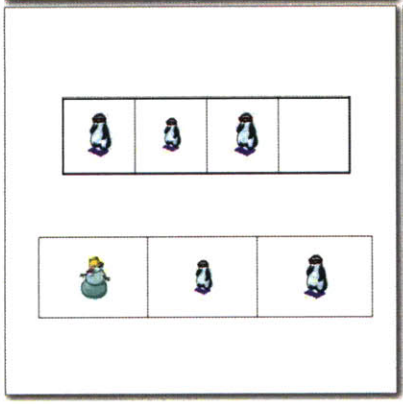
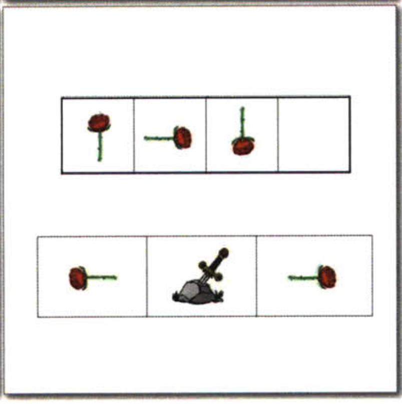




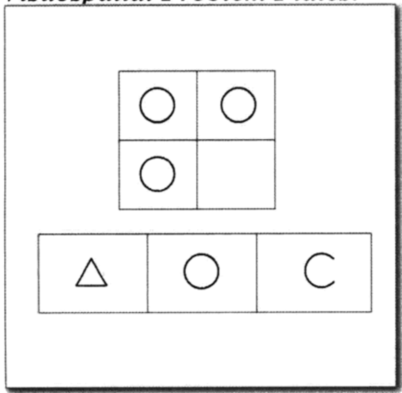
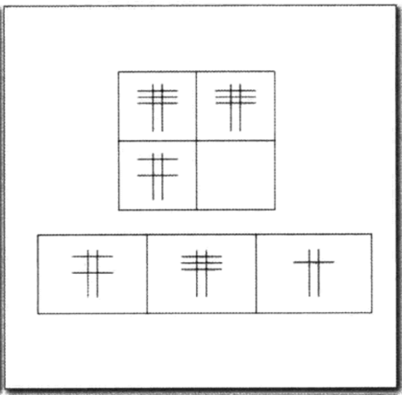
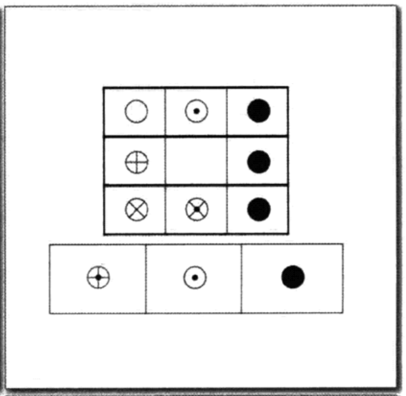
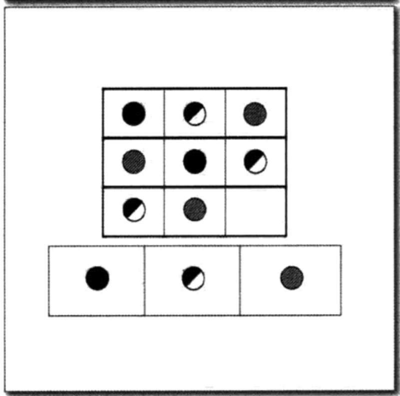
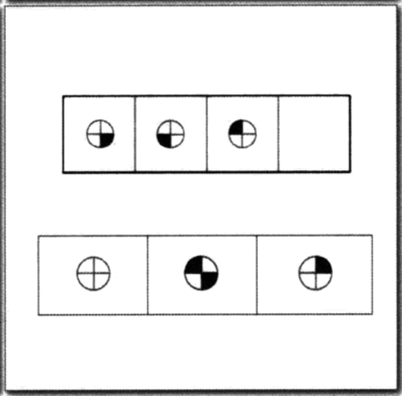
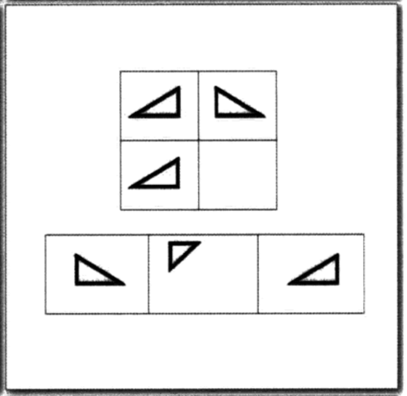
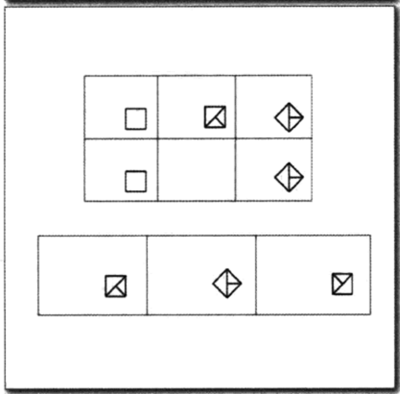
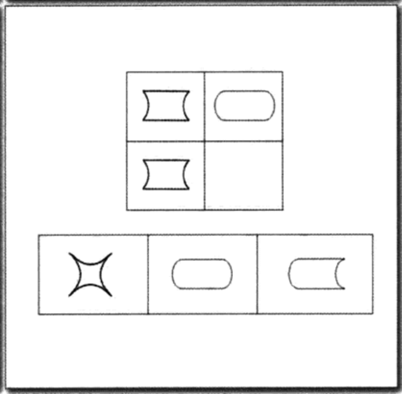
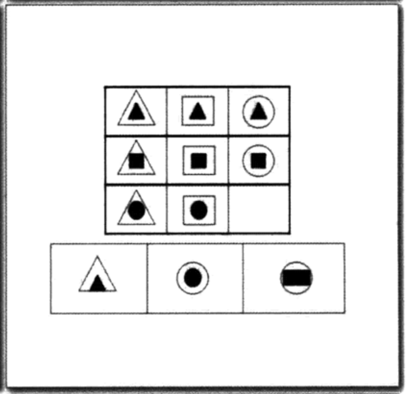
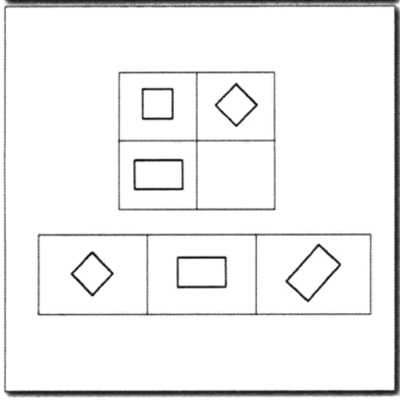
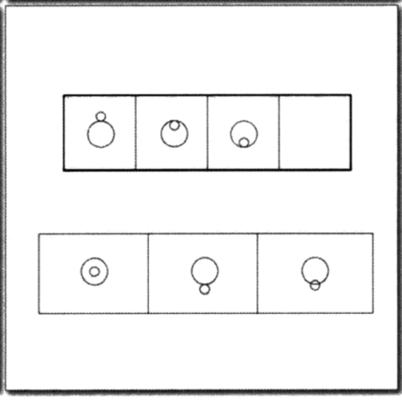
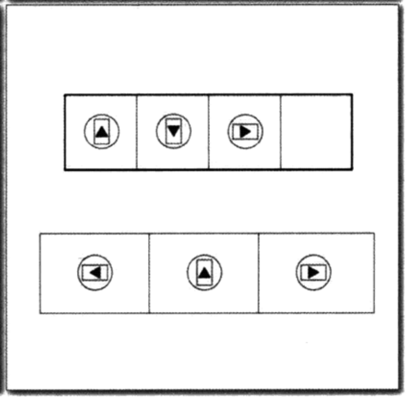


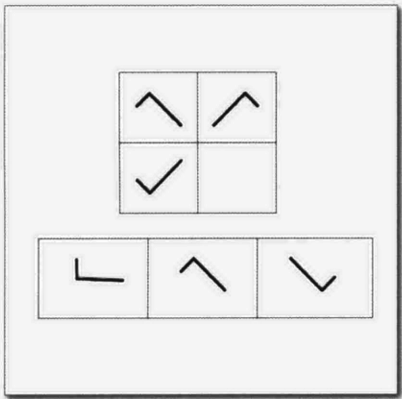
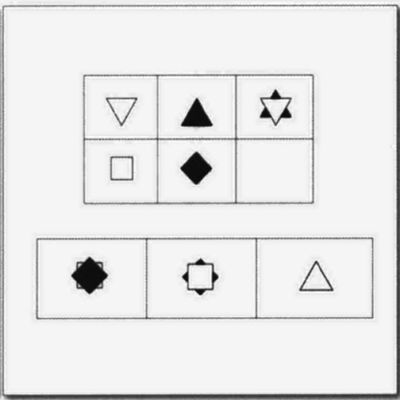
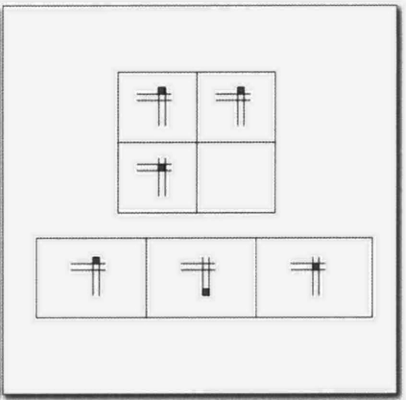
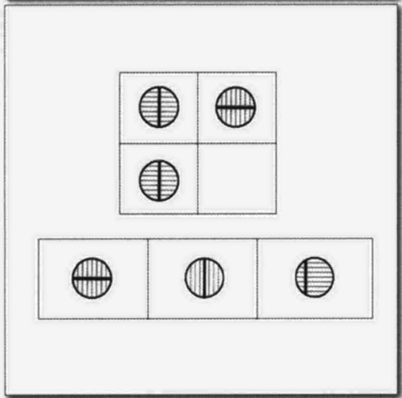
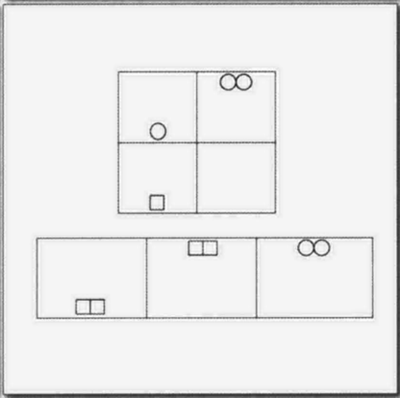
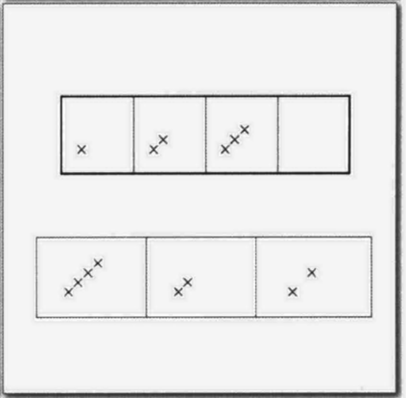
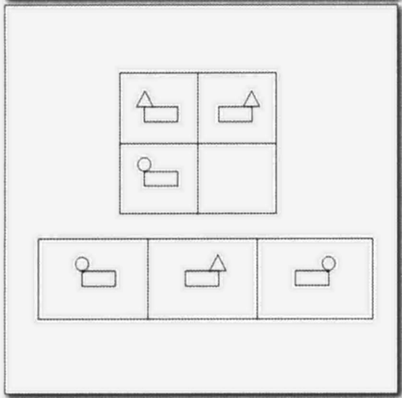
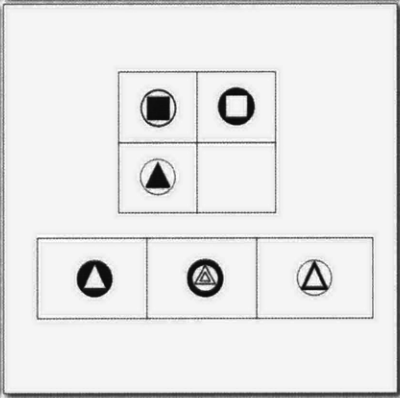
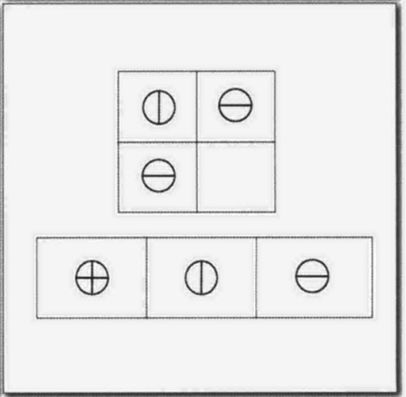
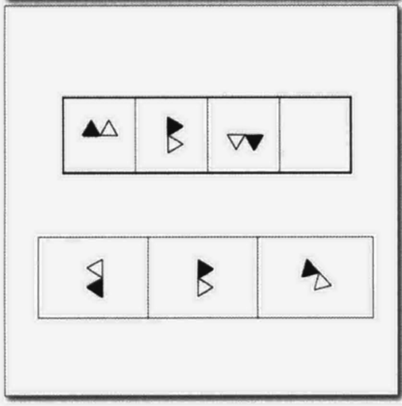
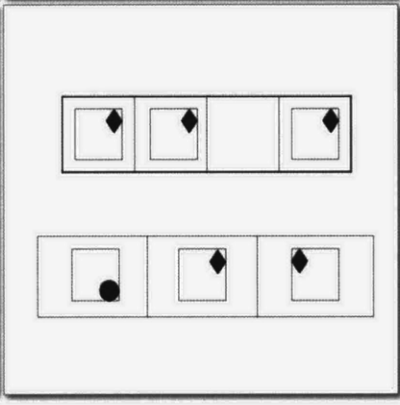
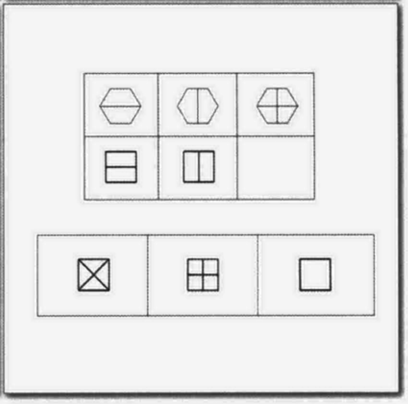


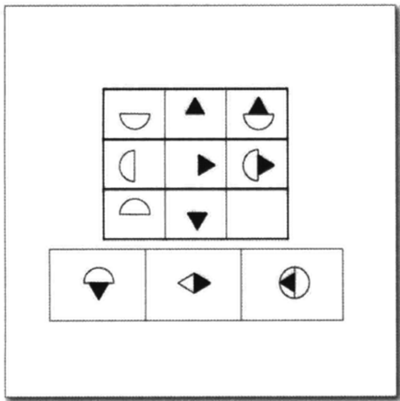
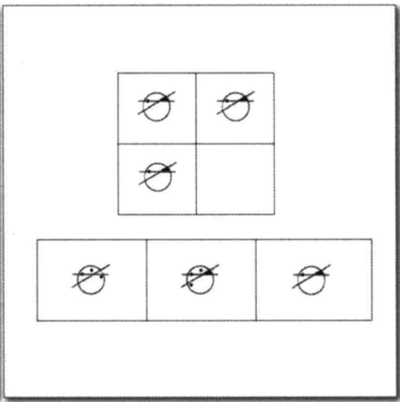
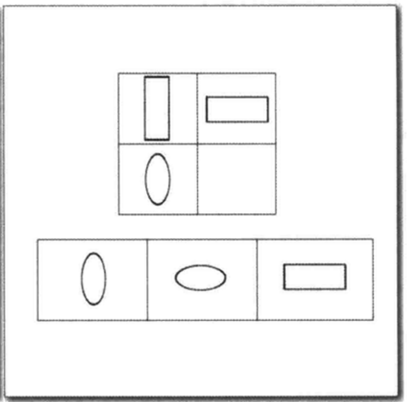
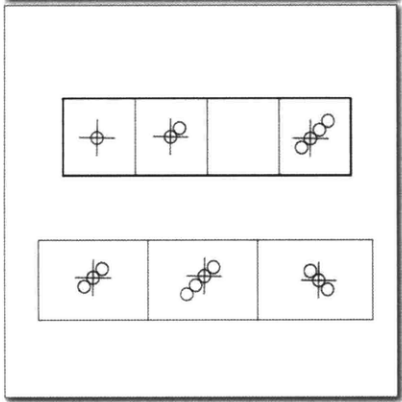
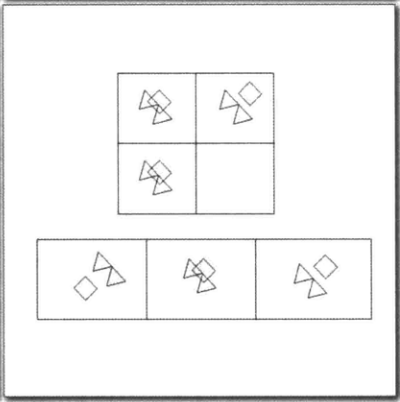
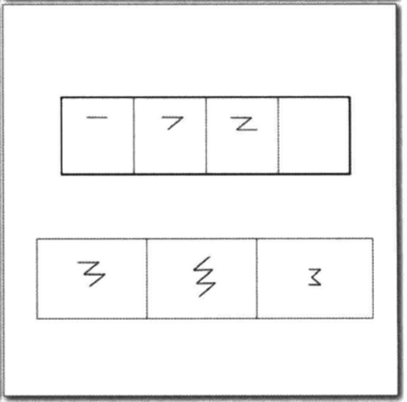
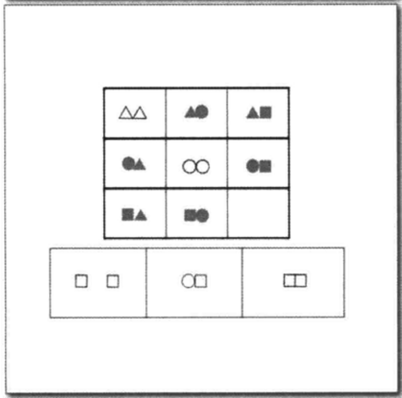
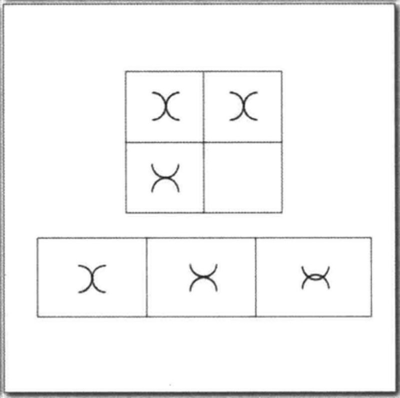
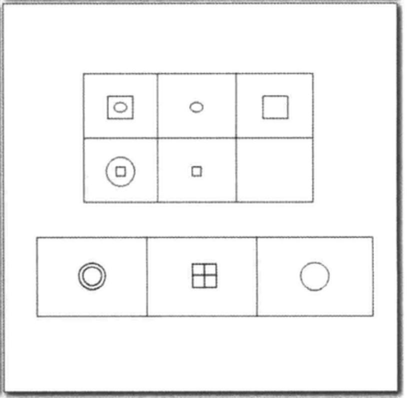
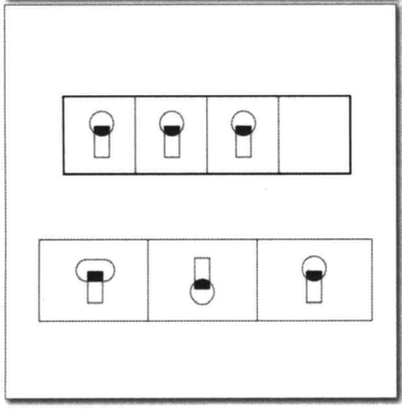
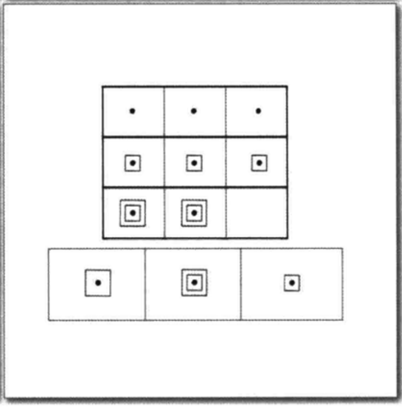
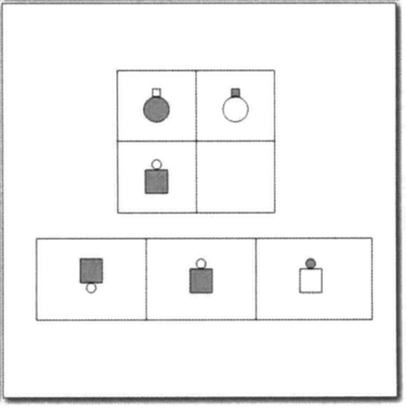


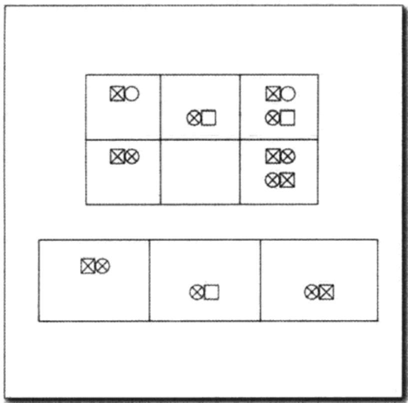












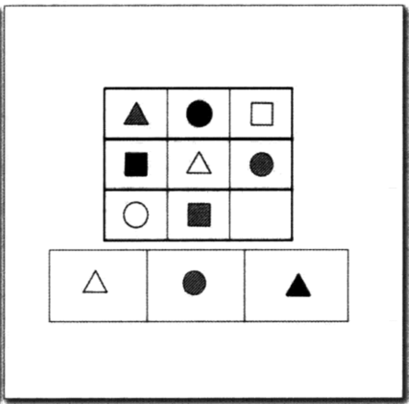

Visuospatial Problem Plates:

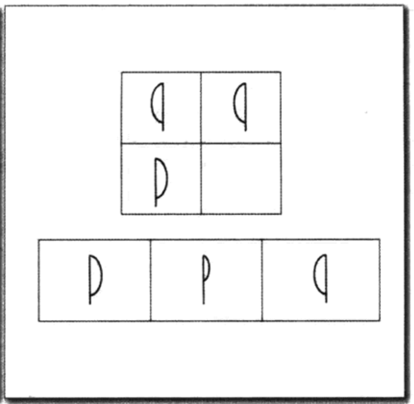













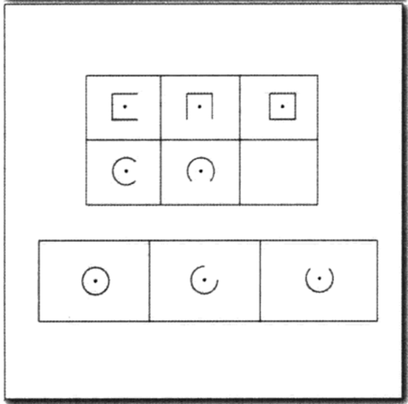













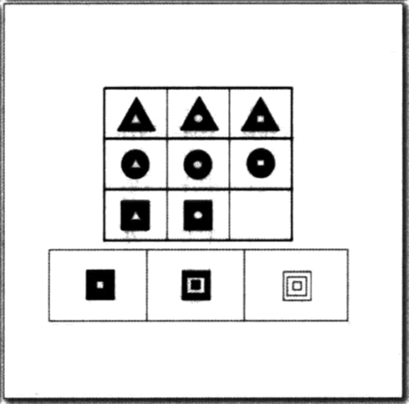













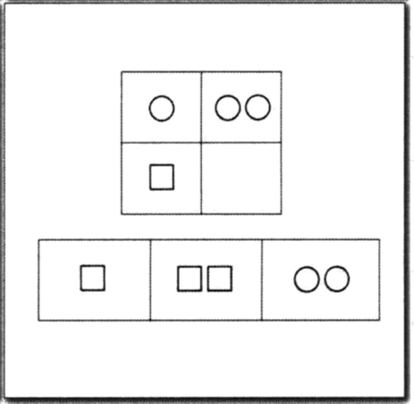


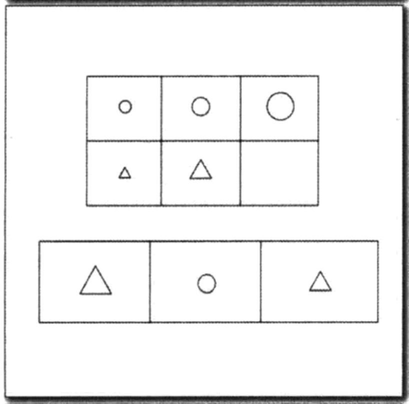


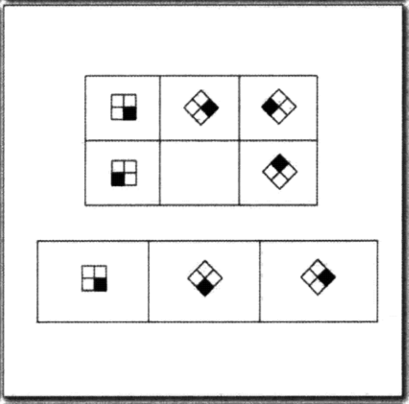


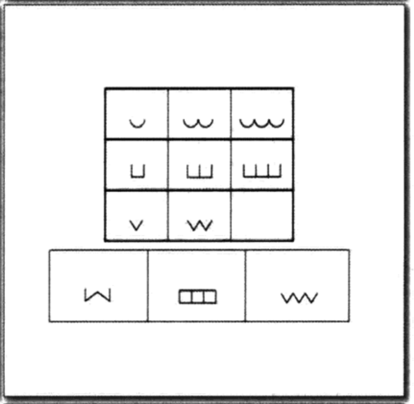


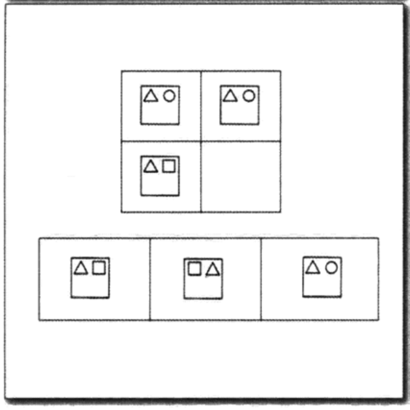


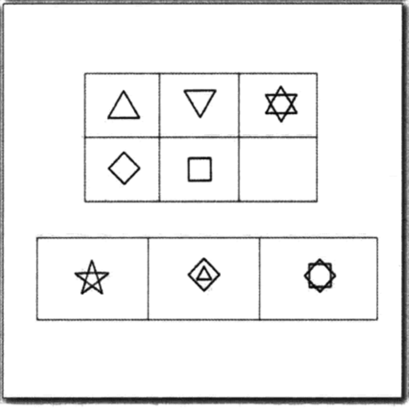


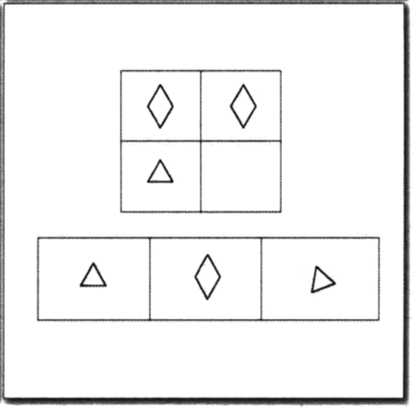












Task Design

We wished to vary the linguistic content of pictorial puzzles according to two factors: 1) whether the input items are linguistic (picture type), and 2) whether the manipulation is linguistic (reasoning/relationship type). In effect, this was carried out by 1) using pictures with/without conceptual (semantic) meaning, and 2) by manipulating whether this meaning of items was necessary for reaching a correct solution.

These considerations therefore required at least 3 conditions (which we will call Visuospatial, Semantic, and Visuospatial+Semantic, as described in chapter 3) which would present the following pairwise distinctions:

- V vs. V+S: Different picture type, same reasoning type
- V+S vs. S: Same picture type, different reasoning type
- V vs. S: Different picture type, different reasoning type

As we were interested only in the linguistic vs. non-linguistic characteristics of pictorial reasoning, the three conditions needed to vary only according to the above manipulations, and therefore needed to be equated for difficulty and lower-level processing. Halford et al. (1998) presented an elegant and powerful theory to define processing capacity in terms of Relational Complexity (RC). While additional factors influence task difficulty (domain expertise, practice, memory capacity...), RC provides a useful metric to compare tasks independently of the "solver". The complexity of a relation depends on the number of arguments to be considered simultaneously (e.g. 2 arguments a and b in the relation "bigger-than(a,b)") as each argument provides a degree of freedom. From this the complexity of a cognitive process or task is the complexity of the most complex step in the process (i.e. the step with the largest number of arguments), which in turn defines the processing demand. Arguments (dimensions to be considered) are used as instances of first order relations (transformations or relationships between arguments), which may be embedded in hierarchical structures (operations on relations).

V and V+S were simple to match for complexity, as all that was needed was to substitute items on a one-to-one basis, keeping the visual manipulation intact (eg. if a V plate shows two rectangles, one being a stretched version of the other, then the corresponding P plate will show say a dog and the same, similarly stretched dog).

Complexity matching between V+S and S was achieved by operationalizing the problem plates. All plates were tabulated, according to the criteria in the table below, in order to match complexity based on dimensions, relationships, and manipulations:

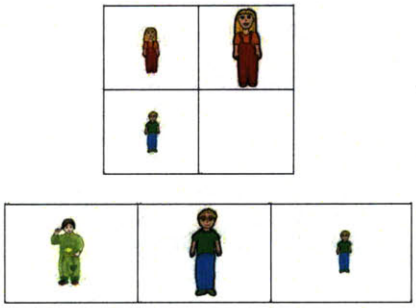
1) dimensions of interest (i.e. the dimensions represented in each plate and that need to be distinguished for successful solving - this includes distractor choices, as these need to be identified as wrong). These are intrinsic attributes used to define the individual items (e.g. color, animal...)

2) Relationships of interest: these are the ways individual items are related to each other in a particular plate (e.g. size increase, rotation, class inclusion)

3) Manipulations of interest: this shows how the different relationships are integrated to solve the problem (e.g. by analogy, by group completion)

	V, V+S			S	
Dimensions	**Relationships**	**Manipulations**	**Dimensions**	**Relationships**	**Manipulations**
size	subpart	addition/ subtraction/ intersection	animals	Meronymic inclusion	addition/ subtraction/ intersection
shape	relative location	group completion	people/ body parts	Spatial inclusion	group completion
color	"kind of"	analogy	professions	Class inclusion	analogy
item identity	growth/ seriality	series completion/ sequence	vehicles	cause-effect/ action-target	series completion/ sequence
line/curve	color match/ identity match		objects	antonym/ synonym	
number/ quantity of subparts	rotation/ flip		food	attribution/ possesion/ attachment	
orientation			sports		
symmetry			clothes		
position			nature		

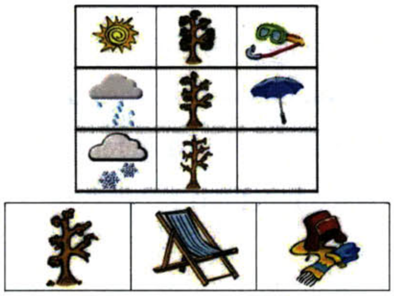
An example of evaluation of the complexity of a V+S problem plate:



dimensions = size+item identity; relationships = growth+identity match; and manipulations = analogy.

As such, this example can be interpreted as "drawing an ANALOGY, based on GROWTH of a particular ITEM, using the concepts of SIZE and ITEM IDENTITY".

Another (now verbal) example:



The above example requires COMPLETING A SERIES by ANALOGY, based on MERONYMIC INCLUSION of ATTRIBUTES, using concepts of NATURE and CLOTHES. (meronymic inclusions are part-whole relationships. in this ex, the attributes of clothing and weather are PART of the season WHOLE).

This full framework then gives an easy way to quantify plate complexity by a simple DIMENSIONS x RELATIONSHIPS x MANIPULATIONS descriptor. In these two examples, P2 is a 2x2x1 plate C2 is a 2x2x2 plate, implying that C2 is more complex than P2.

Plates were matched across conditions based on this descriptor. The average number of dimensions, relationships, and manipulations are also matched across conditions.

Because of the nature of the task, V needed to be presented with black and white geometric forms, and so could not be equivalent to P or C in terms of the amount of lower-level information. However, as solving V required detailed visual comparisons between items, we posed that the amount of lower-level processing would not be significantly different across conditions. In addition, the potential differences in colors and shapes were not critical to our tasks and were not considered meaningful confounds.

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