PERCEPTUAL MNEMONIC MEDIAL TEMPORAL LOBE FUNCTION IN INDIVIDUALS WITH DOWN SYNDROME

By

Goffredina Spanò

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SIGNED: Goffredina Spanò

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

_____	September 17, 2012
Dr. Jamie Ogline Edgin	Date
Assistant Professor	

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ABSTRACT

Behavioral data in individuals with Down syndrome (DS) and mouse models of the syndrome suggest impaired object processing. In this study we examined the component processes that may contribute to object memory deficits. A neuropsychological test battery was administered to individuals with DS (n=28), including tests targeting perirhinal cortex (PRC) and prefrontal cortex (PFC) function, tests of perception (i.e., convexity based figure ground perception), and tests of memory (object recognition and object-in-place learning). To compare to individuals with DS, the same number of typically developing chronological age (CA, n=28) and mental age-matched (MA, n=28) controls were recruited.

We observed object memory deficits in DS ($p < 0.001$). In contrast, the DS group showed relatively intact use of convexity when making figure-ground judgments and spared PRC-dependent function, as compared to MA control. In addition, measures of PFC function seemed to be related to performance on object recognition tasks.

These findings suggest that the inputs into the MTL from low and high level perceptual processing streams may be intact in DS. The object memory deficits we observed might reflect impaired PFC function.

INTRODUCTION

Theoretical Background

The neuropsychological profile of Down syndrome

Down syndrome (DS) is a genetic disorder resulting in a characteristic profile of medical, cognitive, and neuroanatomical differences. DS accounts for up to 40% of cases of moderate to severe intellectual disability, with an incidence of 1 per 700 live births. Ninety-five percent of cases are caused by a meiotic non-disjunction event prior to conception, resulting in an extra copy of chromosome 21 (i.e., trisomy 21). DS may also result from Robertsonian translocation (2-3% of DS cases) or mosaicism (1-2%) (Epstein, 1995).

Turning to the neurological profile, a number of studies have described delayed myelination (Wisniewski & Schmidt-Sidor, 1989), smaller volume of the frontal lobe, and diminished size of the hippocampus and cerebellum (Jernigan et al., 1993; Nadel, 1999; Pinter et al., 2001). From a neuropsychological standpoint, alterations in these regions may potentially explain the specific impairments in cognitive functions associated with this syndrome.

Behavioral data in individuals with DS and mouse models of the syndrome suggests impaired object processing as part of the phenotype. For instance, it has been shown that infants with DS have difficulties in object permanence (OP, Rast et al., 1995). A typical paradigm for assessing OP is the "A-not-B task", in which an object (i.e., a toy) is moved from a specific location to another place for the hiding (complete occlusion of the toy). Infants with DS showed a marked cognitive delay in tracking the object

properly: they reached this level of understanding at 20-43 months of age, compared to typically developing infants, who reach this level at about 8 to 12 months of age (Butterworth, 1977; Diamond, 1985; Piaget, 1954; Uzgiris & Hunt, 1975). These results are consistent with previous findings (Dunst, 1988, 1990; Dunst & Rheingrover, 1983; Kahn, 1978; Mervis & Cardoso-Martins, 198.4; Morss, 1983,1984). These results might suggest that infants with DS have difficulties in maintaining representations of objects and these skills might develop later in this population.

In older children with DS, one of the most replicated deficits is in memory for objects in a spatial context, or a visual spatial paired associates task. For instance, Pennington et al. (2003) and Visu-Petra et al. (2007) reported deficits on immediate pattern recognition tasks (i.e., CANTAB Pattern Recognition Memory), as well as in binding of objects to spatial locations (i.e., CANTAB Paired Associates Learning task, PAL). Specifically, in the CANTAB PRM, after viewing a series of non-verbalizable patterns on the screen, participants are asked to decide which one of a pair of stimuli was previously seen and which was novel. The task is claimed to be sensitive to medial temporal lobe function (Luciana & Nelson 1998). Pennington et al. (2003) found that individuals with DS were impaired in this task compared to mental age-matched controls (MA). These results are consistent with those obtained by Visu-Petra et al. (2007) on the PRM task.

In a recent study in individuals with DS, Jacola et al. (2011) investigated brain regions associated with performance during an object decision task focused on semantic classification. Atypical brain activation was found in the subjects with DS as compared to

controls. Specifically, in the control group (matched by chronological age), bilateral regions in the occipital and parietal lobes usually associated with visual processing and object recognition were significantly more active than in the DS group. In contrast, in the DS group, more activation was detected in bilateral regions of the middle frontal gyrus and regions of the left parietal lobe. These results provide support for the hypothesis that compensatory systems, such as the prefrontal cortex, might be engaged in DS to counteract dysfunction in other systems.

However, not all findings are consistent. For instance, Vicari et al (2000) employed a picture recognition task called "Fragmented Pictures Test", where the participant is asked to recognize an object at different levels of fragmentation: the first level had only a few pieces of the figure, while the seventh showed the complete figure. Children with DS and MA matched controls correctly recognized a similar number of objects in this task in the immediate recognition phase (Vicari et al., 2000), suggesting spared object recognition processing.

Similar results come from findings in the animal literature with the Ts65Dn mouse model. Tasks such as *novel object recognition* (NOR) provide the closest mapping to the deficits in the human literature. Specifically, Hyde and Crnic, (2002) found no difference between older Ts65Dn and wild-type mice utilizing immediate measures of spatial or object novelty, suggesting spared immediate recognition memory, in contrast to the PRM deficits observed in humans (CANTAB PRM, Pennington et al., 2003; Visu-Petra et al., 2007). Along this line, Das and Reeves (2011) showed that object-in-place tasks are not impaired across two models (Ts1Cje and Ts65Dn), contrary to the deficits

on object/place binding measures seen in humans (i.e., CANTAB PAL, Pennington et al., 2003; Visu-Petra et al., 2007, Edgin eta l., 2010a).

Therefore, more work is needed to clarify the profile of object deficits in this population and to examine the component processes that may contribute to object memory deficits. Theories of the neurological bases of object processing suggest the involvement of several neural systems, such as early dorsal and ventral visual streams (i.e., processing visual features of the object and its context), perirhinal cortex (i.e., PRC, involved in the detection of familiarity/novelty of the object, Barense et al., 2011), hippocampus (i.e., engaged in the spatial relationship between objects and their background context, Howard et al. 2011), and prefrontal cortex (i.e., responsible for matching visual input and the best fitting representation of the object stored in LTM, Kosslyn, 1994). Here we review the literature on each of these systems in DS.

Early dorsal and ventral visual stream processing

Several studies showed that individuals with DS perform at the level of MA matched controls on tasks involving immediate memory for spatial locations (i.e., CANTAB Spatial Span or CORSI blocks (Pennington et al., 2003; Visu-Petra et al., 2007; Edgin et al., 2010a), suggesting spared function of early the dorsal visual stream. Furthermore, Fidler et al. (2006) found no difference between children with DS and MA-matched controls on the visual reception scale of the Mullen Scales of Early Learning (e.g., visual tracking and simple visual discriminations). In line with these results, Brown et al. (2003) showed that visual tracking and integration were relatively spared in 2–3

year-olds with DS, in an eye-tracking paradigm. Taken together, these findings suggest relatively spared early ventral and dorsal visual stream processing compared to other cognitive functions.

However, not all findings are consistent. For instance, Vicari et al. (2006) showed that children with DS performed more poorly than MA matched children on visual-perceptual measures such as a task in which the participant is asked to identify a previously seen shape in a confounding context with other shapes. Ikeda et al. (2012) showed that individuals with DS failed in visual-perceptual tasks such as discerning a target from either mirror-imaged or rotated alternatives, in addition to figural-category detection. Consistent with these findings, it has been shown that the mouse model of DS (i.e., Ts65Dn) presents with visual deficits as assessed by pattern visual evoked potentials (Scott-McKean et al., 2010).

Finally, Annaz et al., (2009), showed that children with DS discriminated features (i.e., eyes, nose, mouth) better when these were presented in whole faces than when presented individually. Their need of the context of a whole face to be able to detect features/details suggests "*a holistic processing that compromises discriminability by fusing them with the whole-face context*" (Annaz et al., 2009). In line with this finding, other studies showed that in a drawing task (Bellugi et al., 1999) and in the Delis Hierarchical Processing Test (i.e., where a large letter is made up of smaller letters, Bihrle, et al., 1989), individuals with DS tended to reproduce the global form and failed to report details (Bihrle, Bellugi, Delis, & Marks, 1989). All these studies together

suggest that individuals with DS may show an "*exaggerated part-whole effect*" (Annaz et al., 2009).

Perirhinal cortex

Most of the studies examining object processing in individuals with DS suggest object recognition deficits. For instance, Vicari et al. (2005) examined performance on a visual-object pattern task and a visual-spatial sequence task in 15 individuals with DS. Specifically, in the visual-object paradigm, 15 figures of common objects (e.g. a tree, a knife, a flower) were shown to the participant (each figure for 5 seconds); immediately followed by four different versions of the same object (e.g. four trees, four knives, four flowers). The participant was asked to identify which of these versions of the object was presented earlier. The results suggest a dissociation in individuals with DS: typical learning of visual-spatial sequences but impaired learning of visual-object patterns.

In another study, Miranda et al. (1974) examined novelty/familiarity detection in 28 infants with DS. In the paradigm, two identical targets are presented side by side for a familiarization period of 1 or 2 minutes, immediately followed by two 10-second testing periods in which the familiar picture is paired with a novel stimulus. The results showed that infants with DS have the capacity to acquire, store, and retrieve visual information at an early age (5 months old). However, infants with DS showed a novelty response (i.e., looked longer at a novel than at a familiar target) a week later than typically developing infants. Simple patterns were detected at equivalent levels to controls. However, the DS group had difficulty when making complex discriminations.

Hippocampus

Cognitive functions associated with the hippocampus have been widely investigated in both humans and animal models of DS (Crnic & Pennington, 2000; Uecker, Mangan, Obrzut & Nadel, 1993; Pennington et al., 2003). For instance, Pennington et al. (2003), Visu-Petra et al. (2007), and more recently Edgin et al. (2010a) provided evidence for hippocampal deficits in children with DS in relation to MA controls on tasks such as the CANTAB PAL. Specifically, in the CANTAB PAL task the participant learns associations between non-verbalizable visual patterns and hiding locations on a computer screen.

Prefrontal Cortex

The majority of studies that examined executive functions in individuals with DS reported specific deficits in working memory and attention (Brown et al., 2003; Lanfranchi et al., 2004; Lanfranchi et al., 2010; Visu-Petra et al., 2007; Edgin et al., 2010a) and set-shifting (Zelazo et al., 1996; Edgin, 2003; Rowe et al., 2006; Lanfranchi et al., 2010), with spared function on tasks involved inhibitory control.

Object recognition deficits in DS: potential sources

The literature suggests several theoretical accounts that could help explain object processing problems in this population. First, I review theoretical perspectives regarding the function of the PRC, a region involved in object recognition memory and more

recently implicated in perception. The accounts reviewed here establish frameworks for understanding the types of tasks that should be impaired if PRC is not functioning. Furthermore, other theoretical approaches highlight the extent of networks required in object processing, a network including the PRC and frontal cortex. Given the neuropsychological profile of DS, object memory difficulties could arise from disruption in a number of brain regions.

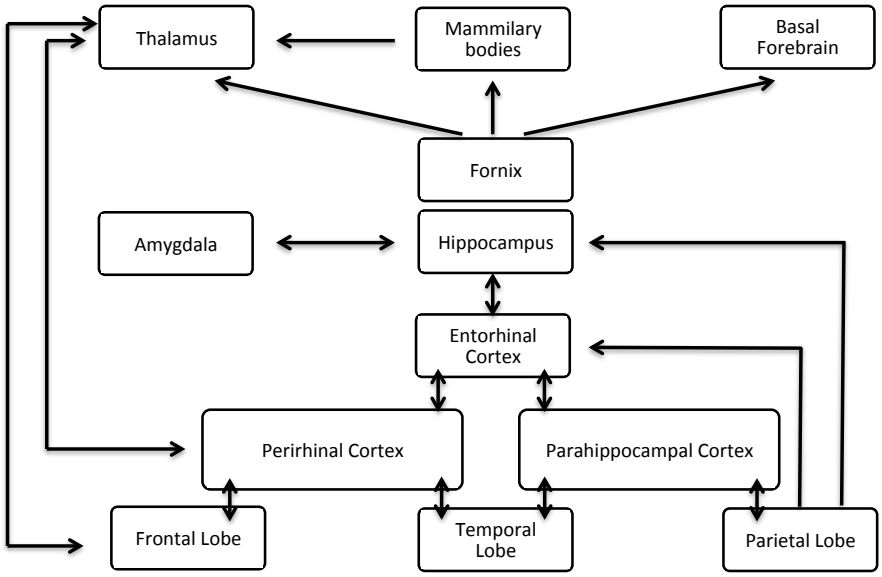

Figure 1: Schematic diagram of the MTL connectivity. The system consists of the hippocampal formation (i.e., the hippocampus proper, the dentate gyrus, the subiculum, and the entorhinal cortex) and the contiguous perirhinal and parahippocampal cortices. Adapted from Nadel and Hardt (2011).

Recent findings from animals and patients with PRC lesions have suggested the involvement of the PRC - which corresponds to Brodmann areas 35 and 36 – in both perception and memory for objects. In fact, PRC seems to be involved in object recognition memory - a "pure" measure of declarative memory - more widely than

hippocampus (Baxter & Murray, 2001b; Winters, Forwood, Cowell, Saksida, & Bussey, 2004). Furthermore, in the animal literature, studies by Murray and Bussey (1999), and later Buckley et al. (2001) showed that macaques with PRC ablation performed worse than controls in oddity tasks involving objects, faces and higher perceptual feature analysis. Each of these tasks was based on the oddity paradigm in which the animal is trained to select the odd stimulus from a visual array for a reward pellet. No differences were observed on color, shape and size complex oddity tasks, however. This finding allowed authors to conclude that PRC lesions cause selective impairments, associated with processing higher perceptual features (e.g., objects, faces, etc.) but not with basic perceptual discrimination (e.g., color, shape, etc.).

The results formed the basis for the perceptual-mnemonic/feature conjunction (PMFC) model of PRC function (Murray and Bussey, 1999; Bussey, Sakida and Murray, 2005), which suggests that the PRC plays the role of binding together complex features of a stimulus. Thus, as Murray and Bussey (p. 146, 1999) stated, "*perirhinal cortex neurons represent the conjunctions of features of visual stimuli – perhaps resulting in a 'gestalt' representation of a complete stimulus – whereas regions earlier in the visual processing stream contain neurons that represent simpler features from which these complex conjunctions are formed".*

Based on the initial PMFC model (Murray and Bussey, 1999; Bussey and Saksida, 2002), Cowell, Bussey and Saksida (2006) recently proposed a revised computational model of the representation of object-features in the ventral visual stream, divided in two main layers:

1. The caudal region of the ventral visual stream (VVS), in which dimensions of the stimulus are combined in order to represent "features";
2. The VVS culminates in the PRC layer, in which all the representations of the stimulus are combined into a single conjunction.

Findings from neuropsychological (Lee et al. 2005, 2006) and neuroimaging studies (Lee et al. 2008), considered in conjunction with evidence from animal data (Buckley et al., 2001), are fully consistent with a model proposing that the PRC may be responsible for conjunctions of object features (Bussey et al. 2002), whereas, as Buckley et al. (2004) suggested, the representation of place conjunctions is hippocampal-dependent. These findings are supported by a complementary study that investigated the performance of patients with Alzheimer's disease (AD) and Semantic dementia (SD) on spatial scene and face discrimination by using a paradigm that did not rely on long-term declarative memory (Lee et al., 2006). Although both AD and SD pathologies are characterized by extensive MTL damage (Chan et al., 2001; Galton et al., 2001), different patterns of global atrophy are present: greater PRC atrophy is associated with SD while the hippocampus is compromised to a greater extent in AD (Davies et al., 2004). The results showed a double dissociation within MTL. While the AD group performed poorly on scene oddity tasks, a selective deficit on oddity judgment for faces was found for SD patients. This observation provides compelling evidence for the critical role played by PRC and hippocampus respectively in the perceptual processing of objects and spatial scenes that expands on their well-established role in long-term memory function. In particular, an interesting aspect of the scene oddity deficit in both studies (Lee et al. 2005,

2006) is the critical role played by the hippocampus in perceptual analysis of the scene even without the involvement of long-term memory. For instance, the presence of hippocampal cells specialized for spatial location and navigation "place cells" has been widely shown in animal (O'Keefe, 1976; Wilson and McNaughton, 1993; Robertson et al., 1998) and human work (Ekstrom et al., 2003) and these cells fire while the animal is actively engaged in navigation as well during the recall of the spatial environment.

However, a fundamental limitation of the oddity task paradigm is the involvement of working memory (WM) due to "*the inability to hold information online across the saccades required to compare simultaneously presented stimuli*" (Ranganath & Blumenfeld, 2005; Ranganath & D'Esposito, 2001). Specifically, Ranganath and Blumenfeld (2005) reported that individuals with amnesia demonstrated impaired working memory, specifically when conjunctions of stimuli (Olson, Page, et al., 2006) or relations amongst elements within a scene (Hannula et al., 2006; Hartley et al., 2007) were involved.

Some experiments have used paradigms that do not tax WM to the same extent. Barense, Ngo, Hung, and Peterson (2011) examined the performance of two groups of amnesic patients (hippocampal damage cases vs. MTL damage cases, comprising PRC) on the test of *effects of familiar configuration on figure assignment* (*the OMEFA test*, Peterson et al. 2000) and a test to assess *the ability to use Gestalt configural cues* (i.e., convexity) *on figure assignment* (Peterson and Salvagio 2008). To eliminate the effect of familiarity, a revised version of the OMEFA with inverted figures including the previous "familiar" segments (Baker et al. 2002) and a test of novelty-familiarity discrimination

were administered to both HC and MTL patients. Across all the tests, MTL patients, compared to healthy controls, showed decreased figure assignment (FA) for familiar configurations and increased FA for novel configurations (part-rearranged novel configurations). Since hippocampal patients showed typical patterns of FA, these effects were attributed to PRC damage. From these data Barense et al. (2011) proposed the *dynamic interaction hypothesis*, which states that feed-forward and feed-backward signals between PRC and area TE result in a "gestalt" representation of a visual stimulus (Murray et al., 1999), with PRC (higher level of the VVS) representing the conjunctions of features/parts of visual stimuli and area TE (regions earlier in the visual processing stream) representing the individual features/parts from which these complex conjunctions are formed. Taken together, these findings suggest that the PRC plays an active role in implicit and explicit discrimination of familiarity and novelty in figure-ground perception.

These results are consistent with a body of evidence suggesting a role in recollection and familiarity for the hippocampus and the PRC, respectively (Aggleton & Brown, 1999). In particular, the model developed by Aggleton & Brown (2006) illustrates the dissociation between the hippocampus, which is mainly involved in the process of encoding and retrieval of episodic information in a spatial context, and the PRC as a "detector" of familiarity in object recognition.

Therefore, MTL regions play a dual role in storing long-term memory of perceptual information and creating representations crucial for perception and memory. Consequently, MTL damage can result from a failure to create and retrieve

representations of objects and spatial features that rely respectively on the PRC and hippocampus.

In this view, Graham, Barense and Lee (2010) proposed the "emergent memory account" (EMA) model, suggesting that:

- MTL regions actively contribute to the formation of complex conjunctive object and scene representations important for perception, firstly, and consequently for memory processing.
- Memory results from an interaction between perceptual representations and prefrontal processes.

In line with this view, the *Object Model Verification Theory* (Kosslyn, 1994; Lowe, 1985; Ganis et al., 2007) suggests that the ventrolateral prefrontal cortex (PFC) plays a crucial role in top-down processes that are responsible for the perceptual matching between visual input and the best fitting representation of the object stored in LTM. Furthermore, Barker et al. (2007) showed evidence for the involvement of both medial PFC and PRC in binding spatial and object information together.

In summary, recent theories of object memory and perception implicate a network of brain regions that could mediate object recognition memory and object in context deficits in DS, including early visual stream function, PRC, hippocampus, and prefrontal cortex.

Aims

There is consistent evidence for impairment in immediate object recognition as well as the binding of objects in spatial locations in DS. In the present work we merge these theoretical perspectives to try to account for the processes underlying object recognition deficits in individuals with DS. Memory problems in individuals with DS could be mediated by MTL structures and/or the prefrontal cortex. Consequently, the present study used paradigms targeting PRC and PFC in individuals with DS in order to determine the extent to which these systems mediated object recognition deficits in this population. As benchmark assessments of object memory, we administered measures most often found to be impaired in DS (Edgin et al., 2010b). In addition, we utilized *the OMEFA test* (Peterson et al., 2000) to test the integrity of PRC function in individuals with DS. Given the specificity of this measure to PRC function and not PFC, deficits on this task would indicate PRC-dependent dysfunction with no explicit requirement for WM. Nonetheless, in order to test the hypothesis of altered prefrontal function we related performance on the PRC measure to validated measures of prefrontal function in this population (Edgin et al. 2010a). Finally, given the lack of information regarding basic visual-perceptual function in DS and the importance of perception to object detection, we administered a test examining global visual processing to determine patterns of strengths and weaknesses. Information from the administration of this sequence of tests helped to determine the source of cognitive difficulties in this population. In fact, deficits on MTL-dependent tasks could result from a) perceptual deficits, b) disruption of PRC function, c) selective hippocampal impairments, d) or altered prefrontal function.

Specifically, the aims of this study are:

1) To test basic visual and perceptual capabilities of individuals with Down syndrome compared to both mental age (MA) and chronological age (CA) matched control samples.
2) To examine the performance on the OMEFA task, a task known to relate to PRC function, in individuals with DS in comparison to both MA and CA matched control samples after control for any variation in perceptual abilities.
3) To relate performance on benchmark tasks of object processing (object recognition, objects in context) to performance on tasks tapping PRC and prefrontal function.

The results from this project will allow a better understanding of the potential "source" of the object memory impairments in individuals with DS.

Hypotheses

Based on the previous aims, the current research was designed with a focus on three hypotheses. First, based on previous literature we expected to find no basic visual and perceptual impairments in individuals with DS. In this study, with regard to the *test of the ability to use Gestalt configural cues on figure assignment*, we expected the DS group to show similar patterns of performance in both 2-region and 8-region displays, in comparison to an MA control sample (who perceive the regions with convex parts as the figure significantly more often than the regions with concave parts). Second, in order to test whether or not the PRC may be the source of object memory difficulties in DS, we examined the pattern of performance on the OMEFA test. If PRC function is compromised in the DS sample we should see similar patterns to patients with damage to

this region. Mainly, we would expect the DS group's figure responses to be reduced for intact familiar configurations, and elevated for part-rearranged novel configurations compared to the MA control group. The elevated performance on part-rearranged novel configurations would be consistent with patient data, and the predictions of dynamic interaction theory. Finally, in an exploratory aim, we assessed the relation between performance on the PRC-dependent measures, a task of prefrontal function and the benchmark assessments of object memory. We expected to replicate deficits in object recognition memory and a task requiring object-in-space binding. Testing the association between the implicit object detection task mediated by PRC, prefrontal functions and each of these benchmark deficits could help to determine the cognitive components causing the deficits in these areas.

METHOD

Participants

Twenty-eight individuals with DS (age range 10.25-24 years; 16 male, 12 female) were recruited through local and parent organizations and advertisement in Tucson, AZ and Phoenix, AZ. With a total of 28 individuals, the study has 80% power to detect medium–large effect sizes for between-group differences ((see Edgin et al., 2010a) Cohen, 1992). Exclusion criteria included the presence of Robertsonian translocation (0 case), mosaicism (0 cases), autistic disorder diagnosis (0 cases), past head injury (0 cases), or incident of loss of consciousness (i.e., greater than 5 minutes in length; 0 cases). The mean KBIT-II IQ of the sample was 45.43±8.93 (range 40–79) and the mean SIB-R scaled score of adaptive behavior was 55.35±23.04 (range 9–94). Additionally, socio-demographic information including family income, maternal ethnicity and education was collected. The mean total family income of the DS sample was ~60,000$ (corresponding to a score of "4.6" on a 10 point scale), with a range starting from $0-15,000 to over $200,000. The distribution of the ethnicity of the child included 39.3% Non-Hispanic or White, 50% Hispanic, 3.6% African-American, 7.1% Biracial/Multiracial. Of the 28 children with DS, fifteen had corrected vision loss, twelve participants had no loss and one was not reported. Down syndrome was verified by karyotype report or medical report (e.g., physician's note on recent-checkup, birth records, psychiatric clinic report) for 19 participants with DS. For the remaining participants, parent endorsed either that their child carried an extra chromosome 21 (n=6)

or (n=3) the parents were unsure of the karyotype of their child with respect to the extra chromosome 21.

To compare to individuals with DS, 28 typically developing chronological age (CA) and 28 mental age (MA) matched controls were recruited. The MA matching was based on both verbal and non-verbal raw score of the KBIT-II test. The CA group was matched for chronological age (see table 2).

With regard to the MA control group, the sample included 28 children (19 male, 9 female), ages 4.08-6.50 years old. The mean KBIT-II IQ of the sample was 112.14±10.45 (range 89– 129); the mean SIB-R scaled score of adaptive behavior was 124.16±18.70 (range 92 – 169). Additionally, socio-demographic information including family income, maternal ethnicity and education was collected. The mean total family income of the MA sample was ~65,000$ (corresponding to a score of "5.25" on a 10 point scale), with a range starting from $0-15,000 to over $200,000. The distribution of the ethnicity of the child included 67.9% Non-Hispanic or White, 17.9% Hispanic, 14.3% Biracial/Multiracial.

The CA control group included 28 adults (16 male, 12 female), ages 9.17-19.75 years old. The mean KBIT-II IQ of the sample was 101.93±11.82 (range 80– 126) and the distribution of the ethnicity included 3.6% American Indian, 7.1% Asian, 50% Non-Hispanic or White; 32.1% Hispanic; 7.1% Biracial/Multiracial.

Stimuli and Apparatus

The measures can be divided into four conceptual domains (see Table 1). In order to assess the representativeness of our group with DS we included both descriptive measures of adaptive behavior and general intellectual ability and benchmark measures (MTL-dependent measures and prefrontal functions) previously investigated in this population (Pennington et al., 2003, Edgin et al., 2010a). The other two conceptual domains were the main focus of our investigation, that is, performance associated with basic visual perceptual tasks and PRC-dependent tasks.

These measures were carefully selected on the basis of the following criteria: 1) each measure had to tap a specific neuropsychological function associated with a brain region (e.g., PRC) or a broader system (e.g., MTL); 2) the measure had to be accessible to all the ages of the samples studied; 3) measures with a non-verbal response were chosen in order to prevent potential confounding of the verbal short-term memory and language deficits in DS (Pennington et al., 2003).

Measures
Descriptive Measures
a) *Kaufman Brief Intelligence Test, Second Edition (KBIT-II)*
b) *The Scales of Independent Behavior-Revised (SIB-R)*
Benchmark Measures
a) *Test of prefrontal function*
1) Modified DOTS task
b) *MTL-dependent tests:*
1) CANTAB Paired-Associates Learning
2) CANTAB Pattern Recognition Memory
3) DAS Recognition of Pictures
4) CANTAB Delayed Matching to Sample
Tests of basic visual perception
a) *A test of the ability to use Gestalt configural cues on figure assignment*
b) *Size oddity task*
Test of PRC function:
a) *A test of effects of familiar configuration on figure assignment*
b) *Inverted manipulation of the OMEFA*
c) *Familiarity Discrimination*

Table 1: Measures divided into the main domains.

Descriptive measures

Kaufman Brief Intelligence Test, Second Edition (KBIT-II) is a measure of verbal (i.e., verbal knowledge and riddles) and nonverbal (i.e., matrices) intelligence and is suitable for individuals from 4 to 90 years old (Kaufman and Kaufman 2004). The outcome measures used in this study are the nonstandardized verbal and non-verbal raw scores for the mental age matching. In addition, the total standardized IQ score has been used for descriptive purposes. Standard scores for the KBIT-II have a mean equal to 100, standard deviation of 15.

The Scales of Independent Behavior-Revised (SIB-R) (Bruininks et al. 1997) is a caregiver completed checklist-style rating scale designed to assess adaptive functioning and everyday skills. This measure has four subtests: Motor, Social/Communication, Personal Living Skills, and Community Living Skills. Bruinicks et al. (1996) showed that this measure is sensitive in differentiating between individuals with severe disabilities and typically developing children individually matched on mental age. The outcome measure used in this study is the overall Broad Independence score (nonstandardized score).

Benchmark measures

Test of prefrontal function:

The Modified DOTS task is a measure of inhibitory control and working memory (4 years to adulthood). There are three phases: 1) the congruent location phase where the participant has to push a button on the same side as the cat on a computer touch screen (cat rule), 2) the incongruent location phase where the participant has to push a button that is in the opposite side of the frog (frog rule) and 3) the combined phase where the cat and frog rules are alternated randomly. Both frogs and cats are presented either on the left or right hand side. In the incongruent phase (frog rule), behavioral inhibition is necessary to over-ride the tendency to push the button on the same side as the stimulus learned in the congruent phase. In the combined phase, the participant has to shift from one rule to the other and avoid adhering to the congruent rule when presented the incongruent rule

and vice versa. The outcome measure used in this study is the percentage of correct responses for each phase of the test (max=100%).

MTL-dependent tests:

In the *CANTAB Paired-Associates Learning (PAL) task* the participant learns associations between non-verbalizable patterns and hiding locations on a computer touch screen. In this subtest the subject is required to remember patterns associated with different locations on the screen. Six white boxes appear around the screen arranged in a circle, and these are opened one at time in a random order for 3 s each. Only one box contains a visual pattern whereas the remaining five boxes are empty. After every box has opened and closed the unique pattern is presented in the center of the screen, and the participant is asked to touch the box in which the pattern was hidden during the presentation phase. The task increases in difficulty from 1 to 8 patterns to be remembered. Three main cognitive processes are required in order to succeed in this task: 1) visual pattern recognition, 2) hippocampal-dependent processes to bind an object with a specific location, and 3) working memory load due to the maintenance of an increasing number of patterns (i.e., executive function component). The outcome measure used in this study is the *mean errors to success* (i.e., to properly bind an object with a specific location). This measure has been shown to be 98% accurate in detecting individuals with Alzheimer's disease in the general population (Swainson et al. 2001). Specifically, the test seems to be sensitive to the hippocampus and surrounding cortex (Swainson et al. 2001). Additionally, it has been shown that children with DS are impaired on this

measure compared to a MA matched control group (Pennington et al., 2003; Visu-Petra et al., 2007; Edgin et al., 2010a).

CANTAB Pattern Recognition Memory (PRM) is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. A series of two blocks of 12 visual patterns are presented for 3 seconds in the center of the computer screen. Every pattern is non-verbalizable and presented individually. After the presentation phase of both blocks, two patterns are presented: one from the series previously shown and a novel pattern with some overlapping features (i.e., color). The participant is asked to recognize and touch the pattern presented in the presentation phase. Previous studies demonstrated that this test is suitable for children and is a reliable measure. Specifically, Luciana and Nelson (1998) showed that 4 years old are able to complete the test and that performance increased with age. Lowe & Rabbitt (1998) reported a test-retest correlation of .84 for this measure. Additionally, it has been shown that children with DS are impaired in this measure compared to a MA matched control group (Pennington et al., 2003; Visu-Petra et al., 2007).

DAS Recognition of Pictures. This subtest assesses short-term visual recognition (normed for ages 2:6 to 17:11). The participant is shown a picture of one object for 5 seconds followed by the presentation of a page with the same object as well as other distracter objects. The participant is asked to point to the object shown previously. The task increases in difficulty from 1 to 4 objects to be remembered and in the number of

distractors. In addition, the difficulty of the task increases with the similarity between the objects (i.e., same semantic category). The subtest contains a total of 20 items, each scored as 1 or 0. The outcome measure used is the number of objects correctly recognized.

CANTAB Delayed Matching to Sample (DMS) is a recognition memory test for non-verbalizable visual patterns, and assesses both simultaneous and visual working memory. In this subtest the subject is asked to match complex visual patterns in either a delayed (0, 4 and 12 seconds) or simultaneous condition. The pattern that represents the sample is located in a red box in the center of the screen and is presented for 3 seconds (except in the simultaneous condition) and beneath this, four white boxes are presented, each containing a different pattern, one of which is identical to the sample. Of the four patterns, two patterns differ from the sample only based on the color and the type of configuration. The remaining box contains a pattern that has minimal overlap with the sample. The participant is asked to touch the pattern that matches the sample. A simplified version for testing children has been used. The outcome measure used is the mean choices to correctly match the sample. In a previous study it has been found that the longest (i.e., 12 seconds) delay condition is most likely sensitive to hippocampal dysfunction (Squire 1992).

Tests of basic visual perception

Size Oddity task: In this test 4 black squares of different sizes are presented. Three squares are of the same dimension, whereas the fourth square is either larger or smaller in size. The positions of the 4 squares in the 2 X 2 array are jittered such that the edges of the squares are not aligned. Each trial is unique. The participant is asked to identify the square of different size. This task has been used as a baseline measure for face and scene oddity tasks (PRC-dependent tasks, Lee et al., 2008). The outcome measure used in his study is the percentage of correct identification.

A test of the ability to use Gestalt configural cues on figure assignment (Peterson & Salvagio, 2008). The displays are composed of either 2 or 8 alternating regions with convex or concave parts framed in a rectangular frame (Barense et al., 2011). Convex regions and concave regions are equally black and white. A medium gray background is used to contrast equally with both black and white regions (for a comprehensive description see Barense et al., 2011). Width and height are calculated based on the viewing angle and the distance from the screen (i.e., $H_{stimuli} = D_{distance\text{-}eye} \times \tan(\theta_{viewing\ angle})$). The stimuli are presented individually and the participant is asked to say whether the black or white segment seems to be a figure. The administration of the 2-region displays and 8-region displays is counterbalanced. The outcome measure used in this study is the percentage of correct identification.

Test of PRC function:

A test of effects of familiar configuration on figure assignment (the OMEFA test, Peterson et al., 2000; Peterson et al., 1998*)*. The test includes a set of 48 displays to assess the effects of familiar configuration on the figure assignment. Each stimulus includes adjacent black and white regions framed in a rectangle. For the experimental stimuli (n = 24), one of the 2 regions portrays an "intact configuration" of a portion of a familiar object (i.e., silhouette) representative of the real object (i.e., good match to the representation of a known object in memory). For the control stimuli (n = 24), one of the regions is created by rearranging the parts of the familiar object configuration of the experimental stimuli; whereas the other region does not portray a familiar object. Part-rearranged and intact familiar configurations are depicted equally in black and in white and on the left and right sides of the central border. In addition, we counterbalanced for side and color (e.g., the silhouette of the snowman was presented in black, in white, and on the left side and the right side between participants). The participant is asked to report whether the black or white region appear to be the figure and to identify any familiar objects they see. The OMEFA test seems to be sensitive to PRC function (Barense et al. 2011).

Additionally, the same stimuli were presented upside down for the inverted version of the test. The orientation manipulation has been used to inform about performance on the OMEFA test, given that the manipulation would affect familiarity but would not affect other figural cues such as protrusion and convexity. In this manipulation

the participant is asked to report whether the black or white region appear to be the figure.

Familiarity Discrimination. This test includes 21 trials; each trial presents both the intact familiar configuration and the corresponding part-rearranged version drawn from the OMEFA test (both depicted in black and superimposed on a white background). In order to avoid position effects, the top/bottom location of the familiar configuration is counterbalanced. In this test, subjects are asked to report whether the black region on the top or on the bottom portrays a familiar object.

In order to introduce participants to figure-ground judgments the participants completed the Gestalt configural cues test of convexity before the OMEFA test. Peterson et al. (2000) showed that exposing the participants to convexity displays made them more confident in figure judgments for displays like those in the OMEFA test. The order of the OMEFA and Familiarity Discrimination was maintained stable. The inverted manipulation was administered before the upright OMEFA test.

In addition, after the administration of the PRC-dependent measures, an object identification task was included in order to test whether the participants identify the objects depicted in the OMEFA stimuli when they are shown in ideal conditions (i.e., colored photos of the objects). In this test, the examiner says a word and the participant points to the picture that best illustrates the word (receptive vocabulary). OMEFA performance was corrected for the number of objects identified in this task. The outcome measure used in this study for all PRC-dependent tests is the percentage of figure reports.

Procedure

Participants took part in a 2.5-hour testing session during which they completed tests of perception, PRC function and an adapted battery from the Arizona Cognitive Test Battery (Edgin et al. 2010a) including MTL-dependent and prefrontal tasks (described in the previous section). The testing session was completed in a laboratory setting or in the home in a location with minimal distractions. The test administration was counterbalanced in order to avoid position effects. However, tests of theoretical interest (i.e., *OMEFA* and the *test of the ability to use Gestalt configural cues on figure assignment*) were given first to obtain optimal performance. Participants were allowed a break when half of the testing was completed; in cases in which participants seemed to lose focus or become fatigued, more breaks were allowed. All procedures were approved by the University of Arizona Biomedical Institutional Review Board.

RESULTS

Statistical analyses

In order to address the aims of this study, we completed the following analyses using SPSS 20.0 for Mac OS X. First, the distributional properties of each measure were examined, including the normality of each measure and the presence of floor/ceiling effects. The measures presented here were mostly normally distributed. We examined the distribution, skewness and kurtosis of each measure for the three groups separately (n for each group = 28). The majority of the measures had a normal distribution, with values of skewness and kurtosis between -1 and 1. Based on findings from previous studies (Edgin et al. 2010a), we expected to find a large effect on the CANTAB PAL *(d*=0.74). At p = 0.05, we had adequate power to detect group differences with large effects (Cohen, 1992).

The results will be divided in the following five sections: a) descriptive measures, for which we compare background factors between the samples using independent t-tests and chi-square analyses b) benchmark measures, for which we compare memory and frontal function between the samples using independent t-tests c) visual-perceptual processing measures (comparison between group by using independent t-tests), d) PRC-dependent measures (comparison between groups by using independent t-tests), and e) relations among measures, in particular the ways in which the PRC and frontal measures may relate to well-replicated benchmark deficits in this population, by using a sequential multiple regression analysis.

Descriptive Measures

In this section we compare the DS group to MA control group on the background factors concerning the participant and his/her family. Table 2 shows that the DS and MA groups were not significantly different on the MA matching variable (verbal and non verbal raw score on the KBIT-II IQ test). Age was significantly different between the DS and MA group ($p < 0.001$), as was gender ($\chi^2(1, n = 56) = 3.54$, $p = 0.05$) and ethnicity ($\chi^2(3, n = 56) = 8.06$, $p = 0.05$). Hence, we controlled for ethnicity and gender in our analyses. Finally, the two groups were similar in total family income ($t(54) = -1.05$, $p = 0.30$); maternal education, ($t(54) = -0.81$, $p = 0.42$)*;* in the raw score on the SIB–R, ($t(52) = -0.55$, $p = 0.58$).

	Down Syndrome group N=28	**Mental age-matched control group N=28**	**t-test/chi-squared test**	***p***
		Child Background Factors		
Age in years M (SD)	16.01 (4.27)	4.57 (.55)	*14.05*	*0.001*
Age range in years	10.25-24	4.08-6.50	*NA*	*NA*
% Female	57.1	32.1	*3.54*	*0.05*
Ethnicity	11 Non-Hispanic or White; 14 Hispanic; 1 African-American, 2 Biracial/Multiracial	19 Non-Hispanic or White; 5 Hispanic; 4 Biracial/Multiracial	*8.06*	*0.05*
Verbal IQ raw score M(SD)	27.43 (10.34)	29.71 (6.83)	*-0.97*	*0.33*
Non Verbal IQ raw score M(SD)	14.46 (5.14)	15 (4.11)	*-0.43*	*0.67*
SIB-R Broad Index Age Equivalent M(SD)	7.62 (2.99)	8.63 (8.90)	*-0.55*	*0.58*
		Family Background Factors		
% Income <25,000	4.68 (2.09)	5.29 (1.63)	*-1.05*	*0.30*
Education *M(SD)*	16.57 (2.25)	17.11 (2.69)	*-0.81*	*0.42*

Table 2: DS and MA Control Group Differences on Descriptive Measures.

The group with DS was almost 11 years older than the MA control group; hence, they had more experience with visual stimuli and objects in the world (i.e., longer exposure). Therefore, we also included a second control group matched on chronological age to the group with DS to specifically control for the effects of experience, as some visual and perceptual tasks may relate more to experience (i.e. years of age) than to

cognitive level. Table 3 shows that the DS and CA groups were not significantly different on the matching variables (i.e., chronological age, t(54) = -0.78, p = 0.44). However, as would be expected, the two groups were different on the KBIT-II IQ test (p < 0.001). The groups were similar in gender ($\chi^2(1, n = 56) = 0.00$, $p = 0.61$) and ethnicity ($\chi^2(5, n = 56) = 5.45$, $p = 0.36$).

	Down Syndrome group N=28	**Chronological age-matched control group N=28**	**t-test/chi-squared test**	***P***
	Child Background Factors			
Age in years M (SD)	16.01 (4.27)	16.81 (3.32)	-0.78	*0.44*
Age range in years	10.25-24	9.17-19.75	NA	*NA*
% Female	57.1	57.1	0.00	*0.61*
Ethnicity	11 Non-Hispanic or White; 14 Hispanic; 1 African-American, 2 Biracial/Multiracial	1 American Indian, 2 Asian-American, 14 Non-Hispanic or White; 9 Hispanic; 2 Biracial/Multiracial	5.45	*0.36*
Verbal IQ raw score M(SD)	27.43 (10.34)	81.43 (10.91)	-19.01	*0.001*
Non Verbal IQ raw score M(SD)	14.46 (5.14)	35.25 (5.20)	-15.04	*0.001*

Table 3: DS and CA Control Group Differences on Descriptive Measures.

Given the significant differences between the DS group and MA control group on gender and ethnicity, we controlled for gender and ethnicity in all the analyses by checking if there are significant differences between females and males in the outcome

measures of main interest. The analyses showed no difference between females and males in benchmark measures, visual-perceptual processing measures and PRC-dependent tests.

Benchmark measures

In order to assess the sample representativeness, we included some benchmark features of the cognitive phenotype, including neuropsychological tasks measuring performance that may relate to prefrontal and medial temporal lobe function (Pennington et al., 2003; Edgin et al. 2010a). Table 4 shows how MA and DS groups compared on the benchmark tests including the hippocampal domain (i.e., CANTAB PAL and CANTAB PRM), MTL-dependent measures (i.e., DAS-II *Recognition of Pictures* and CANTAB DMS), and the prefrontal domain (i.e., *Modified DOTS task*). The groups were significantly different on CANTAB PAL $t(51) = 3.75$, $p = 0.001$, the Modified dots task, $t(54) = -4.10$, $p = 0.001$; and DAS-II Recognition of Pictures, $t(53) = -3.26$, $p = 0.002$. However, the groups were similar on performance in CANTAB PRM, $t(48.95) = 0.77$, $p = 0.45$; and CANTAB DMS, $t(53) = 0.11$, $p = 0.91$.

Measures	**DS Group**			**MA Group**			***p***
	N	*M*	*SD*	*N*	*M*	*SD*	
MTL-dependent Domain							
CANTAB PAL ***Mean Errors to Success*** **M(SD)**	25	7.34	3.07	28	4.13	3.15	*0.001*
CANTAB PRM ***Percent Correct*** **M(SD)**	27	59.88	13.38	28	63.25	18.70	*0.45*
DAS-II Recognition of Pictures ***Number Correct M(SD)***	*27*	7.26	2.68	28	9.86	3.19	*0.002*
CANTAB DMS ***Mean Choices to Correct M(SD)***	27	2.15	0.46	28	2.18	0.34	*0.91*
Prefrontal Domain							
Modified dots task ***Inhibitory Control Phase Percent Correct M(SD)***	28	60.14	37.27	28	82.46	20.72	*0.01*
Modified dots task ***Combined Phase Percent Correct M(SD)***	28	56.26	19.80	28	78.40	20.61	*0.001*

Table 4: DS and MA Control Group Differences on Benchmark Measures.

Therefore, this sample with DS was largely, but not entirely, similar to previous samples in the literature on the main benchmark measures. We did not replicate the deficits in CANTAB PRM reported in Pennington et al., (2003) and Visu-Petra et al. (2007).

Visual-perceptual processing measures

In order to assess basic visual and perceptual capabilities of individuals with Down syndrome we used a *test of the ability to use Gestalt configural cues on figure assignment* (i.e., 2-region and 8-region displays; Peterson & Salvagio, 2008) and a *test of size judgment* (Lee & Graham, 2008). Figure 2 shows how DS performed on the *test of the ability to use Gestalt configural cues on figure assignment*, compared to both MA and CA group controls. As the Figure shows, no significant differences were found between the DS group and the MA control group on either 2-region ($t(47.15) = -1.38$, $p = 0.18$) or 8-region displays ($t(54) = -1.41$, $p = 0.17$). In comparison to the CA control group, the DS group used gestalt cues to assign figure less than the CA control group on both 2-region ($t(34.19) = -2.66$, $p = 0.01$) and 8-region displays ($t(55) = -3.26$, $p = 0.002$).

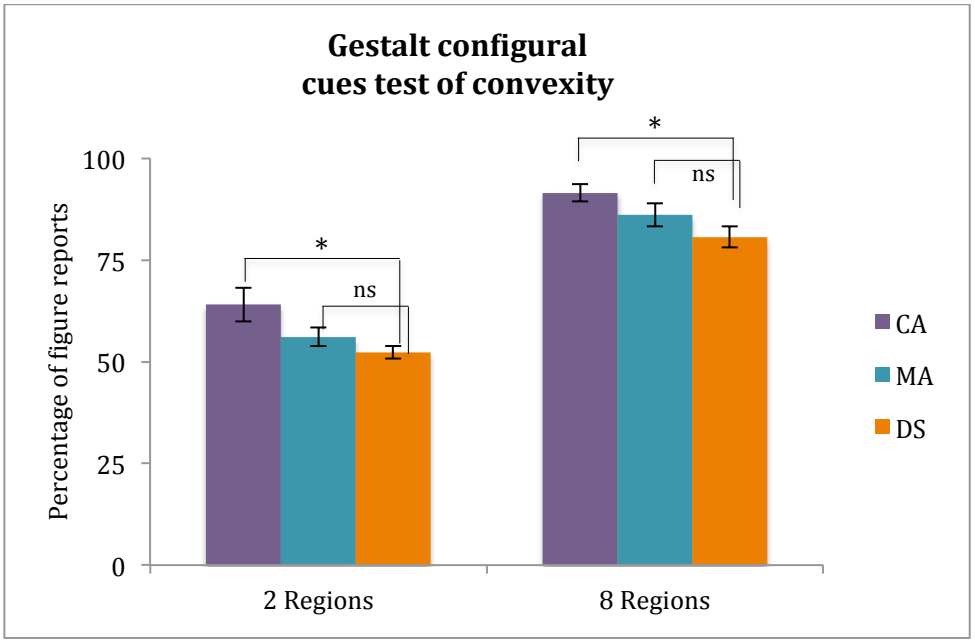

Figure 2: DS group compared to both MA and CA control groups on the *test of the ability to use Gestalt configural cues on figure assignment.*

As figure 7 shows, all three groups were more likely to perceive regions with convex parts as figures in the 8-region displays than in the 2-region displays. For the DS group, a paired-sample t-test indicated that scores were significantly higher for the 8-region displays (M = 80.68, SD = 13.52) than for the 2-region displays (M = 52.32, SD = 8.08), t(27) = -11.10, $p < 0.001$. Also for the MA control group, a paired-sample t-test indicated that scores were significantly higher for the 8-region displays (M = 86.11, SD = 15.33) than for the 2-region displays (M = 56.11, SD = 12.08), t(27) = -9.24, $p < 0.001$. The same pattern was seen in the CA control group. A paired-sample t-test indicated that scores were significantly higher for the 8-region displays (M = 91.54, SD = 11.33) than for the 2-region displays (M = 64.07, SD = 21.96), t(27) = -7.87, $p < 0.001$.

Figure 3 shows how DS performed on the *Size Judgment test*, compared to both MA and CA group controls. As the figure shows, the DS group differed from the MA control group (t(52) = -2.69, $p = 0.01$) and the CA control group (t(42.39) = -13.03, $p = 0.001$) on this test.

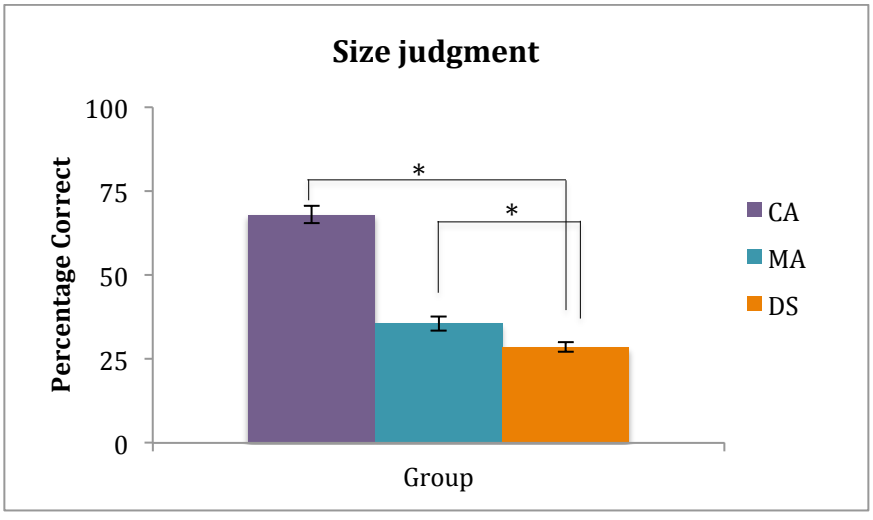

Figure 3: DS group compared to both MA and CA control groups on the *Size Judgment test.*

Additionally, we tested whether this result might remain after controlling for deficits in prefrontal measures. An ANCOVA examining size judgment performance [between-subjects factor: group (DS, MA); covariate: Modified dots task *Combined Phase Percent Correct*] revealed no main effects of the group, $F(1, 51) = 23.11$, $p = 0.57$; and an effect of Modified dots task *Combined Phase Percent Correct*, $F(1, 51) = 15.75$, $p = 0.001$. Therefore, after controlling for the prefrontal-dependent phase of the dots task, no group differences were apparent in size judgment.

PRC-dependent measures

Patients with damage to the PRC display the following pattern of results: they perceive figure significantly less for familiar configurations (due to the loss of facilitation at the parts level) and substantially more for novel configurations (due to the loss of inhibition at the parts level) (Barense et al., 2011). In addition, in an explicit familiarity discrimination task they showed worse performance compared to controls. Therefore, we tested patterns of performance on each of these outcome measures to determine the extent that the group with DS appeared to show difficulties in these functions. In addition, after the administration of the PRC-dependent measures, an object identification task was included in order to test whether the participants identify the objects depicted in the OMEFA stimuli when they are shown in ideal conditions (i.e., colored photos of the objects). OMEFA performance was corrected for the number of objects identified in this task.

1. The standard effect of familiar configuration

All subjects were likely to perceive regions portraying parts of familiar objects as a figure significantly more often than regions portraying novel configurations created by rearranging the parts of familiar objects. In the DS group, a paired-sample t-test indicated that scores were significantly higher for familiar configurations (M = 66.71, SD = 12.93) than for the novel configurations (M = 61.39, SD = 12.56), t(27) = 1.99, $p = 0.05$. Also for the MA control group, a paired-sample t-test indicated that scores were significantly higher for familiar configurations (M = 74.89, SD = 15.70) than for the novel configurations (M = 61.11, SD = 11.72), t(27) = 6.73, $p < 0.001$. The same pattern was found for the CA control group, a paired-sample t-test indicated that scores were significantly higher for familiar configurations (M = 91.39, SD = 7.39) than for the novel configurations (M = 72.89, SD = 7.44), t(27) = 15.89, $p < 0.001$.

2. The familiar minus novel configuration difference scores

As figure 4 shows, significant differences have been detected between the DS group as compared to both the MA control group (t(54) = -2.51, $p = 0.01$) and the CA control group (t(36.85) = -4.51, $p = 0.001$) on the familiar minus novel configuration difference score.

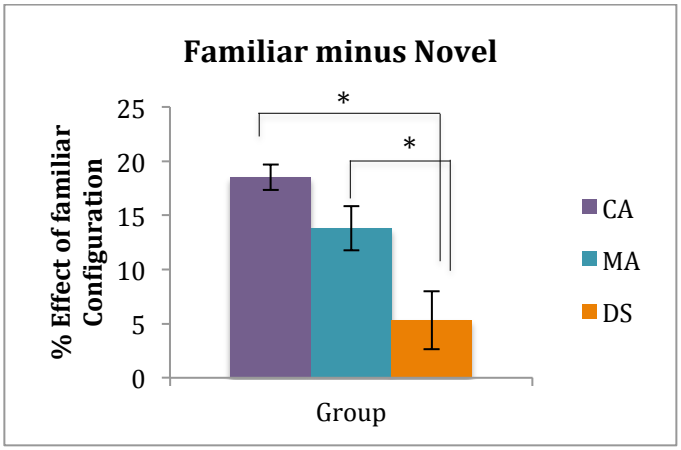

Figure 4: DS group compared to both MA and CA control groups on the *familiar minus novel configuration difference score.*

3. The dynamic interaction hypothesis

Based on our hypotheses, we expected that the DS group would perceive figure significantly less for familiar configurations (due to the loss of facilitation at the part level) and substantially more for novel configurations (due to the loss of inhibition at the part level) (Barense et al., 2011) when compared to both MA and CA control groups. As Figure 5 shows, the DS group perceived regions portraying parts of familiar objects as a figure significantly less often than both MA ($t(54) = -2.13$, $p < 0.03$) and CA ($t(42.93) = -8.78$, $p < 0.001$) control groups. However, the DS group did not perceive regions portraying novel configurations created by rearranging the parts of familiar objects as a figure significantly more in comparison to either the MA ($t(54) = 0.09$, $p < 0.93$) or CA ($t(43.87) = -4.17$, $p < 0.001$) control groups.

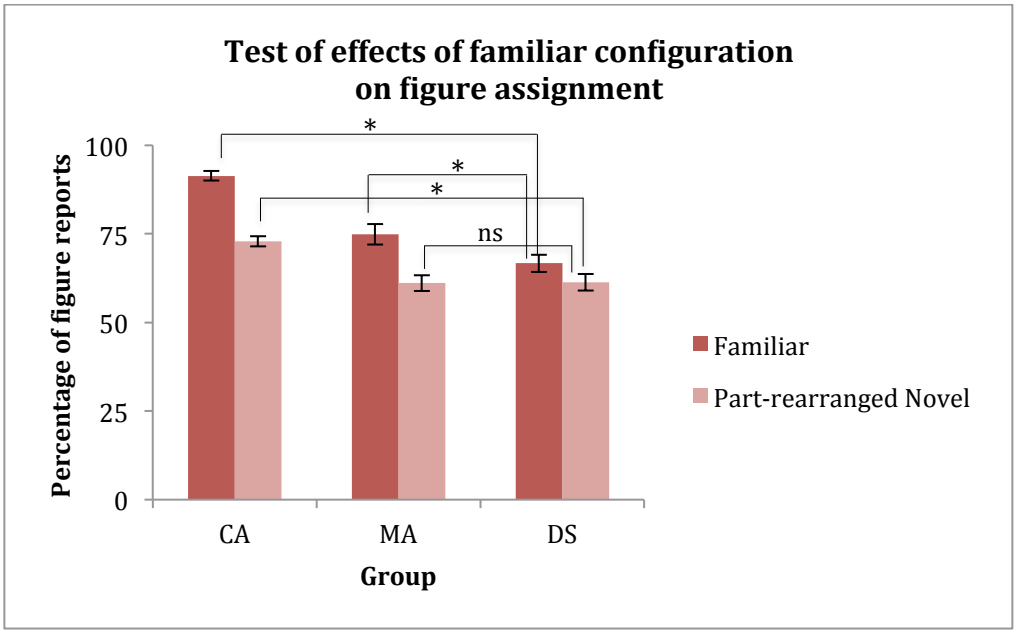

Figure 5: DS group compared to both MA and CA control groups on the *OMEFA test.*

4. Inverted Manipulation

A subgroup of the DS group (n = 9) was tested on the inverted manipulation of the OMEFA test to examine whether or not the DS group would show less familiarity based on object cues than in the upright displays. Only a subset of the MA (n = 7) and CA (n = 8) control groups were tested on the inverted manipulation.

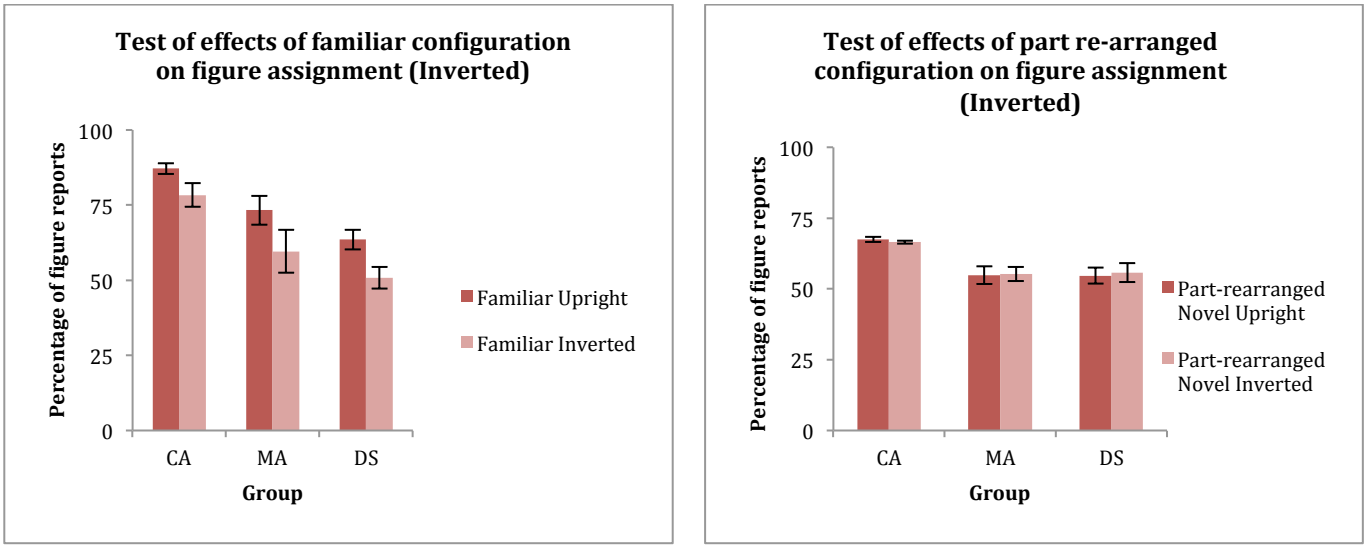

Figure 6: Within group differences between the upright and inverted OMEFA test in the three groups.

With regard to the familiar configurations, we found significant differences for the DS and MA control group, however, for the CA group no differences were detected. As shown in Figure 6, for the DS group, a paired-sample t-test indicated that scores were significantly higher for upright familiar configurations (M = 63.55, SD = 3.29) than the inverted familiar configurations (M = 50.82, SD = 3.59), t(10) = 2.33, p = 0.04. Also for the MA control group, a paired-sample t-test indicated that scores were higher for upright familiar configurations (M = 73.29, SD = 4.81) than the inverted familiar configurations (M = 59.57, SD = 7.13), t(6) = 2.31, p = 0.06 (i.e., trend). However, for the CA control group, a paired-sample t-test indicated that scores for upright familiar configurations (M = 87.13, SD = 1.76) were not significantly higher than the inverted familiar configurations (M = 78.38, SD = 3.93), t(7) = 1.69, p = 0.13.

With regard to the part-rearranged novel configurations, we did not find significant differences between the upright and inverted orientation in any of the three groups. Specifically, for the DS group, a paired-sample t-test indicated that scores for upright novel configurations (M = 54.64, SD = 2.86) were not significantly higher than the inverted novel configurations (M = 55.82, SD = 3.38), t(10) = -0.29, p = 0.78. Also for the MA control group, a paired-sample t-test indicated that scores for upright novel configurations (M = 54.86, SD = 3.11) were not significantly higher than the inverted novel configurations (M = 55.29, SD = 2.53), t(6) = -0.16, p = 0.88. Also for the CA control group, a paired-sample t-test indicated that scores for upright novel configurations (M = 67.50, SD = 0.91) were not significantly higher than the inverted novel configurations (M = 66.50, SD = 0.50), t(7) = 0.80, p = 0.45.

The familiar minus novel configuration difference score for the inverted manipulation is not significantly reduced in the DS group compared to MA control group (t(16) = -1.25, p = 0.23), but does differ when compared to the CA control group (t(17) = -2.94, p = 0.009).

5. Explicit Familiarity discrimination

In order to assess explicit object identification we compared the performance of the DS group to both the MA and CA control groups on the *Explicit Familiarity discrimination test*. As figure 7 shows, familiarity discrimination in the DS group is not significantly different in comparison to the MA control group (t(53) = 0.69, p =

0.49), but does differ in relation to the CA control group, with the DS group showing less ability to determine which figure is more familiar ($t(41.68) = -5.824$, $p = 0.001$).

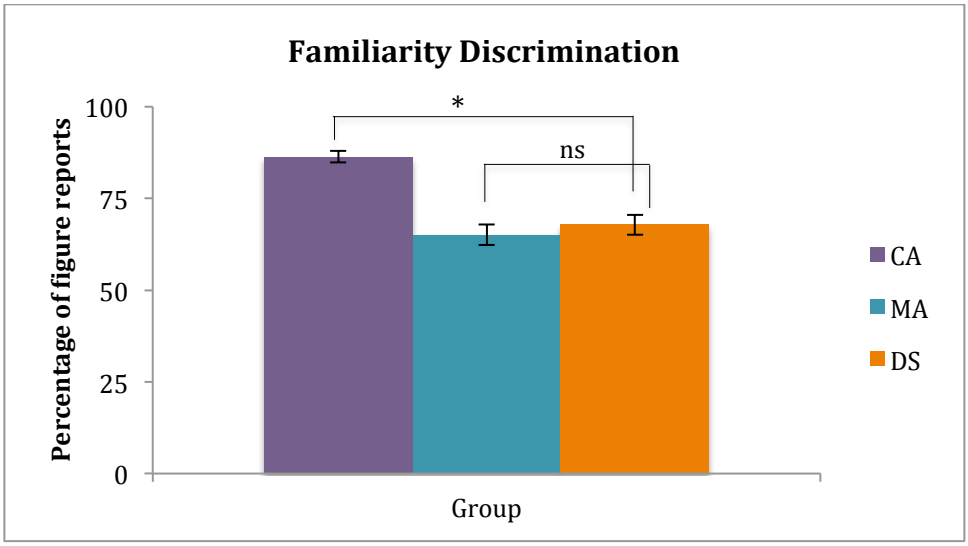

Figure 7: DS group compared to both MA and CA control groups on the *Familiarity Discrimination test.*

Finally, in order to examine potential effects of the administration of both inverted and upright OMEFA conditions in the same session, we ran the analyses excluding the participants from all groups who received the inverted manipulation. The pattern of results was the same when they were removed from the analyses. Roughly equal numbers of children (DS group: 9 subjects; MA control group = 7 subjects) received the inverted condition. Hence, overall group differences on the OMEFA pattern should not have been affected by the addition of this condition.

Relations among measures

A final objective of this study was to determine the cognitive components underlying deficits on benchmark MTL tasks, particularly contributions of frontal or PRC related function.

First, we examined the relation between the use of familiar configurations to guide figure assignment and the benchmark domains (i.e., MTL-dependent, and prefrontal) by performing a Pearson's Product-Moment Correlation (table 5).

Measures	**MTL-dependent**				**Prefrontal**
	CANTAB PAL Mean Errors to Success	*CANTAB PRM Percent Correct*	*CANTAB DMS Mean choices to correct*	*DAS-II Recognition of pictures*	*Modified Dots Combined Phase*
Effect of Familiar Configuration	-.041*	0.42*	-0.51**	-0.16	0.36+

*Correlation is significant at 0.05 level **Correlation is significant at 0.01 level + Correlation = 0.06

Table 5: Age-adjusted partial correlations among cognitive measures in the sample with DS

In addition, we tested relations among measures in the DS group using sequential multiple regression. Specifically, we tested how measures of medial temporal lobe function related to diminished effects of familiar configuration on figure assignment. Additionally, because of well-replicated prefrontal deficits in this population, we controlled for test of executive control (i.e., Modified dots task). A sequential multiple regression analysis was employed to predict performance on CANTAB PAL (i.e., binding of objects in spatial locations) and DAS-II Recognition of Pictures (i.e.,

immediate object recognition) to examine the relationship between MTL-dependent measures and various potential predictors. Two types of analyses were conducted. In the first analysis, we examined whether *executive functions* account for a significant proportion of MTL-dependent measures' variance, when *effect of familiar configuration* is entered first. In the second analysis, we examined the opposite relation: whether the *effect of familiar configuration* continued to account for a significant amount of the MTL-dependent measures variance when *executive functions* were entered first. For *the effect of familiar configuration* score we used the percentage of correct figure assignment on the intact familiar configurations, whereas for the *executive functions* score we used the combined phase of the Modified DOTS task.

		MTL-dependent measures					
		CANTAB PAL ***Mean Trials to Success***			**DAS-II Recognition of Pictures** ***Number Correct***		
	Predictors	R^2	ΔR^2	β	R^2	ΔR^2	β
Analysis 1							
Step 1	*Effect of familiar configuration*	0.16	0.16*	-0.07	0.02	0.02	-0.03
Step 2	*Executive function*	0.32	0.16*	-0.05	0.16	0.14+	0.05
Analysis 2							
Step 1	*Executive function*	0.26	0.26**	-0.06	0.09	0.09	0.04
Step 2	*Effect of familiar configuration*	0.32	0.06	-0.05	0.16	0.08	-0.06

* $p < 0.05$ ** $p < 0.01$ + $p = 0.06$

Table 6: Hierarchical multiple regression analyses predicting MTL-dependent measures by using executive functions and effect of familiar configuration as predictors.

Table 6 summarizes the descriptive statistics and analysis results. First, the results showed that *effect of familiar configuration* was a significant predictor of CANTAB PAL performance when it was entered before the *executive functions* score (Analysis 1, 13 % of the variance, $p = 0.045$). However, when it was entered after the *executive functions* score it was not significant (Analysis 2, 26 % of the variance, $p = 0.18$). In addition, the *effect of familiar configuration* did not contribute significantly to the DAS-II Recognition of Pictures' performance whether it was entered before (Analysis 1, 2 % of the variance, $p = 0.45$) or after (Analysis 2, 15 % of the variance, $p = 0.15$) the *executive functions* score. With regard to executive function, the table showed that there is a significant contribution of this variable to performance on the CANTAB PAL (Analysis 1, 26 % of the variance, $p = 0.04$; Analysis 2, 23 % of the variance, $p = 0.009$) and a trend on DAS-II Recognition of Pictures (Analysis 1, 16 % of the variance, $p = 0.058$). Based on the R^2 change statistic *executive functions* account for 26% of unique variance for CANTAB PAL performance (Analysis 1) and 16% of unique variance for DAS-II Recognition of Pictures (Analysis 1), above and beyond that explained by the *effect of familiar configuration* alone.

In summary, the *effect of familiar configuration* appeared to not be a reliable predictor of variance in the MTL-dependent performance, whereas *executive functions* seemed to be a reliable predictor of variance in the CANTAB PAL. In addition, *executive functions* marginally contribute to the performance on the DAS-II Recognition of Pictures.

DISCUSSION

The main goal of this study was to further our understanding of object memory impairment in individuals with DS. To do this we assessed a number of neuropsychological measures tapping the function of regions theorized to contribute to object memory, including basic visual perceptual capacity, functions of the PRC, and performance on prefrontal tasks. These results were then compared to differences in performance on benchmark assessments of object memory. Consistent with previous results, the group with DS performed significantly worse than the MA control group on one test of immediate object recognition as well as a test of object-in-space binding. Hence, our sample with DS displayed deficits in object memory that were similar to previous samples in the literature. However, we did not replicate deficits on two measures that could be considered PRC-dependent. We found no impairment on a test of immediate pattern recognition or performance on a delayed match to sample task. In the following sections we answer questions regarding the pattern of performance on domains important to object memory performance.

Could MTL-dependent deficits in DS result from basic perceptual impairments at the lower level of the VVS?

As we predicted from the findings of previous studies, we found no evidence for basic visual and perceptual impairments in individuals with DS that could explain difficulties in object memory. With regard to the *test of the ability to use Gestalt*

configural cues on figure assignment, the DS group showed similar patterns of performance in both 2-region and 8-region displays, in comparison to MA control sample. They reported perceiving the regions with convex parts as the figure significantly more often than the regions with concave parts. Based on these findings we can conclude that the use of a generic cue (i.e., convexity, protrusion) for figure assignment is relatively intact in those with DS. In addition, all the three groups were more likely to perceive regions with convex parts as figures in the 8-region displays than in the 2-region displays, consistent with the usual pattern of performance on this task (Peterson & Salvagio, 2008). However, the DS group perceived regions with convex parts as figures in both 8-region displays and 2-region displays significantly less than the CA group. This difference might be explained by levels of attention to the task or the ability to understand instructions. However, the absence of a difference in reference to the MA matched sample suggests relatively intact figure-ground detection on this task.

Another task used to assess visual global processing in the DS group was the Size oddity task. While DS initially showed differences in performance on this task, no group differences were found on this task after controlling for performance on the prefrontal measure, suggesting that this task had a substantial executive component that could have influenced the results. Consistent with past literature and the results on the use of convexity in figure-ground detection (Pennington et al., 2003; Visu-Petra, Bengla, Tincas & Miclea, 2007; Edgin et al., 2010a), these findings suggest relatively intact early visual stream functionality in DS.

Could MTL-dependent deficits in DS result from impoverished perceptual representations in the PRC, at the higher level of the VVS?

We examined PRC function in individuals with DS by using a paradigm shown to relate to PRC function (Barense et al., 2011). We found the group with DS showed decreased figure assignment in the high denotative condition, when the regions portrayed complete configurations of familiar parts. These differences were found in reference to both the CA and MA control sample. Specifically, individuals with DS showed the "*standard effect of familiar configuration*", that is perceiving regions portraying parts of familiar objects as a figure significantly more often than regions portraying novel configurations created by rearranging the parts of familiar objects. However, when we considered the *familiar minus novel configuration difference score*, the DS sample showed a significantly reduced effect of familiar configuration when compared to both MA and CA control groups. Nonetheless, it is important to specify that, unlike in PRC-damaged patients, for the DS group this score was reduced due to decreased figure responses to the intact familiar configurations. Contrary to this sample with DS, for the PRC-damaged patients the reduced score resulted from decreased figure responses to the intact familiar configurations as well as increased figure responses to part-rearranged novel configurations. These data suggest a possible deficit in object recognition/identification due to impoverished representations of the configuration of well-known objects in memory. In fact, individuals with DS identified with higher accuracy the objects depicted in the OMEFA stimuli when they were shown in ideal conditions (i.e., colored photos of the objects), though their ability to assign figure to

familiar objects decreased when presented with few details. In addition, their performance did not differ compared to the MA control group when identifying colored objects; whereas they did assign significantly fewer figures to familiar configurations compared to the MA control group. However, in order to better answer this question we tested the "dynamic interaction hypothesis" in the next section.

Could the deficit in object recognition in DS be due to a lack of feedback mechanism from higher to lower levels in the VVS?

In order to assess our hypothesis of impaired object representation in individuals with DS, the *dynamic interaction theory* was tested (Barense et al., 2011). This theory states that feed-forward and feed-backward signals between PRC and area TE result in a "gestalt" representation of a visual stimulus (Murray et al., 1999), with PRC (higher level of the VVS) representing the conjunctions of features/parts of visual stimuli and area TE (regions earlier in the visual processing stream) representing the individual features/parts from which these complex conjunctions are formed. Based on this theory, an intact PRC a) inhibits familiarity responses at lower levels of the VVS when part-rearranged configurations of object parts are presented b) facilitates familiarity responses at these lower levels when intact familiar configurations are presented (Barense et al., 2011).

By contrast, a damaged PRC:

a) does not detect intact configuration as familiar, and as a consequence there is no enhancement (feedback mechanism) of the low-level part familiarity response from a high-level configuration response. As a result, PRC-damaged

patients perceive the intact familiar configurations as figure significantly less than controls.

b) does not detect the part-rearranged configuration as novel, and as a consequence there is no inhibition (feedback mechanism) of the familiarity responses at lower-levels. As a result, PRC-damaged patients perceive the part-rearranged configurations as figure significantly more than controls.

Consistent with this theory, Barense et al. (2011) showed that performance of the PRC-damaged patients on the OMEFA test were characterized by the loss of facilitation of the PRC at the lower level of the VVS (decrease of responses for familiar configurations) and the loss of inhibition of the PRC at the " individual features" level (increase of responses for part-rearranged novel configurations).

Our data are not consistent with the predictions of the *dynamic interaction theory*. Despite the fact that the DS group's figure responses were reduced for intact familiar configurations compared to the MA control group, elevated responses for part-rearranged novel configurations were not found. There was no evidence for increased familiarity in the part-rearranged novel condition in relation to the DS group's own performance on complete configurations, in comparison to the MA control sample, or in comparison to performance when the inverted conditions were examined. Contrary to the PRC-damaged patients, the DS group perceived the part-rearranged critical regions as figures when they are inverted as much as when they are presented in the upright condition.

This pattern of findings could be explained in one of two ways, including 1) there is no PRC dysfunction in DS and the use of the familiar configuration for figure

assignment reflects impaired object representations at another level of the system, such as the prefrontal cortex or 2) there is PRC dysfunction but damage to the PRC in the developing system may affect facilitation and familiarity detection more so than inhibition and responses to novelty. This explanation would suggest different levels of sensitivity to damage and eventual reorganization of PRC-dependent processes. In PRC patients, the function of this region is highly impacted, so it would be expected to affect both mechanisms equally. However, given the negative findings from our benchmark assessments that may also tap PRC function, we can conclude that the inability to use configurations to guide figure ground decisions must be different in this population not because of dissociated functionality of PRC related mechanisms, but rather from degraded responses of other regions involved, such as the prefrontal cortex.

In addition, we examined the hypothesis that the decrease of familiar configuration effects on figure assignment in the DS group was the result of explicit memory deficits. Contrary to the PRC-damaged patients and our hypothesis, our DS group's performance in discriminating between novel and familiar configurations when presented together (i.e., explicit object identification) was similar to the performance of the MA control group.

Does inability to have implicit access to familiar representations affect MTL-dependent function?

In order to assess the cognitive components that may influence this group's poor performance on some assessments of object memory, we examined the relationship

between measures of object memory that were significantly different in the DS and MA control group (immediate object recognition and object in space paired associates learning) in relation to the effects of familiar configuration on figure assignment and an executive function measure, a prefrontal task. We found that the *effect of familiar configuration* was not a reliable predictor of performance on either task, whereas *executive functions* was a reliable predictor on performance on CANTAB PAL and it was marginally related to performance on the DAS-II Recognition of Pictures. Therefore, deficits on object memory tasks in this population seem not to be dependent on decreased levels of familiarity, and there may be some influence of performance from measures of prefrontal function.

CONCLUSION

The present results converge with previous findings that suggest spared function of the dorsal visual stream in individuals with DS (i.e., CANTAB Spatial Span or CORSI blocks; Pennington et al., 2003; Visu-Petra et al., 2007; Edgin et al., 2010a).

In addition, we found that our DS sample showed a reduced effect for familiar configuration (i.e., intact familiar configuration, the OMEFA test) and immediate object recognition deficits (i.e., DAS-II Recognition of Pictures). Our study is consistent with previous studies that have reported impairment in object recognition, the binding of objects in spatial locations as well as PFC function (i.e., CANTAB PAL; Pennington et al., 2003; Visu-Petra et al., 2007; Edgin et al., 2010a).

Finally, our data suggest that executive functions (i.e., prefrontal cortex) contribute to object-in-place in our DS sample. In addition, executive functions were marginally related to object recognition, only significant at the trend level. Given the marginal significance of these results these analyses need to be replicated in larger samples or with other measures. However, these findings are consistent with the "emergent memory account" model (Graham, Barense and Lee; 2010), and the *Object Model Verification Theory* (Kosslyn, 1994; Lowe, 1985; Ganis et al., 2007) suggesting that the prefrontal cortex plays a crucial role in top-down processes that are responsible for the perceptual matching between visual input and the best fitting representation of the object stored in LTM. Additionally, these results are in line with Jacola et al., (2011), who showed that activation of bilateral regions of the middle frontal gyrus was associated

with performance during an object decision task focused on semantic classification in individuals with DS (Jacola et al., 2011).

Only a few studies have examined familiarity and object representation in this specific population. The inclusion of the CA group aimed at controlling for the effects of experience, as some visual and perceptual tasks may relate more to experience (i.e. years of age) than to cognitive level. However, our findings discouraged any interpretation due to the substantial difference in IQ. The neuropsychological profile of individual with DS can be better examined by including groups with different developmental disabilities, such as William syndrome, matched on both age and IQ. In addition, further studies in individuals with DS are needed to better examine the underlying neural correlates of object recognition deficits, and the role of PFC in object recognition in individuals with DS. The knowledge gained from this study may have significant implications for identifying disrupted neural networks in the DS population.

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