

UC San Diego

UC San Diego Electronic Theses and Dissertations

Title

How we come to process 'what' and 'where' in our visual environment : insights from typical and atypical developmental populations

Permalink

<https://escholarship.org/uc/item/2r1099td>

Author

Paul, Brianna Michelle

Publication Date

2007

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO STATE UNIVERSITY

How We Come to Process ‘What’ and ‘Where’ in Our Visual Environment: Insights
From Typical and Atypical Developmental Populations

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Brianna Michelle Paul

Committee in charge:

University of California, San Diego

Professor Joan Stiles, Chair
Professor Gregory Brown
Professor Sandra Brown
Professor Frank Haist

San Diego State University

Professor Judy Reilly
Professor Beverly Wulfeck


2007

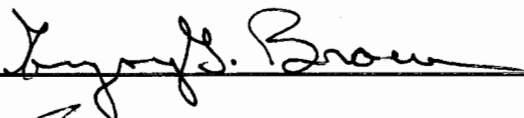
©

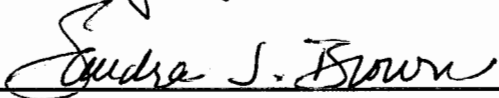
Brianna Michelle Paul, 2007

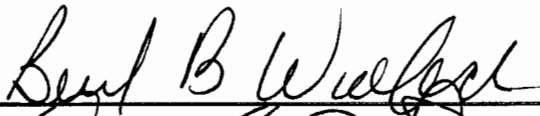
All rights reserved.

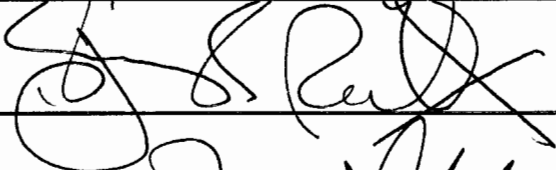
The dissertation of Brianna Michelle Paul is approved, and it is acceptable in quality and form for publication on microfilm:

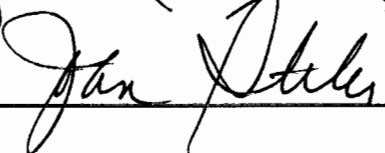











_____ Chair

University of California, San Diego

San Diego State University

2007

For my father.

TABLE OF CONTENTS

Signature Page.....	iii
Dedication.....	iv
Table of Contents.....	v
List of Tables.....	vi
List of Figures.....	vii
Acknowledgments.....	viii
Vita.....	x
Abstract.....	xvii
Chapter 1. General Background.....	1
Chapter 2. Background for the Current Studies.....	26
Chapter 3. Face and Place Processing in Williams Syndrome: Evidence for a Dorsal-Ventral Dissociation.....	35
Chapter 4. Face and Location Processing in Williams Syndrome: Beyond a Dorsal Stream Deficit.....	42
Chapter 5. Amygdala Response to Faces Parallels Social Behavior in a Genetically Determined Syndrome.....	115
Chapter 6. General Discussion.....	135
References.....	150

LIST OF FIGURES

Chapter 3

Figure 3.1. Diagram of Task Design and Sample Stimuli..... 38

Figure 3.2. Task Performance Across Groups..... 39

Chapter 4

Figure 4.1. Task..... 93

Figure 4.2. Amygdala Deficit in WS..... 94

Figure 4.3. Face Identity-Matching Activation in Ventral Occipital-Temporal
Cortex..... 95

Figure 4.4. Ventral Occipito-temporal Region of Interest (ROI) Analyses, Face
Identity-matching..... 97

Figure 4.5. Ventral Occipito-temporal Activation in Typical Children During
Location-matching (Passive Face Viewing)..... 98

Figure 4.6. Parietal Region of Interest (ROI) Analyses, Location-matching..... 99

Figure 4.7. Anomalous Parietal Activation in WS..... 100

Chapter 5

Figure 5.1. Task..... 128

Figure 5.2. Behavioral Session Results (Accuracy and Response Time), Face-
matching Task..... 129

Figure 5.3. Activation in Ventral Occipito-Temporal Regions and the
Amygdala..... 131

LIST OF TABLES

Chapter 4

Table 4.1. Behavioral Results.....	91
Table 4.2. Activation for Identity-matching > Location-matching and Location-matching > Identity-matching contrasts in Each Group.....	92

ACKNOWLEDGEMENTS

There is a long list of individuals who provided invaluable assistance in the completion of this dissertation.

First, my advisor Dr. Joan Stiles, who provided continuous guidance, support and encouragement throughout my graduate tenure. Joan has been an exceptional mentor and role model, and I have learned immeasurably from my experience in her laboratory. She has gone above and beyond in providing me with a number of unique opportunities and it is to her that I owe many of my successes over the last several years. Second, Dr. Frank Haist, who, with unfailing good humor and patience, guided me through many of fMRI analyses for these projects. Third, Janet Shin, who has been a constant source of support and technical knowledge, and who always seemed to have a solution for my many seemingly unsolvable problems.

In addition, this work would not have been possible without the contributions of our gracious and talented collaborators. They include Dr. Ursula Bellugi from the Salk Institute and Drs. Abraham “Avi” Snyder and Marcus Raichle from the Washington University School of Medicine in St. Louis. All of the work with the Williams Syndrome population was inspired by Dr. Bellugi, and was conducted through her laboratory. Drs. Raichle and Snyder gave their time, facilities and knowledge to the neuroimaging portion of this project. Dr. Snyder, in particular, has been particularly generous with his wisdom, and has helped provide me with outstanding training in conducting fMRI investigations.

I would also like to thank my entire dissertation committee. In particular, I acknowledge with great gratitude, the advice and guidance of my clinical mentor, Dr.

Sandra J. Brown. She has been absolutely instrumental in my development professionally and as a clinical neuropsychologist.

On a personal note, I would like to express my deepest appreciation for the patience, love, understanding and encouragement I have received from my friends and family. In particular, I am indebted to my mother, who was always willing to lend her ear, and to my dear friend and companion, Jason Acre, who steadfastly stood by me throughout every moment of my graduate school career. Without him, I would never have accomplished this task.

Chapter 3, in full, is a reprint of the material as it appears in: Paul, Brianna M.; Stiles, Joan; Passarotti, Alessandra; Bavar, Nasim; Bellugi, Ursula (2002). Neuroreport, 13 (9), 1115-1119. The dissertation author was the primary investigator and author of this paper.

Chapter 5 is being prepared for publication as: Paul, Brianna M.; Snyder, Abraham Z.; Haist, Frank; Raichle, Marcus E.; Bellugi, Ursula and Stiles, Joan (in preparation). Amygdala response to faces parallels social behavior in a genetically determined syndrome." The dissertation author was the primary investigator and author of this paper.

the ventral-dorsal stream dissociation in visual processing. Responsible for data acquisition and analysis, presentation of findings at scientific meetings, and manuscript preparation. Assist in grant development and writing. Responsible for selection and mentoring of undergraduate students, including senior honors thesis students, laboratory and research assistants.

1998 - 1999

Pre-doctoral IRTA (Intramural Research Training Award) fellow
Neuropsychology Section, Clinical Brain Disorders Branch
National Institute of Mental Health **Bethesda, Maryland**
Advisors: Terry E. Goldberg, Ph.D. and Daniel R. Weinberger, M.D.

Primary research coordinator and assistant on five research projects. Administered a range of standardized neuropsychological tests to various neuropsychiatric populations (including patients with schizophrenia, Alzheimer's disease and Parkinson's disease) and typical adult and child volunteers. Designed, developed, and implemented experimental neuropsychological tasks. Independently conducted a behavioral study assessing the effects of encoding depth on recognition memory in patients with schizophrenia. Presented findings at a scientific conference and published findings in peer-reviewed journal. Interviewed, selected and supervised research volunteers.

1996 - 1998

Research Assistant, Department of Neural Systems, Memory, and Aging
University of Arizona **Tucson, Arizona**
Advisors: Bruce L. McNaughton, Ph.D. and Carol A. Barnes, Ph.D.

Assisted with projects examining the role of the hippocampus in spatial learning and memory in rodents. Learned basic animal electrophysiological techniques, histological procedures, and ethological methods. *Senior thesis research project*: investigated the effects of immediate early gene products (IEPs) on the maintenance of long-term potentiation (LTP) using a chronic set-up for administration of proteins and recording of potentials in freely-behaving animals.

1997
summer

Research Assistant, Department of Clinical and Preclinical Pharmacology
University of Florence **Florence, Italy**
Advisor: Giancarlo Pepeu, M.D., Ph.D.

Participated in research aimed at developing animal models of Alzheimer's disease. Assisted with projects investigating 1) the effects of amyloid peptide injection in the Nucleus Basalis of Meynert (NBM) on the integrity of cholinergic neurons and the morphology of microglial cells and 2) the effects of NBM interleukin injection on the morphology of microglial and astroglial cells. Performed basic immunohistochemical procedures.

1996
summer

**Research Assistant, Barrow Neurological Institute
St. Joseph's Hospital Phoenix, Arizona**
Advisor: Michal K. Stachowiak, Ph.D.

Participated in research on the synthesis of basic fibroblast human growth factor (BFGF), a protein expressed in the CNS that stimulates growth, motility and differentiation of glial cells and neurons. Assisted with a project aimed at performing site-directed mutagenesis of the BFGF promoter. Implemented basic molecular and cellular biology protocols.

SUPERVISED CLINICAL EXPERIENCE

2005 – 2006

**Psychology Intern, Clinical Neuropsychology Track, Dept. of
Psychiatry and Biobehavioral Sciences, David Geffen School of
Medicine
University of California, Los Angeles**

Supervisors: multiple supervisors both on- and off-site, including Bill Steh, Ph.D., Jessica Horsfall, Ph.D., Thomas Kaleita, Ph.D., Susan Bookheimer, Ph.D., Robert Bilder, Ph.D., ABPP/ABCN, Charles Hinkin, Ph.D., ABPP/ABCN

Clinical internship with an emphasis in neuropsychological and psychodiagnostic assessment of children (outpatient) and adults (outpatient and inpatient) with various medical and psychiatric conditions. Elective intervention experiences included group and individual parent training, autism diagnostic evaluation clinic, and group psychotherapy for adult stroke survivors. Internship meets guidelines for training in neuropsychology, set forth by Division 40 (Clinical Neuropsychology) of the American Psychological Association.

2004 – 2005

**Practicum Student, Child and Adolescent Psychiatric Services (CAPS)
University of California, San Diego**

Supervisor: Sandra J. Brown, Ph.D., ABPP/ABCN

Advanced training in psychological and neuropsychological test interpretation and report-writing in a pediatric inpatient setting. Patient population includes children and adolescents with acute psychiatric conditions, severe behavioral problems, history of abuse/neglect, mental retardation, learning disabilities, substance abuse issues, etc.

2003 – 2005

**Psychometrist, UCSD Neuropsychology Associates
Department of Psychiatry, University of California, San Diego**

Supervisor: Sandra J. Brown, Ph.D., ABPP/ABCN

Test administration and scoring for community dwelling children referred for assessment of neurobehavioral conditions including traumatic brain injury, neurodevelopmental disorders, learning disabilities, etc.

- 2002 - 2005 ***Psychometrist, National Football League (NFL) Neuropsychological Testing
San Diego Chargers***
Supervisor: Robert K. Heaton, Ph.D., ABPP/ABCN
- Test administration and scoring of baseline neuropsychological assessments and post-concussion assessments with team athletes. Determination of readiness to return to play following concussive events.
- 2003 – 2004 ***Practicum Student, UCSD Outpatient Psychiatric Services
Department of Psychiatry, University of California, San Diego***
Supervisor: Robert K. Heaton, Ph.D., ABPP/ABCN
- Advanced training in interpretation and communication of results from neuropsychological evaluations using the expanded Halstead-Reitan battery. Responsibilities included case conceptualization and presentation, and preparation of comprehensive neuropsychological reports. Patients were adults with histories of stroke, traumatic brain injury and a variety of other neurological and psychiatric disorders.
- 2002 - 2003 ***Practicum Student, Neuropsychology Service
VA Medical Center, San Diego***
Supervisors: Gregory G. Brown, Ph.D., ABPP/ABCN, Dean C. Delis, Ph.D., ABPP/ABCN, Mark W. Bondi, Ph.D., ABPP/ABCN, Terry L. Jernigan, Ph.D., J. Vincent Filoteo, Ph.D.
- Training in the administration, interpretation and communication of neuropsychological assessments using a flexible battery approach. Responsible for conducting clinical interviews and comprehensive neuropsychological evaluations, interpreting assessment results, writing reports, presenting cases and providing feedback to patients when requested. Patients were veterans referred for assessment of cognitive difficulties secondary to a variety of neurological and psychiatric illnesses including dementia of the Alzheimer's type, Parkinson's dementia, closed head injury, sleep disorders, substance use disorders, etc. Attended weekly didactic meetings reviewing various topics in neuropsychology.
- 2001 - 2002 ***Practicum Student, Children's Outpatient Psychiatry
Children's Hospital and Health Center, San Diego***
Supervisor: Ann F. Garland, Ph.D.
- Received training in diagnosing and treating children and families within a multidisciplinary outpatient psychiatric setting. Conducted intake interviews, assessments (psychological and neuropsychological) and individual, group and family therapy. Created curriculum and co-facilitated outpatient social skills training group for parents and children. Attended weekly treatment team meetings with medical doctors and social workers/ family therapists, and participated in weekly didactic training and seminars on topics in clinical child psychology.

2000 - 2001 **Practicum Student, Child and Adolescent Psychiatric Services (CAPS)
University of California, San Diego**
Supervisor: Sandra J. Brown, Ph.D., ABPP/ABCN

Training in psychological and neuropsychological assessment of pediatric inpatients. Responsible for test administration, scoring, interpretation of findings and preparation of reports. Co-facilitated social skills training group for children and process group for adolescents. Attended weekly treatment team meetings with medical doctors, nurses, social workers and occupational therapists, and participated in weekly didactic meetings on topics in child psychology/neuropsychology.

TEACHING EXPERIENCE

Winter 2003-2004 **Teaching Assistant, Department of Cognitive Science
University of California, San Diego**
Course: Neurological Development and Cognitive Change, CogSci 115
Faculty: Joan Stiles, Ph.D.

Responsible for exam construction, exam and assignment grading, office-hour consultation, and review lecture preparation and presentation.

Summer 2004 **Guest Lecturer, Academic Connections, Department of Cognitive
Science
University of California, San Diego**
“Profiles of Major Neurobehavioral Syndromes and Disorders”
Course: Developmental Cognitive Neuroscience: How Our Brains
Develop to See the World
Instructor: Wendy Ark, Ph.D.

PUBLICATIONS

Stiles, J., Reilly, J., Paul, B. and Moses, P., and (2005). *Cognitive Development Following Early Brain Injury: Evidence for Neural Adaptation*. Trends in Cognitive Sciences, 9 (3), 136-143.

Paul, B.M., Elvevåg, B., Bokati, C.E., Weinberger, D.R. and Goldberg, T.E. (2005). *Levels of processing effects on recognition memory in patients with schizophrenia*. Schizophrenia Research, 74 (1), 101-110.

Stiles, J., Moses, P., and Paul, B. (2005). *Spatial cognitive development following early focal brain injury*. Cognitive Creier Comportament. Special Issue: Developmental cognitive neuroscience, 9 (2), 383-401.

Passarotti, A.M., Paul, B.M., Bussiere, J., Buxton R., Wong E., and Stiles J. (2003). *The development of face and location processing: an fMRI study*. Developmental Science, 6 (1), 100-117.

Paul, B.M., Stiles, J., Passarotti, A., Bavar, N. and Bellugi, U. (2002). *Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation*. Neuroreport, 13 (9), 1115-1119.

CHAPTERS

- Stiles, J., Paul, B.M., Ark, W. (in press). *Spatial Cognitive Development*. In: Handbook of Developmental Cognitive Neuroscience, 2nd Edition. M. Luciana and C.A. Nelson, eds., MIT Press.
- Stiles, J., Moses, P., and Paul, B.M. (2006). *The Longitudinal Study of Spatial Cognitive Development in Children with Pre- or Perinatal Focal Brain Injury: Evidence for Cognitive Compensation and for the Emergence of Alternative Profiles of Brain Organization*. In: Reprogramming the Cerebral Cortex: Plasticity following central and peripheral lesions. S.G. Lomber and J.J. Eggermont, eds., Oxford University Press.
- Stiles, J., Paul, B., and Hesselink, J. (2006). *Spatial Cognitive Development following Early Focal Brain Injury: Evidence for Adaptive Change in Brain and Cognition*. In Y. Munakata and M.H. Johnson (Eds.), *Process of Change in Brain and Cognitive Development: Attention and Performance XXI* (pp. 535-561). Oxford: Oxford University Press.

MANUSCRIPTS IN PROGRESS

- Paul, B.M., Snyder, A.Z., Haist, F., Bellugi, U., Raichle, M.E., and Stiles, J. (in preparation). *Amygdala response to faces parallels social behavior in a genetically determined syndrome*.
- Paul, B.M., Nass, R., Trauner, D., and Stiles J. (in preparation). *Processing objects and space: Insights from children with early brain injury*.

PUBLISHED ABSTRACTS

- Paul, B.M., Stiles J., Snyder, A.Z., Raichle, M.E., Rose, F.E., Hornbeck, R., Bavar, N., Haist, F., Carapetian, S.A., and Bellugi, U. (2004). *Face and Space Processing in Williams Syndrome (WMS)*. NeuroImage, 22 (suppl 1), S31.
- Paul, B.M. and Stiles J. (2003). *Face Processing: FMRI Case Studies of Children with Focal Lesion*. NeuroImage, 19 (2 suppl 1), S56.
- Passarotti, A.M., Paul, B.M., Bussiere, J., Paparello, S. and Stiles, J. (2002). *Effects of working memory load on anterior and posterior brain networks during What and Where processes: a developmental FMRI study*. NeuroImage, 16 (2 suppl 1), 1345.
- Passarotti, A.M., Paul, B.M., Rudiak-Gould, P. and Stiles J. (2001). *Development affects the ventral and dorsal processing streams differently: a fMRI study on face and location processing in children, teenagers and adults*. Part III. NeuroImage, 13 (6 suppl 1), 345.
- Passarotti, A.M., Paul, B.M., Bussiere, J. and Stiles J. (2000). *Developmental trends in face and spatial processing: A FMRI study, Part I*. NeuroImage, 11 (5 suppl 1), S38.

TALKS AND POSTER PRESENTATIONS

- Haist, F., Paul, B., Duann, J., Jung, T., Makeig, S., and Stiles, J. *Developmental effects on brain networks for face processing studied with independent components analysis*. Poster presented at the 12th Annual meeting of the Organization for Human Brain Mapping. June 2006.
- Paparello, S., Paul, B., Le Grand, R., Maurer, D., Mondloch, C., and Stiles, J. *Children with unilateral focal lesions processing composite faces: Evidence of plasticity*. Poster presented at the 14th Annual meeting of the Cognitive Neuroscience Society. April 2006.

- Paul, B.M. Invited Speaker. *Developmental Change in “What” and “Where”:* Insights from Typical and Atypical Populations. Neuro-Imaging Laboratories, Mallinckrodt Institute of Radiology and School of Medicine, Washington University, St. Louis, MO. July 2003
- Paul, B.M. and Stiles J. *Face and location processing: Evidence from children with focal lesion.* Poster presented at the 11th Annual meeting of the Cognitive Neuroscience Society. April 2003.
- Passarotti, A.M. , Paul, B.M., and Stiles, J. *An FMRI Study on the Developmental Change in the Neural Bases of Face and Location Processing.* Poster presented at the 11th Annual meeting of the Cognitive Neuroscience Society. April 2003.
- Passarotti, A.M., Paul, B.M. and Stiles, J. *How do the ventral and dorsal processing streams develop? A FMRI study.* Poster presented at the 8th Joint Symposium on Neural Computation. May 2001.
- Paul, B.M., Passarotti, A.M., Stiles J. *Face and location processing: A developmental perspective.* Poster presented at the 9th Annual meeting of the Cognitive Neuroscience Society. April 2001.
- Passarotti, A.M., Paul, B.M. and Stiles, J. *Developmental trends in face and spatial processing: A FMRI study, Part II.* Poster presented at the European Science Foundation’s EURESCO Conference on Normal and Abnormal Cortical Functional Specializations: Brain Development and Cognition in Human Infants. July 2000.
- Paul, B.M., Elvevåg, B., Weinberger, D.R. and Goldberg, T.E. *Levels of processing effects on recognition memory in patients with schizophrenia.* Poster presented at the Mt. Sinai Conference on Cognition in Schizophrenia, satellite to the International Congress on Schizophrenia Research (ICOSR). April 1999.
- Paul, B.M., Houston, F.P., Worley, P.F., and Barnes, C.A. *The role of ARC, an immediate early gene, in the maintenance of long-term potentiation.* Poster presented at the 9th Annual Undergraduate Biology Research Conference. January 1998.
- Paul, B.M., Alyan, S.H., Ellsworth, E., White, R.D., and McNaughton, B.L. *A novel test of path integration behavior in rodents.* Poster presented at the 8th Annual Undergraduate Biology Research Conference. January 1997.
- White, R.D., Ellsworth, E., Paul, B.M., Alyan, S.H., and McNaughton, B.L. *Is the hippocampus necessary for path integration?* Poster presented at the 8th Annual Undergraduate Biology Research Conference. January 1997.

PROFESSIONAL MEMBERSHIPS

American Psychological Association (student affiliate)
 Cognitive Neuroscience Society (student affiliate)
 Organization for Human Brain Mapping (student affiliate)
 Society for Neuroscience (student affiliate)
 International Neuropsychological Society (student affiliate)

OTHER EXPERIENCE

2001-2002 Member, Student Selection Committee
 UCSD/SDSU Joint Doctoral Program in Clinical Psychology

ABSTRACT OF THE DISSERTATION

How We Come to Process ‘What’ and ‘Where’ in Our Visual Environment: Insights
From Typical and Atypical Developmental Populations.

by

Brianna Michelle Paul

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2007

San Diego State University, 2007

Professor Joan Stiles, Chair

Human visuoperceptual functions can be divided according to their neuroanatomical substrates: processing ‘what’ an object is depends largely on ventral occipitotemporal regions, whereas processing ‘where’ an object is relies more on dorsal occipitoparietal regions. Although much is known regarding the mature incarnation of this ventral/dorsal dissociation, little is known about how it develops. The current study addressed this with two experiments that involved both typically-developing children and healthy adults, as well as adult individuals with Williams Syndrome (WS), a genetically-based neurodevelopmental disorder for which dissociations in ventral-dorsal stream processing have been reported. The first experiment examined behavioral performance on two matched tasks differing only in

their instructions: attend to stimulus identity (face identity-matching; ventral stream) or to stimulus position (face location-matching; dorsal stream). The second experiment examined patterns of brain activation on these same tasks using functional magnetic resonance imaging (fMRI) with each of the three populations. By virtue of including both typical adults and children (chronological age, CA, and mental age, MA, controls for the WS participants) in addition to WS participants, these experiments were well poised to provide both insight into the normal development of ventral and dorsal stream processing, and critical information regarding the integrity of these systems in WS.

Thirty-three individuals with WS (age $M = 27.2$ years), 19 MA controls (age $M = 9.0$ years), and 24 CA controls (age $M = 20.7$ years) participated in the behavioral experiment. Although overall, typical children (MA controls) responded less accurately and more slowly than adults (CA controls), like adults, their performance did not differ across the identity- and location-matching tasks. By contrast, WS participants showed a pronounced and selective deficit in location-matching when compared with MA controls, but comparable performance on identity-matching. This finding in WS provides empirical support for numerous reports of face processing skills that far exceed general spatial ability in WS. This dissociation is not observed during the course of normal development. Based on this finding, it was hypothesized that the subsequent brain imaging experiment would reveal differentially impacted function in the ventral and dorsal visual streams in WS when compared with typically-developing participants.

In the second experiment, both cognitive and fMRI data were collected from a second set of participants: 15 with WS (age \underline{M} = 30.1 years), 16 MA controls (age \underline{M} = 8.9 years), and 17 CA controls (age \underline{M} = 31.0 years; individually age- and gender-matched to the WS participants). In accordance with their cognitive profile (performance on both tasks that had not quite reached the level of CA controls) MA controls recruited many of the same regions as CA controls, but also differed from them in certain key task-related regions. These regions included the face-preferring temporal fusiform gyrus of the left hemisphere (LH) during identity-matching and superior parietal cortex in the LH during location-matching. Given that most critical task-related regions reside in the right hemisphere (RH) (RH fusiform gyrus for face discrimination, RH parietal cortex for location processing), these findings appear to reflect protracted maturation of task-sensitive regions in the nondominant hemisphere. When compared with profiles of activation in MA and CA controls, brain response in WS participants was abnormal. In accordance with their profound location-matching deficits, WS participants showed a striking lack of location-matching activation in parietal cortex, a finding that is consistent with a dorsal stream deficit hypothesized in this disorder. However, at variance with hypotheses of spared face discrimination and ventral stream function in WS, the brain response was also abnormal for face identity-matching, even though cognitively, WS participants performed this task at the level of MA controls. Abnormalities in WS manifested as a poorly modulated response of the fusiform gyrus, a lack of response in the amygdala, and surprisingly, an abnormally heightened response in a portion of parietal cortex that was not engaged by the task in MA or CA controls. The latter two findings are of particular interest because they may

relate to an unusually strong preference for face-to-face social interaction (often described as “hypersociability”) that has been described in the WS population.

CHAPTER 1

GENERAL BACKGROUND

As sight-driven creatures, we are required to process visual scenes of people, places and objects in order to effectively interact with and make sense of the world from the time we are very young. The course that the developing visual system takes is surprisingly protracted, as some visuospatial functions continue to develop throughout the preschool and school-age years (e.g., Akshoomoff and Stiles 1995; Taylor, McCarthy et al. 1999; Gathercole, Pickering et al. 2004; Luciana, Conklin et al. 2005). In the adult, visuospatial functions can be divided according to the neuroanatomical systems upon which they rely. Specifically, two dissociable pathways have been recognized, a ventral or ‘what’ system for “object vision” and a dorsal or ‘where’ system for “spatial vision” (Mishkin, Ungerleider et al. 1983). While these two types of functions have been simultaneously studied in adults many times, developmental investigators have not routinely employed a single framework to examine the emergence of these abilities. That is, they have tended to restrict their focus to functions subserved by one system *or* the other. Thus, little is known about the ontogeny of these pathways, how they develop in tandem over time and how the adult-like dissociation in behavior and in brain function actually comes about.

Study of individuals with typical or anomalous developmental courses can shed light on the path the visual brain takes in its functional transformation to the adult state. The goal of the studies in this dissertation is to exploit this potential at two complementary levels, behavioral (Chapter 3) and neurophysiological (Chapters 4 and 5), with two developmental populations, typical children and individuals with Williams Syndrome (WS). In each study, a healthy adult comparison group is included to provide information about the mature profile of functioning. The study presented in

Chapter 3 is aimed at addressing unanswered questions regarding performance of ventral and dorsal stream functions in populations that develop these capacities in a typical (school-age children) or an atypical (WS) fashion. An examination of performance differences will help determine whether or not the developmental trajectories for these two processes are indeed dissociable and in the case of typical development, whether one precedes the other in reaching adult status. The study presented in Chapters 4 and 5 uses functional neuroimaging (functional magnetic resonance imaging, fMRI) to explore the neural substrates that underlie performance on the same tasks used in Chapter 3, with the same populations. Information gathered from these studies will permit comparisons of the functional organization of dorsal and ventral streams in typical participants at different points in development (i.e. children and adults) and in a patient population with a genetic abnormality that is associated with dorsal and/or ventral stream compromise. Thus, overall, these studies can speak first to questions about the pattern of development of the two cortical visual pathways. With this knowledge in hand it is then possible to look at the capacity of these pathways to adopt altered patterns of functional organization, and the effects this can have on their ability to support their respective visuo-cognitive functions.

Two Cortical Visual Systems

An influential body of animal work from the late 1960's suggested the utility of dividing visuo-perceptual functions according to whether they guide the animal in space or help the animal discriminate objects in its environment (Ingle 1967; Held 1968; Trevarthen 1968; Schneider 1969). While this early research tended to focus on subcortical contributions to spatial and object vision (Trevarthen 1968; Schneider

1969), later work gave way to interest in cortical mediation of these functions and to Ungerleider and Mishkin's (1982) well-known and influential model of "two cortical visual systems." These two cortical systems were characterized by their distinct extrastriate targets (posterior parietal regions for the dorsal stream and inferior temporal regions for the ventral stream), anatomical connections, functional properties and lesion-based effects on behavior (Ungerleider and Mishkin 1982; Van Essen and Maunsell 1983; Desimone and Ungerleider 1989). Within this framework, the dorsal occipitoparietal pathway is involved in spatial processing, including perception of motion and spatial relations, route-following and visually-guided reaching, whereas the ventral occipitotemporal pathway is implicated in perception, discrimination, and recognition of objects/patterns and their attributes, such as form and color. Despite lively debates over exact definitions and explicit delineations of the types of input/output associated with each cortical pathway in humans (Jeannerod 1999; Creem and Proffitt 2001; Norman 2002), non-human primate work suggests that the dorsal-ventral stream distinction has provided a robust and functionally useful description of the visual brain.

Parvocellular Versus Magnocellular

There is an obvious parallel between the two cortical streams and the division of subcortical visual pathways into two different streams, parvocellular and magnocellular. Briefly, the subcortical parvocellular pathway originates in midget ganglion cells of the retina (P cells) whereas the magnocellular pathway originates in parasol retinal ganglion cells (M cells). P cells are color-selective, whereas M cells are not. M cells, on the other hand, are larger and conduct impulses faster than their

parvocellular counterparts. The anatomical segregation of the two pathways is maintained in the lateral geniculate nucleus (LGN), with P cells projecting to four layers in the LGN that are distinct from the two LGN layers which receive input from M cells. Projections from LGN to cortex also remain segregated, with layer 4a and 4C β of primary visual cortex (V1) receiving parvocellular input and layer 4C α of V1 receiving magnocellular input. While the parvocellular versus magnocellular separation is reflected to some degree in extrastriate regions (e.g. the ‘color pathway’ through cortical area V4 and ‘motion pathway’ through cortical area V5/MT) (Van Essen and Maunsell 1983; Maunsell and Newsome 1987) the parietal and temporal regions for spatial and object processing are not exclusively influenced by either subcortical pathway (Merigan and Maunsell 1993). In addition, the two streams in the cortex are not completely estranged, as there are non-trivial interactions between early and late visual areas from different streams (Van Essen, Anderson et al. 1992). Nonetheless, differences in timing of the development of the parvocellular and magnocellular pathways in humans (Hickey 1977) have been cited as evidence for dissociability in the developmental trajectories of the two cortical visual streams (Atkinson 1992; Atkinson 2000).

Adults: Clinical Studies

Citing the incomplete segregation in the mapping of the parvocellular and magnocellular pathways onto inferior temporal and posterior parietal regions, Goodale & Milner (1992; Milner and Goodale 1995) suggest that both cortical streams receive some of the same basic types of input. In contrast with Ungerleider & Mishkin (1982), they argue that the proper functional distinction between the two cortical streams lies

in different uses of visual information for directing behaviors. In their model of 'perception' versus 'action' or 'what' versus 'how', they assert that the dorsal stream processes information to guide action on objects (e.g. visually-guided grasping), while the ventral stream processes information for the purpose of identifying objects and assigning meaning to them. Much of the impetus for their original proposal stemmed from observations of human patients with selective damage to areas of the visual system. They have written extensively about one patient in particular, D.F. (e.g., Goodale, Milner et al. 1991), a middle-aged woman with damage to ventrolateral occipital regions due to carbon monoxide poisoning. D.F. showed a remarkable dissociation between her ability to discriminate or recognize objects (severely impaired) and the accuracy of her actions on those objects (intact).

Neuropsychological reports of other patients with discrete cortical lesions provide further evidence for a dual-stream representation for vision in the cortex (whether it be according to Ungerleider and Mishkin (1982) or Goodale and Milner (1992; Milner and Goodale 1995)). For example, Hermann et al. (1993) noted decrements in performance on the Benton Facial Recognition test (Benton, Hamsher et al. 1983) following anterior temporal lobe resection in a large group of epileptic patients. Similarly, Warrington and colleagues (Warrington and Rabin 1970; Warrington and James 1988) have documented deficits in the perception of stimuli locations and spatial relations following posterior parietal damage. In addition, evidence for a double dissociation of function has been found (Newcombe and Russell 1969; Newcombe, Ratcliff et al. 1987), with patients with right posterior temporal lesions showing deficits on the Mooney Face task (Mooney 1957) but not on a maze-

learning test, and conversely, right posterior parietal lesion patients showing impaired maze-learning but intact Mooney Face (Mooney 1957) performance.

Adults: Behavioral Studies

While clinical studies have produced evidence in favor of a functional segregation of cortical visual pathways, as mentioned previously, the dissociation is not absolute (Van Essen, Anderson et al. 1992; Merigan and Maunsell 1993). If this is the case, then a valid and essential question becomes whether or not a dissociation can be convincingly demonstrated in neurologically intact individuals using less direct and less invasive procedures. Chen et al. (Chen, Myerson et al. 2000) addressed this question directly by factor analyzing reaction time (RT) data from two sets of tasks designed to rely primarily on either the dorsal or the ventral visual streams. Paralleling the neural organization as it was originally proposed (Ungerleider and Mishkin 1982), discrete factor loadings were revealed with ventral and dorsal tasks loading on separate factors. Thus, while these streams may interact, the extent of their functional independence may be such that their influence on visuospatial behavior can still be differentiated (i.e., one *can* categorize behavioral abilities according to this functional separation). Behavioral interference paradigms have also produced contrasting patterns of performance, such that when a subject performs object or spatial processing, their performance is selectively and negatively influenced by interference stimuli/tasks that contain information processed by the same visual stream (Tresch, Sinnamon et al. 1993; Hecker and Mapperson 1997). Using a change-detection paradigm, Simons (1996) also found performance differences between coding of spatial configuration and coding of object identity. Specifically, subjects' ability to

detect stimulus array changes in the identity of elements dropped to chance when verbal strategies were prevented, however, superior skill in detecting changes in configuration of the elements was maintained.

Adults: Neuroimaging Studies

Several electrophysiological and neuroimaging studies have generated important data confirming the behavioral evidence for the existence of the dorsal/ventral distinction. Electrophysiological studies of working memory with adults suggest that event-related potential (ERP) components elicited during object and location processing tasks differ in their relative timing and spatial/scalp configuration (Mecklinger and Mueller 1996; Ruchkin, Johnson et al. 1997). Neuroimaging studies have also confirmed the segregation, using a variety of paradigms which have included perceptual (Haxby, Horwitz et al. 1994; Kohler, Kapur et al. 1995; Shen, Hu et al. 1999; Rao, Zhou et al. 2003), working memory (Smith, Jonides et al. 1995; Courtney, Ungerleider et al. 1996) and environmental knowledge tasks (Aguirre and D'Esposito 1997).

Wang et al. (Wang, Zhou et al. 1999) suggest that in spite of their specialization, these two systems can work together when stimuli such as 'form-from-motion' patterns are viewed. This is consistent with data from a separate group of neuroimaging studies reporting on brain regions that participate in both types of tasks (Faillenot, Toni et al. 1997; Shen, Hu et al. 1999). For example, Kraut et al. (Kraut, Hart et al. 1997) observed activity in both cortical streams for a shape-based object recognition task (shape selective neurons have also been found in parietal cortex; (Sereno and Maunsell 1998)). Clinical evidence also exists that is consistent with the

idea that both streams may possess the neural machinery necessary to perform, at least under some limited conditions, some functions of the other. Le et al. (2002) reported residual (though limited and overly analytic) object processing capabilities in a patient with lesions to the dorsal pathway in the right hemisphere and the ventral stream bilaterally. They conclude that the “dorsal stream pathway can suffice for basic ‘what’ processing” (p. 72).

Development of Dorsal and Ventral Stream Functions

While the dorsal and ventral visual pathways have been extensively studied in adults, developmental inquiries have yet to produce an adequate response to the need for an account of how development proceeds toward the adult state of two dissociated systems. While there is considerable work examining development of ventral stream functions or dorsal stream functions, separately, there has been no systematic work comparing developmental trajectories for these systems. The task of placing these findings within a common experimental framework, in order to achieve a more complete picture of how ‘what’ and ‘where’ processing develop, is no trivial task. Disparate samples, paradigms, stimuli, etc. make this exceedingly difficult to accomplish. Simultaneous study of the development of the two streams, within the context of a single problem space, is likely to yield the most valuable information in this regard. In the following sections, the existing data attempting to link the development of the individual systems are reviewed, first from studies of infancy, and second, from studies of older children.

Infancy: Object Perception

Studies aimed at elucidating the infant's "object concept" or the infant's understanding of objects and their properties, have undoubtedly augmented our understanding of how cognition and knowledge develop. Studies of this type typically focus on the question of whether early object knowledge is innate or learned (in the context of the familiar 'nature' versus 'nurture' debate). In addition, studies characterizing the infant's object-related abilities have secondary benefits, in that they can provide some insight, albeit limited and indirect, into the development of the "hardware" that supports our knowledge. Specifically, two observations about object processing in infancy provide insight into the functional development of the dorsal and ventral streams. The first involves a dissociation in time, specifically, a developmental lag between when children first achieve an understanding that objects continue to exist after they are occluded, and when children first begin to reach for those same hidden objects. The second entails a dissociation in children's processing of information, specifically, differences in the types of cues that are used for identifying and differentiating objects at different times during development.

'Violation-of-expectation' studies using preference-looking measures have been used extensively to probe the young infant's understanding of occluded objects. Baillargeon's research group has used this paradigm with a variety of experimental conditions [rolling car studies (e.g., Baillargeon and DeVos 1991), sliding rabbit studies (e.g., Baillargeon and Graber 1987) etc.] to investigate infant representations of object properties (e.g. structure, height, location, etc.). She and her colleagues have found that infants as young as 3.5 months (Baillargeon and DeVos 1991) show increased looking (interpreted as "surprise") when properties of hidden objects are

violated. This behavior is thought to indicate an understanding of the impossibility of the event (e.g. two solid objects cannot occupy the same space at the same time). Interestingly, infants don't appear to reach for these same occluded objects until approximately 7 months of age (Diamond 1985) even though they are motorically able to reach at 3 to 4 months. This developmental lag (Baillargeon 1993) has been linked back to the segregated organization of the visual system (Spelke and Hermer 1996; Mareschal, Plunkett et al. 1999) with the perception-based system facilitating object reasoning, but the action-based system still limited in its use of this information. Based on their computational modeling work, Mareschal et al. (1999) suggest that the delay can be attributed to a difficulty integrating ambiguous dorsal and ventral stream information (occlusion renders the object information "imprecise" for the system).

Related studies looking specifically at how the infant tracks the existence of objects, suggest that when object identity is first traced by the infant, surface feature information is not readily used. Rather, before 9-10 months of age infants appear to differentiate objects according to spatiotemporal information (e.g. object's motion or location), and not until 12 months of age do they use object features (e.g. shape or color) or category information for this purpose (Bower 1974; Xu and Carey 1996; Xu 1999; Xu, Carey et al. 1999). A variety of experimental conditions, including those without obvious short-term memory requirements (a potential limitation for very young infants) (Xu, Carey et al. 1999), and those utilizing alternatives to the standard preference-looking paradigms (Van de Walle, Carey et al. 2000), support the claim that infants younger than 10 months cannot use object features to individuate objects. In explaining the mechanism behind this conspicuous change between 10 and 12

months of age, Xu and colleagues (Leslie, Xu et al. 1998; Xu, Carey et al. 1999) invoke the 'what' versus 'where' dissociation in the underlying neural system. They hypothesize that the behavioral transformation between 10 and 12 months is a product of the infant's increasing ability to integrate the originally separate encoding of motion/location and feature/property information. In this formulation, until 10 months of age, "object indexing" (Leslie, Xu et al. 1998) depends on the 'where' system (the object is represented as a 'that', lacking identity based on features). At approximately 12 months of age, 'what' information becomes incorporated by the object indexing system when a connection is established between the two (Kaldy and Leslie 2003). This allows the infant use featural information during object discrimination, even though s/he had been able to perceive many 'what' properties, such as color (Teller and Bornstein 1987) and form (Cook 1987), since approximately 2 months of age.

Infancy: Object Attention and Orienting

The rise of the field of cognitive neuroscience has led to the emergence of a separate developmental literature, looking at attentional processes in infancy. A complicated and multi-faceted entity, attention subsumes many elements, each of which is likely to develop at different times. However, in general, two types of orienting, to objects and to space, both appear to show considerable developmental progress during the first 6 months of life (Colombo 2001). Findings of developmental change in attention and orienting behaviors observed during infancy reflect the influence of two distinct cortical streams.

Colombo et al. (1990) showed that infants at three ages (3, 6 and 9 months) could learn to direct attention to two types of cues, stimulus cues (simple achromatic

forms) and position cues (to right or left of fixation). However, unlike older infants, the 3 month-olds were unable to retain associations with stimulus-based cues after a delay. In a subsequent study, 3 month-old infants were observed to show a strong bias against these stimulus-based cues and toward space-based or position cues. Interestingly, 6 and 9 month-old infants showed the opposite, a bias toward attending to the stimulus-based cues (Colombo, Mitchell et al. 1990). More recently, Harman and colleagues (Harman, Posner et al. 1994) also showed a preference for novel objects in 6 month-old infants. Subsequent studies from this group (Posner, Rothbart et al. 1998), using a paradigm in which participants were shown a single stimulus (object or location) followed by a forced-choice between two objects or two locations, replicated the object novelty preference in 6 month-old infants, but only when the first stimulus was viewed for 3 seconds or more (exposures of one second or less led to a location novelty preference). The authors' (Posner, Rothbart et al. 1998) failure to detect a correlation between the two forms of novelty preference confirms the presence of independent systems for orienting to 'where' and orienting to 'what' in the developing visual system. Further, the changes in attentional bias across ages in these studies (Colombo, Mitchell et al. 1990; Harman, Posner et al. 1994) suggest that these systems may develop according to different timetables.

Infancy: Differential Development of the Ventral and Dorsal Streams?

The studies reviewed thus far, provide convincing evidence that the dissociation between 'what' and 'where' may be evident, even early in infancy. The question now becomes one of relative development: do the dorsal and ventral pathways follow different maturational trajectories? If so, which develops first? Thus

far, very little evidence can address these questions directly (Johnson 2001). Nonetheless, these types of questions have great potential to advance our understanding of how brain and behavior develop in tandem. In addition, they direct us toward avenues of inquiry that can yield important insights into the development of the dual-pathway system, while avoiding the long road of defining in totality the developmental course of each pathway separately (Johnson 1990). Thus, based on the limited information we currently possess, a few investigators have begun speculate as to the answers for these questions.

Some of the strongest pertinent data come from a pair of studies with infant monkeys, conducted by Bachevalier, Mishkin and colleagues (Bachevalier, Hagger et al. 1990; Distler, Bachevalier et al. 1996). Measures of glucose consumption can provide direct information about the functional maturation of the two pathways and in this case, revealed different developmental time courses. While posterior parietal areas and the dorsal pathway reached adult levels of glucose utilization between 2 and 3 months, temporal regions and the ventral pathway did not show this increase until 4 months. This delay in the occipitotemporal pathway is consistent with behavioral findings demonstrating that young monkeys do not appear to be able to solve the delayed nonmatching-to-sample object recognition task until 4 months of age, and do not reach adult levels of performance on the task until 2 years (Bachevalier, Hagger et al. 1990).

Studies of human infant categorization offer complementary results to the non-human primate research. On the whole, categorization research has yielded impressive findings in the infant: categorization ability appears within the first year, before the

emergence of language, and further, adult-like categories are used very early in development (for review, see Quinn and Eimas 1996). Looking at specific types of categorization, Mash and colleagues (Mash, Quinn et al. 1998) found comparable performance in typical infants on object and spatial categorization tasks, but poor performance in same-age preterm infants only on the former. The confluence of better spatial than object categorization performance in Mash et al., (1998), the infant's tendency to use location before featural information to differentiate objects (see above) and faster functional development of the dorsal stream in primate physiology studies (see above) led Quinn (1998) to speculate that the cortical stream for processing spatial information may develop more quickly than the pathway for object features. He further suggests that ventral structures may be more affected by variations in experience and may display more plasticity. We return to this last proposition a bit later.

Based on evidence from behavioral and ERP studies of face processing (ventral stream) and target-directed saccades (dorsal stream), Johnson and colleagues (2001) propose the contrary of Quinn (1998): ventral stream first. Cortical processing of faces is measurable by brain mapping techniques (e.g. ERP, PET) at approximately 2 to 3 months of age (Tzourio-Mazoyer, De Schonen et al. 2002; Halit, de Haan et al. 2003), although the infant's responses to faces are less specific (e.g., monkey faces can trigger a similar response in the infant but not in the adult - de Haan, Pascalis et al. 2002) when compared with adults. By contrast, Johnson et al. find no sign of pre-saccadic spike potentials, a characteristic ERP component typically recorded over adult parietal cortex before the generation of a visual saccade, in infants of the same

age (Csibra, Tucker et al. 1998) or younger (Csibra, Tucker et al. 2001), even though their neural machinery for saccade planning has already become functional (Johnson 1990).

Atkinson (2000) also suggests that the ventral stream develops first. Her model of visual development begins with the independent development of cortical “modules” (Zeki 1993) for processing basic visual information. She proposes that both ventral and dorsal stream modules develop independently during the first few months of life, with ventral stream modules (e.g. for color or orientation) becoming functional slightly earlier than those from the dorsal stream (e.g. for directional motion or disparity). Integration across modules also occurs early in the ventral stream, to allow perceptions of whole, distinct objects. Later stages of the model (5-6 months and on) involve the establishment of connections to the dorsal stream to allow actions to be made on those objects (e.g. reaching, grasping). Divergent preferences in looking and reaching in infants as old as one year (Newman, Atkinson et al. 2001) are consistent with the idea that the two streams maintain some degree of independence even after they are integrated during these last stages of the model.

In light of the paucity of data on which to theorize, Atkinson’s model is one of the most comprehensive. However, she, like some other developmental researchers (Bertenthal 1996) has certainly discussed ‘what’, ‘where’ and ‘how’, but has focused her theory largely on only two of these, ‘what’ versus ‘how’ from Goodale & Milner’s (1992) model of adult vision (see section on Adult Clinical Studies). Given that the actions of a child may be the best indicator of his/her cognitive state during the first year of life, Goodale & Milner’s (1992) model of ‘perception’ versus ‘action’ is

undoubtedly a suitable one. However, if one's interest lies more in the cortical mediation of visual processing only, an examination of the literature looking at the spatial *perceptual* functions of the dorsal stream, in line with the (Ungerleider and Mishkin 1982) model is crucial (Ingle 2002). Unfortunately, to date, some of the most influential human adult studies of 'what' versus 'where' (e.g., Haxby, Horwitz et al. 1994), rather than 'what' versus 'how', have few true developmental counterparts. We look now at later childhood in search of such studies.

School-Age: Objects and Positions

Very few studies simultaneously exploring object and spatial processing in older children have been conducted. A single interference study by Lange-Kuettner & Friederici (2000) found within- but not across-stream interference effects (e.g., place memory is only disrupted by movement judgment) in younger children (4-6 years of age), supporting the idea of segregated processing. This resembles adult findings (Tresch, Sinnamon et al. 1993) of task performance being selectively affected by interference tasks that tap the same stream (e.g. spatial memory disruption by a movement discrimination distractor task and object memory disruption by a color discrimination task). Regarding the relative development of the two streams, studies of older children have shown conflicting results. Some suggest that school-age children and adults more accurately remember positional than object information (Finkel 1973) and that position memory is less susceptible to interference (Lange-Kuttner and Friederici 2000). Others, however, propose that object information is more easily remembered than positional information (Gulya, Rossi-George et al. 2002; Lorsbach and Reimer 2005). In line with the latter results, there also exists some limited

evidence in children at 4 and 7 years of age (Atkinson 1998) of better “matching” than “posting” performance on Milner & Goodale’s (1995) “postbox” task, which requires children to manually post a letter into a slot at a particular angle (dorsal) or to match the perceived angle of the slot (ventral).

School-Age: Psychophysical Studies

Kovacs (Kovacs, Kozma et al. 1999; 2000) has performed several psychophysical investigations of perception with large samples of older children and finds poor performance in children 5 to 14 years of age on a contour-detection task, a task thought to be mediated at least in part by the ventral visual stream. Other work from her group using the Ebbinghaus illusion suggests that young children lack sensitivity to the context effects of the display (perception of which are subserved by the ventral visual stream - Haffenden and Goodale 1998) and as a result, evince less susceptibility to the illusion than adults (Weintraub 1979; Kaldy and Kovacs 2003). Based on these findings she posits a persisting immaturity of the ventral system and has put forth a working hypothesis regarding the relative development of the two streams, with ventral development lagging behind dorsal, as has previously been suggested by non-human primate work (Bachevalier, Mishkin and colleagues, reviewed above) and by more recent visual evoked potential (VEP) studies with humans (Gordon and McCulloch 1999; Madrid and Crognale 2000). However, use of other sets of psychophysical measures such as form and motion coherence or color and motion processing with children suggest instead, that the dorsal stream may be the relatively later stream to reach the adult state (Gunn, Cory et al. 2002; Atkinson, Braddick et al. 2003; Mitchell and Neville 2004; Coch, Skendzel et al. 2005).

Atypical Development of Dorsal and Ventral Stream Functions

While studies of typical development are essential, looking at atypically-developing populations can also be informative in the quest to characterize the development of the dorsal and ventral streams. For example, results from a study of congenital hypothyroidism in adolescence (Leneman, Buchanan et al. 2001) suggest that the two pathways have different critical windows for their sensitivity to the influence of hormones. Studies in schizophrenia (Fuxe, Doniger et al. 2001; Doniger, Fuxe et al. 2002; Kim, Wylie et al. 2006), spina bifida with hydrocephalus (Dennis, Fletcher et al. 2002), and Velocardiofacial/DiGeorge Syndrome (22q11.2 Deletion Syndrome) (Bearden, Wang et al. 2002) suggest that the visual and spatial impairments in these disorders reflect differential involvement of the two streams.

Work with atypically-developing populations can also provide the empirical basis necessary to address other critical developmental questions regarding the visual brain's sensitivity to experience and potential to organize itself in nonstandard ways. For example, ERP studies by Neville and colleagues have shown a greater response in the congenitally deaf to stimuli that elicit activity in dorsal versus ventral systems (peripherally- or centrally-presented squares in (Neville and Lawson 1987; Neville and Lawson 1987); gratings that moved or changed color in (Neville and Bavelier 2002)). Based on their findings, these authors hypothesize that the dorsal system may be more modifiable than the ventral system in response to alterations in early input (Stevens and Neville 2006). Studies in the WS population are particularly germane to questions such as these, regarding the sensitivity of the brain to abnormal

developmental conditions (in this case, the result of genetic error) and the extent of plasticity that can be achieved by each system.

Williams Syndrome (WS)

Atkinson and colleagues (Atkinson, Braddick et al. 2003; Braddick, Atkinson et al. 2003) marshal evidence from a number of developmental disorders, including dyslexia (the ‘magnocellular hypothesis’) (Stein, Talcott et al. 2000), autism (Spencer, O'Brien et al. 2000) and hemiplegic cerebral palsy (Gunn, Cory et al. 2002), in support of a ‘dorsal-stream vulnerability’ hypothesis. Much of Atkinson’s work on this topic has been with Williams Syndrome (e.g., Atkinson, King et al. 1997), a rare genetic disorder caused by a micro-deletion on chromosome 7 (Korenberg, Chen et al. 2000; Korenberg, Chen et al. 2001). This syndrome is characterized by distinctive dysmorphic facial features, mild to moderate mental retardation, distinctive personality characteristics and a unique cognitive profile, which includes strikingly poor visuospatial ability (Bellugi and St. George 2001). Her findings (Atkinson, King et al. 1997) from form versus motion coherence tasks and perceptual matching versus manual posting (“postbox” task described above from Milner and Goodale 1995) tasks implicate reduced or aberrant dorsal stream functioning, at least partly, in the visuospatial deficits in WS (for similar evidence from object versus spatial memory tasks see also Vicari, Bellucci et al. 2006; Vicari and Carlesimo 2006)). Recent evidence of neuroanatomical and neurophysiological abnormalities of the dorsal stream (Galaburda and Bellugi 2001; Galaburda, Schmitt et al. 2001; Galaburda, Holinger et al. 2002; Meyer-Lindenberg, Kohn et al. 2004; Kippenhan, Olsen et al. 2005; Thompson, Lee et al. 2005; Boddaert, Mochel et al. 2006; Van

Essen, Dierker et al. 2006) converges nicely with Atkinson et al.'s behavioral and psychophysical findings.

In the case of WS, it has become apparent that visual functions subserved by different cortical streams have been differentially compromised. However, the functional organization of the WS brain that occurs after such aberrant genetic beginnings, and leads to such poor spatial skills, is still not well-specified. In addition, it is possible that near-normal performance on some visuospatial tasks in WS (i.e. face processing) may be mediated in an abnormal way by underlying brain systems (Karmiloff-Smith 1997; Mills, Alvarez et al. 2000). Thus, the approach taken in the studies presented here is to simultaneously investigate the neural bases of both types of visual functions, those that are impaired (dorsal) and those that may be relatively preserved (ventral).

Summary

In summary, studies from infancy through late childhood suggest two things. First, processing of object and spatial information is subserved by two distinct cortical streams during development, as in adulthood. Second, these two streams most probably mature according to different timelines. However, opinion is mixed over which system seems to hold developmental priority. Several limitations to the current corpus of research contribute to a lack of clarity on this important issue. The first limitation relates to our ability to interpret behavioral change during infancy. Changes occur during the first year of life at an astounding pace, in even very elementary behaviors (e.g. saccading, reaching). In fact, the assumption we make in adults of cortical mediation of object and spatial processing does not hold in very young infants.

There is ample evidence that ‘where’ and ‘how’ functions from are largely mediated by subcortical systems until 2 to 3 months of age, and that cortical mediation emerges after that time (Bronson 1974; Johnson 1990; Atkinson 2000). Unfortunately for researchers, these situations are the source of much complexity. They make it all the more difficult to apprehend even simple perceptual behaviors in infants. For example, with such rapid and dynamic change in multiple domains occurring during infancy, it may not be surprising that novelty preference appears to undergo a complete reversal from 3 to 6 months of age (Harman, Posner et al. 1994). Nevertheless, deducing whether another reversal will appear at a later age, exactly which factors instigate these changes, and how this all relates to the underlying neural substrate is far from simple.

Few studies in older children have utilized designs (i.e. direct comparisons of ‘what’ and ‘where’) capable of providing more definitive information. Those that exist are limited by a failure to concretely define what constitutes a difference between children and adults. For example, Gulya et al., (2002) found that children *and* adults show better item than location memory, while Finkel (1973) found that children *and* adults show better location then item memory. Unfortunately, with adults and children exhibiting performance differences in the same direction in each case, we can summon the alternative and more parsimonious explanation: performance advantages occur on tasks that are easier. Further, allowing adult performance to vary across tasks sets up a situation in which subtle differences between children and adults (i.e. anything other than complete reversals in pattern of performance) may be overlooked. For example, more accurate performance on a spatial than an object task in children may be

dismissed if adults show a difference in the same direction, even if the difference for children is larger. In contrast to the infant, the older child is not expected to show drastic changes in behavior with age, therefore, it is these subtle differences that may be the most informative for work with this age group.

Characterizing development of the ‘what’ and ‘where’ systems is an important endeavor for researchers interested in detailing the maturation of cortically-mediated visuo-perceptual abilities. In addition, the topic has become a focal point for differences in opinion over other, more general, but nonetheless essential topics in brain development. For example, Quinn (1998) and Kovacs (2000) propose a protracted period of maturation for the ventral system, with an associated widening of the critical time period during which the system can actively respond and change to input that is either expected or unexpected. On the other hand, Atkinson (2000) and Neville and colleagues (Neville and Bavelier 2002; Stevens and Neville 2006) suggest the contrary, a prolonged period of development for the dorsal stream, with an extended window during which plasticity and reorganization are possible. Studying atypical populations has great potential for reconciling this debate, yet few such investigations have been conducted to date. Studies with Williams Syndrome provide support for the idea that the functions of one stream may be more vulnerable in particular developmental disorders (Atkinson 2000; Braddick, Atkinson et al. 2003; Kim, Wylie et al. 2006)}. However, the underlying organization of the impacted system has not been fully delineated. What also remains to be seen is whether the relatively less affected system sustains behavior in a typical or an anomalous fashion.

Currently, this is a notable dearth of information with which to resolve the issues that have been highlighted here. The critical gaps in our knowledge and the limitations of current studies imply the usefulness of studies which 1) directly compare dorsal and ventral stream functions in typical children, healthy adults and relevant clinical populations, 2) operationally define differences (e.g. in the typical case, related to age) in the relationship between these two types of functions and 3) explore the neural underpinnings of observed performance differences (e.g. with neuroimaging, for example, using functional magnetic resonance imaging or fMRI). In addition, the pairing of behavioral and neurophysiological measures holds much promise for addressing limitations of previous studies and providing new information regarding behavioral and brain development in these critical perceptual systems.

The Current Studies

The current studies utilize a converging measures approach, examining indices of performance (task accuracy and reaction time) and brain function in typical participants of different ages, as well as in a patient population exhibiting deficits that appear to denote differential compromise of the ventral and dorsal streams. In line with Ungerleider & Mishkin's (1982) model for the adult visual system of 'what' versus 'where', ventral stream function will be indexed by performance on a face discrimination task and dorsal stream function will be indexed by performance on a location discrimination task. In order to confront limitations of prior studies, these investigations make use of a matched-task paradigm. That is, these facial identity and location processing task conditions are matched a priori for stimuli, procedures and required response (see Smith, Jonides et al. 1995 for a similar design with adults). In

addition, by exploiting the fact that the difficulty of any face identity- or location-matching task can be systematically manipulated by varying similarity of the faces or of the on-screen locations, these two tasks were constructed to be comparably difficult for healthy adults. Anchoring the comparability of the basic tasks in adult performance facilitates *direct* comparisons across the two tasks in typical children and WS participants. The metrics of reaction time (RT) and accuracy (Chapter 3) allow performance differences to be concretely defined and then investigated, both between groups and across tasks. Measures of brain activation to modified versions of these same tasks in the Chapters 4 and 5 will allow for an examination of the relationship between profiles of performance and patterns of activation in the brain's systems for processing face ('what') and location ('where') information. In the next chapter, what we currently know about these two types of processing, of faces and locations, will be briefly reviewed.

CHAPTER 2

BACKGROUND FOR THE CURRENT STUDIES

It is evident from the general review of studies in Chapter 1 that despite a sizeable body of adult literature, few direct comparisons of ‘what’ and ‘where’ have been conducted with children and even fewer with atypically-developing populations. Not surprisingly, work comparing the specific functions probed in the current studies, face and location processing, has been virtually nonexistent. Thus, data on the development of these two functions has come from separate bodies of work, which will be briefly reviewed next.

Face Processing

Primate studies indicate that ventral stream regions, inferotemporal cortex in particular, respond to faces more than other objects (Desimone, Albright et al. 1984). Human temporal regions generate ERPs with distinctive topographies in response to faces (e.g., N170 - Bentin, Allison et al. 1996), and damage to this region is associated with prosopagnosia, a selective inability to recognize faces. Neuroimaging studies with adults find activation to faces in bilateral ventral occipitotemporal cortices (Halgren, Dale et al. 1999), with a slight bias toward the right-hemisphere (Sergent, Ohta et al. 1992; McCarthy, Puce et al. 1997; Rossion, Dricot et al. 2000). A particularly active region to faces in the fusiform gyrus has been termed the “fusiform face area” (Kanwisher, McDermott et al. 1997), although more recently, the idea that faces and other objects are processed in a more distributed fashion across occipitotemporal regions has been well-received (Ishai, Ungerleider et al. 1999; Haxby, Gobbini et al. 2001). Face-specific behavioral effects (i.e. inversion effect - Yin 1969) have also been noted and are thought to reflect distinct cognitive mechanisms for faces, namely ‘configural processing’ (i.e. perceiving relational and

distance information about the features contained within a face, which is disrupted when faces are inverted – Maurer, Grand et al. 2002).

Humans appear to enter the world with the ability to distinguish face-like patterns (Johnson, Dziurawiec et al. 1991). Infants as young as 2 to 3 months show brain responses (e.g. using ERPs or PET) suggestive of cortical control of face processing (Tzourio-Mazoyer, De Schonen et al. 2002; Halit, de Haan et al. 2003). In fact, infants have been shown to exhibit an adult-like right-hemisphere bias for faces (de Schonen and Mathivet 1990; Cassia, Kuefner et al. 2006) and respond to face inversion in the same way as adults (Cohen and Cashon 2001). However, in spite of these impressive beginnings, most studies converge on the idea that face processing continues to improve with age (Chung and Thomson 1995), even through adolescence (Taylor, Edmonds et al. 2001; Taylor, Batty et al. 2004). Originally, improvements in performance on face tasks were thought to reflect a change in strategy (Carey and Diamond 1977)), from feature-by-feature analysis to more holistic (Tanaka and Farah 1993) or configuration-based (Diamond and Carey 1986) strategies. However, recent studies support more of a slow, quantitative age-related change (Taylor, McCarthy et al. 1999; Taylor, Batty et al. 2004) and more effective use of the same types of cues used by adults (Flin 1985; Baenninger 1994; Freire and Lee 2001); even though different types of cues (e.g. featural versus configural) may be associated with different developmental timecourses (Mondloch, Le Grand et al. 2002; 2003). This change may be associated with the acquisition of greater expertise in processing faces and other visual objects (Diamond and Carey 1986; Carey 1996; Gauthier and Nelson 2001). Some researchers suggest that the changes in the neural system underlying age-

related performance improvements involve increases in cortical specialization, with increasing specificity of systems for face processing (Johnson, Halit et al. 2002). Recent developmental fMRI studies of face processing (discussed in Chapter 4) support this proposition (Passarotti, Paul et al. 2003; Gathers, Bhatt et al. 2004; Aylward, Park et al. 2005; Golarai, Ghahremani et al. 2007).

Location Processing

Primate studies suggest that neurons in posterior parietal cortex respond when the animal is orienting or attending to locations of stimuli in space, and support representations of personal and extrapersonal space for the guidance of reaching, grasping and saccading behaviors (for review see Colby and Goldberg 1999). Patients with parietal lesions show impairments in several space-based behaviors, including processing of distance or position (von Cramon and Kerkhoff 1993). Unilateral lesions involving the right inferior posterior parietal region have been associated with the clinical syndrome of neglect, the failure to attend to contralesional visual space (Vallar and Perani 1986). Functional imaging studies of healthy adults also suggest a role for posterior parietal regions (e.g. superior parietal) in shifting attention to locations in space (Corbetta, Miezin et al. 1993).

During development, coding of location is initially dominated by egocentric (body-centered) frames of reference until the second half of the first year, at which time infants begin to utilize allocentric (external) frames of reference (Acredolo 1978). Work with older infants (Bushnell, McKenzie et al. 1995; Newcombe, Huttenlocher et al. 1998) suggests a further qualitative shift in allocentric strategies (e.g. from use of ‘direct’ or spatially coincident cues to more ‘indirect’ or distal ones). A more recent

review of the evidence, however, has led Newcombe & Huttenlocher (2000) to reject the idea of developmental shifts in the ability to use different types of spatial information. Rather, they suggest that young infants can exploit all types of spatial information and that what changes with age is the ability to select and use only the most appropriate information for the task at hand.

Studies with toddlers suggest that they can make use of fine-grained distance information in a single dimension in order to direct search for hidden objects (Huttenlocher, Newcombe et al. 1994). In addition, they show a rudimentary form of hierarchical coding (i.e. determining if a location is in a certain region of space, e.g. in the right or left half). Despite these notable early achievements, it does not appear to be until 10 years of age that children show reliable adult-like spatial coding of fine-grained and categorical information in multiple dimensions (Sandberg, Huttenlocher et al. 1996). These latter results are consistent with other studies of school-age children, which find evidence of improvements in location memory through late childhood (Park and James 1983). Together, this group of findings (see also Naveh-Benjamin 1987) suggests that location may not be ‘automatically’ encoded (one criterion for an automatic process is little age-related change in performance), as originally proposed by Hasher & Zacks (1979). However, this has been widely debated in the literature and several studies have found evidence supporting the automaticity theory (Ellis, Katz et al. 1987; Ellis, Woodley-Zanthos et al. 1989; Ellis 1990; Schumann-Hengsteler 1992). Evidence from functional neuroimaging of children’s spatial working memory (discussed in Chapter 4) provide a mixed picture, with some studies finding adult-like patterns of activation in children (Thomas, King et al. 1999; Nelson,

Monk et al. 2000), and others finding evidence for a more protracted period of development through adolescence (Klingberg, Forssberg et al. 2002; Kwon, Reiss et al. 2002; Schweinsburg, Nagel et al. 2005; Klingberg 2006).

Face and Location Processing in Williams Syndrome (WS)

The relationship between research with typical populations and research with clinical populations is a reciprocal one: each informs the study of the other (Cicchetti 1984; Johnson, Griffin et al. 2005)}. The behavioral and neuroimaging studies in this dissertation have the potential to inform questions about the normal developmental course of face and location processing, while also adding to our existing knowledge about key issues in the study of Williams Syndrome.

A core feature of WS is a dissociation between language (a relative strength) and visuospatial cognition (a severe and specific impairment) (Bellugi, Lichtenberger et al. 1999; Mervis, Robinson et al. 2000; Bellugi, Korenberg et al. 2001). When compared with language functioning, this dissociation holds for most types of visuospatial abilities, particularly those with significant visuoconstructional demands (e.g. figure drawing, block design) (Bellugi, Lichtenberger et al. 2001). However, it does not at all apply to face processing, an area where WS show remarkable strength (Rossen, Klima et al. 1996). This disparity in WS, *within* visuospatial cognition, between spatial construction and face processing, has been consistently found across different ages, paradigms and samples (Udwin and Yule 1991; Jones and Lai 1997; Bellugi, Lichtenberger et al. 2001), is not seen in individuals with Down syndrome (DNS) (Wang, Doherty et al. 1995). In face processing, not only do WMS perform far better than age and IQ-matched DNS, they have been found to be no different from normal

age-matched controls on some face discrimination tasks (Bellugi, Klima et al. 1997; Bellugi, Lichtenberger et al. 2001).

The particular tasks chosen for the studies presented here address two critical issues in research on Williams Syndrome. The first (discussed in Chapter 4) relates to the disparity between face and spatial processing in WS, which has not been directly quantified. Studies of face discrimination in WS have typically employed perceptual matching paradigms (e.g. the Benton Faces task), while the spatial tests they are often compared with commonly require visuoconstructional skills. Rather than contrasting levels of performance on very different neuropsychological measures, the current studies use identical perceptual matching tasks, with similar task requirements, that have been designed to yield comparable performance among adult control participants. Further, while the pattern of deficits in WS strongly implicates greater deficits in the dorsal stream (Atkinson, King et al. 1997; Galaburda and Bellugi 2001; Galaburda, Schmitt et al. 2001; Galaburda, Holinger et al. 2002; Kippenhan, Olsen et al. 2005; Thompson, Lee et al. 2005; Boddaert, Mochel et al. 2006; Van Essen, Dierker et al. 2006), only one study has directly compared function in the dorsal and ventral streams (Meyer-Lindenberg, Kohn et al. 2004). This investigation was limited, in that it was conducted with high-functioning participants with WS (i.e. non-retarded), raising the question of whether the results can be generalized to individuals with a level of intellectual functioning that is more typical for the disorder. Given that these authors reported normal function in the ventral stream (in contrast to hypoactivation of the dorsal stream), the possibility of anomalous mediation of face processing by the

‘relatively spared’ ventral stream in these participants remains (Karmiloff-Smith 1997).

The second central issue (discussed in Chapter 5) relates more narrowly to the examination of the brain response to a face perception task in WS. Faces are stimuli with particular social relevance for humans and other primates. Individuals with WS show an exaggerated behavioral response to faces. As young children they display a heightened interest in faces (Laing, Butterworth et al. 2002; Mervis, Morris et al. 2003), and as older children and adults they perform face perception and recognition tasks with greater accuracy than would be expected from their general level of intellectual functioning (Rossen, Klima et al. 1996). The WS preference for faces is especially noteworthy when considered in the context of their intriguing personality. Overall socio-emotional adjustment has been reported as problematic for individuals with WS (Udwin, Yule et al. 1987; Dilts, Morris et al. 1990; Einfeld, Tonge et al. 1997), as they appear to be predisposed for specific phobias (Dykens 2003) and to more general symptoms of anxiety (Einfeld, Tonge et al. 1997). In spite of this, they are often highly sociable and extroverted and demonstrate a very strong affiliative tendency. Individuals with WS have often been described as “overly friendly” and “hypersocial” (Bellugi, Adolphs et al. 1999; Jones, Bellugi et al. 2000), owing to the appearance of an irrepressible inclination to engage others in social interaction. As young children, individuals with WS are rated as less socially reserved (Gosch and Pankau 1994) and seem to lack the normative fear of strangers (Udwin 1990). As adults, they have been shown to offer unusually positive approachability ratings for faces of unfamiliar persons (Bellugi, Adolphs et al. 1999). The combination in WS of

heightened attention and facility with faces in WS, alongside an intense drive for interpersonal contact, provides a unique opportunity to examine the social aspects of face perception.

CHAPTER 3

FACE AND PLACE PROCESSING IN WILLIAMS SYNDROME: EVIDENCE FOR A DORSAL-VENTRAL DISSOCIATION

Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation

Brianna M. Paul,¹ Joan Stiles,² Alessandra Passarotti,² Nasim Bavar³ and Ursula Bellugi^{3,CA}

¹Joint Doctoral Program in Clinical Psychology, San Diego State University/University of California, San Diego; ²Department of Cognitive Science, University of California San Diego, La Jolla, CA; ³Laboratory for Cognitive Neuroscience, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA

^{CA}Corresponding Author

Received 11 April 2002; accepted 24 April 2002

Individuals with Williams syndrome (WMS) show an interesting dissociation of ability within the visuospatial domain, particularly between face perception and other visuospatial tasks. In this population, using tasks matched for stimuli, required response, and difficulty (for controls) is critical when comparing performance across these areas. We compared WMS individuals with a sample of typically developing 8- and 9-year-old children, and with a

sample of adults, closer to the WMS participants in chronological age, in order to investigate performance across two precisely matched perceptual tasks, one assessing face processing and the other assessing proficiency in processing stimuli location. The pattern of performance seen in WMS, but not in controls, implicates a specific deficit of dorsal stream functioning in this syndrome. *NeuroReport* 13:1115–1119 © 2002 Lippincott Williams & Wilkins.

Key words: Dorsal and ventral streams; Face processing; Molecular genetics; Neural systems; Spatial processing; Williams syndrome

INTRODUCTION

Research in typically developing children suggests that face processing undergoes a protracted period of development [1]. Interestingly, from quite early on, individuals with Williams syndrome (WMS) seem to perform better at face processing tasks than at other visual cognitive tasks [2]. However, reports of a dissociation between face and other kinds of visuospatial processing have not equated processing demands across tasks. Studies of face processing typically employ perceptual matching paradigms, while the tasks they are often compared with commonly require visuoconstructional skills. The current study used identical perceptual matching tasks for both experimental tasks, one assessing face processing and the other assessing location processing, thus equating demands across task domains and allowing us to directly assess the issue of a dissociation in WMS between these two cognitive skills.

WMS is a rare disorder that occurs in 1/25 000 births and is caused by a hemizygous deletion encompassing the elastin gene at 7q11.23 and <20 other genes [3,4]. This syndrome is characterized by distinctive dysmorphic facial features, mild to moderate mental retardation, distinctive personality characteristics and a unique cognitive profile [5]. A major hallmark of WMS is the dissociation between language (a relative strength) and spatial cognition (a severe and specific impairment) [2,6].

One of the most intriguing aspects of the WMS cognitive profile is a dissociation within the visual processing domain, what Bellugi *et al.* have called a chasm within visuospatial cognition. In drawings and block designs made by individuals with WMS, spatial construction is often severely and specifically impaired. However, these same individuals

with WMS show remarkable strength in face processing. This disparity in WMS between spatial construction and face processing, consistently found across different ages, paradigms and samples [7–9], is not seen in individuals with Down syndrome (DNS), who are equally impaired in both. In face processing, not only do WMS perform far better than age and IQ-matched DNS, they have been found to be no different from normal age-matched controls on face recognition tasks [5,10].

This distinction between face and space processing within a specific genetically based population is of great interest, since it may map onto different neural systems in the brain. The primate visual system is subdivided into two anatomically and functionally separate systems [11]. Specifically, the ventral stream (occipito-temporal lobes) is principally involved in processing object properties, whereas the dorsal stream (occipito-parietal lobes) is mainly involved in spatial processes such as object localization and movement detection. Many researchers have examined the functional segregation of these two streams with adults [12,13] and to a lesser degree in children [14,15]. The weight of the evidence to date for the distinction in WMS between face processing and location processing has strongly implicated relative sparing in the ventral stream and a clear deficit in the dorsal stream [16–21].

While there may be relative strength in face processing among individuals in this special population, no study to date has directly quantified the above differences. Most studies of face processing with WMS individuals rely on visuo-perceptual tasks and pointing responses, while spatial tasks have been mostly visuoconstructional, such as copying from a model, drawing, block design, etc. These latter

spatial tasks involve a significant spatial constructional component, whereas the face identification tasks have minimal motor demands. In the current study we directly confront these limitations of previous research. Instead of contrasting levels of performance on very different neuropsychological measures, we have utilized a paradigm in which the two tasks we use are precisely matched for stimuli and procedures. Further, the face and location tasks were specifically designed to yield comparable performance among adult control participants [13]. With this paradigm, we assess and directly compare face processing skills with proficiency in another strictly visuo-perceptual area, processing the location of visually presented stimuli.

The current study compares performance accuracy of a group of WMS participants to that of an adult control group and to a group of mental age-matched children (specifically 8- to 9-year-olds), on a face- and a location-matching task. Findings from an earlier study using this testing protocol with typical adults and children aged 6–12 years showed that although overall accuracy improved with age, performance across the two task conditions was comparable at each age tested [22]. These results demonstrate the effectiveness of the basic task design in balancing face and location processing demands. Given the hypersociability of WMS participants and their tendency to orient preferentially toward faces [23], we wanted to rule out the possibility that any deficits that may be seen on the location-matching task in WMS could be attributed to distraction by the face stimuli themselves. Hence, in addition to the face- and location-matching tasks, a third location control task, using scrambled patterns rather than faces, was also included.

MATERIALS AND METHODS

Participants: Data from 33 individuals diagnosed with WMS aged 12–51 years (mean 27.2; 18 females and 15 males), 19 typically developing right-handed 8- and 9-year old children (mean age 9.0 years; nine females and 10 males) and 24 typical right-handed adults (mean age 20.7 years; 12 females and 12 males) are reported here. The WMS group, recruited as part of an ongoing large program project (P01 HD33113 to UB), received a small monetary sum for participating. They were inducted into the project based on both a clinical diagnosis of WMS and a FISH test (fluorescent *in situ* hybridization) for absence of one copy of the gene for elastin on chromosome 7. Adult controls were college students who were given course credit for participating. Child controls were recruited from local schools, and were given a toy for participating.

In the WMS sample, the mean (\pm s.d.) WAIS-R Full Scale IQ score was (68.4 ± 8.9). The characteristic disparity among WMS between language and visuospatial ability, also evident in this sample, makes the decision of an appropriate control group a challenging one [24]. Mental age for this WMS sample was calculated using the Peabody Picture Vocabulary Test–III (PPVT-III) [25], and scores ranged from 6.02 to 30.7 years (mean 12.04 ± 4.91). In addition, age equivalent scores from the Beery Developmental Test of Visuomotor Integration, 4th edn (VMI) [26] were calculated, and ranged from 4.1 to 8.0 years (mean 5.78 ± 1.10). Based upon these findings, the WMS group in this study was compared to two different samples of controls, a sample

close in approximate mental age: typical children with a mean age of 9 years; and a sample close in chronological age: typical adults with a mean age of 20 years.

Experimental design: Each participant in the study performed the same three tasks, specifically, a face-matching task, a location-matching task and a location control task. The basic design of the three tasks was identical. First, two reference stimuli appeared in sequence in different locations on a computer screen. After a short delay (blank screen), a third (probe) stimulus appeared (Fig. 1). The participant was required to decide whether the probe stimulus matched either of the first two reference stimuli. In the face-matching task, matching was based on identity of the stimulus. In the location tasks, matching was based on location of the stimuli on the screen. In the face-matching and location-matching tasks an identical set of face stimuli were used; thus, these two tasks differed only in the decision the participant was asked to make. In the location control task, matching was also based on location, but the stimuli were scrambled faces. Order of administration for the face-matching and location-matching tasks was counterbalanced across subjects. Because the location control task was created specifically for the WMS population for this study, it was given last to all participants.

The difficulty of any face- or location-matching task can be systematically manipulated by varying similarity of the faces or of the on-screen locations. In the current study, it was important to ensure that the face- and location-matching tasks were comparable in difficulty. To achieve this end, in a preliminary study with typical adults, RT and accuracy scores were collected on a large sample of face- and location-matching trials that varied systematically in difficulty. Items included in our face- and location-matching tasks were selected to yield comparable levels of response time and accuracy performance across the two tasks. Findings from the adult controls in the current study replicated those of the preliminary study. Having anchored the comparability of the basic tasks for adults, we could then test for selective differences in response across the two tasks in our children and in the WMS participants.

Procedure: Figure 1 illustrates the basic procedure for the three tasks in this study. Participants were seated 60 cm from the screen of a Macintosh computer running Psycscope version 1.2 [27]. In all three conditions, the reference and probe stimuli subtended 4.76° visual angle in the vertical dimension and 5.06° in the horizontal. Each type of task was associated with a distinct warning cue displayed to identify the subsequent test trials (green smiley face for the face-matching task and red tic-tac-toe grid for both location tasks). One task block consisted of one warning cue followed by six test trials. Each test trial began with a 500 ms fixation, followed by a 1000 ms interstimulus interval (ISI). Next, the two reference stimuli appeared in sequence for 500 ms each, separated by a 250 ms ISI, and then, after a 500 ms delay, the probe stimulus was presented. During presentation of the probe, participants made a button press (yes or no) indicating whether the probe stimulus matched either of the two reference stimuli with respect to the attended property (identity or location). Adult controls were

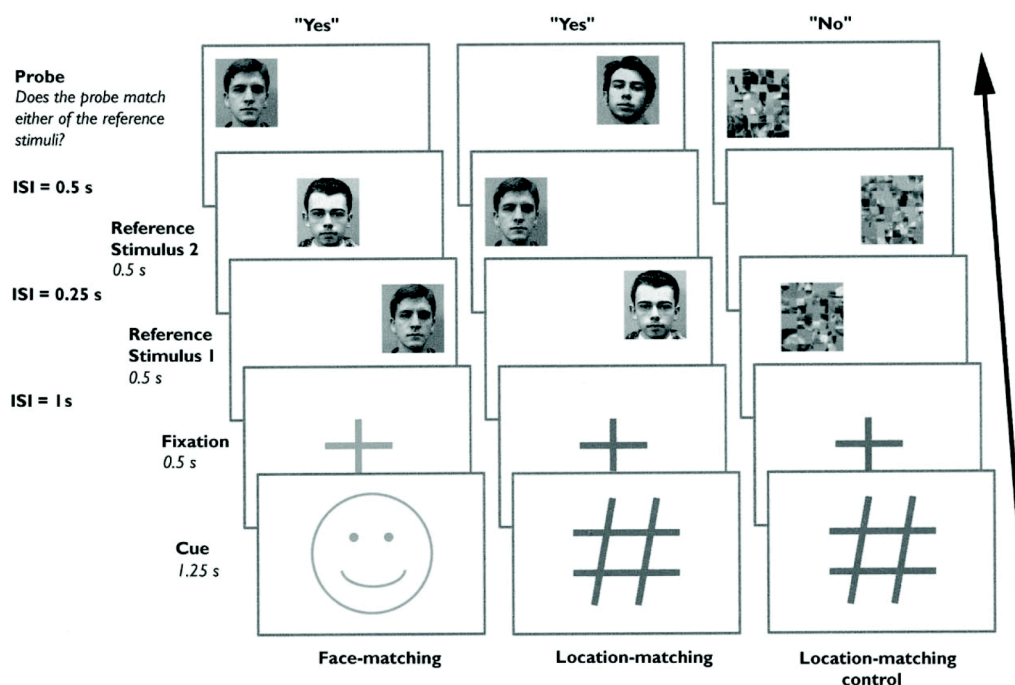


Fig. 1. Diagram of task design and sample stimuli. For all tasks, a warning cue appeared at the beginning of a block of six trials. The green smiley face in the face-matching task cued the participant to attend to the identity of the stimuli. The red grid icon in the location tasks cued the participant to attend to the location of the stimuli. Stimuli could appear in 12 possible locations. An inter-trial interval of 0.5 s separated one trial from the next in all three tasks.

allowed a maximum of 2000 ms to respond, while child controls were allowed 2500 ms and WMS 3500 ms. It is likely that this difference did not truly alter the tasks since both control groups responded well within their allotted times.

Stimuli used in both the face-matching and location-matching tasks were black and white photographs of male faces. For the location control task, scrambled black and white patterns were used. These scrambled stimuli contained the same range of spatial frequencies as the regular face photographs, but were not recognizable as faces. For all three tasks, half the trials contained matching probes and half did not. During the face-matching task, reference and probe stimuli locations never matched; during location tasks, reference and probe stimuli never matched in identity. For the control adults and children, 48 trials per task were given (eight blocks). To maximize performance among the WMS, shortened versions of the three tasks were used. They consisted of 18 trials each, identical to the first 18 trials of each task given to controls. To take into account the difference in task lengths across groups (48 versus 18 trials per task), the analyses reported here were also performed using control data from only the first 18 trials per task; the results did not change.

The WMS and child control groups were given a minimum of eight practice trials per task and the adult group, four practice trials. During the practice and experimental tasks, typical adults and children were provided

with feedback (a computer beep) for incorrect answers. WMS participants were given feedback only during their practice trials in order to minimize distractions, since WMS individuals tend to be hypersensitive to sounds [28].

Participants were excluded if their performance was below chance on all three tasks (four out of the original sample of 37 WMS). With 48 trials, chance performance for controls was ~ 0.59 ($p=0.05$) or below according to the binomial probability distribution (note: given that WMS had fewer trials, in order to maintain a comparable range of scores across the study groups, WMS were retained with performance of 0.67 ($p=0.07$) or higher. All but two WMS scored well above the 0.05 chance level for 18 trials on at least one task). Mean substitution (of the appropriate participant group mean) was used to deal with missing data points; this was performed on only one cell (one WMS participant on the location control task). Because WMS is such a rare clinical group, that group was not restricted by handedness. Five non-right-handed WMS individuals were included in these analyses. When the analyses were rerun excluding these five subjects, the results did not change.

RESULTS

Accuracy was investigated with a $3 \times 2 \times 2 \times 2$ (group \times order \times gender \times task) mixed design ANOVA. Group (WMS, adult controls, child controls), order (face-matching

first, location-matching first) and gender were between subject variables. Task (face-matching, location-matching, location control) was the within subject variable. Preliminary analyses revealed that order and gender were not involved in any of the significant effects, and were dropped from further analyses. In the resulting 3×2 (group \times task) ANOVA, the groups \times task interaction was significant ($F(4,146) = 16.52, p < 0.001$). Analysis of simple effects (by group) indicated that performance across the three tasks differed significantly only in the WMS group ($F(2,64) = 31.21, p < 0.001$; Fig. 2). Bonferroni's correction was applied to correct for multiple comparisons. A follow-up Tukey HSD test for all pairwise comparisons revealed that WMS performance on face-matching was significantly better than performance on both the location-matching ($p < 0.001$) and the location control tasks ($p < 0.001$). Performance on the two location tasks was not different ($p > 0.6$). This pattern of performance is striking and uniform across subjects; 30 of the 33 WMS participants show the pattern regardless of age and overall ability level. Performance in the adult and child control groups did not differ across tasks.

DISCUSSION

The findings from this study document a striking disparity between face and location processing in a large sample of WMS individuals under experimental conditions in which processing demands were carefully balanced. The findings (Fig. 2) are consistent with results from previous studies on face and location processing in WMS and confirm the spatial deficit even in the absence of a motor component [2]. One possible account of the WMS poor performance on the location-matching task in this study could have been that because the stimuli in the location-matching task were always faces, WMS were unable to repress face processing and were simply off task. By this account, the disparity in performance observed between the face- and location-matching tasks could reflect a strong attraction to face stimuli rather than deficits in location processing. Three findings argue against this account. First, if WMS individuals

were in fact engaged in face matching during location-matching trials, their accuracy scores should have been substantially lower. Recall that during location-matching, the reference and probe faces never matched, thus if WMS individuals attempted to match faces during these trials, all of their responses should have been "no" and their performance should have been at 50%. In fact, their performance during location matching was substantially higher than 50%. Further, examination of individual patterns of responses showed a comparatively even distribution of yes and no responses for WMS participants during location matching, suggesting that they were not simply defaulting to a face matching strategy. Second, the performance of the WMS group on the location control task was virtually identical to that on the location-matching task. Thus, even when no distracting face stimuli were present, location processing performance was still impaired. Lastly, the selective impairment of location processing cannot be characterized as an immature processing strategy. In a study of typically developing 6–12 year olds using tasks similar to those reported here, but with increased processing demands, we demonstrated that the increase in difficulty led to a selective decline in face, but not location processing [22]. Thus, the performance profile for the WMS represents a pattern of selective deficit rather than developmental delay.

CONCLUSIONS

The major finding of this study confirms previous reports of strong face processing in the WMS population, as well as reports of a spatial deficit. However, it extends the documentation of poor performance in the spatial domain to include a perceptually based location-processing task matched precisely in stimulus and response demands to the face-processing task. The findings from this study thus highlight in a new and more compelling way the contrast between face processing and spatial processing abilities in the WMS group. Our findings serve to confirm the existence of a chasm within visuospatial cognition, as well as to characterize it in greater depth. The current findings add further support to claims of a functional dissociation in WMS which is reflected in contrasting patterns of strength and deficit in processes mediated by different visual processing streams. Specifically, WMS appear to manifest deficits in processes associated with the dorsal stream, while exhibiting relative strengths in processes, such as face processing, that are mediated by the ventral stream. The current findings are consistent with the hypothesis of a dissociation in dorsal versus ventral stream processing that is beginning to gain support from neurophysiological, neuromorphological and cellular studies of WMS underlying brain systems.

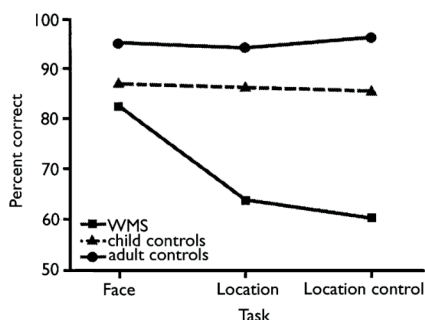


Fig. 2. Task performance across groups. It appears that WMS participants and controls close in mental age performed at similar levels of accuracy on the face-matching task (82.2% for WMS vs 86% for child controls), while their performance levels on the location-matching task were markedly different (62.7% for WMS vs 85.6% for child controls).

REFERENCES

- De Haan M. The neuropsychology of face processing during infancy and childhood. In: Nelson CA and Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience*. Cambridge, MA: MIT Press; 2001, pp. 381–398.
- Bellugi U, Lichtenberger L, Mills D *et al.* *Trends Neurosci* 22, 197–207 (1999).
- Korenberg JR, Chen X-N, Hirota H *et al.* Genome structure and cognitive map of Williams syndrome. In: Bellugi U and George MS, eds. *Journey*

- from *Cognition to Brain to Gene: Perspectives from Williams Syndrome*. Cambridge, MA: MIT Press; 2001, pp. 147–177.
4. Korenberg JR, Chen X-N, Zheng Y *et al.* *Am Soc Hum Genet* **14**(4), Suppl. 2 (2000).
 5. Bellugi U and St. George M, eds. *Journey from Cognition to Brain to Gene: Perspectives from Williams Syndrome*. Cambridge, MA: MIT Press; 2001.
 6. Bellugi U, Korenberg JR and Klima ES. *Clin Neurosci Res* **1**, 217–229 (2001).
 7. Bellugi U, Lichtenberger L, Jones W *et al.* The neurocognitive profile of williams syndrome: A complex pattern of strengths and weaknesses. In: Bellugi U and George MS, eds. *Journey from Cognition to Brain to Gene: Perspectives from Williams Syndrome*. Cambridge, MA: MIT Press; 2001, pp. 1–41.
 8. Donnai D and Karmiloff-Smith A. *Am J Med Genet* **97**, 164–71 (2000).
 9. Jones W and Lai ZC. *Int Behav Neurosci Soc Abstr* **6**, P2–51 (1997).
 10. Bellugi U, Klima ES and Wang PP. Cognitive and neural development: Clues from genetically based syndromes. In: Magnusson D, ed. *The Lifespan Development of Individuals: Behavioral, Neurobiological, and Psychosocial Perspectives: A Synthesis*. New York, NY: Cambridge University Press; 1997, pp. 223–243.
 11. Ungerleider LG and Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA and Mansfield RJW, eds. *Analysis of Visual Behavior*. Cambridge, MA: MIT Press; 1982, pp. 549–586.
 12. Haxby JV, Horwitz B, Ungerleider LG *et al.* *J Neurosci* **14**, 6336–6353 (1994).
 13. Smith EE, Jonides J, Koeppe RA *et al.* *J Cogn Neurosci* **7**, 337–356 (1995).
 14. Nelson CA, Monk CS, Lin J *et al.* *Dev Psychol* **36**, 109–116 (2000).
 15. Passarotti AM, Paul BM, Stiles J *et al.* *Neuroimage* **11**, S38 (2000).
 16. Atkinson J, King J, Braddick O *et al.* *Neuroreport* **8**, 1919–1922 (1997).
 17. Galaburda A, Holinger DP, Bellugi U *et al.* *Arch Gen Neurol* (2002), in press.
 18. Galaburda AM and Bellugi U. Cellular and molecular cortical neuroanatomy in Williams syndrome. In: Bellugi U and George MS, eds. *Journey from Cognition to Brain to Gene: Perspectives from Williams Syndrome*. Cambridge, MA: MIT Press; 2001, pp. 123–145.
 19. Galaburda AM, Schmitt JE, Atlas SW *et al.* *Arch Neurol* **58**, 1865–1869 (2001).
 20. Mills DL, Alvarez TD, St George M *et al.* *J Cogn Neurosci* **12** (Suppl. 1), 47–64 (2000).
 21. Rose FE and Bellugi U. *Soc Neurosci Abstr* **27** (2001), San Diego, CA 2001.
 22. Paul BM, Passarotti AM and Stiles J. *Cogn Neurosci Soc Abstr* 70C (2001).
 23. Jones W, Bellugi U, Lai Z *et al.* Hypersociability: The social and affective phenotype of williams syndrome. In: Bellugi U and George MS, eds. *Journey from Cognition to Brain to Gene: Perspectives from Williams Syndrome*. Cambridge, MA: MIT Press; 2001, pp. 43–71.
 24. Losh M, Bellugi U, Reilly J *et al.* *Narrative Inquiry* **10**, 265–290 (2000).
 25. Dunn LM and Dunn LM. *Peabody Picture Vocabulary Test*. Circle Pines, MN: American Guidance Service; 1997.
 26. Beery KE. *The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)*. Parsippany, NJ: Modern Curriculum Press; 1997.
 27. Cohen JD, MacWhinney B, Flatt M *et al.* *Behav Res Methods Instr Computers* **25**, 257–271 (1993).
 28. Levitin DJ, Bellugi U and Cole K. Aversion, awareness and attraction: Understanding hyperacusis in Williams syndrome. *Technical Report 2113*. University of California, San Diego: Institute for Neural Computation, 2002.

Acknowledgements: This research was supported by NIH grant PO1 HD33113 and a grant from the James S. McDonnell Foundation to Ursula Bellugi; by NIH NS22343, Project 5 to Joan Stiles and Project 3 to Ursula Bellugi; and by NIH HD25077 to Joan Stiles. We thank Fred Rose, Edward Klima, Yvonne Searcy, Diana Kikuchi and Janet Shin for help in analysis, figures, and comments. We are also grateful to the Williams Syndrome Association and to all the individuals and families who participated in these studies.

This chapter is a reprint of the material as it appears in:

Paul, B.M., Stiles, J., Passarotti, A., Bavar, N. and Bellugi, U. (2002). Neuroreport, 13 (9), 1115-1119. Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation.

The dissertation author was the primary investigator and author of this paper.

CHAPTER 4

FACE AND LOCATION PROCESSING IN WILLIAMS SYNDROME: BEYOND A DORSAL STREAM DEFICIT

Abstract

We used functional magnetic resonance imaging (fMRI) to explore the neural basis of the frequently cited dissociation between skilled face processing but impaired spatial abilities in Williams Syndrome (WS), a genetically-determined neurodevelopmental disorder. A pair of face identity- and location-matching tasks, equated for stimuli, timing and response, were used to examine differences in engagement of ventral and dorsal stream visual processing systems. Importantly, by including both a chronological age-matched control group (healthy adults) and a group of typically-developing child controls (8- to 9-years-old) a consideration of potential WS-related differences in ventral and dorsal stream recruitment in the context of normal developmental change was afforded.

Unlike both control groups, WS participants failed to show the expected profile of greater ventral region activity during facial identity processing and greater dorsal region activity during location processing. The most marked divergence from the brain response observed in both control groups was the absence of activation in posterior parietal cortex during location-matching, a finding that is consistent with previous reports of functional and structural abnormalities in the dorsal pathway in WS. However, despite the relatively strong face discrimination abilities often seen in WS, the underlying brain response during the identity-matching task also appeared atypical. Ventral stream activation centering on the fusiform gyrus was mildly abnormal. In addition, a striking deficit in amygdala activation was seen in the WS group, along with an unexpectedly increased response in an area of parietal cortex

typically associated with visuospatial attention. Implications for both typical and atypical development of visual processing pathways are discussed.

Background

Williams syndrome (WS) is a rare neurodevelopmental disorder caused by a hemizygous microdeletion on chromosome 7, which includes the gene for elastin (ELN), among others (Ewart, Morris et al. 1993; Frangiskakis, Ewart et al. 1996; Korenberg, Chen et al. 2000). In addition to distinctive facies (Jones and Smith 1975) and heightened risk for cardiac and other organ system pathology (Jones and Smith 1975; Morris, Demsey et al. 1988; Pober and Dykens 1996) the syndrome is characterized by mild to moderate mental retardation (Arnold, Yule et al. 1985; Howlin, Davies et al. 1998; Mervis, Morris et al. 1999), a unique social demeanor (Vonarnim and Engel 1964; Dilts, Morris et al. 1990; Gosch and Pankau 1994; Jones, Bellugi et al. 2000) and a heterogeneous profile of neuropsychological strengths and weaknesses (Bellugi, Lichtenberger et al. 2000). Given the substantial understanding of the underlying genetic abnormality, the study of WS holds promise for addressing questions regarding the genetic bases of human cognition and behavior (Bellugi, Lichtenberger et al. 1999; Mervis, Morris et al. 1999; Bellugi and St. George 2001).

With respect to the cognitive profile observed in individuals with WS, a notable disparity between language and spatial abilities is typically seen (Bennett, LaVeck et al. 1978; Udwin, Yule et al. 1987; Bellugi, Wang et al. 1994; Mervis, Robinson et al. 2000). These individuals often present with relatively strong language skills, including speech production (Udwin and Yule 1990; Gosch, Stading et al. 1994) and receptive vocabulary (Bellugi, Bihle et al. 1990; Vicari, Bates et al. 2004; Brock 2007). Their visuomotor and spatial abilities, however, are exceedingly poor (Bellugi, Sabo et al. 1988; MacDonald and Roy 1988). Particular deficits are seen with

visuospatial tasks involving drawing and block design (Bellugi, Sabo et al. 1988; Bertrand, Mervis et al. 1997). Importantly, individuals with WS show deficits even on visuospatial measures that do not require a significant motor or constructional component (e.g. Benton Judgment of Line Orientation) (Crisco, Dobbs et al. 1988; Wang, Doherty et al. 1995). Moreover, these deficits are unrelated to sensory vision problems that are also seen with some frequency in this disorder (Atkinson, Anker et al. 2001).

Deficits in visuoperceptual function in WS, while striking in certain subdomains, are not present for all types of stimuli. Specifically, the face processing abilities of individuals with WS remain relatively unaffected (Bellugi, Lichtenberger et al. 2000). In the first years of life individuals with WS show a heightened interest in faces over other classes of stimuli (Laing, Butterworth et al. 2002; Mervis, Morris et al. 2003). During the later stages of development, they demonstrate impressive accuracy on face perception and recognition tasks (Udwin and Yule 1991; Rossen, Klima et al. 1996). They often outperform mental age controls (including those with other forms of mental retardation) on measures of face processing (Udwin and Yule 1991), and have even been found to score at or near the level of chronological age controls on certain tasks [(e.g., the Benton Test of Facial Recognition (Benton, Hamsher et al. 1983)], (Bellugi, Wang et al. 1994; Wang, Doherty et al. 1995).

As noted previously, the notable skill and interest in processing faces observed in WS is in sharp contrast with the significant deficits in spatial cognition. The existence of such a marked discrepancy within a specific genetically based population is of great interest, since it may provide insight regarding the relationship between

genes and the organization of the neural systems that mediate visuospatial processing abilities. The primate cortical visual system is subdivided into two anatomically and functionally separate systems. Specifically, the ventral stream (occipito-temporal lobes) is principally involved in processing the properties of objects such as faces, whereas the dorsal stream (occipito-parietal lobes) is involved in spatial processes such as object localization, movement detection, and visually-guided action (Ungerleider and Mishkin 1982; Goodale and Milner 1992; Milner and Goodale 1995). Evidence in support of the dual-stream representation of vision has emerged both from studies of patients with brain lesions (Newcombe and Russell 1969; Newcombe, Ratcliff et al. 1987), and from psychophysiological (Tresch, Sinnamon et al. 1993; Hecker and Mapperson 1997) and neuroimaging studies with healthy adults (Haxby, Horwitz et al. 1994; Kohler, Kapur et al. 1995; Smith, Jonides et al. 1995; Courtney, Ungerleider et al. 1996; Mecklinger and Mueller 1996; Aguirre and D'Esposito 1997; Ruchkin, Johnson et al. 1997; Shen, Hu et al. 1999; Rao, Zhou et al. 2003).

It has been frequently suggested that the considerable discrepancy between face and spatial processing implicates impairment of the dorsal stream, with relative sparing of the ventral stream (Wang, Doherty et al. 1995; Atkinson, King et al. 1997; Nakamura, Watanabe et al. 2001; Paul, Stiles et al. 2002; Atkinson, Braddick et al. 2003; Atkinson, Braddick et al. 2006). Indeed, evidence gathered to date suggests that impairment of dorsal stream function is a prominent and enduring feature of this disorder. Many children with WS show significantly poorer performance on visuo-perceptual and visuo-cognitive tasks that place greater demands on the dorsal

rather than the ventral cortical stream (Atkinson, King et al. 1997; Atkinson, Braddick et al. 2003). Recent evidence suggests that these deficits persist into adulthood and are unlikely to represent a simple lag in development, rather a persistent neurocognitive deficit (Atkinson, Braddick et al. 2003; Atkinson, Braddick et al. 2006). In fact, data from WS and several other neurodevelopmental disorders, including dyslexia (the ‘magnocellular hypothesis’) (Stein and Walsh 1997; but see Skottun 2000; Stein, Talcott et al. 2000), autism (Spencer, O'Brien et al. 2000), and schizophrenia (Kim, Wylie et al. 2006), bolster the proposition that, in general, the dorsal stream may be more modifiable and/or more vulnerable to perturbation (Braddick, Atkinson et al. 2003; Stevens and Neville 2006), possibly as a result of abnormal ontogenetic competition between the two pathways (Atkinson, Braddick et al. 2003).

In recent years, neuroimaging studies of WS have lent support to the hypothesis of greater dorsal stream involvement in this disorder. Structural imaging work in WS has shown unambiguous abnormalities in dorsal cortical regions. Specifically, inspection of gross anatomical features in WS indicates that the central sulcus is foreshortened in its dorsal aspect near the interhemispheric fissure, but not in its ventral extension toward the sylvian fissure (Galaburda and Bellugi 2000; Galaburda, Schmitt et al. 2001; Jackowski and Schultz 2005; Van Essen, Dierker et al. 2006). Measures of gyrification have yielded complementary results, revealing abnormalities in occipital and parietal cortex, but not temporal cortex, in WS (Schmitt, Watts et al. 2002; Gaser, Luders et al. 2006). In addition, regional volume reductions have been found in the occipital and parietal lobes with some consistency (Jernigan and Bellugi 1990; Reiss, Eliez et al. 2000; Reiss, Eckert et al. 2004; Eckert, Hu et al.

2005; Thompson, Lee et al. 2005), including grey matter reductions in the superior parietal lobule (Reiss, Eckert et al. 2004; Eckert, Hu et al. 2005) and the region in and around the intraparietal sulcus (Meyer-Lindenberg, Kohn et al. 2004; Kippenhan, Olsen et al. 2005; Boddaert, Mochel et al. 2006). Measures of sulcal depth have provided evidence of that the intraparietal sulcus, among other sulci, is abnormally shallow in WS (Kippenhan, Olsen et al. 2005; Van Essen, Dierker et al. 2006), and efforts have been made to link structural deficits in this area with the spatial cognitive impairments in WS (Meyer-Lindenberg, Kohn et al. 2004).

While cognitive and neuroimaging studies converge nicely on the existence of dorsal stream impairment in WS, the evidence for relative sparing of the ventral stream in WS is less consistent. Behavioral findings of proficient processing of objects (at the level of chronological age controls) (Wang, Doherty et al. 1995; Landau, Hoffman et al. 2006), in addition to faces, provide some evidence for ventral stream integrity. However, the possibility that individuals with WS rely on atypical underlying cognitive mechanisms has been raised (Karmiloff-Smith, Thomas et al. 2004). Specifically, an impaired ability to utilize configural information (distances among face features), which is considered essential for normal face processing (Maurer, Grand et al. 2002), has been posited (Deruelle, Mancini et al. 1999; Karmiloff-Smith, Thomas et al. 2004). Electrophysiological studies in WS have provided data regarding the neural mechanisms that might be associated with this impairment. In the first event-related potential (ERP) study of face processing in WS, Mills and colleagues (2000) found that the brain response to faces in WS was noticeably atypical, particularly with respect to the early response components (e.g.

the N100 was of a smaller amplitude than expected, while the N200 had an extremely large amplitude). Moreover, the ERP components for upright and inverted faces did not differ, suggesting that unlike healthy controls, WS participants did not engage distinct neural systems when processing the two types of stimuli. Grice et al. (2001) made a similar discovery with gamma band electroencephalography (EEG). In a group of WS adults they observed a markedly atypical response to upright faces (a complete absence of normal gamma activity bursts), in addition to abnormally similar EEG activity when processing upright and inverted faces (unlike controls whose EEG activity was modulated by changes in face orientation). Given that differences in processing of upright versus inverted faces in typical participants are thought to be linked to configural processing (i.e., the reliable performance decrement induced by face inversion, known as the face inversion effect, is thought to reflect the perceiver's inability to process the configural aspects of the face when it is presented upside-down - Yin 1969; Valentine 1988; Rhodes 1993), these findings are consistent with deviance in the cognitive mechanisms associated with face processing. Further, they raise the possibility that the ventral stream may mediate face processing in an abnormal way.

Although the two electrophysiological studies of face processing in WS have produced relatively consistent findings, functional neuroimaging studies of ventral stream processes in WS have been much less concordant. For example, no evidence for ventral stream dysfunction was found in a functional magnetic resonance imaging (fMRI) study by Meyer-Lindenberg and colleagues (2004), using two tasks, a shape-matching task and a visual attention task with face and house stimuli, in a select group of WS individuals with normal IQ (i.e. non-retarded). In contrast, a fMRI study by

Mobbs et al. (2004) examining face gaze processing in a more typical WS sample (mild mental retardation), observed activation deficits in primary and secondary visual cortices, but not in the fusiform gyrus, a ventral temporal region critical for normal face perception (Allison, Ginter et al. 1994; Puce, Allison et al. 1995). Structural MRI studies have revealed a handful of differences between WS and healthy control participants in the ventral stream, although not all of them have been consistently replicated, at least in part due to methodological differences across studies (Eckert, Tenforde et al. 2006). These findings in WS include increased grey matter density in bilateral fusiform gyri (Reiss, Eckert et al. 2004), and increased cortical thickness in a nearby region of inferior temporal cortex (right hemisphere only) extending into the temporal fusiform gyrus (Thompson, Lee et al. 2005). Thus far, measures of sulcal depth have been most consistent, with two studies finding decreased depth within the collateral sulcus, which runs along the medial border of the fusiform gyrus (Kippenhan, Olsen et al. 2005; Van Essen, Dierker et al. 2006). Given the likelihood that faces are represented in a distributed manner along the ventral side of the temporal and occipital lobes (Ishai, Ungerleider et al. 1999; Haxby, Gobbini et al. 2001), this finding is of potential importance to the study of face processing in WS.

The current investigation examined dorsal and ventral stream processing in WS using functional magnetic resonance imaging (fMRI) in an effort to address some of the inconsistencies among studies that have been conducted to date. Only one other study has examined task-related brain activation on measures with differential sensitivity to ventral or dorsal stream function in WS (Meyer-Lindenberg, Kohn et al. 2004). As previously alluded to, Meyer-Lindenberg and colleagues (2004) compared

BOLD activation in WS and chronological age- and gender-matched controls during a visual task that required that participants attend to either the identity or position of a pair of stimuli (faces or houses). Clear hypofunction of the dorsal stream, particularly in the region surrounding the intraparietal sulcus, was observed. No differences from controls were seen in ventral stream response of WS participants. However, because the WS participants included in this study were of normal-range IQ (i.e., non-retarded, common in individuals with partial deletions - Mervis, Morris et al. 1999) it remains unclear how characteristic these findings are of the typical individual with WS, who exhibit mild-to-moderate intellectual impairment (Arnold, Yule et al. 1985; Howlin, Davies et al. 1998). The current study, therefore, included a WS group chosen to be representative of the broader population of WS individuals with respect to overall cognitive ability.

Another limitation in our understanding of the neural basis of the pattern visuo-spatial/perceptual deficits manifested in WS has been a dearth of information regarding the normal developmental trajectory of the ventral and dorsal visual processing systems. Despite the plethora of studies focusing on the mature incarnation of the ventral/dorsal visual stream dichotomy, little is known about its emergence during the course of development (Passarotti, Paul et al. 2003). A limited corpus of psychophysical investigations (Gordon and McCulloch 1999; Madrid and Crognale 2000; Gunn, Cory et al. 2002; Atkinson, Braddick et al. 2003; Mitchell and Neville 2004; Coch, Skendzel et al. 2005) provides some evidence that the two systems may reach maturity at differing rates, however, there is no consensus as to a more exact chronology. By virtue of including two healthy control groups (a group of typically-

developing 8- to 9-year-old children and a group of healthy adults), in addition to WS participants, the present study is well poised to provide both insight into the normal development of ventral and dorsal stream processing, and critical information regarding the integrity of these systems in WS.

Following work in healthy adults (Haxby, Horwitz et al. 1994; Courtney, Ungerleider et al. 1996), to probe ventral and dorsal stream processing, respectively, we employed a pair of face identity-matching and location-matching tasks. To facilitate across task comparisons, the tasks were matched on key variables, including stimulus presentation and response requirements. Performance of individuals with WS on these experimental tasks has been well-documented (Paul, Stiles et al. 2002; Paul, Snyder et al. in preparation), and shows the characteristic dissociation (Bellugi, Wang et al. 1994; Bellugi, Lichtenberger et al. 2000) between relatively strong face-matching performance and severe impairment in matching stimuli based on their location. While we expected to see a pervasive deficit in dorsal stream responsivity in WS, the ventral stream response was expected to more closely resemble that seen in unaffected controls, particularly for the face identity-matching task (Paul, Stiles et al. 2002; Paul, Snyder et al. in preparation). However, given the prospect of process-based abnormalities of face and object perception in WS (Karmiloff-Smith, Thomas et al. 2004), we did not exclude the possibility that more subtle differences in ventral stream response might be observed. Some of the results for the face identity processing task included here have appeared in a preliminary report (Paul, Snyder et al. in preparation).

Two types of group comparisons were drawn for these tasks, with typically-developing school-age children enabling a comparison based on approximate mental age (MA), and the healthy adults matched to the WS participants on age and gender enabling a chronological age (CA) comparison. The inclusion of a typically-developing child control group, which is unique to the present study, allowed for the consideration of the pattern of brain activity in WS within a broader developmental context. This type of approach is warranted (Paterson and Schultz 2007) because the developmental course in this genetically-based disorder is likely to be altered from the very earliest stages (Karmiloff-Smith 2001). Such group comparisons allowed for clearer determination of whether any differences in brain response are similar to that seen in immature systems, or whether they represent the functioning of a system organized in a fundamentally atypical fashion. This distinction has been debated extensively in studies of this population and we hoped to provide the first brain imaging data to address these questions as applied to visuoperceptual processing in WS.

Methods

PARTICIPANTS

Williams Syndrome (WS) group. Fifteen individuals with Williams Syndrome (9 females, 6 males; $M = 30.1$ years, $SD = 12.0$) were recruited and evaluated at the Salk Institute as part of a comprehensive multi-disciplinary research project. Imaging data from three additional subjects were not used because of excessive head movement (one participant) or because they did not complete both task conditions (two participants). The diagnosis of WS was made on the basis of FISH (fluorescence

in situ hybridization; absence of one copy of the elastin gene on chromosome 7) and presence of phenotypic features defined by the American Academy of Pediatrics (2001). WS participants were administered the Weschler Adult Intelligence Scale – Revised (WAIS-R), with the exception of two participants under the age of 17 who were administered the Weschler Intelligence Scale for Children – Revised (WISC-R). One participant with WS did not participate in IQ testing at the time of the study. Mean IQ scores for the group (Full Scale = 66.1, SD = 9.7; Verbal = 71.8, SD = 7.8; Performance = 62.8, SD = 9.6) fell within the range typically reported for individuals with WS (Howlin, Davies et al. 1998; Searcy, Lincoln et al. 2004). All WS participants completed the Peabody Picture Vocabulary Test – 3rd edition (PPVT-III), (M = 75.5, SD = 12.8; range 40 – 92), indicating that the receptive vocabulary Age-Equivalent for the WS group was about 12 years of age (M = 12.3 years, SD = 4.7; range = 5.83 – 22.0 years). In addition, all WS participants completed the Developmental Test of Visuomotor Integration (VMI) (Beery 1997) (M = 48.7, SD = 8.2; range < 45 – 75; four participants scored below the basal score of 45). The Age-Equivalent for visuomotor integration for the WS group was about 6 years of age (M = 5.8 years, SD = 1.6; range = 4.1 – 11.25 years).

Mental age (MA) matched comparison group. The MA group consisted of 16 typically-developing 8- to 9-year-old children (M = 8.9 years, SD = 0.7; 9 females, 7 males) recruited from elementary schools in San Diego County. Five additional children were excluded because of excessive head motion during MRI. The chronological age of the MA group mean fell midway between the mean language and visuospatial age-equivalent estimates of the WS group (see above).

Chronological age (CA) matched comparison group. A second comparison group consisted of neurologically normal adults matched to the WS group for gender and age. In all but two cases participants were matched to within 1 year of age (the two exceptions were pairs of participants differing in age by 1 year, 4 months in one case, and 2 years, 10 months in the second case). The CA group was comprised of 17 individuals ($M = 31.0$ years, $SD = 11.2$; 10 females, 7 males) recruited from the University of California, San Diego and surrounding community. One additional male was excluded due to technically compromised imaging data (excessive electronic noise).

None of the control participants had a history of neurological, psychiatric or major medical conditions, learning disability, head trauma, or current use of psychotropic drugs. The study was approved by the Institutional Review Boards of the Salk Institute, the University of California, San Diego (UCSD) and San Diego State University (SDSU). Adult participants and parents/guardians of WS and child participants gave written informed consent; in addition, children and WS participants gave assent to participate. Participants were compensated for their participation with a small monetary sum.

BEHAVIORAL TASK

Task stimuli were black and white photographs of male faces with neutral expression displayed on a uniform grey background (see Figure 4.1) obtained from the University of Essex online face database. Participants were seated 60 cm from the computer screen. Stimuli subtended $4.76^\circ \times 5.06^\circ$ visual angle in the vertical and

horizontal dimensions. Each stimulus appeared in one of twelve possible positions on the screen.

To obtain an accurate measure of each participant's face identity- and location-matching abilities, the tasks were administered prior to the imaging session in a quiet room at the Salk Institute. Figure 4.1 illustrates the two task conditions. Each task was associated with a distinct warning cue displayed to identify the subsequent test trials (green "smiley face" for face identity-matching trials and red tic-tac-toe grid for location-matching trials). Trials were presented in blocks of six, with each block preceded by a warning cue. Six blocks were administered for a total of 36 trials per task condition. Each task trial began with a fixation cross, followed by a series of two reference stimuli (500 ms duration per stimulus). After a delay of either 500 or 1750 ms, a third (test) stimulus appeared until the participant responded, or until 3500 ms elapsed. Participants indicated by pressing one of two buttons ("yes" or "no") whether the identity or location of the test stimulus matched either of the two reference stimuli. A match was presented in half of the trials. During the face identity-matching condition, reference and test stimuli never matched in location; during the location-matching condition, reference and test stimuli never matched in identity. Participants were encouraged to respond as quickly but as accurately as possible. Both accuracy and response times were recorded. The first 18 trials for each task condition used a 500 ms delay between the second reference stimulus and the test stimulus, in accordance with our previous study using these tasks with WS (Paul, Stiles et al. 2002). The second 18 trials used a 1750 ms delay, in line with the functional neuroimaging paradigm (see below) that has been successfully employed in the UCSD

laboratory for several years (Passarotti, Paul et al. 2003; Stiles, Paul et al. 2006). Comparison of accuracy data from the two delay conditions across the three participant groups did not reveal a significant group \times delay interaction effect ($P > 0.5$). These data therefore were collapsed over the two delay conditions in the analyses presented here.

To ensure adequate understanding of the task procedure, all participants were given practice (at least eight trials per task condition for MA and WS groups and at least four trials per condition for the CA group). Additional practice and explanation were given as needed. Feedback for incorrect answers (computer-generated beep) was provided on all trials for the MA and CA groups. However, because of hyperacusis in WS, feedback for incorrect answers was given to WS participants only during practice.

FUNCTIONAL NEUROIMAGING

Task. The behavioral task described above was adapted for block design fMRI (Figure 4.1b). Based on preliminary data from 12 WS participants (not included in the current study), trials from the behavioral task were modified slightly to promote optimal task performance during fMRI runs. This involved increasing the presentation of the reference stimuli to 1000 ms, and requiring a button press only on positive identity or location matches (to avoid using two different buttons without direct visualization). In addition, to achieve scanning runs of constant length, the third (test) stimulus was presented for a fixed duration of 3250 ms. Control trials followed the same stimulus sequence but did not require a match decision; participants were instructed to simply wait for the third stimulus and press the mouse button. Control

stimuli were scrambled face images. Each participant completed at least two runs per task condition, or as many as tolerated up to a limit of eight total runs. WS participants were trained in a mock-scanner immediately prior to fMRI to improve compliance (e.g., reduce head and body motion) and ensure understanding of the task.

Image acquisition. Images were acquired at UCSD, on a Siemens 1.5 Tesla Vision System (Erlangen, Germany) with a standard clinical head coil. A thermoplastic mask was used for head stabilization. Both earplugs and noise-canceling headphones were used to attenuate scanner noise. Stimuli were rear-projected onto a screen located at the subject's feet, which the subject viewed with a small mirror secured to the head coil above their eyes. Participants responded to the tasks with a hand-held mouse connected to a laptop computer.

Functional images were acquired with a single-shot echo-planar (EPI) pulse sequence sensitive to blood oxygenation level dependent (BOLD) contrast (FOV=220 mm, TR=2500 ms, TE=40 ms, flip angle=90°). Whole head coverage was obtained with 27 5 mm slices (in-plane resolution 3.44 x 3.44 mm). Each fMRI run included 116 volumes (frames). T1-weighted structural images were obtained using an MP-RAGE sequence (TR=11.4 ms, TE=4.4 ms, flip angle=10°, resolution=1 mm³; 180 sagittal slices).

fMRI data preprocessing. Image preprocessing was performed with algorithms developed at Washington University (A.Z. Snyder, R.L. Buckner and others). MP-RAGE images from each individual were registered (12 parameter affine transformation) to an atlas-representative target conforming to the atlas of Talairach &

Tournoux (1988) as defined by the SN method of Lancaster et al. (1995). A study-specific atlas-representative target image was prepared from MP-RAGE data representing all three participant groups (20 WS, 10 CA adults and 10 MA children) using a previously described strategy (Buckner, Head et al. 2004). This approach to atlas normalization was adopted to minimize the influence of structural differences between groups on functional responses measured in common regions of interest (ROI) in atlas space. Structural differences between 8- to 9-year-old children and young adults are minor after 12-parameter affine transformation to a common atlas space (Burgund, Kang et al. 2002). Structural differences in WS include abnormal cortical folding, most prominently in dorsal parietal regions (Schmitt, Watts et al. 2002; Reiss, Eckert et al. 2004; Eckert, Hu et al. 2005; Kippenhan, Olsen et al. 2005; Thompson, Lee et al. 2005; Van Essen, Dierker et al. 2006).

Preprocessing of the fMRI data involved (1) correction of central spike artifact caused by signal drift, (2) compensation for asynchronous slice acquisition, (3) elimination of odd versus even slice intensity differences due to interleaved acquisition, (4) rigid body head motion correction within and across fMRI runs and (5) intensity scaling to a whole-brain mode value of 1,000. Atlas transformation of the functional data was computed via each subject's MP-RAGE. The final preprocessing step combined motion correction and atlas transformation in one step to yield volumetric time series resampled to 3 mm cubic voxels.

Individual fMRI analyses. As a quality assurance (QA) step, the standard deviation of the signal over the course of each functional run was calculated and runs with excessive variability (mean whole brain standard deviation greater than 2.5%: 6,

3, and 1 runs in MA, CA and WS groups, respectively) were excluded from the statistical results. Analysis of individual fMRI time series was performed using AFNI (Cox 1996). The data were spatially smoothed (6.88 mm full width at half maximum Gaussian kernel). Multiple regression analysis was performed assuming a canonical hemodynamic response function (HRF) of the gamma type (Cohen 1997). Head motion correction parameters (three translation, three rotation), as well as the global mean and linear drift were included as nuisance regressors. Voxel-wise t -statistic images (one per task condition for a total of two per individual) representing BOLD modulation attributable to task performance were computed and converted to equivalently probable z -scores.

Group fMRI analyses. Group-level analyses were performed in AFNI (Cox 1996). A voxel-wise two-way mixed design ANOVA (between subjects factor of group x within-subjects factor of task condition, with the random factor of subjects nested within the group factor) was conducted using the z -score images obtained from the multiple regression analyses to generate task contrast maps (face identity-matching versus location-matching) for each of the three groups. The results were masked to include only voxels in which a group x task condition interaction was present at $P < 0.05$ per voxel. After masking, the task contrast maps were corrected for multiple comparisons using the cluster threshold technique (individual voxel threshold at $P \leq 0.005$, two-tailed; cluster size = 14 voxels, 378 μ L) (Forman, Cohen et al. 1995) to obtain an overall corrected alpha level of 0.05. To confirm apparent group differences and characterize activation for each task condition separately, follow-up one-way ANOVAs were conducted for each task condition (face identity-matching versus

control, and location-matching versus control) using the z-score images obtained from the individual multiple regression analyses. This generated mean activation maps for each group, as well as pairwise group contrasts. Pairwise group contrast maps were masked and corrected for multiple comparisons in the same manner as the task contrast maps. Group mean activation maps for each task were corrected for multiple comparisons using the cluster threshold technique over the whole brain (individual voxel threshold at $P \leq 0.005$, two-tailed; cluster size = 31 voxels, 837 μ L).

Results

BEHAVIORAL TASK

Performance accuracy was represented by d' , a measure of accuracy that considers the frequency of “hits” as well as “false alarms”, and thus takes into consideration participant bias in responding. A standard correction was employed for false alarm and hit rates of 0 or 1 (Macmillan and Creelman 1991). Response data from one CA control and three WS participants were not available due to equipment malfunction (CA control, one WS participant) or administration of a different version of the behavioral task (two WS participants). Data from one additional WS participant was excluded due to difficulty staying on task during the behavioral session (although his accuracy scores during the imaging session were the fourth highest in the WS group, suggesting that he was capable of understanding and performing the tasks). Accuracy (d') and response time (RT) were each investigated with a 3 x 2 (group x task condition) mixed design analysis of variance (ANOVA).

Results (Table 4.1) revealed a group x task condition interaction effect ($F(2,40) = 6.21, P < 0.005$), which qualified main effects of group ($F(2,40) = 51.42, P <$

0.001) and task condition ($F(1,40) = 27.80, P < 0.001$; overall higher accuracy for identity-matching). Follow-up Tukey HSD tests for the identity-matching condition showed that both the WS and MA groups were outperformed by the CA group ($P < 0.005$ for both t -tests), while the performances of the WS and MA groups were not significantly different from one another ($P > 0.09$). By contrast, in the location-matching condition, WS participants performed significantly worse than both MA and CA controls ($P < 0.001$ for both t -tests); MA controls also performed more poorly than CA controls, although this comparison did not quite attain significance ($P = 0.07$). RT results revealed only a main effect of group ($F(2,40) = 26.8, P < 0.001$). Follow-up Tukey HSD showed that both the WS and MA groups had overall significantly slower RTs than the CA group ($P < 0.001$ for both t -tests of marginal means). However, the WS and MA groups were not different from one another ($P > 0.1$). Thus, on the whole, the WS and MA groups performed less accurately and with greater response latency than CA controls. However, whereas the WS and MA groups did not differ from each other with respect to response latency, they performed at comparable levels of accuracy only for face-identity-matching. This replicates a previous behavioral study using these tasks with different samples of WS participants, 8- to 9-year-old typically-developing children, and healthy adults (Paul, Stiles et al. 2002), and is consistent with the poor spatial abilities that characterize WS.

FUNCTIONAL NEUROIMAGING

Behavioral performance. Response data from three CA controls during the imaging session were not available due to an error during acquisition. Performance (d') and RT on task trials during the imaging session (control trials not analyzed) were

each investigated with a 3 x 2 (group x task condition) mixed design ANOVA. Results showed a significant main effect of group ($F(2,42) = 48.33, P < 0.001$), with the WS participants performing more poorly than the MA and CA controls on both the identity- and location-matching conditions (Tukey HSD tests of marginal means, both $P < 0.001$). MA controls were also outperformed by CA controls (Tukey HSD test, $P < 0.05$). The main effect of task condition ($F(1,42) = 98.19, P < 0.001$) was also significant, due to better performance for all three groups on identity-matching trials (WS identity-matching $d' = 1.28$, location-matching $d' = 0.46$; MA identity-matching $d' = 2.69$, location-matching $d' = 1.49$; CA identity-matching $d' = 3.17$, location-matching $d' = 2.01$). Response time results revealed a main effect of group ($F(2,42) = 7.46, P < 0.005$), modified by a significant group x task condition interaction effect ($F(2,42) = 4.33, P < 0.05$). Follow-up Tukey HSD tests (for each task condition, separately) showed that for both identity- and location-matching, response time in the WS participants and CA controls was not significantly different. MA controls, however, were significantly slower to respond than both other groups during identity-matching ($P < 0.05$ for both comparisons). During location-matching, MA controls were significantly slower than only CA controls ($P < 0.001$; WS and MA groups were not different, $P > 0.1$). Thus, overall, compared with their performance outside of the scanner, WS took less time to respond (RTs comparable to CA controls) during the imaging session. However, for face identity-matching trials, this appeared to result in a speed versus accuracy trade-off (declining by 0.43 discriminability points).

FMRI. Results of task contrasts (face identity-matching versus location-matching) for each group are presented in Table 4.2. Considering the particular active

and control task conditions included in the current study (Figure 4.1), results from these contrasts are thought to represent activation that is unique to discriminating either facial identity or location, rather than to more general aspects of performing a visuo-perceptual discrimination task. In the remainder of this section, patterns of activation revealed by task contrasts (Table 4.2; face identity-matching versus location-matching) are described. This is followed by a more specific reporting of findings from key task-related regions in the ventral and dorsal streams (ventral occipito-temporal and parietal regions). These findings draw on patterns of activation observed for each task (identity-matching versus scrambled control, and location-matching versus scrambled control), as well as direct pairwise group contrasts for each task. In addition, results from specifically targeted region-of-interest (ROI) analyses of response magnitude are also reported (comparisons of percent signal change within regions of interest placed around peak foci within ventral occipito-temporal and parietal regions).

FMRI – task contrasts. Generally, both control groups displayed the expected ventral versus dorsal stream pattern of greater occipito-temporal lobe recruitment during identity-matching, and greater parietal lobe involvement during location-matching (Haxby, Horwitz et al. 1994; Courtney, Ungerleider et al. 1996). This pattern emerged in both CA and MA control groups, despite overall differences in the amount of activation observed (the CA group exhibited greater overall activation than the MA and WS groups). Brain regions displaying the most conspicuous identity-matching > location-matching differences in both the CA and MA control groups included the amygdala and the hippocampus. In contrast, the brain regions that showed the most

significant location-matching > identity-matching difference in the control groups were located in the superior parietal and intraparietal regions.

Unlike both CA and MA controls, WS participants did not show the expected ventral versus dorsal stream pattern of activation. Although WS participants exhibited greater identity- versus location-matching activation in a small region of the inferior temporal gyrus, unexpectedly, this pattern was also found in parietal cortex. In addition, during identity-matching (versus location-matching), WS participants did not recruit the amygdala and the hippocampal region, as did both control groups (Figure 4.2). No regions showed greater activation for location-matching (versus identity-matching) in the WS group.

FMRI - ventral occipito-temporal regions. In line with the critical role of ventral occipito-temporal cortex in processing objects and patterns, including faces, this area of the brain was heavily recruited by all three groups during face identity-matching (versus scrambled control) (Figure 4.3). However, as was the case in most brain regions, both WS participants and MA controls displayed somewhat lower levels of activation than CA controls.

To more specifically characterize activation within ventral occipito-temporal cortex, we focused on regions within this part of the brain that responded most robustly during facial identity discrimination. We placed a region of interest (ROI; sphere with radius = 4.5 mm) (Figure 4.4) around the most reliably activated voxel (across all participants, the voxel with the highest mean z-statistic representing the identity-matching versus control contrast) in the ventral stream. This region fell within the middle fusiform gyrus (right hemisphere [40, -57, -21], left hemisphere [-38, -54, -

21]), which is known to be critically involved in face processing (Puce, Allison et al. 1995; Haxby, Hoffman et al. 2000). The fusiform face area (FFA), usually found within the middle fusiform gyrus, has been of particular interest because it responds preferentially to faces over other classes of stimuli (e.g. objects, scenes, textures) (Kanwisher, McDermott et al. 1997). The FFA is typically defined according to functional responses, using data from a “localizer” task comparing activation to faces with other objects. Although we did not include a “localizer” task to enable the localization of a classically-defined FFA, prior reports of the location of this area suggest that our ROIs fell within the general vicinity of the FFA. Results from these two ROIs (one per hemisphere; Figure 4.4a) during the two task conditions revealed a similar pattern of results for CA and MA controls. In both control groups, a pattern emerged of significantly greater response amplitude during face identity-matching than location-matching (each task compared with the scrambled control). In addition, in line with the evidence of a right hemisphere (RH) bias in the FFA (Kanwisher, McDermott et al. 1997), there was a fairly consistent trend toward greater response amplitude in the right than the left hemisphere ROI for both CA and MA controls. Despite substantial activation in ventral temporal regions that appeared grossly similar to that seen in controls (Figure 4.3), this more fine-grain ROI analysis revealed an abnormal pattern of activation in WS. This involved, first, the absence of significantly more intense activation during identity-matching (versus location-matching). Second, a RH > LH trend was not observed in WS.

To examine how closely these two ROIs representing peak activation across all participants corresponded to peak activation in each individual group, we located local

identity-matching (versus scrambled control) peaks for each of the three participant groups. For both control groups the most reliably active voxel in the dominant RH ventral temporal region coincided with the voxel around which the ROI was centered (this voxel fell within the center of a large cluster of highly significant activation for both CA and MA controls). By contrast, the peak voxel in the WS group was located several slices more superior and posterior [40, -69, -12] (again, a large cluster of reliably active voxels fell around this central peak). This tendency for ventral occipitotemporal activation in WS to be shifted superiorly was noted throughout our fMRI analyses.

Given the anatomical abnormalities seen in WS, it is possible that this superior shift in activation could have been related to structural differences among the groups. To address this possibility we explored activation within group-specific ROIs (one per hemisphere, placed at the site of the most reliably active ventral occipitotemporal voxel for each individual group; see Figure 4.3). We reasoned that if the abnormal pattern of activation in WS were related to anatomical differences that caused the FFA in WS to be displaced, we would observe a more typical pattern within ROIs placed at the most active sites in the WS group. However, this was not the case (Figure 4.4b). Again, response magnitudes for location-matching were equivalent to those observed for identity-matching in the WS group only. In addition, although a nonsignificant RH > LH trend emerged for identity-matching, this pattern did not hold for location-matching. In fact, unlike controls, activation within the fusiform gyrus and surrounding cortex appeared to follow a LH > RH pattern for this task in WS.

The ROI analyses further revealed some interesting findings germane to our understanding of how functionality in face-sensitive brain regions evolves during typical development. For adults (CA group), the most reliably active focus in the fusiform gyrus occurred in the same location for both face identity-matching and location-matching, a finding that held bilaterally. This suggests that adults are reliant on the same fusiform region when viewing a face, regardless of the task they are performing (i.e. active face processing as in the identity-matching task, or more passive viewing as in the location-matching task). Thus, differences across task conditions arose not in location of activation, but instead in response magnitude, i.e., activation was of lesser intensity when the task required less active processing of the face stimulus (this is seen in the graphs of Figure 4.4, as lower percent signal change in the RH and LH ROIs during location-matching compared to face identity-matching). Similarly, typical children (MA group) showed less intense activation in the fusiform ROIs during passive versus active face processing. In addition, during active face processing, the most reliably activated RH and LH voxels in typical children were the same peak voxels observed in adults. However, during passive face processing, typical children diverged from adults, predominantly in the LH. The most reliably active focus was the same for adults and children in the RH (although, unlike adults for whom this voxel represented the center of a large cluster of reliably active, contiguous voxels in the RH, children showed more thinly distributed activation along the anterior to posterior extent of the fusiform gyrus). However, in the LH the most active voxel for children occurred at a more posterior site, falling in the occipital portion of the fusiform gyrus (with a large cluster of reliably active, contiguous voxels

extending laterally from this peak; Figure 4.5). In other words, for children, in the LH, the location of the most reliable fusiform activation differing depending on the particular type of face processing being performed.

Parietal regions. In line with prior studies in healthy adults showing prominent parietal cortex activation during spatial localization (Haxby, Horwitz et al. 1994), both control groups displayed reliable activation in inferior and superior parietal regions (Figure 4.6). This activation occurred during location-matching (versus scrambled control), to a greater extent than during identity-matching. In adult controls (CA group), this activation was largely bilateral, with a RH > LH pattern during location-matching. In the typically-developing children (MA group), this location-matching activation was only significant in the RH, and it did not reach statistical significance during identity-matching. Direct comparison of CA and MA controls revealed a small region of parietal cortex that was more active in CA than MA controls during identity-matching ([20, -72, 51]). More substantial differences (CA > MA) were noted for location-matching, particularly in bilateral superior parietal regions (differences in LH > RH).

Unlike the ventral occipito-temporal activation in WS participants, which partly resembled MA controls, posterior parietal cortex activation in WS followed an entirely abnormal pattern. Most strikingly, WS participants did not display significant parietal region activation during location-matching (Figure 4.6). Voxel-wise group contrasts revealed statistically significant differences between WS and CA controls throughout posterior parietal cortex. Although MA controls showed somewhat less reliable parietal activation (than CA controls) during location-matching, when directly

comparing the MA controls with WS participants significantly greater parietal activation in MA controls, particularly within the inferior and intraparietal region, was still evident. This lack of parietal activation during the location-matching task in WS is consistent with a prior report of parietal region hypoactivation during spatial position processing in this population (Meyer-Lindenberg, Kohn et al. 2004).

As previously mentioned, functional abnormalities in posterior parietal cortex in WS, particularly in the intraparietal region, are thought to be related to spatially coincident structural abnormalities. In light of this, a highly unexpected finding was the presence of significant parietal region activation during face identity-matching (but not location-matching) in the WS group. Two foci were significantly activated during identity-matching in WS. The more lateral focus (inferior parietal [28, -55, 46]) was present in the CA group. However, the more medial, posterior focus (superior parietal [14, -67, 45]) was not observed in either control group during identity-matching and was found to be significantly different in pairwise group contrasts (WS > MA and WS > CA; Figure 4.7). This more medial, posterior region, however, was recruited by both control groups during the location-matching condition (Figure 4.6).

To characterize more fully activation in parietal cortex across participant groups, we looked at response magnitude in the regions showing the greatest voxel-wise group x task interaction (Figure 4.6; RH superior parietal, LH superior parietal, RH inferior parietal) by placing ROIs (spheres with radius = 6.0 mm) around these local peaks. One-way ANOVAs of response magnitude within these regions showed a main effect of group for location-matching in all three ROIs (RH superior parietal [(F (2,45) = 28.5, $P < 0.001$); LH superior parietal [(F (2,45) = 10.6, $P < 0.001$); RH

inferior parietal [$F(2,45) = 14.7, P < 0.001$]. Follow-up Tukey HSD tests demonstrated significantly greater response magnitude for the CA group than for both the MA and WS groups (all $P < .005$) in all three ROIs. In the RH and LH superior parietal ROIs, the MA and WS groups were not significantly different ($P > .4$). However, in the RH inferior parietal region, MA controls showed significantly greater response magnitude than WS participants ($P < .05$). Analysis of peak regions for location-matching showed that the two bilateral superior parietal regions showing highly significant group x task interaction effects represented the two most reliably active regions for location-matching in CA controls. The most reliably active region for location-matching in MA controls also overlapped with the RH superior parietal locus. However, for the LH superior parietal region, activation for MA controls was less reliable and non-significant after correcting for multiple comparisons. The next most reliably active parietal loci for MA controls were all in the RH, i.e. in the precuneus [4, -57, 45] and the inferior parietal region [32, -45, 45]. Less reliable activation in LH parietal cortex has been reported in children (versus adults) during spatial working memory tasks; this activation has also been found to correlate with spatial working memory task performance in children (Klingberg, Forssberg et al. 2002; Nagel, Barlett et al. 2005). This was also the case for the current data, as response magnitude within the LH superior parietal ROI showed a significant correlation with location-matching performance (d' from the behavioral session) in MA controls ($r = .55, P < .05$), but not in CA controls or WS participants, suggesting that greater LH superior parietal recruitment is related to developmental gains in

location-matching performance. Activation in the RH superior and inferior parietal ROIs did not correlate with location-matching performance in any of the groups.

Discussion

Using fMRI, we investigated the neural correlates of the characteristic disparity seen in WS between strength in face discrimination abilities, in the context of deficient spatial cognition. Specifically, we employed a pair of complementary tasks tapping ventral and dorsal stream function, respectively, which were matched for key variables such as stimulus presentation, timing, and required response. The two-pathway model has frequently been invoked to explain the pattern of visuo-spatial/perceptual strengths and weakness in WS, as the weight of the evidence to date has strongly implicated a deficit in the dorsal pathway with relative sparing of the ventral pathway. By comparing a cognitively typical (mild-to-moderate mental retardation) group of WS participants to controls matched for chronological age (CA) and controls matched for approximate mental age (MA), the present study aimed to characterize the response of ventral and dorsal stream brain regions in a representative WS sample. Importantly, by including the MA group, differences in neural recruitment in the WS sample can be considered within the context of information regarding normal developmental change.

Results of this study revealed several differences between WS participants and both the MA and CA control groups that are suggestive of abnormalities in the functional organization of both dorsal and ventral cortical visual processing systems in this disorder. Furthermore, our analyses uncovered key findings pertinent to the

understanding of normal developmental change in brain regions underlying ventral and dorsal stream processes.

VENTRAL STREAM

As visual objects, faces place primary processing demands on inferior occipito-temporal regions of the ventral visual pathway, which mediate perception, discrimination, and recognition of visual objects and patterns (Haxby, Horwitz et al. 1994). Indeed, all participant groups showed reliable activation of these regions, particularly when the task required visual analysis and when attention was directed to the properties that are most critical to this process (i.e. during facial identity versus location discrimination).

Ventral stream – fusiform region. Within the ventral stream, the most reliably active region across participants fell within the middle fusiform gyrus, a region (particularly in the right hemisphere) consistently found to be highly responsive to faces (Kanwisher, McDermott et al. 1997). Although there is some variability within the extant WS neuroimaging literature (electrophysiological, as well as structural and functional MRI) regarding a sparing of the ventral stream, including the fusiform gyrus, previous fMRI studies in WS have not reported functional abnormalities in these structures (Meyer-Lindenberg, Kohn et al. 2004; Mobbs, Garrett et al. 2004; Meyer-Lindenberg, Hariri et al. 2005). Therefore, we predicted an essentially normal pattern of activation in these regions in WS, at least during face discrimination. Indeed, like the two control groups, we found that the fusiform gyrus and surrounding cortex was reliably recruited by the WS group, results which accord with prior studies (Meyer-Lindenberg, Kohn et al. 2004; Mobbs, Garrett et al. 2004). Evidence for

attentional modulation of the fusiform response to faces (Palermo and Rhodes 2007) has led others (Mobbs, Garrett et al. 2004) to speculate that increased interest and attention to social stimuli, such as faces, in WS, may facilitate normal levels of fusiform activation. Although the current study does not directly test this hypothesis, our results accord with such a formulation (see Section 3.1 below for a discussion of a potential parietal correlate).

Given the significance of the fusiform gyrus for face processing, we undertook a more in-depth examination of activation in this structure. ROIs placed within the most face-responsive fusiform region (likely corresponding to the FFA, bilaterally; defined according to activation across all participants) revealed evidence for differences between WS participants and controls that were not apparent in our initial analyses. Furthermore, this analysis uncovered differences between the two healthy control groups that have implications for our knowledge of the normal development of face processing.

Ventral stream – typical adult and child response profile within the fusiform gyrus. An examination of peak activation in the fusiform gyrus showed that typical adults recruited the same segment of the middle fusiform gyrus (bilaterally, RH > LH) for both face identity- and location-matching, with more active face processing (i.e. identity-matching) eliciting increased response magnitude within these areas. Typical children also relied most on these same loci when actively processing facial identity. The consistency with which these sites emerged as the most reliable face-responsive ventral stream regions in controls of all ages confirms the primacy of the middle fusiform gyrus in face processing, and suggests that this basic relationship develops

some time before the middle childhood years (the age of the MA controls). A recent fMRI study that employed an active face discrimination task (one-back discrimination) with children of this age range (7-11 years) also uncovered local peaks of activation within the middle fusiform gyrus (Golarai, Ghahremani et al. 2007).

Two other fMRI studies with school-age children, however, have not identified typical face-preferring loci within the temporal fusiform gyrus [ages 5-8 in (Gathers, Bhatt et al. 2004); ages 8-10 in (Aylward, Park et al. 2005)]. The pattern of results for the tasks included here, which differ in the level of facial analysis required (active discrimination in the identity-matching task versus more passive viewing in the location-matching task), suggests that this discrepancy might be related to differences in task requirements rather than to imaging methodology (e.g., use of spatial normalization of adults and children to a common template, a previously validated procedure - Burgund, Kang et al. 2002), as has been proposed by some (Golarai, Ghahremani et al. 2007). In contrast to the similarity in fusiform activation seen in children and adults during active face discrimination, passive viewing of faces yielded more divergent results. Like the adult group, the child group showed lower response amplitude within our fusiform regions of interest in both hemispheres during passive viewing. However, children also differed from the adult profile, particularly in the LH, in that the most reliably activated region occurred at a more posterior location (occipital, rather than temporal portion of the fusiform gyrus, extending into lateral aspects of inferior occipital cortex). In other words, depending on the task, children recruited different foci within the LH than adults who consistently engaged the same, more anterior locus regardless of how actively they processed the identity of the face

stimuli. This variability observed during passive face processing in children could explain the lack of fusiform activation observed in the two prior studies (Gathers, Bhatt et al. 2004; Aylward, Park et al. 2005), both of which utilized a passive viewing task that did not require individuation of the face stimuli during the imaging session. ERP studies have also demonstrated that certain face-sensitive components (e.g. P1 - Halit, de Haan et al. 2000) show greater changes with age for implicit versus explicit face processing tasks (Taylor, Batty et al. 2004). Our findings also raise the possibility that the middle fusiform region may be engaged less automatically by a face image during development, or that simple detection of a face may not always be sufficient to induce robust activation in this area in children.

The more adult-like consistency of peak activation in the fusiform gyrus of the RH in typically-developing children fits well with what is known about the development of face processing and its underlying neural substrate. The fusiform gyrus region of the RH appears to play a more central role in face processing, as seen for example in cases of acquired prosopagnosia from unilateral right-sided extrastriate cortical dysfunction (De Renzi, Perani et al. 1994), in the RH advantage for face processing commonly observed in hemi-field reaction times studies (Sergent and Bindra 1981; Rhodes 1993), or the frequent pattern of greater RH than LH ventral temporal response to faces in functional imaging studies (e.g., Sergent, Ohta et al. 1992; McCarthy, Puce et al. 1997; Rossion, Dricot et al. 2000). In addition, the RH bias for face processing appears to emerge very early in the course of development (de Schonen and Mathivet 1990). It follows, then, that the location of activation in the RH might appear more mature in the typical 8- to 9-year-old MA controls, and that these

children might begin to show signs of a RH > LH bias (Figure 4.3). However, the less consistent response in these children suggests that function in this region has not quite achieved the more localized status of the adult.

Our finding of peak activation in a more posterior, occipital LH locus for children is consistent with the emerging view from within the developmental literature of a relatively more distributed neural system for faces in children. For example, Gathers et al., (2004) observed a “developmental shift” in the ventral stream response to faces from posterior occipital regions in children to more anterior temporal regions in adolescents and adults (for a similar finding with magnetoencephalography see also Kylliainen, Braeutigam et al. 2006). In addition, developmental ERP studies of the face-sensitive N170 (Bentin, Allison et al. 1996) have shown that while a single N170 component appears in adults, children often exhibit two subcomponents of the N170 (merging during adolescence) that are thought to reflect distinct anatomical sources (Taylor, Batty et al. 2004). Two ERP components for faces have also been reported in infants, which are believed to be the precursors of the adult N170 (de Haan, Pascalis et al. 2002; Halit, de Haan et al. 2003). Collectively, these changes seem to parallel developmental improvements in the ability to differentiate objects that are highly similar to one another (such as faces - Gathers, Bhatt et al. 2004). Some have hypothesized that this gradual consolidation of activation with age, alongside steady improvements in behavioral proficiency, is related to changes in cognitive strategy with age, specifically, less reliance on featural or part processing, in favor of configural processing (Aylward, Park et al. 2005; Joseph, Gathers et al. 2006). Part-based processing is thought to be engaged during object perception, and may be more

selective to occipital regions that show heightened responsivity to objects over other stimuli (Lerner, Hendler et al. 2001). Consistent with our finding within the LH, previous neuroimaging studies of the response of lateral occipito-temporal regions to hierarchical stimuli (multiple small shapes or letters configured to form a large, global shape or letter) indicate that the LH shows a preference for local-level or part-based processing (Fink, Halligan et al. 1996; Martinez, Moses et al. 1997). Behavioral and electrophysiological studies with infants and children (Henderson, McCulloch et al. 2003), however, suggest that any functional or cognitive changes with development are more likely to entail a shift in the weighting of different strategies (Mondloch, Le Grand et al. 2002) or a general increase in efficiency of strategy use (Pedelty, Levine et al. 1985; Chung and Thomson 1995; Itier and Taylor 2004), rather than an absolute, qualitative change in which children begin with a piecemeal approach that is later abandoned in favor of a more configural one [(Carey and Diamond 1977) but see (Schwarzer 2000; Schwarzer 2002)].

Ventral stream – Williams Syndrome response profile within the fusiform gyrus. Despite grossly normal-appearing recruitment of ventral occipito-temporal cortex, more careful examination of the activation within these regions indicates that WS participants exhibited neither of the patterns described above for the control groups. Bilaterally, peak activation within the fusiform gyrus tended to occur at a different location in WS than in controls, particularly in the dominant RH (Figure 4.3). In addition, WS participants engaged face-responsive regions to the same degree for both tasks (no differences for active compared with passive face processing), and further, they failed to show consistent evidence of a RH > LH profile of laterality.

This same general pattern of results was found within the regions representing the most active fusiform loci across all participants, and within the loci in which as a group, WS participants showed peak activation.

Although the WS and typical child participants showed generally comparable face discrimination performance, the pattern of fusiform activation observed in participants with WS differed from that seen in the child controls. The most remarkable feature of the response in typical children was more distributed activation across tasks in the fusiform of the LH, possibly reflecting regional specialization that emerges in a more protracted fashion. Findings from the WS group imply that while these individuals tended to engage the same peak foci for both tasks, these foci were not located in the same place as controls. In addition, they were part of a large portion of cortex centered around the fusiform gyrus, which tended to be over-recruited in WS during passive face processing, the task for which controls showed lower levels of fusiform activation.

These findings are consistent with a less finely-tuned face processing system in WS. As previously noted in this population for other measures of brain response to visual objects (Grice, Haan et al. 2003), these findings are reminiscent of the decreased specialization of the brain response to faces seen in very young infants (de Haan, Pascalis et al. 2002; Johnson 2007), which changes rapidly within the first year of life (Halit, de Haan et al. 2003; Johnson, Griffin et al. 2005). Electrophysiological data from WS has also shown abnormal specialization of the brain response to faces, for example, decreased RH lateralization and a lack of response modulation according to changes in the stimulus (e.g., upright versus inverted faces, or faces versus cars -

Mills, Alvarez et al. 2000; Grice, Spratling et al. 2001; Karmiloff-Smith 2007). This is supported by evidence from behavioral studies suggesting that persons with WS use similar cognitive mechanisms with faces and other objects (Donnai and Karmiloff-Smith 2000), mechanisms that entail analysis of the features of a visual stimulus, rather than its configuration (Deruelle, Mancini et al. 1999; Karmiloff-Smith, Thomas et al. 2004). The relationship of structural abnormalities in the ventral stream (i.e. reduced grey matter volume in bilateral parahippocampal gyri - Reiss, Eckert et al. 2004) (decreased depth of the collateral sulcus - Kippenhan, Olsen et al. 2005; Van Essen, Dierker et al. 2006) to functional abnormalities in this region may be informative in elucidating factors that contribute to this unique behavioral profile.

It is important to note that from a qualitative standpoint, some of the features of the ventral stream response in WS participants did resemble typically-developing children. Specifically, while children did show a tendency toward greater RH fusiform activation during active face discrimination, like WS participants, they tended to show more bilateral activation during passive face viewing. Thus, it is possible that the other features of the WS profile that diverge from that seen in the 8- to 9-year-old group may be characteristic of children of a much younger age. In the future, it will be important to directly compare brain responses in WS to those of younger typically-developing children, in addition to investigating the responses of younger WS participants (Karmiloff-Smith, Thomas et al. 2004).

DORSAL STREAM

While data from the current study do provide evidence for abnormalities of ventral stream processing, it is important to consider these findings in context. That is,

the observed differences in WS were relatively subtle, and do not diverge dramatically from patterns of ventral stream activation in typical adults and children. Activation was present in the same general regions and with an overall intensity that falls within the range seen in controls. By contrast, the response of dorsal stream regions was markedly atypical in WS participants, even in very basic ways.

Dorsal stream – parietal response during spatial localization, normal development. Much of the limited knowledge that exists regarding the normal development of the neural correlates of spatial processing comes from studies using spatial working memory paradigms. Early studies of spatial working memory in school-age children have demonstrated that children and adults recruited largely similar brain regions, including dorsal regions of the pre-frontal cortex, as well as superior and inferior parietal cortex (Thomas, King et al. 1999; Nelson, Monk et al. 2000). However, it is difficult to determine if more subtle differences existed in these studies, as they did not directly compare task-related brain activation in children and adults. Subsequent studies of spatial working memory in children and adults have revealed increases in pre-frontal and parietal activation related to age and location memory performance (Klingberg, Forssberg et al. 2002; Kwon, Reiss et al. 2002; Schweinsburg, Nagel et al. 2005). We also found a positive relationship between location processing accuracy and response within the superior parietal cortex, a LH region that previous studies have reported greater activation associated with developmental improvements in spatial working memory (Klingberg, Forssberg et al. 2002; Nagel, Barlett et al. 2005) and increases in measures of fronto-parietal white matter (Olesen, Nagy et al. 2003). Klingberg and colleagues (Olesen, Nagy et al.

2003; Klingberg 2006) concluded that the lateralization of these findings reflects a fronto-parietal network for spatial working memory that matures later in the left hemisphere, in the same way that fronto-temporal white and grey matter show protracted periods of development in the left hemisphere (Paus, Zijdenbos et al. 1999; Sowell, Thompson et al. 2004). A similar finding by Kucian and colleagues (2006) of less LH intraparietal activation in children than adults (mirroring our findings, adults showed bilateral activation while children showed significant activation only in the RH) during a mental rotation task with no working memory component suggests that the delayed emergence of a reliable response in parietal cortex in the LH may also be related to developmental changes in spatial processing (independent of working memory).

Dorsal stream – parietal response during spatial localization, Williams Syndrome. Unlike the response of ventral stream regions during location-matching in WS, which was abnormally elevated, a complete lack of reliable activation was observed in parietal cortex in this group. Although this finding is limited in some respect by the low performance accuracy of these participants, there is nevertheless evidence that they were still engaged in the task, but simply had great difficulty performing it. Specifically, the robust ventral occipito-temporal activation observed during location-matching, which was of similar intensity to that seen during face identity-matching, implying that these participants were indeed processing the stimuli. Moreover, upon scrutiny of the responses of the WS participants during image acquisition, it did not appear that they were doing something dramatically different, such as defaulting to a face identity-matching strategy, which they were more

proficient in (i.e., they did not show an overwhelming ‘no’ response bias since the identity of the faces in the location-matching trials never matched). Rather, the behavioral data is suggestive of participants’ attempts to complete a location-matching task that was exceptionally challenging for them. In addition, the observed lack of parietal response is highly consistent with fMRI results from a similar position-matching task (Meyer-Lindenberg, Kohn et al. 2004), and complements nicely a growing number of structural imaging studies showing anatomical abnormalities in this region (Schmitt, Watts et al. 2002; Reiss, Eckert et al. 2004; Eckert, Hu et al. 2005; Kippenhan, Olsen et al. 2005; Thompson, Lee et al. 2005; Boddaert, Mochel et al. 2006; Gaser, Luders et al. 2006; Van Essen, Dierker et al. 2006).

The additional finding of over-recruitment in the ventral stream resembles the pattern of compensatory activation seen in elderly adults performing a similar location-matching task (Grady, Maisog et al. 1994). For WS, this activation may represent an attempt to engage relatively more intact regions while performing a task for which the most functionally essential regions (i.e. parietal cortex) are compromised. Taken together, these findings provide a convincing neuroanatomical and neurophysiological underpinning of the significant deficits in spatial cognitive skills characteristic of WS.

Dorsal stream – parietal response during facial identity processing. Perhaps the most unexpected finding of the current study was the presence of significant dorsal stream activation in the WS group during face identity-matching. Whereas the absent parietal response to spatial tasks in WS appears to indicate an effectively non- or minimally functional area, this finding suggests that impairment of this region may

manifest in a more complex way than initially thought. The engagement of a parietal region not observed in either control group during the same task suggests that at least this section of cortex may be functional, but incorporated in an unusual way into the brain system for face perception in WS. Unfortunately, activity in parietal regions is not typically discussed when face processing tasks do not vary gaze direction, since the most well-accepted role for this region in face processing is in mediating spatial attention shifts in response to averted gaze (Haxby, Hoffman et al. 2000; George, Driver et al. 2001). Using positron emission tomography (PET), Tzourio-Mazoyer et al., (2002) observed heightened parietal recruitment in a small sample of newborns during face processing, although it is difficult to discern from this study whether this corresponds to the region we found to be different in WS. Nonetheless, this does raise the possibility that the parietal activation seen in our WS participants is indicative of a profoundly immature dorsal stream system, with the activation representing something of a developmental remnant that is normally eliminated as the brain systems supporting face processing become more specialized with age.

Certain behavioral features of WS, however, support an alternative account for this curious finding. As previously discussed, it has been hypothesized that increased social interest and attention to faces in WS may facilitate face discrimination performance and normal levels of fusiform activation (Mobbs, Garrett et al. 2004). However, the neural instantiation of this conceptualization remains unspecified. The region of parietal cortex engaged by the WS group is indeed one of several parietal loci involved in attention, specifically for visuospatial information (Kastner and Ungerleider 2000; Corbetta and Shulman 2002). Although neither control group

recruited this region during face identity-matching, both control groups did show significant activation at this locus during the location-matching task, which places a greater burden on spatial attention by requiring that distinct locations on the screen be explicitly compared. Recent work has shown that this particular parietal region (Figure 4.7) plays an integral role when visual attention is distributed across the visual field (Natale, Marzi et al. 2006; Sturm, Schmenk et al. 2006), as might be the case in our tasks, in that face stimuli are presented unpredictably at 12 possible positions across the visual field. This added spatial attention demand may be more significant for persons with WS, leading to the engagement of this region in order to effectively perform the basic discrimination task with visual stimuli that, for them, are particularly salient and attention-capturing.

OTHER REGIONS

Amygdala. Although the amygdala is a subcortical structure and hence is not typically included within the ventral visual stream, its anatomical and functional connections with ventral occipital-temporal cortex (Amaral and Price 1984) highlight the importance of the finding (as previously reported - Paul, Snyder et al. in preparation) of a failure to recruit this structure during facial identity processing in WS. The amygdala's role in face perception, particularly of emotionally salient stimuli, has been well-documented (Breiter, Etcoff et al. 1996; Morris, Frith et al. 1996). In addition, the amygdala is thought to process other aspects of a face stimulus that are important for social interaction, such as gaze direction (Kawashima, Sugiura et al. 1999). As seen in the current study, the amygdala also responds to faces that are unfamiliar to the viewer (Gobbini, Leibenluft et al. 2004) but lack overt emotional

content (i.e. neutral expression faces - Kesler/West, Andersen et al. 2001; Fitzgerald, Angstadt et al. 2006; Wright and Liu 2006) or other explicit social cues. This suggests a more general role for the amygdala in responding to the social value or meaning of faces (Haxby, Hoffman et al. 2002; Leibenluft, Gobbini et al. 2004; Adolphs and Spezio 2006).

The difference between WS participants and controls in amygdala response to faces was especially striking because even typically-developing children showed significant activation of this structure, which did not differ from healthy adults. Although one study has shown hypoactivity of this structure to fearful faces in WS (Meyer-Lindenberg, Hariri et al. 2005), another study of face and gaze processing (Mobbs, Garrett et al. 2004) failed to observe differences between WS and chronological age-matched controls in amygdalar activation, although it appeared that neither group evidenced significant activation in this region. Given the amygdala's sensitivity to information communicated by the eyes (Kawashima, Sugiura et al. 1999; Morris, deBonis et al. 2002), it is possible that explicitly directing attention to this feature (as in Mobbs, Garrett et al. 2004) elicits more robust amygdala activation, and thus diminishes WS versus control differences. However, this has yet to be studied directly in WS. Further, the WS propensity to seek eye contact and face-to-face interaction (Laing, Butterworth et al. 2002; Mervis, Morris et al. 2003), and a finding of amygdala hyper-reactivity to non-face stimuli (i.e. threatening scenes) (Meyer-Lindenberg, Hariri et al. 2005), suggests that a failure to direct attention to the eyes in WS (e.g., as has been hypothesized for fusiform hypoactivation in autism - Dalton, Nacewicz et al. 2005) is unlikely to provide a sufficient explanation for this finding.

RELATIONSHIP OF RESULTS TO WS PARTICIPANT CHARACTERISTICS

Variability in the WS population. Although this is the first study to systematically examine dorsal *and* ventral stream activation in a typically defined group of individuals with WS, one previous study used a similar pair of tasks with WS participants of normal-range IQ (Meyer-Lindenberg, Kohn et al. 2004). Like the WS individuals in our study who possessed a mild level of mental retardation (typical for WS), the participants in the Meyer-Lindenberg et al. (2004) study showed a striking lack of parietal activation during a spatial position-matching task. However, these authors did not report abnormalities in ventral stream activation during object identity-matching (houses and faces), nor did they report any indication of anomalous parietal recruitment in this condition. Since behavioral data for these tasks was not reported, it is not possible to determine whether performance-related differences could account for these discrepancies. However, the most obvious difference in the two samples lies in their level of intellectual functioning, raising the possibility that affected individuals possessing the modal cognitive profile for the disorder (i.e. mild mental retardation with relatively strong face discrimination skills but poor spatial abilities) are more likely to evince functional abnormalities in the neural systems underlying even well-performed skills (i.e. face discrimination).

Overall levels of activation across groups. Although WS participants and typically-developing 8- to 9-year-old children (MA controls) appeared similar in the overall intensity and extent of activation for the two task conditions, this level of activation was in most cases lower than that observed in healthy adult participants (CA controls). The source of this difference between CA controls and the two other groups,

while relevant to the interpretation of the data, is not readily apparent. It is possible that the brain systems subserving facial identity perception and spatial localization share a commonly protracted course of normal development, with activation for face identity-matching and location-matching reaching adult levels some time after 8-9 years of age (the age of the MA controls), but in WS never progressing beyond this point. However, processing of the baseline task condition (motor response after presentation of scrambled images) is also an important consideration. Because it is potentially more engaging than a passive baseline state (e.g., visual fixation), it may be processed less automatically by typically-developing children or persons with WS. This may lead to levels of activation that appear broadly similar across these two groups, but different from the level of activation in a group of adults for whom processing of the baseline condition is performed more automatically. Although this issue may be less likely to impact comparisons between the WS and MA groups, it is nonetheless a factor deserving consideration in future fMRI studies of both typically-developing children and individuals with WS.

Acknowledgements

This research was supported in part by NIH Program Project HD33113 and a McDonnell Foundation Award to UB, NIH grant NS06833 (MER, AZS), NIH grant P50-NS22343 (JS), and an NIH Kirschstein Research Fellowship Award to BMP. The authors wish to thank Janet Shin for technical assistance with this work, as well as Eric Fine and Yvonne Searcy for helpful comments.

Table 4.1 Behavioral results.

Group	Task Condition	Accuracy ($d' \pm SD$)	Response Time (ms \pm SD)
CA controls	Identity-matching	3.22 \pm 0.36	1026.2 \pm 208
($n = 17$)	Location-matching	2.61 \pm 0.47	963.5 \pm 148
MA controls	Identity-matching	2.29 \pm 0.72	1526.4 \pm 322
($n = 16$)	Location-matching	2.17 \pm 0.60	1468.4 \pm 305
WS	Identity-matching	1.71 \pm 0.95	1626.3 \pm 278
($n = 15$)	Location-matching	0.46 \pm 0.56	1694.2 \pm 305

Table 4.2 Activation for Identity-Matching > Location-Matching and Location-Matching > Identity-Matching contrasts in each group. Coordinates listed, according to the Talairach and Tournoux (1988) atlas, correspond to foci of maximum task difference. Brain regions spanned within each cluster are included.

Identity-matching > Location-matching		Talairach Coordinates			*z-value	Location-matching > Identity-matching		Talairach Coordinates			
Region		X	Y	Z		Region		X	Y	Z	*z-value
CA controls					CA controls						
R Cerebellum, Fusiform Gyrus		40.5	-60	-24	2.67	R Mid Occipital Gyrus		31.5	-81	33	2.57
L Cerebellum, Fusiform Gyrus / BA 37		-37.5	-51	-21	3.40	R Cingulate		13.5	-36	33	2.09
R Cerebellum, Fusiform Gyrus		34.5	-45	-21	3.28	R Precentral Gyrus		52.5	6	36	1.97
L Cerebellum		-7.5	-48	-18	1.59	Sup Frontal Sulcus / BA 6		25.5	-9	51	2.68
L Inf Occipital Gyrus / BA 17		-25.5	-99	-15	2.79	R Sup Parietal, Precuneus / BA 7		10.5	-69	57	4.07
L Inf Occipital Gyrus / Fusiform Gyrus		-40.5	-78	-15	2.57	R Inf Parietal / BA 40		37.5	-42	42	2.86
L Amygdala, Hippocampus		-19.5	-9	-15	2.13	L Sup Parietal, Precuneus / BA7		-16	-76	48	3.08
L Hippocampus		-22.5	-19	-12	2.24						
R Amygdala, Hippocampus		19.5	-12	-12	2.35						
R Inf Occipital Gyrus / BA 17, 18		34.5	-93	-9	2.55						
L Mid Temporal Gyrus		-46.5	-33	-6	1.86						
R Inf Frontal Gyrus (pars orbitalis)		46.5	21	-3	1.73						
R Lingual Gyrus, Cuneus / BA 17,18		-1.5	-78	6	2.55						
L Inf, Mid Frontal Gyrus		-40.5	3	27	2.01						
R Inf, Mid Frontal Gyrus		49.5	24	30	2.46						
Sup Frontal Sulcus, SMA		1.5	9	66	2.05						
MA controls					MA controls						
L Hippocampus		-19.5	-21	-15	1.80	L Mid Occipital Gyrus / BA 17		-31.5	-90	12	1.77
R Mid Temporal Gyrus / BA 21		61.5	-12	-12	2.14	R Inf Parietal Lobule		40.5	-39	42	1.49
R Amygdala, Hippocampus		19.5	-9	-12	2.12	R Sup Parietal, Precuneus / BA 7		16.5	-72	48	2.68
R Hippocampus / Parahippocampal Gyrus		19.5	-27	-12	1.65	L Sup Frontal Gyrus, Sulcus		-13.5	-63	57	2.02
R Calcarine Sulcus		4.5	-75	9	2.22	L Sup Parietal, Precuneus / BA 7		-25.5	-6	63	2.06
WS participants					WS participants						
Sup Temporal Sulcus, Mid Temporal Gyrus		43.5	-57	9	1.91	None					
Intraparietal Sulcus		28.5	-54	42	1.57						
Fusiform Gyrus		37.5	-63	-9	1.81						

*z-value corresponding to task difference

L = Left, R = Right, Inf = Inferior, Sup = Superior, Mid = Middle

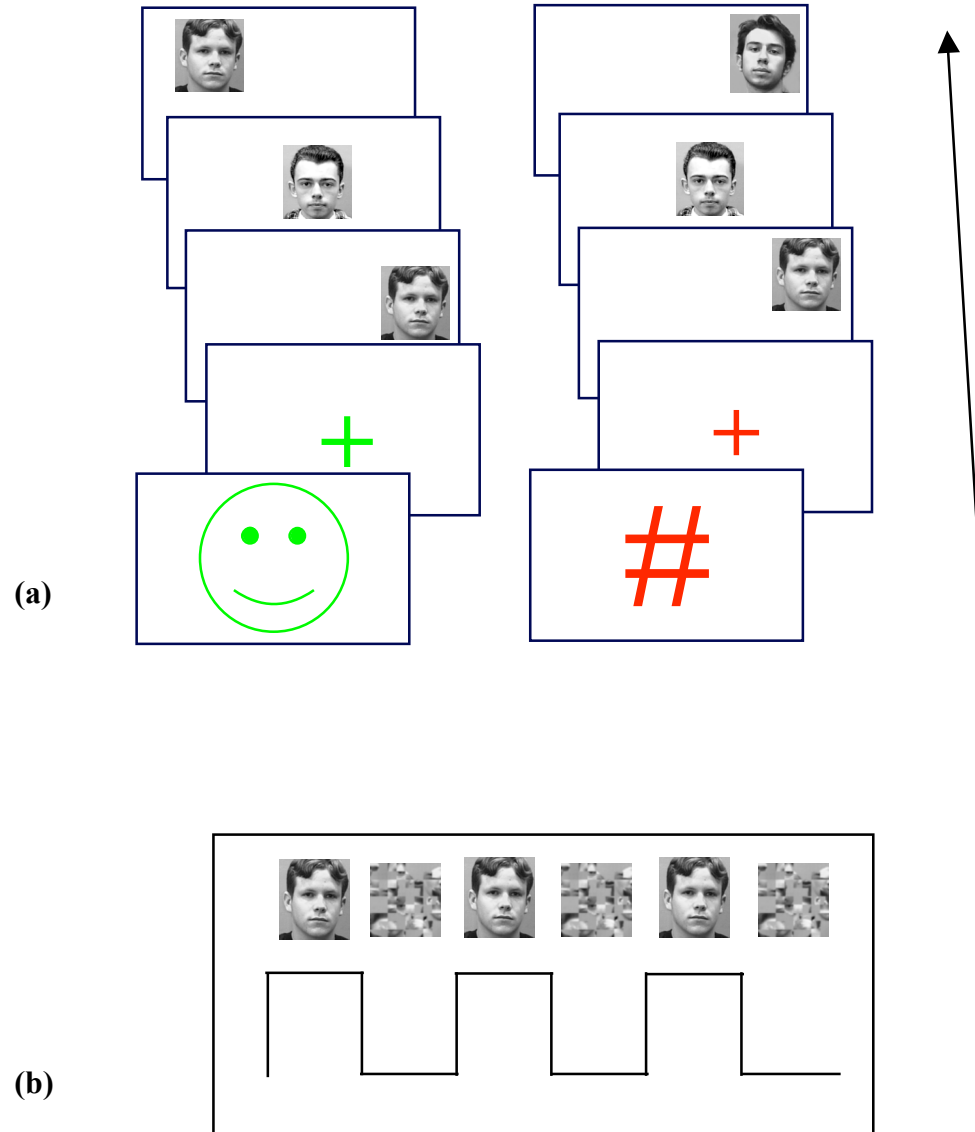


Figure 4.1 Task. (a) Trials were presented in blocks of six with each block preceded by a warning cue. Participants indicated whether the third (test) stimulus matched either of the two reference stimuli. Matching was based on stimulus identity in the face identity-matching task (left) or on the position of the stimulus on the screen in the location-matching task (right). (b) Each 4 minute, 50 second fMRI scanning run consisted of six 47.5 sec blocks (5 trials) of task and control trials, in an interleaved fashion. Control trials followed the same presentation sequence as task trials; participants were instructed to simply wait for the third scrambled image and press the mouse button. Control trial blocks were also preceded by a distinct cue (an image of a black handprint, not shown), in order to warn participants as to which trial type would be shown in the upcoming task block.

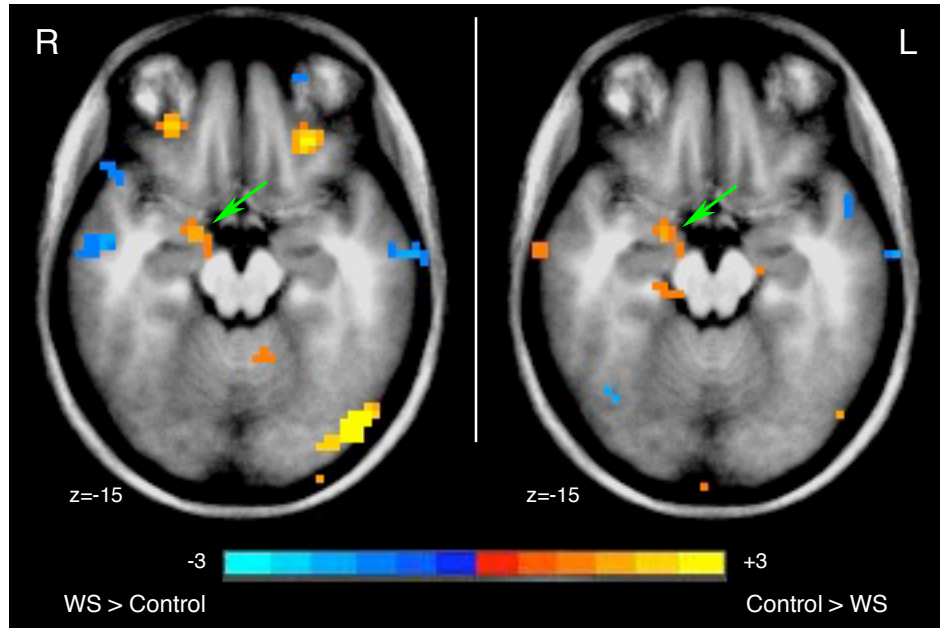


Figure 4.2 Amygdala deficit in WS. In a prior study (Paul, Stiles et al. 2002; Paul, Snyder et al. in preparation) of face identity-matching in WS that included many of the same study participants, we reported an absence of amygdala activation in WS participants. The same analyses (see Paul, Snyder et al. in preparation) with the current participant groups confirmed this finding, as both control groups evidenced significantly greater activation of the amygdala during facial identity processing than the WS group (arrows), which showed no significant amygdala activation. Shown are pairwise group Z-score contrast images for the identity-matching task, corrected for multiple comparisons at $P < .05$. Data are displayed in radiological convention (right is on left). Left = CA controls vs. WS, right = MA controls vs. WS

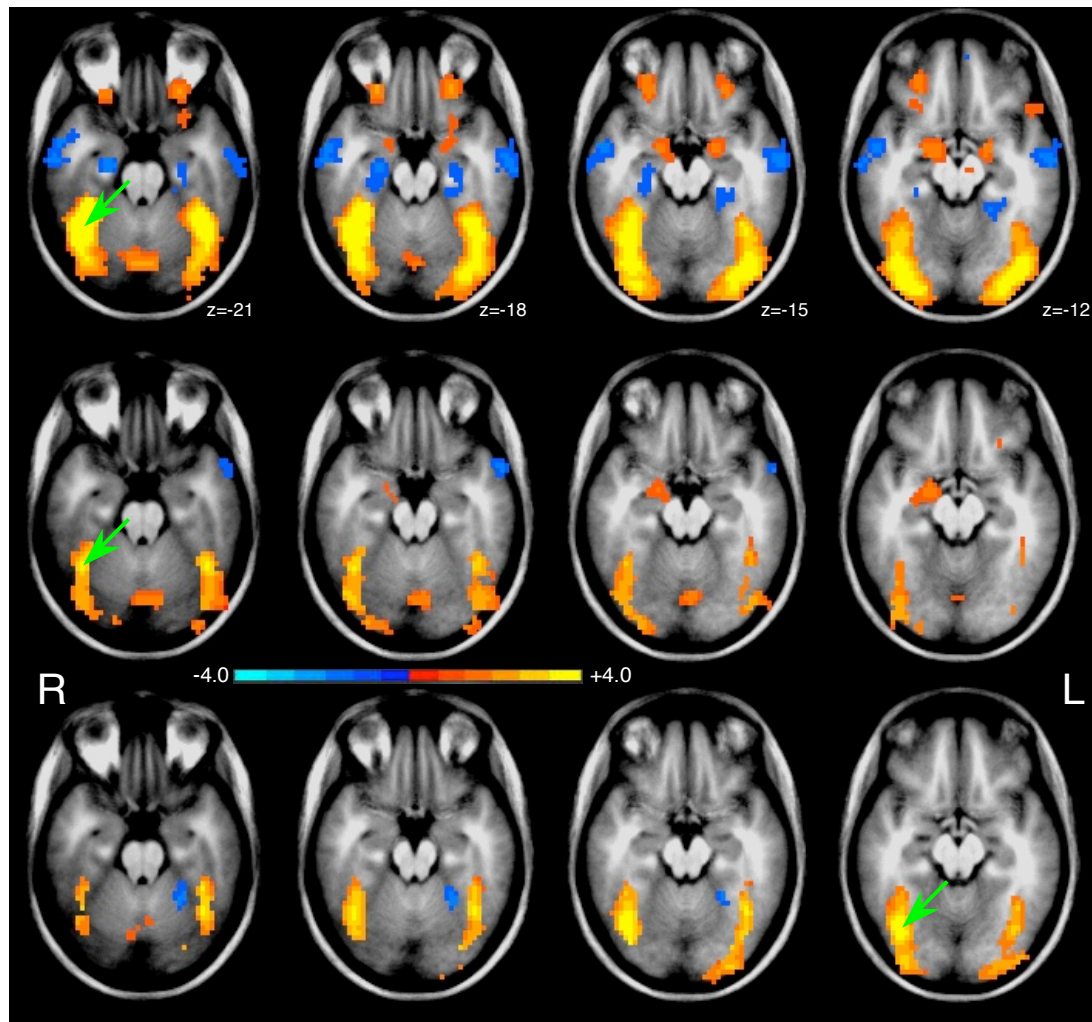


Figure 4.3 Face identity-matching activation in ventral occipito-temporal cortex. Mean Z-score images depicting active voxels ($P < 0.05$, corrected) in chronological age-matched (CA) controls (top), mental age-matched (MA) controls (middle) and WS (bottom). Data are displayed in radiological convention (right is on left). Green arrows denote loci of peak activation for each group. Results from region-of-interest (ROI) analyses at these loci are presented in Figure 4.4 (panel b).

Figure 4.4 Ventral occipito-temporal region of interest (ROI) analyses, face identity-matching. (a) Mean activation intensity within a spherical region-of-interest (ROI) (radius = 4.5 mm) in the fusiform gyrus region (defined based on all participants) of the right (RH) and left (LH) hemispheres. CA and MA controls show a main effect of task (identity-matching > location-matching, both $P < .001$) but WS do not ($P = .28$; trend is in opposite direction, location-matching > identity-matching); a RH > LH pattern (i.e. main effect of hemisphere) is apparent (but non-significant) in controls (CA, $P = .06$; MA, $P = .27$) but not WS ($P = .74$). (b) Mean activation intensity within spherical ROI (radius = 4.5 mm) in the most reliably face-active ventral occipitotemporal regions of the RH and LH, defined separately for each participant group (see Figure 4.3). Again, CA and MA controls still show main effect of task (identity-matching > location-matching, both $P < .001$) but WS do not ($P = .78$). Again, a RH > LH pattern (i.e. main effect of hemisphere) is apparent (but non-significant) in controls (CA, $P = .06$; MA, $P = .33$) but not WS ($P = .98$).

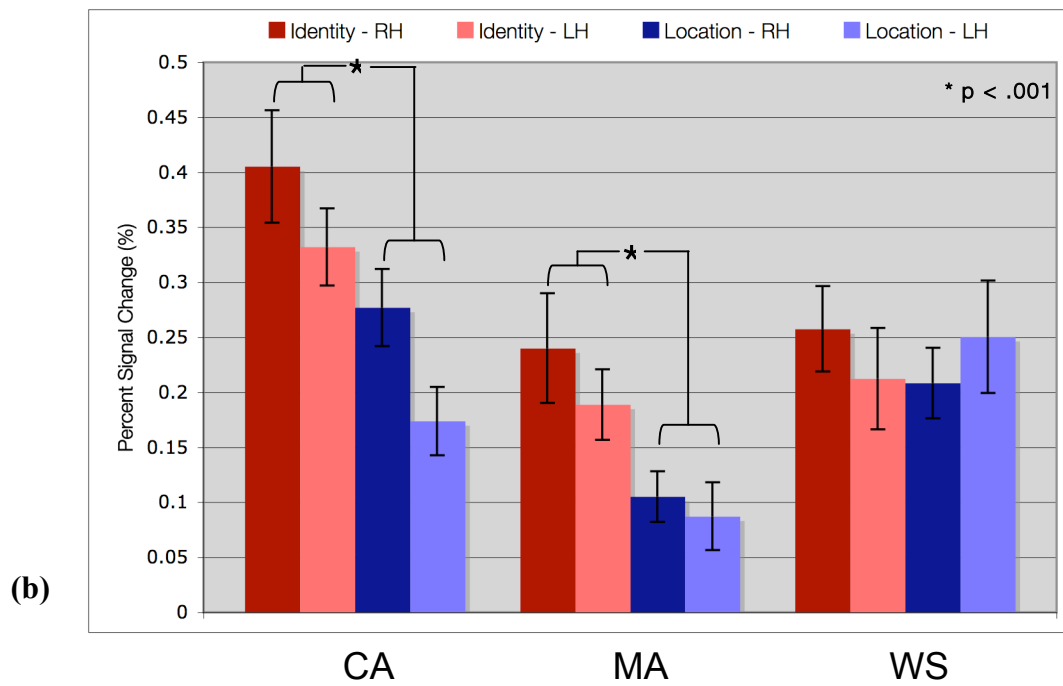
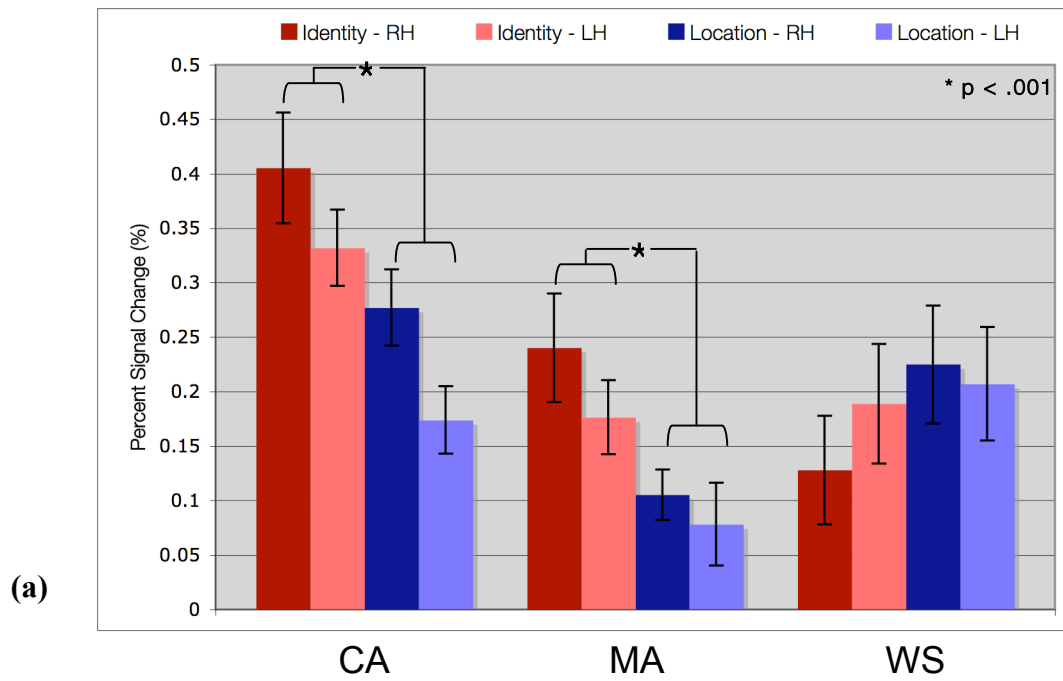




Figure 4.5 Ventral occipito-temporal activation in typical children during location-matching (passive face viewing). Mean Z-score image ($P < 0.05$, corrected) for the MA group showing the region of most reliable activation in the left hemisphere (LH). Even though children engage the same anterior/middle fusiform gyrus regions (in the right and left hemispheres) as adults during active face discrimination (i.e. identity-matching), during passive face viewing (location-matching) peak activation is shifted posteriorly in the LH. Data are displayed in radiological convention (right is on left).

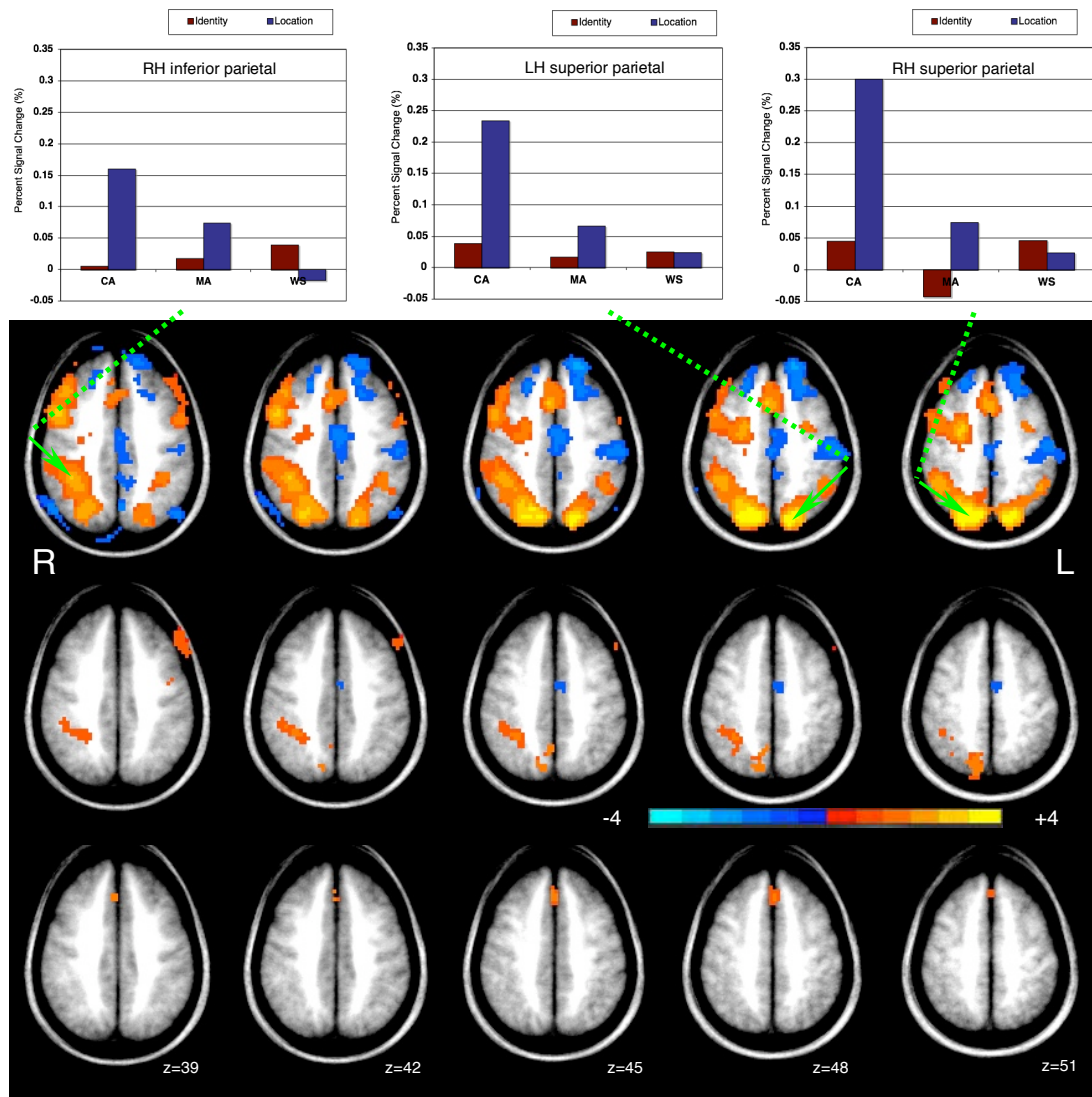


Figure 4.6 Parietal region of interest (ROI) analyses, location-matching. Mean Z-score images ($P < 0.05$, corrected) for the three participant groups are displayed (top = CA controls, middle = MA controls, bottom = WS). Voxels with the greatest group x task interaction (RH superior parietal [20, -69, 51], LH superior parietal [-14, -75, 48], RH inferior parietal [38, -42, 39]) served as peak foci for ROIs (spheres with radius = 6.0 mm). Results (see text) from the location-matching task revealed greater response magnitude for CA controls than both MA controls and WS in all three ROIs. MA controls showed greater response magnitude than WS in RH inferior parietal ROI.

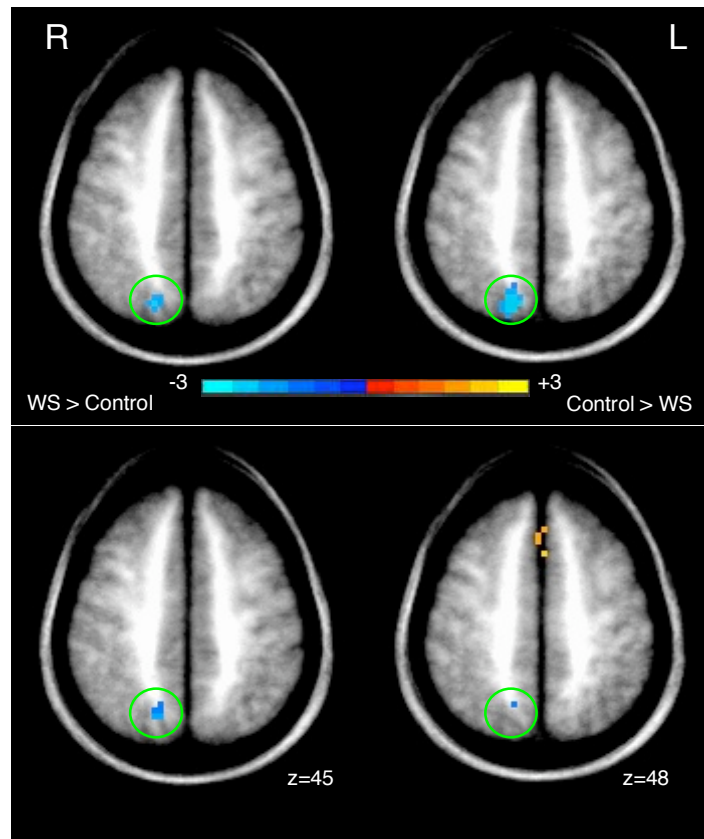


Figure 4.7 Anomalous parietal activation in WS. Pairwise group Z-score contrast images for the identity-matching task, showing regions of significantly greater activation in WS than controls. This region was recruited by controls during location-matching (Figure 4.5) but not during the identity-matching task. Data are displayed in radiological convention (right is on left). Images corrected for multiple comparisons at $P < .05$. Bottom = CA controls vs. WS; Top = MA controls vs. WS

References

- Adolphs, R. and M. Spezio (2006). "Chapter 20 Role of the amygdala in processing visual social stimuli." Prog Brain Res **156**: 363-78.
- Aguirre, G. K. and M. D'Esposito (1997). "Environmental knowledge is subserved by separable dorsal/ventral neural areas." Journal of Neuroscience **17**(7): 2512-2518.
- Allison, T., H. Ginter, et al. (1994). "Face recognition in human extrastriate cortex." Journal of Neurophysiology **71**(2): 821-5.
- Amaral, D. G. and J. L. Price (1984). "Amygdalo-cortical projections in the monkey (*Macaca fascicularis*)." J Comp Neurol **230**(4): 465-96.
- Arnold, R., W. Yule, et al. (1985). "The psychological characteristics of infantile hypercalcaemia: a preliminary investigation." Dev Med Child Neurol **27**(1): 49-59.
- Atkinson, J., S. Anker, et al. (2001). "Visual and visuospatial development in young children with Williams syndrome." Dev Med Child Neurol **43**(5): 330-7.
- Atkinson, J., O. Braddick, et al. (2003). "Neurobiological models of visuospatial cognition in children with Williams syndrome: Measures of dorsal-stream and frontal function." Developmental Neuropsychology. Special Issue: Williams syndrome **23**(1-2): 139-172.
- Atkinson, J., O. Braddick, et al. (2006). "Dorsal-stream motion processing deficits persist into adulthood in Williams syndrome." Neuropsychologia **44**(5): 828-33.
- Atkinson, J., J. King, et al. (1997). "A specific deficit of dorsal stream function in Williams' syndrome." Neuroreport **8**(8): 1919-22.
- Aylward, E. H., J. E. Park, et al. (2005). "Brain activation during face perception: evidence of a developmental change." J Cogn Neurosci **17**(2): 308-19.
- Beery, K. E. (1997). The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI). Parsippany, NJ, Modern Curriculum Press.
- Bellugi, U., A. Bihrlle, et al. (1990). "Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome." Am J Med Genet Suppl **6**: 115-25.

- Bellugi, U., L. Lichtenberger, et al. (2000). "I. The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses." J Cogn Neurosci **12 Suppl 1**: 7-29.
- Bellugi, U., L. Lichtenberger, et al. (1999). "Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome." Trends Neurosci **22(5)**: 197-207.
- Bellugi, U., H. Sabo, et al. (1988). Spatial deficits in children with Williams Syndrome. Spatial cognition: Brain bases and development. E. Mark Kritchvsky and et al., Hillsdale, NJ, USA: 273-298.
- Bellugi, U. and M. St. George, Eds. (2001). Journey from cognition to brain to gene: Perspectives from Williams syndrome. Cambridge, MA, The MIT Press.
- Bellugi, U., P. P. Wang, et al. (1994). Williams syndrome: An unusual neuropsychological profile. Atypical cognitive deficits in developmental disorders: Implications for brain function. S. H. Broman and J. Grafman. Hillsdale, NJ, England, Lawrence Erlbaum Associates, Inc: 23-56.
- Bennett, F. C., B. LaVeck, et al. (1978). "The williams elfin facies syndrome: the psychological profile as an aid in syndrome identification." Pediatrics **61(2)**: 303-6.
- Bentin, S., T. Allison, et al. (1996). "Electrophysiological studies of face perception in humans." Journal of Cognitive Neuroscience **8(6)**: 551-565.
- Benton, A. L., K. d. Hamsher, et al. (1983). Contributions to neuropsychological assessment: A clinical manual. New York, Oxford University Press.
- Bertrand, J., C. B. Mervis, et al. (1997). "Drawing by children with Williams syndrome: A developmental perspective." Developmental Neuropsychology **13(1)**: 41-67.
- Boddaert, N., F. Mochel, et al. (2006). "Parieto-occipital grey matter abnormalities in children with Williams syndrome." Neuroimage **30(3)**: 721-5.
- Braddick, O., J. Atkinson, et al. (2003). "Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'." Neuropsychologia **41(13)**: 1769-84.
- Breiter, H. C., N. L. Etcoff, et al. (1996). "Response and habituation of the human amygdala during visual processing of facial expression." Neuron **17(5)**: 875-87.

- Brock, J. (2007). "Language abilities in Williams syndrome: a critical review." Dev Psychopathol **19**(1): 97-127.
- Buckner, R. L., D. Head, et al. (2004). "A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume." Neuroimage **23**(2): 724-38.
- Burgund, E. D., H. C. Kang, et al. (2002). "The feasibility of a common stereotactic space for children and adults in fMRI studies of development." Neuroimage **17**(1): 184-200.
- Carey, S. and R. Diamond (1977). "From piecemeal to configurational representation of faces." Science **195**(4275): 312-314.
- Chung, M.-S. and D. M. Thomson (1995). "Development of face recognition." British Journal of Psychology **86**(1): 55-87.
- Coch, D., W. Skendzel, et al. (2005). "Motion and color processing in school-age children and adults: an ERP study." Dev Sci **8**(4): 372-86.
- Cohen, M. S. (1997). "Parametric analysis of fMRI data using linear systems methods." Neuroimage **6**(2): 93-103.
- Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nat Rev Neurosci **3**(3): 201-15.
- Courtney, S. M., L. G. Ungerleider, et al. (1996). "Object and spatial visual working memory activate separate neural systems in human cortex." Cerebral Cortex **6**(1): 39-49.
- Cox, R. W. (1996). "AFNI: software for analysis and visualization of functional magnetic resonance neuroimages." Computers and Biomedical Research **29**(3): 162-73.
- Crisco, J. J., J. M. Dobbs, et al. (1988). "Cognitive processing of children with Williams syndrome." Dev Med Child Neurol **30**(5): 650-6.
- Dalton, K. M., B. M. Nacewicz, et al. (2005). "Gaze fixation and the neural circuitry of face processing in autism." Nat Neurosci **8**(4): 519-26.
- de Haan, M., O. Pascalis, et al. (2002). "Specialization of neural mechanisms underlying face recognition in human infants." Journal of Cognitive Neuroscience **14**(2): 199-209.

- De Renzi, E., D. Perani, et al. (1994). "Prosopagnosia can be associated with damage confined to the right hemisphere: An MRI and PET study and a review of the literature." Neuropsychologia **32**(8): 893-902.
- de Schonen, S. and E. Mathivet (1990). "Hemispheric asymmetry in a face discrimination task in infants." Child Development **61**(4): 1192-1205.
- Deruelle, C., J. Mancini, et al. (1999). "Configural and local processing of faces in children with Williams syndrome." Brain Cogn **41**(3): 276-98.
- Dilts, C. V., C. A. Morris, et al. (1990). "Hypothesis for development of a behavioral phenotype in Williams syndrome." Am J Med Genet Suppl **6**: 126-31.
- Donnai, D. and A. Karmiloff-Smith (2000). "Williams syndrome: from genotype through to the cognitive phenotype." American Journal of Medical Genetics **97**(2): 164-71.
- Eckert, M. A., D. Hu, et al. (2005). "Evidence for superior parietal impairment in Williams syndrome." Neurology **64**(1): 152-3.
- Eckert, M. A., A. Tenforde, et al. (2006). "To modulate or not to modulate: differing results in uniquely shaped Williams syndrome brains." Neuroimage **32**(3): 1001-7.
- Ewart, A. K., C. A. Morris, et al. (1993). "Hemizyosity at the elastin locus in a developmental disorder, Williams syndrome." Nat Genet **5**(1): 11-6.
- Fink, G. R., P. W. Halligan, et al. (1996). "Where in the brain does visual attention select the forest and the trees?" Nature **382**(6592).
- Fitzgerald, D. A., M. Angstadt, et al. (2006). "Beyond threat: amygdala reactivity across multiple expressions of facial affect." Neuroimage **30**(4): 1441-8.
- Forman, S. D., J. D. Cohen, et al. (1995). "Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold." Magnetic Resonance in Medicine **33**(5): 636-47.
- Frangiskakis, J. M., A. K. Ewart, et al. (1996). "LIM-kinase1 hemizyosity implicated in impaired visuospatial constructive cognition." Cell **86**(1): 59-69.
- Galaburda, A. M. and U. Bellugi (2000). "V. Multi-level analysis of cortical neuroanatomy in Williams syndrome." J Cogn Neurosci **12 Suppl 1**: 74-88.
- Galaburda, A. M., J. E. Schmitt, et al. (2001). "Dorsal forebrain anomaly in Williams syndrome." Archives of Neurology **58**(11): 1865-1869.

- Gaser, C., E. Luders, et al. (2006). "Increased local gyrification mapped in Williams syndrome." Neuroimage **33**(1): 46-54.
- Gathers, A. D., R. Bhatt, et al. (2004). "Developmental shifts in cortical loci for face and object recognition." Neuroreport **15**(10): 1549-53.
- George, N., J. Driver, et al. (2001). "Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing." Neuroimage **13**(6 Pt 1): 1102-12.
- Gobbini, M. I., E. Leibenluft, et al. (2004). "Social and emotional attachment in the neural representation of faces." Neuroimage **22**(4): 1628-35.
- Golarai, G., D. G. Ghahremani, et al. (2007). "Differential development of high-level visual cortex correlates with category-specific recognition memory." Nat Neurosci **10**(4): 512-22.
- Goodale, M. A. and A. D. Milner (1992). "Separate visual pathways for perception and action." Trends in Neurosciences **15**(1, 163): 20-25.
- Gordon, G. E. and D. L. McCulloch (1999). "A VEP investigation of parallel visual pathway development in primary school age children." Doc Ophthalmol **99**(1): 1-10.
- Gosch, A. and R. Pankau (1994). "Social-emotional and behavioral adjustment in children with Williams-Beuren syndrome." Am J Med Genet **53**(4): 335-9.
- Gosch, A., G. Stading, et al. (1994). "Linguistic abilities in children with Williams-Beuren syndrome." Am J Med Genet **52**(3): 291-6.
- Grady, C. L., J. M. Maisog, et al. (1994). "Age-related changes in cortical blood flow activation during visual processing of faces and location." J Neurosci **14**(3 Pt 2): 1450-62.
- Grice, S. J., M. D. Haan, et al. (2003). "ERP abnormalities of illusory contour perception in Williams syndrome." Neuroreport **14**(14): 1773-7.
- Grice, S. J., M. W. Spratling, et al. (2001). "Disordered visual processing and oscillatory brain activity in autism and Williams syndrome." Neuroreport **12**(12): 2697-700.
- Gunn, A., E. Cory, et al. (2002). "Dorsal and ventral stream sensitivity in normal development and hemiplegia." Neuroreport **13**(6): 843-7.

- Halit, H., M. de Haan, et al. (2000). "Modulation of event-related potentials by prototypical and atypical faces." Neuroreport: For Rapid Communication of Neuroscience Research **11**(9): 1871-1875.
- Halit, H., M. de Haan, et al. (2003). "Cortical specialisation for face processing: face-sensitive event-related potential components in 3- and 12-month-old infants." Neuroimage **19**(3): 1180-93.
- Haxby, J. V., M. I. Gobbini, et al. (2001). "Distributed and overlapping representations of faces and objects in ventral temporal cortex." Science **293**(5539): 2425-30.
- Haxby, J. V., E. A. Hoffman, et al. (2000). "The distributed human neural system for face perception." Trends Cogn Sci **4**(6): 223-233.
- Haxby, J. V., E. A. Hoffman, et al. (2002). "Human neural systems for face recognition and social communication." Biol Psychiatry **51**(1): 59-67.
- Haxby, J. V., B. Horwitz, et al. (1994). "The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations." Journal of Neuroscience **14**(11, Pt 1): 6336-6353.
- Hecker, R. and B. Mapperson (1997). "Dissociation of visual and spatial processing in working memory." Neuropsychologia **35**(5): 599-603.
- Henderson, R. M., D. L. McCulloch, et al. (2003). "Event-related potentials (ERPs) to schematic faces in adults and children." Int J Psychophysiol **51**(1): 59-67.
- Howlin, P., M. Davies, et al. (1998). "Cognitive functioning in adults with Williams syndrome." J Child Psychol Psychiatry **39**(2): 183-9.
- Ishai, A., L. G. Ungerleider, et al. (1999). "Distributed representation of objects in the human ventral visual pathway." Proceedings of the National Academy of Sciences of the United States of America **96**(16): 9379-84.
- Itier, R. J. and M. J. Taylor (2004). "Face inversion and contrast-reversal effects across development: in contrast to the expertise theory." Dev Sci **7**(2): 246-60.
- Jackowski, A. P. and R. T. Schultz (2005). "Foreshortened dorsal extension of the central sulcus in Williams syndrome." Cortex **41**(3): 282-90.
- Jernigan, T. L. and U. Bellugi (1990). "Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome." Arch Neurol **47**(5): 529-33.

- Johnson, M. H. (2007). "Developing a social brain." Acta Paediatr **96**(1): 3-5.
- Johnson, M. H., R. Griffin, et al. (2005). "The emergence of the social brain network: evidence from typical and atypical development." Dev Psychopathol **17**(3): 599-619.
- Jones, K. L. and D. W. Smith (1975). "The Williams elfin facies syndrome. A new perspective." J Pediatr **86**(5): 718-23.
- Jones, W., U. Bellugi, et al. (2000). "II. Hypersociability in Williams Syndrome." J Cogn Neurosci **12 Suppl 1**: 30-46.
- Joseph, J. E., A. D. Gathers, et al. (2006). "Neural developmental changes in processing inverted faces." Cogn Affect Behav Neurosci **6**(3): 223-35.
- Kanwisher, N., J. McDermott, et al. (1997). "The fusiform face area: a module in human extrastriate cortex specialized for face perception." Journal of Neuroscience **17**(11): 4302-11.
- Karmiloff-Smith, A. (2001). Development itself is the key to understanding developmental disorders. Language development: The essential readings. Essential readings in developmental psychology. M. Tomasello and E. Bates. Malden, MA, US, Blackwell Publishing: 331-350.
- Karmiloff-Smith, A. (2007). "Atypical epigenesis." Dev Sci **10**(1): 84-8.
- Karmiloff-Smith, A., M. Thomas, et al. (2004). "Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories." J Child Psychol Psychiatry **45**(7): 1258-74.
- Kastner, S. and L. G. Ungerleider (2000). "Mechanisms of visual attention in the human cortex." Annu Rev Neurosci **23**: 315-41.
- Kawashima, R., M. Sugiura, et al. (1999). "The human amygdala plays an important role in gaze monitoring. A PET study." Brain **122 (Pt 4)**: 779-83.
- Kesler/West, M. L., A. H. Andersen, et al. (2001). "Neural substrates of facial emotion processing using fMRI." Cognitive Brain Research **11**(2): 213-226.
- Kim, D., G. Wylie, et al. (2006). "Magnocellular contributions to impaired motion processing in schizophrenia." Schizophr Res **82**(1): 1-8.
- Kippenhan, J. S., R. K. Olsen, et al. (2005). "Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome." J Neurosci **25**(34): 7840-6.

- Klingberg, T. (2006). "Development of a superior frontal-intraparietal network for visuo-spatial working memory." Neuropsychologia **44**(11): 2171-7.
- Klingberg, T., H. Forssberg, et al. (2002). "Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood." Journal of Cognitive Neuroscience **14**(1): 1-10.
- Kohler, S., S. Kapur, et al. (1995). "Dissociation of pathways for object and spatial vision: a PET study in humans." Neuroreport **6**(14): 1865-8.
- Korenberg, J. R., X. N. Chen, et al. (2000). "VI. Genome structure and cognitive map of Williams syndrome." J Cogn Neurosci **12 Suppl 1**: 89-107.
- Kucian, K., M. von Aster, et al. (2006). "Brain activation during mental rotation in school children and adults." J Neural Transm.
- Kwon, H., A. L. Reiss, et al. (2002). "Neural basis of protracted developmental changes in visuo-spatial working memory." Proceedings of the National Academy of Sciences of the United States of America **99**(20): 13336-41.
- Kylliäinen, A., S. Braeutigam, et al. (2006). "Face and gaze processing in normally developing children: a magnetoencephalographic study." Eur J Neurosci **23**(3): 801-10.
- Laing, E., G. Butterworth, et al. (2002). "Atypical development of language and social communication in toddlers with Williams syndrome." Developmental Science **5**(2): 233-246.
- Lancaster, J. L., T. G. Glass, et al. (1995). "A modality-independent approach to spatial normalization of tomographic images of the human brain." Human Brain Mapping **3**(3): 209-223.
- Landau, B., J. E. Hoffman, et al. (2006). "Object recognition with severe spatial deficits in Williams syndrome: sparing and breakdown." Cognition **100**(3): 483-510.
- Leibenluft, E., M. I. Gobbini, et al. (2004). "Mothers' neural activation in response to pictures of their children and other children." Biol Psychiatry **56**(4): 225-32.
- Lerner, Y., T. Hendler, et al. (2001). "A hierarchical axis of object processing stages in the human visual cortex." Cereb Cortex **11**(4): 287-97.
- MacDonald, G. W. and D. L. Roy (1988). "Williams syndrome: a neuropsychological profile." J Clin Exp Neuropsychol **10**(2): 125-31.

- Macmillan, N. A. and C. D. Creelman (1991). Detection theory: A user's guide, Cambridge University Press, NY, USA.
- Madrid, M. and M. A. Crognale (2000). "Long-term maturation of visual pathways." Vis Neurosci **17**(6): 831-7.
- Martinez, A., P. Moses, et al. (1997). "Hemispheric asymmetries in global and local processing: evidence from fMRI." Neuroreport **8**(7): 1685-1689.
- Maurer, D., R. L. Grand, et al. (2002). "The many faces of configural processing." Trends Cogn Sci **6**(6): 255-260.
- McCarthy, G., A. Puce, et al. (1997). "Face-specific processing in the human fusiform gyrus." Journal of Cognitive Neuroscience **9**(5): 605-610.
- Mecklinger, A. and N. Mueller (1996). "Dissociations in the processing of "what" and "where" information in working memory: An event-related potential analysis." Journal of Cognitive Neuroscience **8**(5): 453-473.
- Mervis, C. B., C. A. Morris, et al. (1999). Williams Syndrome: Findings from an integrated program of research. Neurodevelopmental disorders. H. Tager-Flusberg. Cambridge, MA, The MIT Press: 65-110.
- Mervis, C. B., C. A. Morris, et al. (2003). "Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions." Dev Neuropsychol **23**(1-2): 243-68.
- Mervis, C. B., B. F. Robinson, et al. (2000). "The Williams syndrome cognitive profile." Brain Cogn **44**(3): 604-28.
- Meyer-Lindenberg, A., A. R. Hariri, et al. (2005). "Neural correlates of genetically abnormal social cognition in Williams syndrome." Nat Neurosci **8**(8): 991-3.
- Meyer-Lindenberg, A., P. Kohn, et al. (2004). "Neural basis of genetically determined visuospatial construction deficit in Williams syndrome." Neuron **43**(5): 623-31.
- Mills, D. L., T. D. Alvarez, et al. (2000). "III. Electrophysiological studies of face processing in Williams syndrome." Journal of Cognitive Neuroscience **12 Suppl 1**(6): 47-64.
- Milner, A. D. and M. A. Goodale (1995). "The visual brain in action."

- Mitchell, T. V. and H. J. Neville (2004). "Asynchronies in the development of electrophysiological responses to motion and color." *J Cogn Neurosci* **16**(8): 1363-74.
- Mobbs, D., A. S. Garrett, et al. (2004). "Anomalous brain activation during face and gaze processing in Williams syndrome." *Neurology* **62**(11): 2070-6.
- Mondloch, C. J., R. Le Grand, et al. (2002). "Configural face processing develops more slowly than featural face processing." *Perception* **31**(5): 553-66.
- Morris, C. A., S. A. Demsey, et al. (1988). "Natural history of Williams syndrome: physical characteristics." *J Pediatr* **113**(2): 318-26.
- Morris, J. S., M. deBonis, et al. (2002). "Human amygdala responses to fearful eyes." *Neuroimage* **17**(1): 214-22.
- Morris, J. S., C. D. Frith, et al. (1996). "A differential neural response in the human amygdala to fearful and happy facial expressions." *Nature* **383**(6603): 812-5.
- Nagel, B. J., V. C. Barlett, et al. (2005). "Neuropsychological predictors of BOLD response during a spatial working memory task in adolescents: what can performance tell us about fMRI response patterns?" *J Clin Exp Neuropsychol* **27**(7): 823-39.
- Nakamura, M., K. Watanabe, et al. (2001). "Williams syndrome and deficiency in visuospatial recognition." *Dev Med Child Neurol* **43**(9): 617-21.
- Natale, E., C. A. Marzi, et al. (2006). "ERP and fMRI correlates of endogenous and exogenous focusing of visual-spatial attention." *Eur J Neurosci* **23**(9): 2511-21.
- Nelson, C. A., C. S. Monk, et al. (2000). "Functional neuroanatomy of spatial working memory in children." *Developmental Psychology* **36**(1): 109-116.
- Newcombe, F., G. Ratcliff, et al. (1987). "Dissociable visual and spatial impairments following right posterior cerebral lesions: Clinical, neuropsychological and anatomical evidence." *Neuropsychologia* **25**(1-B): 149-161.
- Newcombe, F. and W. R. Russell (1969). "Dissociated visual perceptual and spatial deficits in focal lesions of the right hemisphere."
- Olesen, P. J., Z. Nagy, et al. (2003). "Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network." *Brain Res Cogn Brain Res* **18**(1): 48-57.

- Palermo, R. and G. Rhodes (2007). "Are you always on my mind? A review of how face perception and attention interact." Neuropsychologia **45**(1): 75-92.
- Passarotti, A. M., B. M. Paul, et al. (2003). "The development of face and location processing: An fMRI study." Developmental Science **6**(1): 100-117.
- Paterson, S. J. and R. T. Schultz (2007). "Neurodevelopmental and behavioral issues in williams syndrome." Curr Psychiatry Rep **9**(2): 165-71.
- Paul, B. M., A. Z. Snyder, et al. (in preparation). "Amygdala response to faces parallels social behavior in a genetically determined syndrome."
- Paul, B. M., J. Stiles, et al. (2002). "Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation." Neuroreport **13**(9): 1115-1119.
- Paus, T., A. Zijdenbos, et al. (1999). "Structural maturation of neural pathways in children and adolescents: in vivo study." Science **283**(5409): 1908-11.
- Pedely, L., S. C. Levine, et al. (1985). "Developmental changes in face processing: results from multidimensional scaling." J Exp Child Psychol **39**(3): 421-36.
- Pober, B. R. and E. M. Dykens (1996). "Williams syndrome: An overview of medical, cognitive, and behavioral features." Child and Adolescent Psychiatric Clinics of North America **5**(4): 929-943.
- Puce, A., T. Allison, et al. (1995). "Face-sensitive regions in human extrastriate cortex studied by functional MRI." Journal of Neurophysiology **74**(3): 1192-9.
- Rao, H., T. Zhou, et al. (2003). "Spatiotemporal Activation of the Two Visual Pathways in Form Discrimination and Spatial Location: A Brain Mapping Study." Human Brain Mapping **18**(2): 78-89.
- Reiss, A. L., M. A. Eckert, et al. (2004). "An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome." J Neurosci **24**(21): 5009-15.
- Reiss, A. L., S. Eliez, et al. (2000). "IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study." Journal of Cognitive Neuroscience **12 Suppl 1**(6): 65-73.
- Rhodes, G. (1993). "Configural coding, expertise, and the right hemisphere advantage for face recognition." Brain & Cognition **22**(1): 19-41.
- Rossen, M., E. S. Klima, et al. (1996). Interaction between language and cognition: Evidence from Williams Syndrome. Language, Learning, and Behavior

Disorders: Developmental, Biological, and Clinical Perspectives. E. Joseph H. Beitchman and et al. Cambridge University Press, NY, USA: 367-392.

- Rossion, B., L. Dricot, et al. (2000). "Hemispheric asymmetries for whole-based and part-based face processing in the human fusiform gyrus." Journal of Cognitive Neuroscience **12**(5): 793-802.
- Ruchkin, D. S., R. Johnson, Jr., et al. (1997). "Multiple visuospatial working memory buffers: evidence from spatiotemporal patterns of brain activity." Neuropsychologia **35**(2): 195-209.
- Schmitt, J. E., K. Watts, et al. (2002). "Increased gyrification in Williams syndrome: evidence using 3D MRI methods." Dev Med Child Neurol **44**(5): 292-5.
- Schwarzer, G. (2000). "Development of face processing: the effect of face inversion." Child Dev **71**(2): 391-401.
- Schwarzer, G. (2002). "Processing of Facial and Non-facial Visual Stimuli in 2-5-year-Old Children." Infant and Child Development **11**: 253-269.
- Schweinsburg, A. D., B. J. Nagel, et al. (2005). "fMRI reveals alteration of spatial working memory networks across adolescence." J Int Neuropsychol Soc **11**(5): 631-44.
- Searcy, Y. M., A. J. Lincoln, et al. (2004). "The relationship between age and IQ in adults with Williams syndrome." Am J Ment Retard **109**(3): 231-6.
- Sergent, J. and D. Bindra (1981). "Differential hemispheric processing of faces: Methodological considerations and reinterpretation." Psychological Bulletin **89**(3): 541-554.
- Sergent, J., S. Ohta, et al. (1992). "Functional neuroanatomy of face and object processing. A positron emission tomography study." Brain **115 Pt 1**: 15-36.
- Shen, L., X. Hu, et al. (1999). "Neural correlates of visual form and visual spatial processing." Human Brain Mapping **8**(1): 60-71.
- Skottun, B. C. (2000). "On the conflicting support for the magnocellular-deficit theory of dyslexiaResponse to Stein, Talcott and Walsh (2000)." Trends Cogn Sci **4**(6): 211-212.
- Smith, E. E., J. Jonides, et al. (1995). "Spatial versus object working memory: PET investigations." Journal of Cognitive Neuroscience **7**(3): 337-356.

- Sowell, E. R., P. M. Thompson, et al. (2004). "Longitudinal mapping of cortical thickness and brain growth in normal children." J Neurosci **24**(38): 8223-31.
- Spencer, J., J. O'Brien, et al. (2000). "Motion processing in autism: evidence for a dorsal stream deficiency." Neuroreport **11**(12): 2765-7.
- Stein, J., J. Talcott, et al. (2000). "Controversy about the visual magnocellular deficit in developmental dyslexics." Trends Cogn Sci **4**(6): 209-211.
- Stein, J. and V. Walsh (1997). "To see but not to read; the magnocellular theory of dyslexia." Trends in Neurosciences **20**(4): 147-52.
- Stevens, C. and H. Neville (2006). "Neuroplasticity as a double-edged sword: deaf enhancements and dyslexic deficits in motion processing." J Cogn Neurosci **18**(5): 701-14.
- Stiles, J., B. Paul, et al. (2006). Spatial Cognitive Development following Early Focal Brain Injury: Evidence for Adaptive Change in Brain and Cognition. Processes of Change in Brain and Cognitive Development: Attention and Performance XXI. Y. Munakata and M. H. Johnson. Oxford, Oxford University Press: 535-561.
- Sturm, W., B. Schmenk, et al. (2006). "Spatial attention: more than intrinsic alerting?" Exp Brain Res **171**(1): 16-25.
- Talairach, J. and P. Tournoux (1988). Co-planar stereotaxic atlas of the human brain. New York, Thieme.
- Taylor, M. J., M. Batty, et al. (2004). "The faces of development: a review of early face processing over childhood." J Cogn Neurosci **16**(8): 1426-42.
- Thomas, K. M., S. W. King, et al. (1999). "A developmental functional MRI study of spatial working memory." Neuroimage **10**(3 Pt 1): 327-38.
- Thompson, P. M., A. D. Lee, et al. (2005). "Abnormal cortical complexity and thickness profiles mapped in Williams syndrome." J Neurosci **25**(16): 4146-58.
- Tresch, M. C., H. M. Sinnamon, et al. (1993). "Double dissociation of spatial and object visual memory: Evidence from selective interference in intact human subjects." Neuropsychologia **31**(3): 211-219.
- Tzourio-Mazoyer, N., S. De Schonen, et al. (2002). "Neural correlates of woman face processing by 2-month-old infants." Neuroimage **15**(2): 454-61.

- Udwin, O. and W. Yule (1990). "Expressive language of children with Williams syndrome." Am J Med Genet Suppl **6**: 108-14.
- Udwin, O. and W. Yule (1991). "A cognitive and behavioural phenotype in Williams syndrome." J Clin Exp Neuropsychol **13**(2): 232-44.
- Udwin, O., W. Yule, et al. (1987). "Cognitive abilities and behavioural characteristics of children with idiopathic infantile hypercalcaemia." J Child Psychol Psychiatry **28**(2): 297-309.
- Ungerleider, L. G. and M. Mishkin (1982). Two cortical visual systems. Analysis of visual behavior. D. J. Ingle, M. A. Goodale and R. J. W. Mansfield. Cambridge, MA, MIT Press: 549-586.
- Valentine, T. (1988). "Upside-down faces: a review of the effect of inversion upon face recognition." Br J Psychol **79 (Pt 4)**: 471-91.
- Van Essen, D. C., D. Dierker, et al. (2006). "Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses." J Neurosci **26**(20): 5470-83.
- Vicari, S., E. Bates, et al. (2004). "Neuropsychological profile of Italians with Williams syndrome: an example of a dissociation between language and cognition?" J Int Neuropsychol Soc **10**(6): 862-76.
- Vonarnim, G. and P. Engel (1964). "Mental Retardation Related To Hypercalcaemia." Dev Med Child Neurol **89**: 366-77.
- Wang, P. P., S. Doherty, et al. (1995). "Unique profile of visuo-perceptual skills in a genetic syndrome." Brain and Cognition **29**(1): 54-65.
- Wright, P. and Y. Liu (2006). "Neutral faces activate the amygdala during identity matching." Neuroimage **29**(2): 628-36.
- Yin, R. K. (1969). "Looking at upide-down faces." Journal of Experimental Psychology **81**(1): 141-145.

CHAPTER 5

AMYGDALA RESPONSE TO FACES PARALLELS SOCIAL BEHAVIOR IN A GENETICALLY DETERMINED SYNDROME

Abstract

Individuals with Williams Syndrome (WS), a genetically determined disorder, show impressive face processing abilities despite poor visuospatial skills and depressed intellectual function. Interestingly, beginning early in childhood they also show an unusually high level of interest in face-to-face social interaction. We employed functional magnetic resonance imaging (fMRI) to investigate physiological responses in face-sensitive brain regions, including ventral occipito-temporal cortex and the amygdala, in this unique genetic disorder. Participants included 17 individuals with WS, 17 age- and gender-matched healthy adults (chronological age match controls, CA), and 17 typically-developing 8- to 9-year-old children (mental age match controls, MA). While engaged in a face discrimination task, WS participants failed to recruit the amygdala, unlike both CA and MA controls. WS fMRI responses in ventral occipito-temporal cortex, however, were comparable to those of MA controls. These results reveal evidence for a neural correlate of the abnormally high sociability that characterizes WS.

Introduction

WS is a neurodevelopmental disorder caused by a known chromosomal microdeletion (Ewart, Morris et al. 1993; Korenberg, Chen et al. 2000). Individuals with WS typically show mild-to-moderate mental retardation, poor spatial abilities, and comparatively strong language skills. In addition, WS individuals exhibit a unique, highly affiliative social style. This remarkable behavioral profile together with knowledge of the genetic abnormality indicate that WS has strong potential for linking genes to human cognition (Bellugi and St. George 2001).

Individuals with WS also possess a notable interest and skill in face processing, an essential aspect of social interaction. The WS predilection for faces is marked early in life by heightened interest in faces over other stimuli (Laing, Butterworth et al. 2002), and later by impressive accuracy on face discrimination tasks (Bellugi, Wang et al. 1994), coupled with an irrepressible inclination to engage in social exchange (Bellugi and St. George 2001).

The nature of the neurocognitive mechanisms employed during face processing in WS has been debated (Tager-Flusberg, Plesa-Skwerer et al. 2003; Karmiloff-Smith, Thomas et al. 2004). Electrophysiological recordings show that the WS response to faces is morphologically atypical (Mills, Alvarez et al. 2000) and abnormally modulated by changes in stimulus orientation (Grice, Spratling et al. 2001). Extant functional magnetic resonance imaging (fMRI) studies investigating WS face processing have produced inconsistent findings in prototypical face-responsive brain regions. Specifically face-related activation in ventral occipito-temporal cortex (including the fusiform gyrus), a region responsive to visual patterns such as faces

(Haxby, Hoffman et al. 2002), has been reported to be normal in WS (Meyer-Lindenberg, Kohn et al. 2004; 2005). By contrast, the amygdala, a limbic structure that guides socio-emotional behavior and plays a role in the perception of facial identity and emotion (Haxby, Hoffman et al. 2002; Adolphs and Spezio 2006), is reported to be hypoactive in WS in response to negative facial affect (Meyer-Lindenberg, Hariri et al. 2005) but not during gaze processing (Mobbs, Garrett et al. 2004). Thus, previous studies have produced conflicting results and further, have used tasks that present powerful social signals (e.g., affect, gaze changes). In addition, several of these studies were based on WS individuals with normal-range IQ (i.e., non-retarded) (Meyer-Lindenberg, Kohn et al. 2004; 2005), raising concern regarding whether these findings are typical of persons with WS. This leaves open questions about the neural systems underlying typical WS proficiency in processing facial identity.

We addressed this using fMRI in a representative WS sample and two healthy control groups to enable both chronological age (CA) and mental age (MA) comparisons. We focused on ventral occipito-temporal cortex and the amygdala, two brain regions that act in concert to support the perceptual and social-affective demands of face processing (Haxby, Hoffman et al. 2002). The juxtaposition of good face discrimination with atypical socio-emotional behaviors in WS suggests that if differences are observed, the amygdala may show relatively more functional compromise than ventral occipito-temporal cortex.

Methods and Materials

PARTICIPANTS

The WS sample ($n=17$, 10 females; $M=31.2$ -years, $SD=11.0$) was representative with respect to overall cognitive ability, with mean IQ scores (WAIS-R/WISC-R) falling within the typical WS range (Howlin, Davies et al. 1998; Searcy, Lincoln et al. 2004) (Full Scale= 67.4 , $SD=\pm 9.7$; Verbal= 72.4 , $SD=7.8$; Performance= 64.5 , $SD=10.0$). The diagnosis of WS was established by FISH (fluorescence in situ hybridization probes for the elastin gene on chromosome 7) and the presence of phenotypic features defined by the American Academy of Pediatrics (2001). Peabody Picture Vocabulary Test (PPVT-III) scores for the WS sample revealed a receptive vocabulary age-equivalent of 13 years ($SD=4.4$). Developmental Test of Visuomotor Integration (VMI) (Beery 1997) scores revealed an age-equivalent of 5.9 years ($SD=1.6$). The CA group consisted of neurologically normal adults (17 age- and gender-matched individuals; $M=31.0$ -years, $SD=11.2$). The MA group consisted of 17 typically-developing children (9 females) selected such that their mean age (8.8-years, $SD=0.7$) fell midway between the language and visuospatial age-equivalent estimates for the WS group. Also, past results (Paul, Stiles et al. 2002) suggested that 8- to 9-year-old children would perform the face identity-matching task with accuracy comparable to the WS group while also being able to complete the imaging study.

TASK

To obtain measures of each participant's face-matching abilities, the task was administered prior to the imaging session. The task required visual-matching of facial identity over a series of three neutral expression stimuli (Figure 5.1). Participants were

encouraged to respond as quickly and accurately as possible. Both accuracy (d') and response times (RT) were recorded.

FUNCTIONAL NEUROIMAGING

Task. The behavioral task was adapted for block design fMRI (Figure 5.1) and modified slightly to promote optimal task performance (viz., increasing duration of the reference stimuli to 1000 ms and requiring a button press only for positive identity matches). In the control condition three scrambled images appeared sequentially and participants made a motor response without any match/mismatch decision. All participants completed at least two task runs.

Image acquisition. Images were acquired on a Siemens 1.5-Tesla System according to a procedure described elsewhere (Passarotti, Paul et al. 2003). Functional images were acquired with a single-shot echo-planar (EPI) pulse sequence sensitive to blood oxygenation level dependent (BOLD) contrast (FOV=220 mm, TR=2500 ms, TE=40 ms, flip angle=90°). Whole head coverage was obtained with 27 5 mm slices (in-plane resolution 3.44x3.44 mm). Each fMRI run included 116 volumes. T1-weighted structural images were obtained using a MP-RAGE sequence (TR=11.4 ms, TE=4.4 ms, flip angle=10°, resolution=1 mm³; 180 sagittal slices).

fMRI data preprocessing. Image preprocessing was performed with algorithms developed at Washington University (A.Z. Snyder, R.L. Buckner and others). Individual MP-RAGE images were registered (12-parameter affine transformation) to an atlas-representative target conforming to the Talairach & Tournoux atlas (1988). A study-specific atlas-representative target image was

prepared from MP-RAGE data representing all three participant groups using a previously described strategy (Buckner, Head et al. 2004). This approach was adopted to minimize the influence of structural differences between groups. Atlas transformation of the functional data was computed via each subject's MP-RAGE and combined with motion correction in one step to yield volumetric time series resampled to 3 mm cubic voxels. Further details of the fMRI data preprocessing have been detailed elsewhere (Fox, Snyder et al. 2005).

fMRI analyses. Functional runs with excessive variability (mean whole brain standard deviation over a run >2.5%: 4, 1, and 0 runs in MA, CA and WS groups, respectively) were excluded. Individual and group fMRI analyses were performed using AFNI (Cox 1996). Data were spatially smoothed (Gaussian kernel at FWHM=6.88 mm). Multiple regression analysis was performed assuming a canonical hemodynamic response function of the gamma type (Cohen 1997). Six head motion correction parameters, as well as the global mean and linear drift were included as nuisance regressors. Voxel-wise *t*-statistic images representing BOLD modulation attributable to task performance were computed and converted to equivalently probable *z*-scores. A voxel-wise one-way ANOVA then was conducted to generate pairwise group contrasts (3). The results were masked to include only voxels in which a main effect of group was present at $P < 0.01$ per voxel. The functional maps then were corrected for multiple comparisons using the False Discovery Rate procedure (Genovese, Lazar et al. 2002) to obtain an overall alpha level of 0.05. Foci including less than five contiguous voxels (<135 μ L) were discounted.

Results

BEHAVIORAL TASK

Behavioral session data were not available for five WS participants. One WS participant's data were excluded because he had difficulty attending to the task during the behavioral session. Results (Figure 5.2) showed that the WS group was less accurate and slower than the older CA group. No differences were found between the WS and MA groups for accuracy or RT.

FUNCTIONAL NEUROIMAGING

fMRI task accuracy and RTs were similar to patterns of data collected during the behavioral session, confirming that all groups were engaged in the task during imaging. fMRI responses generally were similar in WS participants and MA controls, with both groups displaying less robust activations than CA controls (Supplementary Table 1 lists occipito-temporal lobe regions displaying group differences). This pattern held in many ventral occipito-temporal regions as well (Figure 5.3), suggesting that the WS responses generally were immature. However, the amygdala response in WS was distinctly abnormal, as both the MA and CA groups showed significant activation, while the WS group did not (Figure 5.3).

Discussion

The typically-developing child controls did not display the adult pattern of ventral occipito-temporal activation observed in the CA group. This difference is consistent with the idea that face processing normally follows a protracted developmental course (Chung and Thomson 1995). As the WS responses in this part of the brain resembled those of the MA group, this effect can be understood as reflecting developmental delay. The presence in WS of fMRI responses (albeit,

immature) in cortical regions associated with face and object identification is consistent with the observation that these functions may be comparatively well preserved (Bellugi, Wang et al. 1994).

While the MA and CA control groups alike showed robust activation in the amygdala, this response was absent in the WS group. The amygdala is thought to participate at an early developmental stage in the establishment of brain systems for face processing. As part of a fast subcortical pathway that includes the superior colliculus and the pulvinar (a thalamic structure that may contribute to the profound spatial deficits in WS (Eckert, Galaburda et al. 2006)), the amygdala is thought to mediate the human newborn's precocious ability to detect and orient to faces (Johnson 2005). This pathway responds selectively to low-spatial frequencies, which carry coarse configural information about faces. Interestingly, it is configural information that may be processed abnormally in WS (Karmiloff-Smith, Thomas et al. 2004).

In light of the strong activation for faces in WS observed in ventral occipito-temporal cortex, which is heavily connected with the amygdala (Amaral and Price 1984), the absence of amygdalar activation is striking. In addition to its importance in emotional processing, the amygdala is involved in detecting social relevance (Sander, Grafman et al. 2003) and regulating approach behavior (Amaral 2002). The amygdala normally shows heightened activity during discrimination of unfamiliar faces (Gobbini, Leibenluft et al. 2004). Absent amygdala responses to faces in WS is therefore consistent with unusually positive approachability ratings of strangers' faces (Bellugi, Adolphs et al. 1999). A similar positive approachability bias has been seen in patients with amygdala damage (Adolphs, Tranel et al. 1998). It remains unclear

whether the current amygdala finding represents a correlate of reduced vigilance when assessing unfamiliar faces or a more primary deficit.

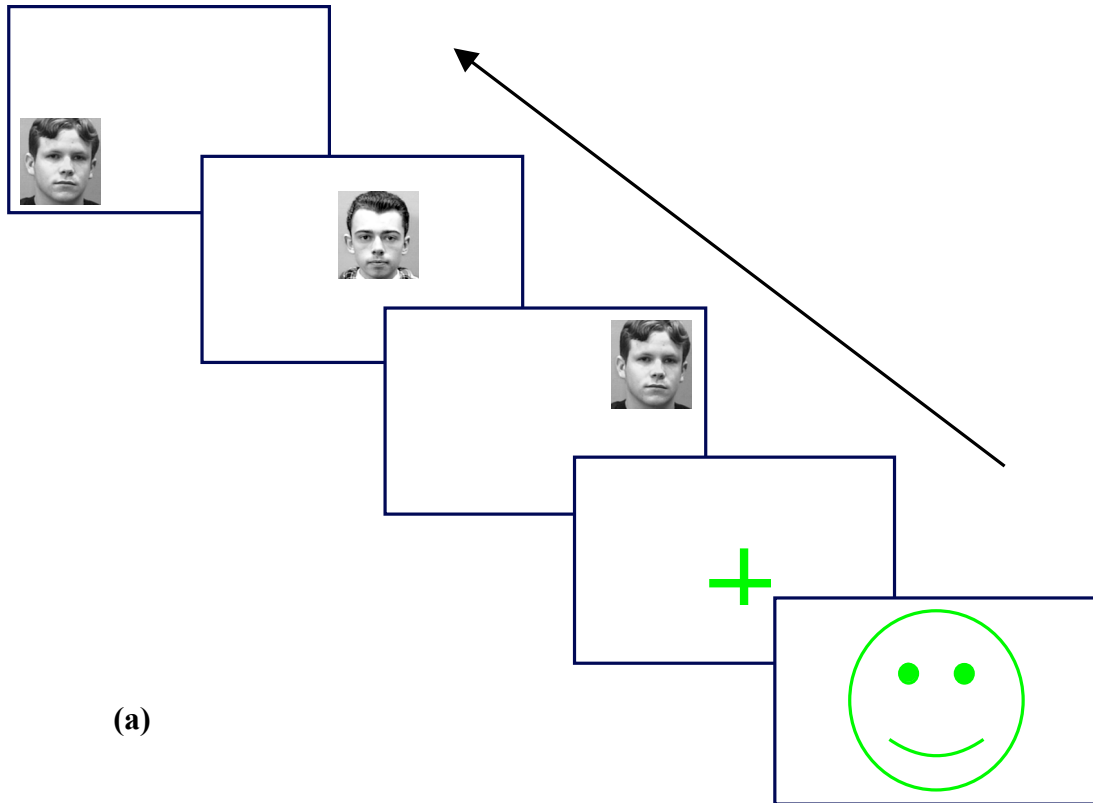
The addition of these findings to recent neuroimaging results in WS adults (Meyer-Lindenberg, Kohn et al. 2004; Mobbs, Garrett et al. 2004; 2005) argues for a complex interplay among several factors, each of which may be associated with early, anomalous functioning of the amygdala. Meyer-Lindenberg and colleagues (2005) reported attenuated amygdala response in WS adults to threatening faces but elevated response to threatening scenes, suggesting a disordered association between socio-emotional stimuli and the amygdala (rather than absence of function). They suggested (Meyer-Lindenberg, Hariri et al. 2005; 2006) that dysfunction in an amygdala-prefrontal cortex system for social behavior results in abnormal responses to stimuli that are potentially harmful or threatening in WS. Given that the amygdala may also be critically involved very early in life in a subcortical pathway for face processing (amygdala-thalamus-superior colliculus - Johnson 2005), impairment of this structure could have far-reaching effects on the development of the adult “social brain” network (Skuse 2003). Our findings suggest that the amygdala is functional in the processing of social information, in this case faces, at least by middle childhood (seen in the robust amygdala response in MA controls). In WS, however, genetic influences may impair amygdala function early in development, impacting emergence of the ability to process information from faces. This may contribute to the complex constellation of social-cognitive and behavioral abnormalities observed during development in WS. Because development is a dynamic process, these characteristics themselves may interact in a complicated way (Karmiloff-Smith, Thomas et al. 2004), to influence

what are ultimately observed as the distinctive and intriguing features of the adult WS phenotype.

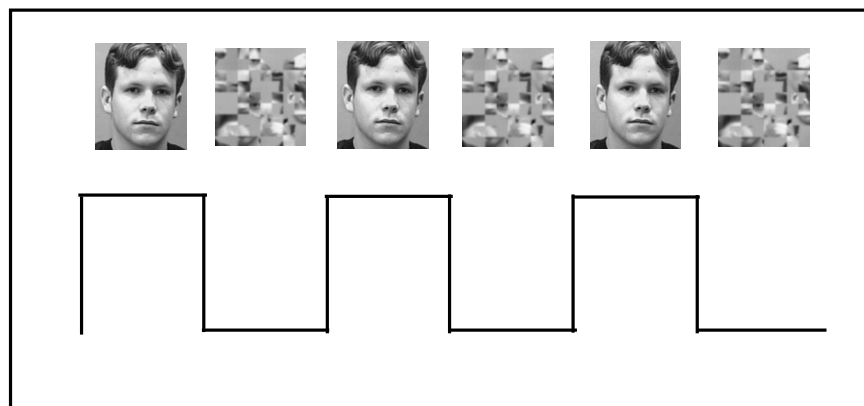
Acknowledgements

This research was supported in part by NIH Program Project HD33113 and a McDonnell Foundation Award to UB, NIH grant NS06833 (MER, AZS), NIH grant P50-NS22343 (JS), and an NIH Kirschstein Research Service Award to BMP. The authors wish to thank Fred Rose, Janet Shin, Nasim Bavar, Russ Hornbeck and Justin Vincent for technical assistance with this work, as well as Yvonne Searcy and Silvia Paparello for helpful comments.

Figure 5.1 Task. (a) Trials were presented in blocks of six (6 blocks, 36 trials total), with each block preceded by a warning cue (green “smiley face”). A delay of either 500 or 1750 ms followed a series of two reference stimuli (500 ms duration per stimulus). After the delay the third (test) stimulus appeared until the participant responded, or until 3500 ms elapsed. Participants indicated by pressing one of two buttons (“yes” or “no”) whether the identity of the test stimulus matched either of the two reference stimuli. A match was presented in half of the trials. The first 18 trials used a 500 ms delay between the second reference stimulus and the test stimulus, in accordance with our previous face processing study of WS. The second 18 trials used a 1750 ms delay, in line with the functional magnetic resonance imaging (fMRI) paradigm that has been successfully employed in the UCSD laboratory for several years. Comparison of accuracy data from the two trial types across the three participant groups did not reveal a significant group \times trial type interaction effect ($P > 0.1$). These data therefore were collapsed over the two trial types in the present analyses. (b) Each 4 minute, 50 second fMRI scanning run consisted of six 47.5 sec blocks (5 trials) of identity-matching and control trials, in an interleaved fashion. Unlike the behavioral task, the third (test) stimulus was presented for a fixed duration of 3250 ms in order to achieve scanning runs of constant length. Control trials followed the same presentation sequence as identity-matching trials. Control trial blocks were preceded by a distinct cue (an image of a black handprint, not shown), in order to warn participants as to which trial type would be shown in the upcoming task block.



(a)



(b)

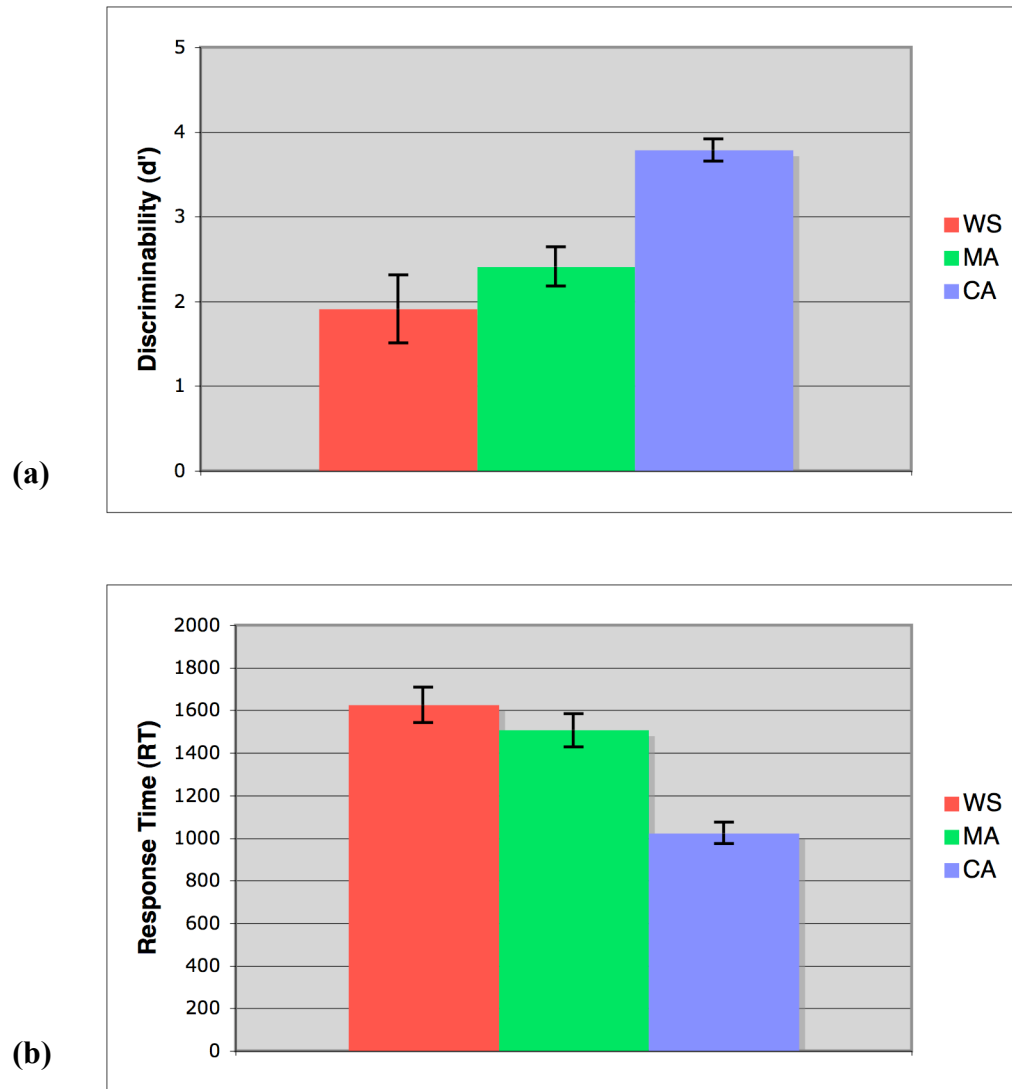
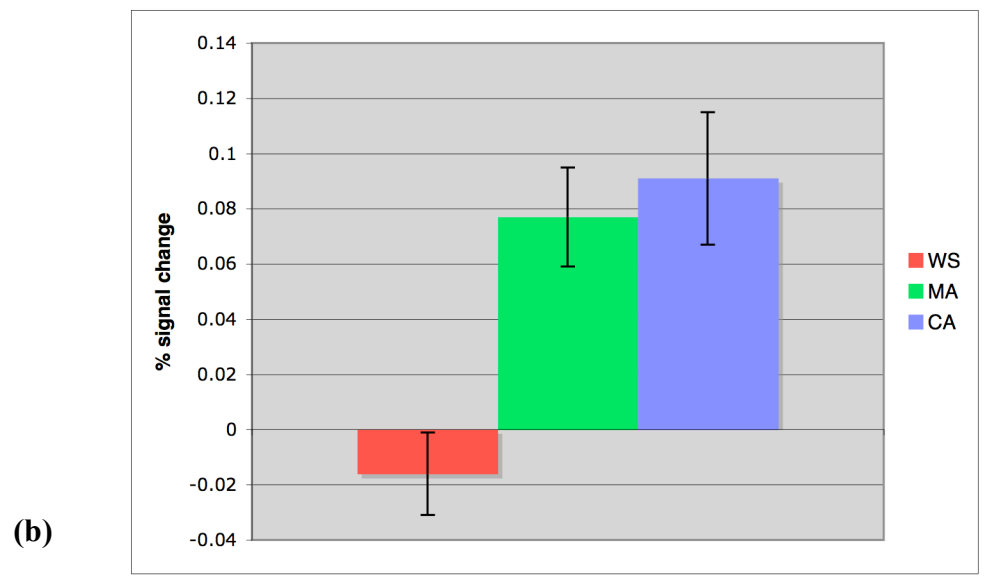
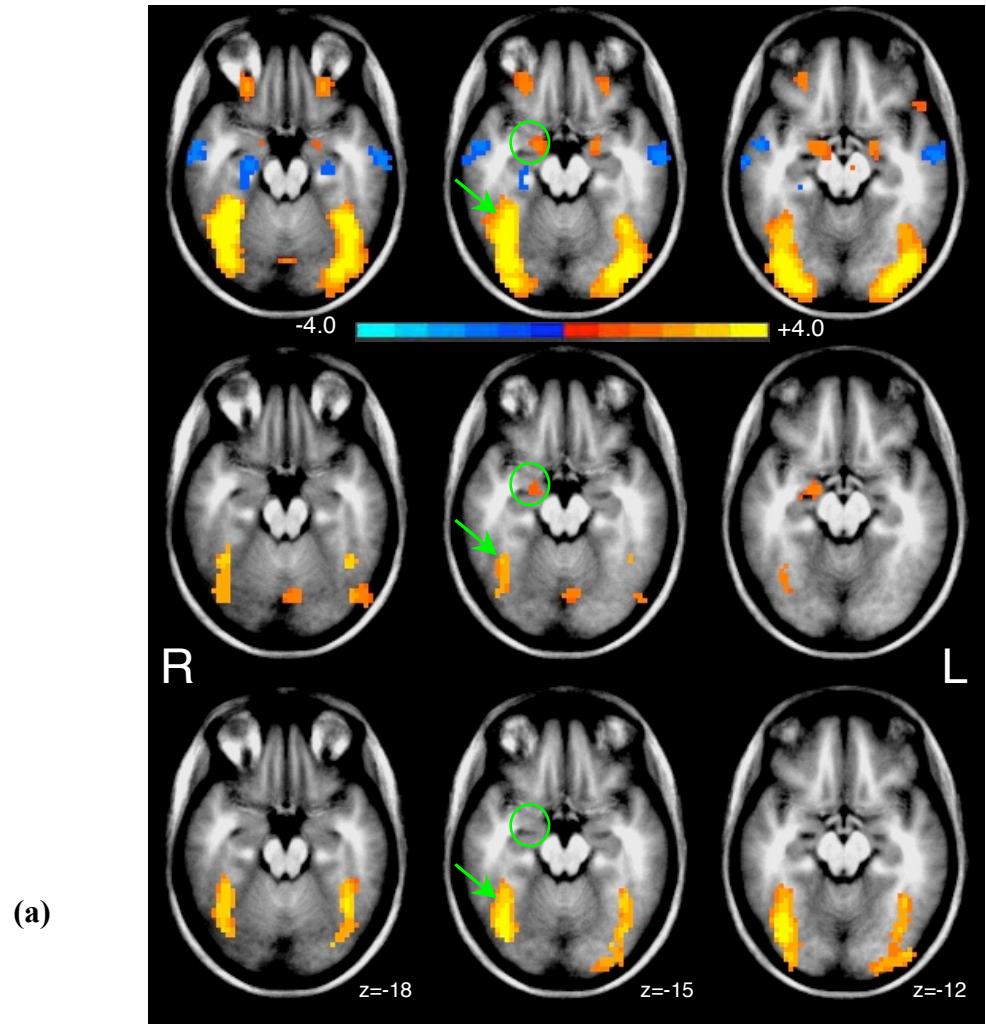


Figure 5.2 Behavioral session results, face-matching task. (a) Accuracy (b) Response Time (RT). Results revealed an effect of group membership for both dependent variables (d' : $F(2,42) = 15.78, P < 0.001$; RT: $F(2,42) = 20.64, P < 0.001$). Follow-up Tukey HSD tests revealed the same pattern of results for both variables: both the WS and MA groups were outperformed by the CA group, with respect to both accuracy and RT ($P < 0.001$ for all t -test comparisons). The performances of the WS participants and MA controls, as expected, were not different ($P > 0.3$ for both d' and RT).

Figure 5.3 Activation in ventral occipito-temporal regions and the amygdala. (a) Mean Z-score images depicting active voxels ($P < 0.05$, corrected) in chronological age-matched controls (top), mental age-matched controls (middle) and WS (bottom). Data are displayed in radiological convention (right is on left). Green circles denote significant activation in both control groups in the right amygdalar region, absent in the WS group. Green arrows denote activation in all three groups in the fusiform gyrus, a region in ventral occipito-temporal cortex that is highly sensitive to faces. Except for one focus in a more superior aspect of the fusiform gyrus, where the WS group showed more robust activation than both control groups (Talairach coordinates [38, -69, -9]; % signal change = 0.21 for WS, 0.079 for MA controls, and 0.13 for CA controls), most ventral occipito-temporal regions showed comparable levels of activation between the WS and MA groups. (b) Mean activation intensity within a spherical region-of-interest (ROI) (radius = 4.5 mm) placed within the right amygdalar region.



References

- Adolphs, R. and M. Spezio (2006). "Chapter 20 Role of the amygdala in processing visual social stimuli." Prog Brain Res **156**: 363-78.
- Adolphs, R., D. Tranel, et al. (1998). "The human amygdala in social judgment." Nature **393**(6684): 470-4.
- Amaral, D. G. (2002). "The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety." Biol Psychiatry **51**(1): 11-7.
- Amaral, D. G. and J. L. Price (1984). "Amygdalo-cortical projections in the monkey (*Macaca fascicularis*)." J Comp Neurol **230**(4): 465-96.
- Beery, K. E. (1997). The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI). Parsippany, NJ, Modern Curriculum Press.
- Bellugi, U., R. Adolphs, et al. (1999). "Towards the neural basis for hypersociability in a genetic syndrome." Neuroreport: For Rapid Communication of Neuroscience Research **10**(8): 1653-1657.
- Bellugi, U. and M. St. George, Eds. (2001). Journey from cognition to brain to gene: Perspectives from Williams syndrome. Cambridge, MA, The MIT Press.
- Bellugi, U., P. P. Wang, et al. (1994). Williams syndrome: An unusual neuropsychological profile. Atypical cognitive deficits in developmental disorders: Implications for brain function. S. H. Broman and J. Grafman. Hillsdale, NJ, England, Lawrence Erlbaum Associates, Inc: 23-56.
- Buckner, R. L., D. Head, et al. (2004). "A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume." Neuroimage **23**(2): 724-38.
- Chung, M.-S. and D. M. Thomson (1995). "Development of face recognition." British Journal of Psychology **86**(1): 55-87.
- Cohen, M. S. (1997). "Parametric analysis of fMRI data using linear systems methods." Neuroimage **6**(2): 93-103.
- Cox, R. W. (1996). "AFNI: software for analysis and visualization of functional magnetic resonance neuroimages." Computers and Biomedical Research **29**(3): 162-73.

- Eckert, M. A., A. M. Galaburda, et al. (2006). "The neurobiology of Williams syndrome: cascading influences of visual system impairment?" Cell Mol Life Sci **63**(16): 1867-75.
- Ewart, A. K., C. A. Morris, et al. (1993). "Hemizyosity at the elastin locus in a developmental disorder, Williams syndrome." Nat Genet **5**(1): 11-6.
- Fox, M. D., A. Z. Snyder, et al. (2005). "Transient BOLD responses at block transitions." Neuroimage **28**(4): 956-66.
- Genovese, C. R., N. A. Lazar, et al. (2002). "Thresholding of statistical maps in functional neuroimaging using the false discovery rate." Neuroimage **15**(4): 870-8.
- Gobbini, M. I., E. Leibenluft, et al. (2004). "Social and emotional attachment in the neural representation of faces." Neuroimage **22**(4): 1628-35.
- Grice, S. J., M. W. Spratling, et al. (2001). "Disordered visual processing and oscillatory brain activity in autism and Williams syndrome." Neuroreport **12**(12): 2697-700.
- Haxby, J. V., E. A. Hoffman, et al. (2002). "Human neural systems for face recognition and social communication." Biol Psychiatry **51**(1): 59-67.
- Howlin, P., M. Davies, et al. (1998). "Cognitive functioning in adults with Williams syndrome." J Child Psychol Psychiatry **39**(2): 183-9.
- Johnson, M. H. (2005). "Subcortical face processing." Nat Rev Neurosci **6**(10): 766-74.
- Karmiloff-Smith, A., M. Thomas, et al. (2004). "Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories." J Child Psychol Psychiatry **45**(7): 1258-74.
- Korenberg, J. R., X. N. Chen, et al. (2000). "VI. Genome structure and cognitive map of Williams syndrome." J Cogn Neurosci **12 Suppl 1**: 89-107.
- Laing, E., G. Butterworth, et al. (2002). "Atypical development of language and social communication in toddlers with Williams syndrome." Developmental Science **5**(2): 233-246.
- Meyer-Lindenberg, A., A. R. Hariri, et al. (2005). "Neural correlates of genetically abnormal social cognition in Williams syndrome." Nat Neurosci **8**(8): 991-3.

- Meyer-Lindenberg, A., P. Kohn, et al. (2004). "Neural basis of genetically determined visuospatial construction deficit in Williams syndrome." Neuron **43**(5): 623-31.
- Meyer-Lindenberg, A., C. B. Mervis, et al. (2006). "Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour." Nat Rev Neurosci **7**(5): 380-93.
- Mills, D. L., T. D. Alvarez, et al. (2000). "III. Electrophysiological studies of face processing in Williams syndrome." Journal of Cognitive Neuroscience **12 Suppl 1**(6): 47-64.
- Mobbs, D., A. S. Garrett, et al. (2004). "Anomalous brain activation during face and gaze processing in Williams syndrome." Neurology **62**(11): 2070-6.
- Passarotti, A. M., B. M. Paul, et al. (2003). "The development of face and location processing: An fMRI study." Developmental Science **6**(1): 100-117.
- Paul, B. M., J. Stiles, et al. (2002). "Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation." Neuroreport **13**(9): 1115-1119.
- Sander, D., J. Grafman, et al. (2003). "The human amygdala: an evolved system for relevance detection." Rev Neurosci **14**(4): 303-16.
- Searcy, Y. M., A. J. Lincoln, et al. (2004). "The relationship between age and IQ in adults with Williams syndrome." Am J Ment Retard **109**(3): 231-6.
- Skuse, D. (2003). "Fear recognition and the neural basis of social cognition." Child and Adolescent Mental Health **8**(2): 50-60.
- Stiles, J., B. Paul, et al. (2006). Spatial Cognitive Development following Early Focal Brain Injury: Evidence for Adaptive Change in Brain and Cognition. Processes of Change in Brain and Cognitive Development: Attention and Performance XXI. Y. Munakata and M. H. Johnson. Oxford, Oxford University Press: 535-561.
- Tager-Flusberg, H., D. Plesa-Skwerer, et al. (2003). "People with Williams syndrome process faces holistically." Cognition **89**(1): 11-24.
- Talairach, J. and P. Tournoux (1988). Co-planar stereotaxic atlas of the human brain. New York, Thieme.

CHAPTER 6

GENERAL DISCUSSION

The studies described in the previous chapters have presented findings from behavioral and functional imaging investigations with a pair of face identity- and location-processing tasks differentially tapping ventral and dorsal stream processing, respectively, in typical participants and in participants affected by a Williams Syndrome (WS), neurodevelopmental disorder. These investigations have yielded critical information about the normal development of these functions. In turn, this information has provided a context within which to examine these functions in WS, a genetic disorder with a deficit profile that parallels the ventral/dorsal processing distinction. Findings from WS have augmented our understanding of atypical developmental processes that can occur within these two streams, in addition to providing further insight into the mechanisms underlying normal developmental change. This final chapter will briefly summarize the key findings from these studies, and discuss their implications first for Williams Syndrome, and second, for our knowledge of the ontogeny of the human visuoperceptual system.

Summary of Findings

The behavioral study presented in Chapter 3 yielded two findings of import. The first concerned typical children: despite a difference from adults in the overall level of performance (lower accuracy, slower response times), children did not show a different pattern of performance across the face identity- and location-matching tasks, i.e. like adults, their performance was not different on the two tasks. Although the size of the typically-developing sample of 8- to 9-year-old children was somewhat limited in this particular investigation (N=19), this result is in agreement with findings from a

large scale study of 100 children ages 8 to 12 (N=20 per age year) which showed comparable across-task performance in children of all age groups.

The second principal finding from Chapter 3 concerned patients with WS: when compared with the child participants (selected, as a group, to be of similar mental age to the WS participants), these individuals exhibited a selective, profound deficit in location processing. This finding provides empirical support, from a well-controlled comparison using tasks matched precisely in stimulus and response demands, for the numerous reports in the literature of face processing skills that far exceed general spatial ability in WS (Bellugi, Lichtenberger et al. 2001). Moreover, it lays the groundwork for an investigation of the neural correlates of this disparity, which was hypothesized to reveal differentially impacted function in the ventral and dorsal visual systems.

The results of such an investigation, using functional magnetic resonance imaging (fMRI) to examine the neural underpinning of face identity- and location-processing, were described in Chapters 4 and 5. Specifically, Chapter 4 detailed several key results from typically-developing children and from persons with WS, regarding ventral and dorsal visual stream activation underlying the profiles of behavioral performance presented for these two groups in Chapter 3. For typically-developing children, patterns of activation mirrored their behavioral profile of comparable performance on the two tasks, which overall, had not yet reached the level of healthy adults. Although children engaged many of the same regions as adults, they showed noteworthy differences in the ventral and dorsal streams. For example, activation in the face-sensitive fusiform gyrus of the temporal lobe was similar for

children and adults during active face discrimination (i.e. identity-matching), but not during passive face viewing (i.e. location-matching), as activation in this area during passive viewing was less consistent in children. This was particularly apparent in the left hemisphere (LH), where child participants relied most heavily on a more posterior, ventral occipital region, instead of on the anterior to middle temporal portions of the fusiform gyrus. This finding implies greater task dependence in the recruitment of ventral stream regions during face processing in children. Further, it is consistent with prior reports of relatively greater engagement of posterior ventral regions during face and object processing in younger children (Gathers, Bhatt et al. 2004; Aylward, Park et al. 2005), which may be due to more rapid maturation of function in these regions (Golarai, Ghahremani et al. 2007). As with ventral stream function, dorsal stream activity in typical children was not fully adult-like. Most notably, whereas peak regions of activation during location-matching fell in the superior parietal region of both hemispheres in adults, children showed reliable activation only in the RH. In the LH, activation in superior parietal cortex was less consistent and was positively correlated with performance accuracy. Very similar observations have been made in prior neuroimaging studies of spatial working memory in children (Klingberg, Forssberg et al. 2002; Olesen, Nagy et al. 2003; Nagel, Barlett et al. 2005). However, in combination with a recent, similar finding from a spatial task without a working memory component (i.e. mental rotation, Kucian, von Aster et al. 2006), this finding suggests that these differences may reflect protracted maturation of the LH parietal mediation of spatial processing, independently of working memory.

Knowledge of the patterns of ventral and dorsal stream activation in typical adults and children enabled an identification of abnormal function in individuals with WS. As discussed in Chapter 4, both streams showed some evidence of abnormal responsivity, with the degree of abnormality paralleling the degree of deficit in behavioral performance observed in Chapter 3. In line with the behavioral profile of significantly better face identity-matching than location-matching performance seen in WS, ventral stream regions exhibited less dramatically atypical function than dorsal stream regions. Importantly, however, given hypotheses that face processing is achieved normally (Tager-Flusberg, Plesa-Skwerer et al. 2003) and is mediated in a usual way by the ventral stream (Meyer-Lindenberg, Kohn et al. 2004), ventral stream activation in our WS participants was not entirely normal. Specifically, the response of the face-sensitive fusiform was not properly modulated by the demands of the task (i.e. response magnitude did not differ for active face discrimination versus passive face viewing) and was less lateralized than expected.

Regarding the dorsal stream, as might be expected from their impaired performance on the location-matching task, highly conspicuous abnormalities were observed in the response of these regions. In agreement with evidence for significant structural (Reiss, Eckert et al. 2004; Eckert, Hu et al. 2005; Kippenhan, Olsen et al. 2005; Thompson, Lee et al. 2005; Van Essen, Dierker et al. 2006) and functional (Meyer-Lindenberg, Kohn et al. 2004) abnormalities of this system, a striking failure to engage parietal cortex was observed during location processing. Surprisingly, however, during face identity-matching WS showed abnormally increased activity in a portion of this region that was not engaged by the task in typical adults or children. As

will be discussed in the next section, this may represent the first fMRI evidence for a neural correlate of the exaggerated attentional response to faces in WS.

Chapter 5 discussed a final important finding that emerged from analyses of the brain response during face identity-matching in WS. Despite significant engagement of ventral occipito-temporal and parietal cortex during this task, WS participants evinced a marked deficit in activation of the amygdala. This contrasted with the robust amygdala response in controls, which did not differ in the two age groups (children, adults). This finding extends a prior report of decreased amygdala activation in WS during perception of threatening faces (Meyer-Lindenberg, Hariri et al. 2005) to processing of a basic visual stimulus with high social salience, but without an overtly affective component. As discussed in the next section, attenuated response of the amygdala during face perception may relate to the remarkably sociable, uninhibited WS personality.

Implications for Williams Syndrome

The previously described brain activation findings from WS represent two intriguing dimensions of the disorder. The first, relates to the behavioral phenotype of WS, while the second relates to the cognitive manifestations of the disorder. Based on the findings presented in Chapters 4 and 5, the possibility that these two elements may be related to dysfunction of a common neural system(s), is put forth.

Since WS was first identified (Williams, Barratt-Boyes et al. 1961; Beuren, Apitz et al. 1962), the “hypersociability” of individuals affected by the disorder has continually been cited as an unusual, defining characteristic. This involves a tendency to approach, without hesitation, unfamiliar individuals for the purpose of engaging in

face-to-face social interaction (Doyle, Bellugi et al. 2004), and, early in life, a tendency to orient to the faces of individuals even when the more adaptive response is to direct attention to a different environmental stimulus (e.g. an object of common interest, Laing, Butterworth et al. 2002; Mervis, Morris et al. 2003). Given the amygdala's responsivity to face stimuli, especially those that are emotionally arousing (Breiter, Etcoff et al. 1996; Morris, Frith et al. 1996), convey ambiguous socially-relevant information (Whalen 1998; Thomas, Drevets et al. 2001), or are simply unfamiliar to the viewer (Gobbini, Leibenluft et al. 2004), the neural finding of most relevance to the social behavior seen in WS is the absence of an amygdalar response to faces. Although the current data do not enable a more definitive conclusion regarding whether this failure is merely a correlate of the behavioral characteristics of WS, or whether it plays a more causative role, this finding likely represents an abnormality of primary interest for future research on this disorder.

Variability within a small group of functional imaging findings involving the amygdala in WS suggests this structure plays a complex role in the phenotype of the disorder. Based on fMRI evidence of decreased amygdala activation to fearful face stimuli but increased activity to threatening visual scenes, Meyer-Lindenberg et al., (2005; 2006) have submitted that amygdala dysfunction in WS contributes to the behavioral profile seen in the disorder, namely, increased approach of unfamiliar individuals but an elevated level of general anxiety and more frequent phobic response to non-social stimuli. However, another fMRI study examining the WS brain response to music (contrasted with noise) (Levitin, Menon et al. 2003), a stimulus, like faces, that seems to be especially appealing to WS individuals (Levitin, Cole et al. 2004),

showed amygdala activation that was significantly *greater* than in controls. Thus, the lack of amygdala response to faces reported in the current investigation may not easily be explained as a reaction to a stimulus that elicits a more favorable emotional response in this population.

Recent work in the macaque (Gothard, Battaglia et al. 2007) suggests that amygdala may contain a sub-population of neurons that are selectively responsive to facial identity, independent of facial emotion. This implies that the amygdala may play a more general role in face processing, as had previously been suggested by numerous fMRI reports in typical adults of amygdala activation to faces that are affectively neutral (Kesler/West, Andersen et al. 2001; Fitzgerald, Angstadt et al. 2006; Wright and Liu 2006). This role for the amygdala most probably involves the perception of information from faces that may be used by the viewer in formulating an appropriate social response (Adolphs and Spezio 2006). A failure to correctly perceive this information could explain the WS tendency to be less wary of strangers, and more indiscriminate in their approach. Given the prominence of visuoperceptual deficits in this disorder, it is logical to consider a relationship between these deficits and the perception of, and behavioral response to, social information in WS. Elgar & Campbell (2001) were some of the first authors to speculate about possibility (see also Johnson 2001). They focused on impairments in magnocellular function, which have traditionally been associated with the spatial deficits (dorsal stream) in WS. They suggested that since the ventral visual stream receives magnocellular input, in addition to parvocellular input, anomalous magnocellular function might impact face recognition abilities, likely through an adverse effect on configural processing. More

recently, Eckert et al. (2006) suggested that visual system deficits stemming from defects in the dorsal stream, posterior thalamus (particularly the pulvinar), and cerebellar vermis, may have cascading developmental effects, one of which might be an impairment in the ability to process the information contained within a face. Specifically, these authors posited that dysfunction of the pulvinar could impact the amygdala (via a direct anatomical connection), and consequently, the ability to detect facial emotion information. Indeed, these two structures, the pulvinar and the amygdala, are part of a fast subcortical pathway (also including the superior colliculus) that is likely to be responsible for the automatic detection of threat, as in facial displays of negative facial affect (Morris, Ohman et al. 1999; de Gelder, Frissen et al. 2003). Interestingly, this same pathway may mediate the response to faces seen in newborns, who are heavily reliant on subcortical pathways due to the immaturity of cortical visual areas at birth (Johnson 2005). This subcortical pathway responds selectively to low-spatial frequency information (Vuilleumier, Armony et al. 2003), probably transmitted through magnocellular channels (Vuilleumier and Pourtois 2007), which carries crude configural information about faces. Thus, given the confluence of impairments in functioning of the dorsal stream/magnocellular system, the amygdala, and the pulvinar, it is perhaps no accident that previous studies have found evidence that individuals with WS have difficulty with configural face processing (Deruelle, Mancini et al. 1999; Karmiloff-Smith, Thomas et al. 2004) (but not configural processing of objects - Deruelle, Rondan et al. 2006) and facial emotion processing (Gagliardi, Frigerio et al. 2003). In addition to direct connections between the pulvinar and the amygdala, the pulvinar also sends substantial projections to the

dorsal visual stream (Kaas and Lyon 2007). These projections might represent yet another component of the neuroanatomical basis for the hypothesized association between deficits in visuoperceptual and social-emotional functioning in WS (Eckert, Galaburda et al. 2006).

Looking next at the nexus of face processing and social behavior in WS from the perspective of sparing, a second question becomes, what might sustain the relative strength in face processing seen in certain tasks? The most frequently cited answer to this questions is that WS appear to exhibit a local, or part-based, processing bias (Bihrlle, Bellugi et al. 1989) that might be sufficient for successful performance of certain face perception tasks (e.g. the Benton Face Task Benton, Hamsher et al. 1983) (Deruelle, Mancini et al. 1999). However, as with many aspects of the research with this population, the existence of a local processing bias in WS has been vigorously debated (Mervis, Morris et al. 1999; Farran and Jarrold 2003; Farran and Jarrold 2005). The current investigation indicates that a viable (but not necessarily mutually exclusive) alternative lies in another of the intriguing neural findings in WS, namely, the abnormal recruitment a region of right superior parietal cortex during face discrimination. This finding suggests a highly unusual role for the dorsal stream in visual processing in WS; while gross impairment of this stream may result in generalized spatial dysfunction and impinge upon the ability to process configural and/or socially relevant information from within a face, function in certain circumscribed regions may be decoupled from the larger pathway. Specifically, the superior parietal region identified in the current study may function in a compensatory-like fashion to direct the attention of WS participants to the face

stimuli. A prior report of “sticky fixation” (trouble disengaging attention) to face-like objects in young children (6 years and under) with WS (Atkinson, Braddick et al. 2003; see also Brown, Johnson et al. 2003), coupled with a tendency in WS toddlers to look with unusually extreme intensity at the faces of others (Mervis, Morris et al. 2003), suggests that this attention may be deployed in an almost obligatory manner. Typically-developing infants also have difficulty disengaging attention from visual objects early on, but this resolves within the first few months of life (Atkinson 2000). Brain imaging studies with younger children affected by WS will be required to help determine if the abnormal persistence of the “sticky fixation” phenomenon in WS is related to an abnormal response to faces in the parietal region. A functional imaging study of face processing in infancy (using PET) (Tzourio-Mazoyer, De Schonen et al. 2002) raises the possibility that the parietal response to faces in WS also represents an abnormal persistence of a phenomenon that is observed very early on, but subsequently disappears during development. This study found that a small group of 2-month-old infants showed significant activation in a region of right parietal cortex that is not usually observed in adults viewing faces with neutral expression and invariant direction of gaze (varying gaze does, however, elicit intraparietal region activation in adults Haxby, Hoffman et al. 2000; George, Driver et al. 2001). Future research will be necessary to determine whether either or both of these factors, abnormalities in attentional function and in the response of the parietal region during face processing, play a key role in the perception of, and behavioral response to, faces in WS.

Although research on WS is still in a nascent stage, and little, if any, direct evidence exists to confirm these hypotheses, they nonetheless provide a good starting point for future research. In the context of the current set of studies, these hypotheses also highlight a few considerations for future work with this population. First, in accordance with suggestion that genetic anomalies can have widespread effects on the developing organism, it may be most informative to ‘cast a wide net’ and carefully probe functions that may on the surface appear to be unaffected (e.g. face processing), in addition to those that show clear evidence of compromise (Karmiloff-Smith, Thomas et al. 2004). It is the thorough examination of precisely these seemingly unaffected functions that may unveil additional cognitive or neural factors with the potential to fill gaps in the broader conceptualization of the disorder. Essential to this broader conceptualization of WS is a consideration of developmental context (Karmiloff-Smith, Scerif et al. 2002; Karmiloff-Smith 2007; Paterson and Schultz 2007). Although some have attempted to forge direct links from genes to adult behavior and cognition, this genotype-phenotype relationship is likely to be prohibitively complex (Gray, Karmiloff-Smith et al. 2006). A more tractable approach might entail ‘working backward’ from the adult WS phenotype, a process that can proceed in at least two complementary ways: first, by investigating the developmental precursors of the adult phenotype in a relatively straightforward manner through the study of younger participants with WS, and second, by considering how certain aspects of the adult WS phenotype might be represented during the course of normal development (e.g., in the typically-developing, but immature, organism).

Implications for Typical Development of Two Cortical Streams

On the whole, the findings from normal 8- to 9-year-old children that were presented in this investigation suggest that these higher-order visual functions are associated with a very gradual process of developmental change, as both behavior and brain function were not quite adult-like in this group for either face or location processing. This is consistent with behavioral studies that have looked independently at these skills, and concluded that both continue to mature at least through the school-age years (Chung and Thomson 1995; Zald and Iacono 1998; Taylor, Batty et al. 2004; Luciana, Conklin et al. 2005). However, the factors that influence this process of change are just starting to be described more fully, as developmental research has only recently begun to benefit from increasingly sophisticated technology, such as neuroimaging, that has enabled an examination of changes in brain structure and function that may underlie improvements in behavioral performance (Casey, Tottenham et al. 2005).

Results from the current investigation suggest that several factors affect how developmental change manifests in the ventral and dorsal streams. Perhaps not surprisingly, task-related differences represent one of these factors. This was observed in the ventral stream response to faces in typical children, which differed according to whether the task demanded active discrimination or passive viewing of the face stimuli. In Chapter 4 it was proposed that this difference might account for some of the discrepancies in the findings from the few developmental neuroimaging studies of face processing that have been conducted to date (Gathers, Bhatt et al. 2004; Aylward, Park et al. 2005; Golarai, Ghahremani et al. 2007). Although these differences in task demands may differentially impact how difficult the task is to perform, more

importantly, they may promote the use of distinct cognitive strategies in children and adults (e.g. attending more to the features rather than the configuration of a face) that can contribute to noticeable differences in brain activation.

Task differences (and strategy differences) may also result in variability in the particular set of brain regions engaged, with different regions having their own, independently variable maturational rates and/or trajectories. For example, a recent study looking at the response specificity of different functionally-defined ventral stream regions (the ‘fusiform face area’ or ‘FFA’ in the anterior/middle temporal fusiform gyrus (Kanwisher, McDermott et al. 1997); the ‘parahippocampal place area’ or ‘PPA’ in the temporal parahippocampal gyrus (Epstein and Kanwisher 1998); and the object-sensitive ‘lateral occipital complex’ or ‘LOC’ in the inferior/middle occipital gyrus (Malach, Reppas et al. 1995)) in typical children suggests that not all regions within the same visual stream develop at the same rate. The sequence of development in these regions suggested by the results of this study (the LOC showed adult-like functional specificity before the FFA or the PPA) seems to correspond, at least roughly, with certain general principles of structural brain development (i.e. primary sensory areas first, with higher-order associative areas lagging behind - Huttenlocher and Dabholkar 1997; Gogtay, Giedd et al. 2004). This type of function-structure correspondence also emerged in the current investigation, for example, in evidence for prolonged maturation of the response of intraparietal cortex within the left hemisphere (LH) (Chapter 4), a cortical region that, bilaterally, appears to be one of the last to fully myelinate (Yakovlev and Lecours 1967; Klingberg, Forssberg et al. 2002). The laterality of the intraparietal finding (LH only) suggests that an additional

factor may be the degree to which a given region is critical to performance of the task. In the current studies, this was seen in the patterns of brain activation in both visual streams. Among the most essential regions for face identity- and location-matching in adults were the right middle fusiform gyrus and the right intraparietal/superior parietal region, respectively. Interestingly, the response of these regions in children appeared more adult-like; rather, it was the responses of homologous (but possibly less critical, e.g. see Sack, Sperling et al. 2002) regions in the left hemisphere that were less consistent.

In summary, the number and complexity of the factors that can affect our observations of developmental change indicates that until more data are available, it may be most helpful to focus attention *within* each visual stream, rather than attempting to characterize each stream in its entirety. Because an understanding of normal developmental processes is of critical importance to questions involving atypical development, vulnerability, plasticity, reorganization and compensation, an analogous approach, focusing more on the similarities and differences among task-specific processes within each stream, may be most fruitful. Finally, the complicated nature of the interrelationships among the factors discussed above suggests that a great deal can be gained from applying multiple measures (e.g. neuropsychological tasks combined with brain imaging of both structure and function), simultaneously, to the study of cognitive and brain development.

References

- Acredolo, L. P. (1978). "Development of spatial orientation in infancy." *Developmental Psychology* **14**(3): 224-234.
- Adolphs, R. and M. Spezio (2006). "Chapter 20 Role of the amygdala in processing visual social stimuli." *Prog Brain Res* **156**: 363-78.
- Aguirre, G. K. and M. D'Esposito (1997). "Environmental knowledge is subserved by separable dorsal/ventral neural areas." *Journal of Neuroscience* **17**(7): 2512-2518.
- Akshoomoff, N. A. and J. Stiles (1995). "Developmental trends in visuospatial analysis and planning: I. Copying a complex figure." *Neuropsychology* **9**(3): 364-377.
- Atkinson, J. (1992). "Early visual development: differential functioning of parvocellular and magnocellular pathways." *Eye* **6 (Pt 2)**: 129-35.
- Atkinson, J. (1998). The 'where and what' or 'who and how' of visual development. The development of sensory, motor and cognitive capacities in early infancy: From perception to cognition. F. Simion and G. Butterworth. Hove, England, Psychology Press/Erlbaum (UK) Taylor & Francis: 3-24.
- Atkinson, J. (2000). The developing visual brain. Oxford; New York, Oxford University Press.
- Atkinson, J., O. Braddick, et al. (2003). "Neurobiological models of visuospatial cognition in children with Williams syndrome: Measures of dorsal-stream and frontal function." *Developmental Neuropsychology. Special Issue: Williams syndrome* **23**(1-2): 139-172.
- Atkinson, J., J. King, et al. (1997). "A specific deficit of dorsal stream function in Williams' syndrome." *Neuroreport* **8**(8): 1919-22.
- Aylward, E. H., J. E. Park, et al. (2005). "Brain activation during face perception: evidence of a developmental change." *J Cogn Neurosci* **17**(2): 308-19.
- Bachevalier, J., C. Hagger, et al. (1990). Functional maturation of the occipitotemporal pathway in infant rhesus monkeys. Copenhagen, proceedings of the Alfred Benzon Symposium 31.

- Baenninger, M. (1994). "The development of face recognition: Featural or configurational processing?" *Journal of Experimental Child Psychology* **57**(3): 377-396.
- Baillargeon, R. (1993). The object concept revisited: New direction in the investigation of infants' physical knowledge. *Visual perception and cognition in infancy*. Carnegie Mellon symposia on cognition. C. Granrud. Hillsdale, NJ, England, Lawrence Erlbaum Associates, Inc: 265-315.
- Baillargeon, R. and J. DeVos (1991). "Object permanence in young infants: further evidence." *Child Development* **62**(6): 1227-46.
- Baillargeon, R. and M. Graber (1987). "Where's the rabbit? 5.5-month-old infants' representation of the height of a hidden object." *Cognitive Development* **2**(4): 375-392.
- Bearden, C. E., P. P. Wang, et al. (2002). "Williams syndrome cognitive profile also characterizes Velocardiofacial/DiGeorge syndrome." *Am J Med Genet* **114**(6): 689-92.
- Bellugi, U., R. Adolphs, et al. (1999). "Towards the neural basis for hypersociability in a genetic syndrome." *Neuroreport: For Rapid Communication of Neuroscience Research* **10**(8): 1653-1657.
- Bellugi, U., E. S. Klima, et al. (1997). *Cognitive and neural development: Clues from genetically based syndromes. The lifespan development of individuals: Behavioral, neurobiological, and psychosocial perspectives: A synthesis*. D. Magnusson. New York, NY, Cambridge University Press: 223-243.
- Bellugi, U., J. R. Korenberg, et al. (2001). "Williams syndrome: An exploration of neurocognitive and genetic features." *Clinical Neuroscience Research* **1**: 217-229.
- Bellugi, U., L. Lichtenberger, et al. (2001). *The neurocognitive profile of Williams syndrome: A complex pattern of strengths and weaknesses. Journey from cognition to brain to gene: Perspectives from Williams syndrome*. U. Bellugi and M. S. George. Cambridge, MA, The MIT Press: 1-41.
- Bellugi, U., L. Lichtenberger, et al. (1999). "Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome." *Trends in Neurosciences* **22**(5): 197-207.

- Bellugi, U. and M. St. George, Eds. (2001). *Journey from cognition to brain to gene: Perspectives from Williams syndrome*. Cambridge, MA, The MIT Press.
- Bentin, S., T. Allison, et al. (1996). "Electrophysiological studies of face perception in humans." *Journal of Cognitive Neuroscience* **8**(6): 551-565.
- Benton, A. L., K. d. Hamsher, et al. (1983). *Contributions to neuropsychological assessment: A clinical manual*. New York, Oxford University Press.
- Bertenthal, B. I. (1996). "Origins and early development of perception, action, and representation." *Annu Rev Psychol* **47**: 431-59.
- Beuren, A. J., J. Aritz, et al. (1962). "Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance." *Circulation* **26**: 1235-40.
- Bihrlé, A. M., U. Bellugi, et al. (1989). "Seeing either the forest or the trees: dissociation in visuospatial processing." *Brain Cogn* **11**(1): 37-49.
- Boddaert, N., F. Mochel, et al. (2006). "Parieto-occipital grey matter abnormalities in children with Williams syndrome." *Neuroimage* **30**(3): 721-5.
- Bower, T. G. (1974). *Development in infancy*. Oxford, England, W.H. Freeman.
- Braddick, O., J. Atkinson, et al. (2003). "Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'." *Neuropsychologia* **41**(13): 1769-84.
- Breiter, H. C., N. L. Etcoff, et al. (1996). "Response and habituation of the human amygdala during visual processing of facial expression." *Neuron* **17**(5): 875-87.
- Bronson, G. (1974). "The postnatal growth of visual capacity." *Child Dev* **45**(4): 873-90.
- Brown, J. H., M. H. Johnson, et al. (2003). "Spatial representation and attention in toddlers with Williams syndrome and Down syndrome." *Neuropsychologia* **41**(8): 1037-46.
- Bushnell, E. W., B. E. McKenzie, et al. (1995). "The spatial coding strategies of one-year-old infants in a locomotor search task." *Child Development* **66**(4): 937-958.

- Carey, S. (1996). Perceptual classification and expertise. *Perceptual and cognitive development*. R. Gelman and T. Kit-Fong. San Diego, CA, Academic Press, Inc: 49-69.
- Carey, S. and R. Diamond (1977). "From piecemeal to configurational representation of faces." *Science* **195**(4275): 312-314.
- Casey, B. J., N. Tottenham, et al. (2005). "Imaging the developing brain: what have we learned about cognitive development?" *Trends Cogn Sci* **9**(3): 104-10.
- Cassia, V. M., D. Kuefner, et al. (2006). "A behavioural and ERP investigation of 3-month-olds' face preferences." *Neuropsychologia* **44**(11): 2113-25.
- Chen, J., J. Myerson, et al. (2000). "Behavioral evidence for brain-based ability factors in visuospatial information processing." *Neuropsychologia* **38**(4): 380-387.
- Chung, M.-S. and D. M. Thomson (1995). "Development of face recognition." *British Journal of Psychology* **86**(1): 55-87.
- Cicchetti, D. (1984). "The emergence of developmental psychopathology." *Child Dev* **55**(1): 1-7.
- Coch, D., W. Skendzel, et al. (2005). "Motion and color processing in school-age children and adults: an ERP study." *Dev Sci* **8**(4): 372-86.
- Cohen, L. B. and C. H. Cashon (2001). "Do 7-month-old infants process independent features or facial configurations?" *Infant & Child Development* **10**(1-2): 83-92.
- Colby, C. L. and M. E. Goldberg (1999). "Space and attention in parietal cortex." *Annual Review of Neuroscience* **22**: 319-349.
- Colombo, J. (2001). "The development of visual attention in infancy." *Annu Rev Psychol* **52**: 337-67.
- Colombo, J., W. Mitchell, et al. (1990). "Discrimination Learning During the First Year: Stimulus and Positional Cues." *Journal of Experimental Psychology: Learning, Memory and Cognition* **16**(1): 98-109.
- Cook, M. (1987). The origins of form perception. *Perceptual development in early infancy: Problems and issues*. Child psychology. B. E. McKenzie and R. H. Day. Hillsdale, NJ, England, Lawrence Erlbaum Associates, Inc: 93-123.
- Corbetta, M., F. M. Miezin, et al. (1993). "A PET study of visuospatial attention." *Journal of Neuroscience* **13**(3): 1202-1226.

- Courtney, S. M., L. G. Ungerleider, et al. (1996). "Object and spatial visual working memory activate separate neural systems in human cortex." *Cerebral Cortex* **6**(1): 39-49.
- Creem, S. H. and D. R. Proffitt (2001). "Defining the Cortical Visual Systems: "what", "where", and "how"." *Acta Psychologica* **107**(1-3): 43-68.
- Csibra, G., L. A. Tucker, et al. (1998). "Neural correlates of saccade planning in infants: A high-density ERP study." *International Journal of Psychophysiology* **29**(2): 201-215.
- Csibra, G., L. A. Tucker, et al. (2001). "Differential frontal cortex activation before anticipatory and reactive saccades in infants." *Infancy* **2**(2): 159-174.
- de Gelder, B., I. Frissen, et al. (2003). "A modulatory role for facial expressions in prosopagnosia." *Proc Natl Acad Sci U S A* **100**(22): 13105-10.
- de Haan, M., O. Pascalis, et al. (2002). "Specialization of neural mechanisms underlying face recognition in human infants." *J Cogn Neurosci* **14**(2): 199-209.
- de Schonen, S. and E. Mathivet (1990). "Hemispheric asymmetry in a face discrimination task in infants." *Child Development* **61**(4): 1192-1205.
- Dennis, M., J. M. Fletcher, et al. (2002). "Object-based and action-based visual perception in children with spina bifida and hydrocephalus." *J Int Neuropsychol Soc* **8**(1): 95-106.
- Deruelle, C., J. Mancini, et al. (1999). "Configural and local processing of faces in children with Williams syndrome." *Brain Cogn* **41**(3): 276-98.
- Deruelle, C., C. Rondan, et al. (2006). "Do children with Williams syndrome fail to process visual configural information?" *Res Dev Disabil* **27**(3): 243-53.
- Desimone, R., T. D. Albright, et al. (1984). "Stimulus-selective properties of inferior temporal neurons in the macaque." *Journal of Neuroscience* **4**(8): 2051-62.
- Desimone, R. and L. G. Ungerleider (1989). Neural mechanisms of visual perception in monkeys. *Handbook of Neuropsychology*. H. Goodglass and A. R. Damasio. New York, Elsevier. **2**: 267-299.
- Diamond, A. (1985). "Development of the ability to use recall to guide action, as indicated by infants' performance on AB." *Child Development* **56**(4): 868-883.

- Diamond, R. and S. Carey (1986). "Why faces are and are not special: an effect of expertise." *J Exp Psychol Gen* **115**(2): 107-17.
- Dilts, C. V., C. A. Morris, et al. (1990). "Hypothesis for development of a behavioral phenotype in Williams syndrome." *Am J Med Genet Suppl* **6**: 126-31.
- Distler, C., J. Bachevalier, et al. (1996). "Functional development of the corticocortical pathway for motion analysis in the macaque monkey: a 14C-2-deoxyglucose study." *Cereb Cortex* **6**(2): 184-95.
- Doniger, G. M., J. J. Foxe, et al. (2002). "Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia." *Arch Gen Psychiatry* **59**(11): 1011-20.
- Doyle, T. F., U. Bellugi, et al. (2004). "'Everybody in the world is my friend' hypersociability in young children with Williams syndrome." *Am J Med Genet A* **124**(3): 263-73.
- Dykens, E. M. (2003). "Anxiety, fears, and phobias in persons with Williams syndrome." *Dev Neuropsychol* **23**(1-2): 291-316.
- Eckert, M. A., A. M. Galaburda, et al. (2006). "The neurobiology of Williams syndrome: cascading influences of visual system impairment?" *Cell Mol Life Sci* **63**(16): 1867-75.
- Eckert, M. A., D. Hu, et al. (2005). "Evidence for superior parietal impairment in Williams syndrome." *Neurology* **64**(1): 152-3.
- Einfeld, S. L., B. J. Tonge, et al. (1997). "Behavioral and emotional disturbance in individuals with Williams syndrome." *Am J Ment Retard* **102**(1): 45-53.
- Elgar, K. and R. Campbell (2001). "Annotation: the cognitive neuroscience of face recognition: implications for developmental disorders." *J Child Psychol Psychiatry* **42**(6): 705-17.
- Ellis, H. D. (1992). The development of face processing skills. Processing the facial image. V. Bruce, A. Cowey and et al. New York, NY, Clarendon Press/Oxford University Press: 105-111.
- Ellis, N. R. (1990). "Is memory for spatial location automatically encoded?" *Memory & Cognition* **18**(6): 584-592.

- Ellis, N. R., E. Katz, et al. (1987). "Developmental aspects of memory for spatial location." *J Exp Child Psychol* **44**(3): 401-12.
- Ellis, N. R., P. Woodley-Zanthos, et al. (1989). "Memory for spatial location in children, adults, and mentally retarded persons." *American Journal on Mental Retardation* **93**(5): 521-526.
- Epstein, R. and N. Kanwisher (1998). "A cortical representation of the local visual environment." *Nature* **392**(6676): 598-601.
- Faillenot, I., I. Toni, et al. (1997). "Visual pathways for object-oriented action and object recognition: functional anatomy with PET." *Cereb Cortex* **7**(1): 77-85.
- Farran, E. K. and C. Jarrold (2003). "Visuospatial cognition in Williams syndrome: Reviewing and accounting for the strengths and weaknesses in performance." *Developmental Neuropsychology. Special Issue: Williams syndrome* **23**(1-2): 173-200.
- Farran, E. K. and C. Jarrold (2005). "Evidence for unusual spatial location coding in Williams syndrome: an explanation for the local bias in visuo-spatial construction tasks?" *Brain Cogn* **59**(2): 159-72.
- Finkel, D. L. (1973). "A Developmental Comparison of the Processing of Two Types of Visual Information." *Journal of Experimental Child Psychology* **16**(2): 250-266.
- Fitzgerald, D. A., M. Angstadt, et al. (2006). "Beyond threat: amygdala reactivity across multiple expressions of facial affect." *Neuroimage* **30**(4): 1441-8.
- Flin, R. H. (1985). "Development of face recognition: An encoding switch?" *British Journal of Psychology* **76**(1): 123-134.
- Foxe, J. J., G. M. Doniger, et al. (2001). "Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping." *Neuroreport* **12**(17): 3815-20.
- Freire, A. and K. Lee (2001). "Face recognition in 4- to 7-year-olds: processing of configural, featural, and paraphernalia information." *J Exp Child Psychol* **80**(4): 347-71.
- Gagliardi, C., E. Frigerio, et al. (2003). "Facial expression recognition in Williams syndrome." *Neuropsychologia* **41**(6): 733-8.

- Galaburda, A. M. and U. Bellugi (2001). Cellular and molecular cortical neuroanatomy in Williams syndrome. *Journey from cognition to brain to gene: Perspectives from Williams syndrome*. U. Bellugi and M. S. George. Cambridge, MA, The MIT Press: 123-145.
- Galaburda, A. M., D. P. Holinger, et al. (2002). "Williams syndrome: neuronal size and neuronal-packing density in primary visual cortex." *Arch Neurol* **59**(9): 1461-7.
- Galaburda, A. M., J. E. Schmitt, et al. (2001). "Dorsal forebrain anomaly in Williams syndrome." *Archives of Neurology* **58**(11): 1865-1869.
- Gathercole, S. E., S. J. Pickering, et al. (2004). "The structure of working memory from 4 to 15 years of age." *Dev Psychol* **40**(2): 177-90.
- Gathers, A. D., R. Bhatt, et al. (2004). "Developmental shifts in cortical loci for face and object recognition." *Neuroreport* **15**(10): 1549-53.
- Gauthier, I. and C. A. Nelson (2001). "The development of face expertise." *Current Opinion in Neurobiology* **11**(2): 219-224.
- George, N., J. Driver, et al. (2001). "Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing." *Neuroimage* **13**(6 Pt 1): 1102-12.
- Gobbini, M. I., E. Leibenluft, et al. (2004). "Social and emotional attachment in the neural representation of faces." *Neuroimage* **22**(4): 1628-35.
- Gogtay, N., J. N. Giedd, et al. (2004). "Dynamic mapping of human cortical development during childhood through early adulthood." *Proc Natl Acad Sci U S A* **101**(21): 8174-9.
- Golarai, G., D. G. Ghahremani, et al. (2007). "Differential development of high-level visual cortex correlates with category-specific recognition memory." *Nat Neurosci* **10**(4): 512-22.
- Goodale, M. A. and A. D. Milner (1992). "Separate visual pathways for perception and action." *Trends in Neurosciences* **15**(1, 163): 20-25.
- Goodale, M. A., A. D. Milner, et al. (1991). "A neurological dissociation between perceiving objects and grasping them." *Nature* **349**(6305): 154-156.

- Gordon, G. E. and D. L. McCulloch (1999). "A VEP investigation of parallel visual pathway development in primary school age children." *Doc Ophthalmol* **99**(1): 1-10.
- Gosch, A. and R. Pankau (1994). "Social-emotional and behavioral adjustment in children with Williams-Beuren syndrome." *Am J Med Genet* **53**(4): 335-9.
- Gothard, K. M., F. P. Battaglia, et al. (2007). "Neural responses to facial expression and face identity in the monkey amygdala." *J Neurophysiol* **97**(2): 1671-83.
- Gray, V., A. Karmiloff-Smith, et al. (2006). "In-depth analysis of spatial cognition in Williams syndrome: A critical assessment of the role of the LIMK1 gene." *Neuropsychologia* **44**(5): 679-85.
- Gulya, M., A. Rossi-George, et al. (2002). "The development of explicit memory for basic perceptual features." *J Exp Child Psychol* **81**(3): 276-97.
- Gunn, A., E. Cory, et al. (2002). "Dorsal and ventral stream sensitivity in normal development and hemiplegia." *Neuroreport* **13**(6): 843-7.
- Haffenden, A. M. and M. A. Goodale (1998). "The effect of pictorial illusion on prehension and perception." *J Cogn Neurosci* **10**(1): 122-36.
- Halgren, E., A. M. Dale, et al. (1999). "Location of human face-selective cortex with respect to retinotopic areas." *Hum Brain Mapp* **7**(1): 29-37.
- Halit, H., M. de Haan, et al. (2003). "Cortical specialisation for face processing: face-sensitive event-related potential components in 3- and 12-month-old infants." *Neuroimage* **19**(3): 1180-93.
- Harman, C., M. I. Posner, et al. (1994). "Development of orienting to locations and objects in human infants." *Canadian Journal of Experimental Psychology* **48**(2): 301-318.
- Hasher, L. and R. T. Zacks (1979). "Automatic and effortful processes in memory." *Journal of Experimental Psychology: General* **108**(3): 356-388.
- Haxby, J. V., M. I. Gobbini, et al. (2001). "Distributed and overlapping representations of faces and objects in ventral temporal cortex. [Comment In: *Science*. 2001 Sep 28;293(5539):2405-7 UI: 21461328]." *Science* **293**(5539): 2425-30.

- Haxby, J. V., E. A. Hoffman, et al. (2000). "The distributed human neural system for face perception." *Trends Cogn Sci* **4**(6): 223-233.
- Haxby, J. V., B. Horwitz, et al. (1994). "The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations." *Journal of Neuroscience* **14**(11, Pt 1): 6336-6353.
- Hecker, R. and B. Mapperson (1997). "Dissociation of visual and spatial processing in working memory." *Neuropsychologia* **35**(5): 599-603.
- Held, R. (1968). "Dissociation of Visual Functions by Deprivation and Rearrangement."
- Hermann, B. P., M. Seidenberg, et al. (1993). "Dissociation of object recognition and spatial localization abilities following temporal lobe lesions in humans." *Neuropsychology* **7**(3): 343-350.
- Hickey, T. L. (1977). "Postnatal development of the human lateral geniculate nucleus: relationship to a critical period for the visual system." *Science* **198**(4319): 836-8.
- Huttenlocher, J., N. Newcombe, et al. (1994). "The coding of spatial location in young children." *Cognitive Psychology* **27**(2): 115-148.
- Huttenlocher, P. R. and A. S. Dabholkar (1997). "Regional differences in synaptogenesis in human cerebral cortex." *Journal of Comparative Neurology* **387**(2): 167-78.
- Ingle, D. (1967). "Two visual mechanisms underlying the behavior of fish." *Psychol Forsch* **31**(1): 44-51.
- Ingle, D. (2002). "A wider view of the spatial mode of vision." *Behav Brain Sci* **25**(1): 108-109.
- Ishai, A., L. G. Ungerleider, et al. (1999). "Distributed representation of objects in the human ventral visual pathway." *Proceedings of the National Academy of Sciences of the United States of America* **96**(16): 9379-84.
- Jeannerod, M. (1999). "A Dichotomous Visual Brain? (Commentary on *The Visual Brain in Action* (D. Milner & M. Goodale))." *Oxford Psychology Series*(27).
- Johnson, M., Mareschal, Denis, Csibra, Gergely (2001). *The Functional Development and Integration of the Dorsal and Ventral Visual Pathways: A*

Neurocomputational Approach. Handbook of Developmental Cognitive Neuroscience. M. L. Charles A. Nelson. Cambridge, MIT Press: 339-350.

- Johnson, M. H. (1990). "Cortical maturation and the development of visual attention in early infancy." *Journal of Cognitive Neuroscience* **2**(2): 81-95.
- Johnson, M. H. (2005). "Subcortical face processing." *Nat Rev Neurosci* **6**(10): 766-74.
- Johnson, M. H., S. Dziurawiec, et al. (1991). "Newborns' preferential tracking of face-like stimuli and its subsequent decline." *Cognition* **40**(1-2): 1-19.
- Johnson, M. H., R. Griffin, et al. (2005). "The emergence of the social brain network: evidence from typical and atypical development." *Dev Psychopathol* **17**(3): 599-619.
- Johnson, M. H., H. Halit, et al. (2002). "Neuroimaging of typical and atypical development: a perspective from multiple levels of analysis." *Dev Psychopathol* **14**(3): 521-36.
- Jones, W., U. Bellugi, et al. (2000). "II. Hypersociability in Williams Syndrome." *Journal of Cognitive Neuroscience* **12 Suppl 1**: 30-46.
- Jones, W. and Z. C. Lai (1997). "The relationship between intact face processing and impaired spatial cognition in Williams syndrome." *International Behavioral Neuroscience Society Abstracts* **6**(59): #P2-51.
- Kaas, J. H. and D. C. Lyon (2007). "Pulvinar contributions to the dorsal and ventral streams of visual processing in primates." *Brain Res Rev*.
- Kaldy, Z. and I. Kovacs (2003). "Visual context integration is not fully developed in 4-year-old children." *Perception* **32**(6): 657-66.
- Kaldy, Z. and A. M. Leslie (2003). "Identification of objects in 9-month-old infants: Integrating 'what' and 'where' information." *Developmental Science* **6**(3): 360-373.
- Kanwisher, N., J. McDermott, et al. (1997). "The fusiform face area: a module in human extrastriate cortex specialized for face perception." *Journal of Neuroscience* **17**(11): 4302-11.

- Karmiloff-Smith, A. (1997). "Crucial differences between developmental cognitive neuroscience and adult neuropsychology." *Developmental Neuropsychology* **13**(4): 513-524.
- Karmiloff-Smith, A. (2007). "Atypical epigenesis." *Dev Sci* **10**(1): 84-8.
- Karmiloff-Smith, A., G. Scerif, et al. (2002). "Different approaches to relating genotype to phenotype in developmental disorders." *Dev Psychobiol* **40**(3): 311-22.
- Karmiloff-Smith, A., M. Thomas, et al. (2004). "Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories." *J Child Psychol Psychiatry* **45**(7): 1258-74.
- Kesler/West, M. L., A. H. Andersen, et al. (2001). "Neural substrates of facial emotion processing using fMRI." *Cognitive Brain Research* **11**(2): 213-226.
- Kim, D., G. Wylie, et al. (2006). "Magnocellular contributions to impaired motion processing in schizophrenia." *Schizophr Res* **82**(1): 1-8.
- Kippenhan, J. S., R. K. Olsen, et al. (2005). "Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome." *J Neurosci* **25**(34): 7840-6.
- Klingberg, T. (2006). "Development of a superior frontal-intraparietal network for visuo-spatial working memory." *Neuropsychologia* **44**(11): 2171-7.
- Klingberg, T., H. Forssberg, et al. (2002). "Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood." *J Cogn Neurosci* **14**(1): 1-10.
- Kohler, S., S. Kapur, et al. (1995). "Dissociation of pathways for object and spatial vision: a PET study in humans." *Neuroreport* **6**(14): 1865-8.
- Korenberg, J. R., X.-N. Chen, et al. (2001). Genome structure and cognitive map of Williams syndrome. *Journey from cognition to brain to gene: Perspectives from Williams syndrome*. U. Bellugi and M. S. George. Cambridge, MA, The MIT Press: 147-177.
- Korenberg, J. R., X.-N. Chen, et al. (2000). Williams syndrome: Genes and pathway responsible for human cognition. American Society for Human Genetics.

- Kovacs, I. (2000). "Human development of perceptual organization." *Vision Research* **40**(10-12): 1301-1310.
- Kovacs, I., P. Kozma, et al. (1999). "Late maturation of visual spatial integration in humans." *Proc Natl Acad Sci U S A* **96**(21): 12204-9.
- Kraut, M., J. Hart, Jr., et al. (1997). "Object shape processing in the visual system evaluated using functional MRI." *Neurology* **48**(5): 1416-1420.
- Kucian, K., M. von Aster, et al. (2006). "Brain activation during mental rotation in school children and adults." *J Neural Transm.*
- Kwon, H., A. L. Reiss, et al. (2002). "Neural basis of protracted developmental changes in visuo-spatial working memory." *Proc Natl Acad Sci U S A* **99**(20): 13336-41.
- Laing, E., G. Butterworth, et al. (2002). "Atypical development of language and social communication in toddlers with Williams syndrome." *Developmental Science* **5**(2): 233-246.
- Lange-Kuttner, C. and A. D. Friederici (2000). "Modularity of object and place memory in children." *Brain Cogn* **43**(1-3): 302-5.
- Le, S., D. Cardebat, et al. (2002). "Seeing, since childhood, without ventral stream: a behavioural study." *Brain* **125**(Pt 1): 58-74.
- Leneman, M., L. Buchanan, et al. (2001). "Where and what visuospatial processing in adolescents with congenital hypothyroidism." *J Int Neuropsychol Soc* **7**(5): 556-62.
- Leslie, A. M., F. Xu, et al. (1998). "Indexing and the object concept: developing 'what' and 'where' systems." *Trends in Cognitive Science* **2**(1).
- Levitin, D. J., K. Cole, et al. (2004). "Characterizing the musical phenotype in individuals with Williams Syndrome." *Child Neuropsychol* **10**(4): 223-47.
- Levitin, D. J., V. Menon, et al. (2003). "Neural correlates of auditory perception in Williams syndrome: an fMRI study." *Neuroimage* **18**(1): 74-82.
- Lorsbach, T. C. and J. F. Reimer (2005). "Feature binding in children and young adults." *J Genet Psychol* **166**(3): 313-27.

- Luciana, M., H. M. Conklin, et al. (2005). "The development of nonverbal working memory and executive control processes in adolescents." *Child Dev* **76**(3): 697-712.
- Madrid, M. and M. A. Crognale (2000). "Long-term maturation of visual pathways." *Vis Neurosci* **17**(6): 831-7.
- Malach, R., J. B. Reppas, et al. (1995). "Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex." *Proceedings of the National Academy of Sciences of the United States of America* **92**(18): 8135-9.
- Mareschal, D., K. Plunkett, et al. (1999). "A computational and neuropsychological account of object-oriented behaviours in infancy." *Developmental Science* **2**(3): 306-317.
- Mash, C., P. C. Quinn, et al. (1998). "Global influences on the development of spatial and object perceptual categorization abilities: Evidence from preterm infants." *Developmental Science* **1**(1): 85-102.
- Maunsell, J. H. and W. T. Newsome (1987). "Visual processing in monkey extrastriate cortex." *Annual Review of Neuroscience* **10**(3): 363-401.
- Maurer, D., R. L. Grand, et al. (2002). "The many faces of configural processing." *Trends Cogn Sci* **6**(6): 255-260.
- McCarthy, G., A. Puce, et al. (1997). "Face-specific processing in the human fusiform gyrus." *Journal of Cognitive Neuroscience* **9**(5): 605-610.
- Mecklinger, A. and N. Mueller (1996). "Dissociations in the processing of "what" and "where" information in working memory: An event-related potential analysis." *Journal of Cognitive Neuroscience* **8**(5): 453-473.
- Merigan, W. H. and J. H. Maunsell (1993). "How parallel are the primate visual pathways?" *Annual Review of Neuroscience* **16**: 369-402.
- Mervis, C. B., C. A. Morris, et al. (1999). *Williams Syndrome: Findings from an integrated program of research. Neurodevelopmental disorders*. H. Tager-Flusberg. Cambridge, MA, The MIT Press: 65-110.
- Mervis, C. B., C. A. Morris, et al. (2003). "Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions." *Dev Neuropsychol* **23**(1-2): 243-68.

- Mervis, C. B., B. F. Robinson, et al. (2000). "The Williams syndrome cognitive profile." *Brain Cogn* **44**(3): 604-28.
- Meyer-Lindenberg, A., A. R. Hariri, et al. (2005). "Neural correlates of genetically abnormal social cognition in Williams syndrome." *Nat Neurosci* **8**(8): 991-3.
- Meyer-Lindenberg, A., P. Kohn, et al. (2004). "Neural basis of genetically determined visuospatial construction deficit in Williams syndrome." *Neuron* **43**(5): 623-31.
- Meyer-Lindenberg, A., C. B. Mervis, et al. (2006). "Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour." *Nat Rev Neurosci* **7**(5): 380-93.
- Mills, D. L., T. D. Alvarez, et al. (2000). "III. Electrophysiological studies of face processing in Williams syndrome." *Journal of Cognitive Neuroscience* **12 Suppl 1**(6): 47-64.
- Milner, A. D. and M. A. Goodale (1995). "The visual brain in action."
- Mishkin, M., L. G. Ungerleider, et al. (1983). "Object vision and spatial vision: Two cortical pathways." *Trends in Neurosciences* **6**(10): 414-417.
- Mitchell, T. V. and H. J. Neville (2004). "Asynchronies in the development of electrophysiological responses to motion and color." *J Cogn Neurosci* **16**(8): 1363-74.
- Mondloch, C. J., S. Geldart, et al. (2003). "Developmental changes in face processing skills." *Journal of Experimental Child Psychology* **86**(1): 67-84.
- Mondloch, C. J., R. Le Grand, et al. (2002). "Configural face processing develops more slowly than featural face processing." *Perception* **31**(5): 553-66.
- Mooney, C. M. (1957). "Closure as affected by viewing time and multiple visual fixation." *Canadian Journal of Psychology* **11**: 21-28.
- Morris, J. S., C. D. Frith, et al. (1996). "A differential neural response in the human amygdala to fearful and happy facial expressions." *Nature* **383**(6603): 812-5.
- Morris, J. S., A. Ohman, et al. (1999). "A subcortical pathway to the right amygdala mediating "unseen" fear." *Proc Natl Acad Sci U S A* **96**(4): 1680-5.
- Nagel, B. J., V. C. Barlett, et al. (2005). "Neuropsychological predictors of BOLD response during a spatial working memory task in adolescents: what can

- performance tell us about fMRI response patterns?" *J Clin Exp Neuropsychol* **27**(7): 823-39.
- Naveh-Benjamin, M. (1987). "Coding of spatial location information: an automatic process?" *J Exp Psychol Learn Mem Cogn* **13**(4): 595-605.
- Nelson, C. A., C. S. Monk, et al. (2000). "Functional neuroanatomy of spatial working memory in children." *Developmental Psychology* **36**(1): 109-116.
- Neville, H. and D. Bavelier (2002). Specificity and Plasticity in Neurocognitive Development in Humans. *Brain Development and Cognition: A Reader*. M. H. Johnson, Y. Munakata and R. O. Gilmore. Oxford, Blackwell Publishing: 544.
- Neville, H. J. and D. Lawson (1987). "Attention to central and peripheral visual space in a movement detection task: An event-related potential and behavioral study: I. Normal hearing adults." *Brain Research* **405**(2): 253-267.
- Neville, H. J. and D. Lawson (1987). "Attention to central and peripheral visual space in a movement detection task: An event-related potential and behavioral study: II. Congenitally deaf adults." *Brain Research* **405**(2): 268-283.
- Newcombe, F., G. Ratcliff, et al. (1987). "Dissociable visual and spatial impairments following right posterior cerebral lesions: Clinical, neuropsychological and anatomical evidence." *Neuropsychologia* **25**(1-B): 149-161.
- Newcombe, F. and W. R. Russell (1969). "Dissociated visual perceptual and spatial deficits in focal lesions of the right hemisphere."
- Newcombe, N., J. Huttenlocher, et al. (1998). "The development of spatial location coding: Place learning and dead reckoning in the second and third years." *Cognitive Development* **13**(2): 185-200.
- Newcombe, N. S. and J. Huttenlocher (2000). *Making space: the development of spatial representation and reasoning*. Cambridge, Mass., MIT Press.
- Newman, C., J. Atkinson, et al. (2001). "The development of reaching and looking preferences in infants to objects of different sizes." *Dev Psychol* **37**(4): 561-72.
- Norman, J. (2002). "Two visual systems and two theories of perception: An attempt to reconcile the constructivist and ecological approaches." *Behav Brain Sci* **25**(1): 73-96; discussion 96-144.

- Olesen, P. J., Z. Nagy, et al. (2003). "Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network." *Brain Res Cogn Brain Res* **18**(1): 48-57.
- Park, D. C. and C. Q. James (1983). "Effect of encoding instructions on children's spatial and color memory: Is there evidence for automaticity?" *Child Development* **54**(1): 61-68.
- Passarotti, A. M., B. M. Paul, et al. (2003). "The development of face and location processing: An fMRI study." *Developmental Science* **6**(1): 100-117.
- Paterson, S. J. and R. T. Schultz (2007). "Neurodevelopmental and behavioral issues in williams syndrome." *Curr Psychiatry Rep* **9**(2): 165-71.
- Posner, M. I., M. Rothbart, et al. (1998). "The Development of Orienting to Locations and Objects." *Visual Attention*: 269-287.
- Quinn, P. C. (1998). Object and spatial categorisation in young infants: "What" and "Where" in early visual perception. *Perceptual Development: Visual, Auditory, and Speech Perception in Infancy*. A. Slater. London, Psychology Press: 131-165.
- Quinn, P. C. and P. D. Eimas (1996). *Perceptual Organization and Categorization in Young Infants*. *Advances in Infancy Research*. C. Rovee-Collier and L. P. Lipsitt. Norwood, New Jersey, Ablex Publishing Corporation. **10**: 1-31.
- Rao, H., T. Zhou, et al. (2003). "Spatiotemporal Activation of the Two Visual Pathways in Form Discrimination and Spatial Location: A Brain Mapping Study." *Human Brain Mapping* **18**(2): 78-89.
- Reiss, A. L., M. A. Eckert, et al. (2004). "An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome." *J Neurosci* **24**(21): 5009-15.
- Rossen, M., E. S. Klima, et al. (1996). Interaction between language and cognition: Evidence from Williams Syndrome. *Language, Learning, and Behavior Disorders: Developmental, Biological, and Clinical Perspectives*. E. Joseph H. Beitchman and et al. Cambridge University Press, NY, USA: 367-392.
- Rossion, B., L. Dricot, et al. (2000). "Hemispheric asymmetries for whole-based and part-based face processing in the human fusiform gyrus." *Journal of Cognitive Neuroscience* **12**(5): 793-802.

- Ruchkin, D. S., R. Johnson, Jr., et al. (1997). "Multiple visuospatial working memory buffers: evidence from spatiotemporal patterns of brain activity." *Neuropsychologia* **35**(2): 195-209.
- Sack, A. T., J. M. Sperling, et al. (2002). "Tracking the mind's image in the brain II: transcranial magnetic stimulation reveals parietal asymmetry in visuospatial imagery." *Neuron* **35**(1): 195-204.
- Sandberg, E. H., J. Huttenlocher, et al. (1996). "The development of hierarchical representation of two-dimensional space." *Child Development* **67**(3): 721-739.
- Schneider, G. E. (1969). "Two visual systems." *Science* **163**(870): 895-902.
- Schumann-Hengsteler, R. (1992). "The development of visuo-spatial memory: How to remember location." *International Journal of Behavioral Development* **15**(4): 455-471.
- Schweinsburg, A. D., B. J. Nagel, et al. (2005). "fMRI reveals alteration of spatial working memory networks across adolescence." *J Int Neuropsychol Soc* **11**(5): 631-44.
- Sereno, A. B. and J. H. Maunsell (1998). "Shape selectivity in primate lateral intraparietal cortex." *Nature* **395**: 500-503.
- Sergent, J., S. Ohta, et al. (1992). "Functional neuroanatomy of face and object processing. A positron emission tomography study." *Brain* **115 Pt 1**: 15-36.
- Shen, L., X. Hu, et al. (1999). "Neural correlates of visual form and visual spatial processing." *Human Brain Mapping* **8**(1): 60-71.
- Simons, D. J. (1996). "In sight, out of mind: When object representations fail." *Psychological Science* **7**(5): 301-305.
- Smith, E. E., J. Jonides, et al. (1995). "Spatial versus object working memory: PET investigations." *Journal of Cognitive Neuroscience* **7**(3): 337-356.
- Spelke, E. S. and L. Hermer (1996). Early cognitive development: Objects and space. Perceptual and cognitive development. *Handbook of perception and cognition* (2nd ed.). R. Gelman and T. Kit-Fong. San Diego, CA, Academic Press, Inc: 71-114.
- Spencer, J., J. O'Brien, et al. (2000). "Motion processing in autism: evidence for a dorsal stream deficiency." *Neuroreport* **11**(12): 2765-7.

- Stein, J., J. Talcott, et al. (2000). "Controversy about the visual magnocellular deficit in developmental dyslexics." *Trends Cogn Sci* **4**(6): 209-211.
- Stevens, C. and H. Neville (2006). "Neuroplasticity as a double-edged sword: deaf enhancements and dyslexic deficits in motion processing." *J Cogn Neurosci* **18**(5): 701-14.
- Tager-Flusberg, H., D. Plesa-Skwerer, et al. (2003). "People with Williams syndrome process faces holistically." *Cognition* **89**(1): 11-24.
- Tanaka, J. W. and M. J. Farah (1993). "Parts and wholes in face recognition." *Quarterly Journal of Experimental Psychology: Human Experimental Psychology* **46A**(2): 225-245.
- Taylor, M. J., M. Batty, et al. (2004). "The faces of development: a review of early face processing over childhood." *J Cogn Neurosci* **16**(8): 1426-42.
- Taylor, M. J., G. E. Edmonds, et al. (2001). "Eyes first! Eye processing develops before face processing in children." *Neuroreport* **12**(8): 1671-6.
- Taylor, M. J., G. McCarthy, et al. (1999). "ERP evidence of developmental changes in processing of faces." *Clinical Neurophysiology* **110**(5): 910-5.
- Teller, D. Y. and M. H. Bornstein (1987). Infant color vision and color perception. *Handbook of infant perception: From sensation to perception*. P. Salapatek and L. B. Cohen. Orlando, Academic Press. **1**: 185-236.
- Thomas, K. M., W. C. Drevets, et al. (2001). "Amygdala response to facial expressions in children and adults." *Biological Psychiatry* **49**(4): 309-316.
- Thomas, K. M., S. W. King, et al. (1999). "A developmental functional MRI study of spatial working memory." *NeuroImage* **10**(3 Pt 1): 327-38.
- Thompson, P. M., A. D. Lee, et al. (2005). "Abnormal cortical complexity and thickness profiles mapped in Williams syndrome." *J Neurosci* **25**(16): 4146-58.
- Tresch, M. C., H. M. Sinnamon, et al. (1993). "Double dissociation of spatial and object visual memory: Evidence from selective interference in intact human subjects." *Neuropsychologia* **31**(3): 211-219.
- Trevarthen, C. B. (1968). "Two Mechanisms of Vision in Primates." *Psychologische Forschung* **31**(4): 299-337.

- Tzourio-Mazoyer, N., S. De Schonen, et al. (2002). "Neural correlates of woman face processing by 2-month-old infants." *Neuroimage* **15**(2): 454-61.
- Udwin, O. (1990). "A survey of adults with Williams syndrome and idiopathic infantile hypercalcaemia." *Dev Med Child Neurol* **32**(2): 129-41.
- Udwin, O. and W. Yule (1991). "A cognitive and behavioural phenotype in Williams syndrome." *J Clin Exp Neuropsychol* **13**(2): 232-44.
- Udwin, O., W. Yule, et al. (1987). "Cognitive abilities and behavioural characteristics of children with idiopathic infantile hypercalcaemia." *J Child Psychol Psychiatry* **28**(2): 297-309.
- Ungerleider, L. G. and M. Mishkin (1982). Two cortical visual systems. Analysis of visual behavior. D. J. Ingle, M. A. Goodale and R. J. W. Mansfield. Cambridge, MA, MIT Press: 549-586.
- Vallar, G. and D. Perani (1986). "The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man." *Neuropsychologia* **24**(5): 609-22.
- Van de Walle, G. A., S. Carey, et al. (2000). "Bases for object individuation in infancy: Evidence from manual search." *Journal of Cognition & Development* **1**(3): 249-280.
- Van Essen, D. C., C. H. Anderson, et al. (1992). "Information processing in the primate visual system: An integrated systems perspective." *Science* **255**(5043): 419-423.
- Van Essen, D. C., D. Dierker, et al. (2006). "Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses." *J Neurosci* **26**(20): 5470-83.
- Van Essen, D. C. and J. H. Maunsell (1983). "Hierarchical organization and functional streams in the visual cortex." *Trends in Neurosciences* **6**(9): 370-375.
- Vicari, S., S. Bellucci, et al. (2006). "Evidence from two genetic syndromes for the independence of spatial and visual working memory." *Dev Med Child Neurol* **48**(2): 126-31.
- Vicari, S. and G. A. Carlesimo (2006). "Short-term memory deficits are not uniform in Down and Williams syndromes." *Neuropsychol Rev* **16**(2): 87-94.

- von Cramon, D. and G. Kerkhoff (1993). On the cerebral organization of elementary visuo-spatial perception. Functional organisation of the human visual cortex. D. O. Balázs Gulyas, and Per E. Roland. Oxford, Pergamon Press.
- Vuilleumier, P., J. L. Armony, et al. (2003). "Distinct spatial frequency sensitivities for processing faces and emotional expressions." *Nat Neurosci* **6**(6): 624-31.
- Vuilleumier, P. and G. Pourtois (2007). "Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging." *Neuropsychologia* **45**(1): 174-94.
- Wang, J., T. Zhou, et al. (1999). "Relationship between ventral stream for object vision and dorsal stream for spatial vision: An fMRI + ERP study." *Human Brain Mapping* **8**(4): 170-181.
- Wang, P. P., S. Doherty, et al. (1995). "Unique profile of visuo-perceptual skills in a genetic syndrome." *Brain Cogn* **29**(1): 54-65.
- Warrington, E. K. and M. James (1988). "Visual apperceptive agnosia: a clinico-anatomical study of three cases." *Cortex* **24**(1): 13-32.
- Warrington, E. K. and P. Rabin (1970). "Perceptual matching in patients with cerebral lesions." *Neuropsychologia* **8**(4): 475-87.
- Weintraub, D. J. (1979). "Ebbinghaus illusion: Context, contour, and age influence the judged size of a circle amidst circles." *Journal of Experimental Psychology: Human Perception & Performance* **5**(2): 353-364.
- Whalen, P. J. (1998). "Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala." *Current Directions in Psychological Science* **7**(6): 177-188.
- Williams, J. C., B. G. Barratt-Boyes, et al. (1961). "Supravalvular aortic stenosis." *Circulation* **24**: 1311-8.
- Wright, P. and Y. Liu (2006). "Neutral faces activate the amygdala during identity matching." *Neuroimage* **29**(2): 628-36.
- Xu, F. (1999). "Object individuation and object identity in infancy: the role of spatiotemporal information, object property information, and language." *Acta Psychol (Amst)* **102**(2-3): 113-36.

- Xu, F. and S. Carey (1996). "Infants' metaphysics: the case of numerical identity." *Cognit Psychol* **30**(2): 111-53.
- Xu, F., S. Carey, et al. (1999). "Infants' ability to use object kind information for object individuation." *Cognition* **70**(2): 137-66.
- Yakovlev, P. I. and A. R. Lecours (1967). The myelogenetic cycles of regional maturation of the brain. *Regional Development of the Brain in Early Life*. A. Mankowski. Philadelphia, Davis: 3-69.
- Yin, R. K. (1969). "Looking at upide-down faces." *Journal of Experimental Psychology* **81**(1): 141-145.
- Zald, D. H. and W. G. Iacono (1998). "The development of spatial working memory abilities." *Developmental Neuropsychology* **14**(4): 563-578.
- Zeki, S. (1993). *A vision of the brain*. Cambridge, MA, Blackwell Scientific Publications, Inc.