UNIVERSITY OF CALIFORNIA, SAN DIEGO

Embodied Perception: Neuropsychological and Neuroimaging Studies of Language, Vision, and Attention

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in

Cognitive Science

by

Ayşe Pınar Saygın

Committee in charge:

Professor Martin I. Sereno (Chair)
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Professor Marta Kutas

2005

The dissertation of Ayse Pinar Saygin is approved, and it is acceptable in quality and form for publication on microfilm.

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Chair

University of California, San Diego

2005

Dedicated to

Hülya and Sinan Saygın

and

In memory of Elizabeth Bates

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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I also wish to thank members of my dissertation committee for their guidance and helpful comments on this work, as well as in general on my academic career. In addition, I am grateful to Marta Kutas for all her advice on matters scientific and personal; Virginia de Sa for helping me to embark upon psychophysics projects; and Geoff Boynton and his lab for being so friendly and not minding me often attending their lab dinners and parties.

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Morana Alac, friend and collaborator, for sharing with me the peaks, the valleys and also the absurdities of academia; for all our conversations on life, work, feminism, art, androids; and for a whole lot more I cannot express in words.

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Chapter 1, in full, is a reprint of Saygin, A.P., Dick, F., Wilson, S.M., Dronkers, N. & Bates, E. (2003) Neural resources for processing language and environmental sounds: Evidence from aphasia. *Brain, 126*, 928-945. Permission to reprint was granted by the copyright holder, Oxford University Press, and all co-authors.

Chapter 2, in full, is a reprint of Saygin, A.P., Wilson, S.M., Dronkers, N.F., Bates, E. (2004). Action comprehension in aphasia: Linguistic and non-linguistic deficits and their lesion correlates. *Neuropsychologia, 42,* 1788-1804. Permission to reprint was granted by the copyright holder, Elsevier, and all co-authors.

Chapter 4, in full, is a reprint of Saygin, A.P., Wilson, S.M., Hagler, D.J. Jr., Bates, E. & Sereno, M.I. (2004). Point-light biological motion perception activates human premotor cortex. *Journal of Neuroscience, 24*, 6181-6188. Permission to reprint was granted by the copyright holder, Society for Neuroscience, and all co-authors.

Chapter 3 and Chapter 5 are included as they are being prepared for submission for publication, with the dissertation author as first author, the latter chapter co-authored with the dissertation committee chair.

CURRICULUM VITAE

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EDUCATION

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AWARDS AND HONORS

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2004 Fellow, Summer Institute in Cognitive Neuroscience at Dartmouth College, Hanover, NH (McDonnell Foundation).

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2002 Dean's Social Sciences Research Travel Award (UCSD Social Sciences Dean's Office).

2002 Departmental Travel Award to attend Academy of Aphasia Meeting (UCSD, Department of Cognitive Science).

2001 Fellow, Linguistic Society of America Summer Institute at UCSB, Santa Barbara, CA (Linguistic Society of America).

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RESEARCH FUNDING AWARDED

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Agency: European Commission (Marie Curie Intra-European Fellowship FP6-2004-Mobility 5)
Duration: 24 months

Title: Investigating Human Brain Responses to the Movements of Humanoid Robots and Androids
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PROFESSIONAL EXPERIENCE

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TEACHING EXPERIENCE

2004	Instructor, Brain Disorders and Cognition, Department of Cognitive Science, University of California, San Diego, CA.
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PROFESSIONAL MEMBERSHIPS

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Center for Research in Language Newsletter

Minds and Machines

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PROFESSIONAL ACTIVITIES AND SERVICE

Organizer for the UCSD Cognitive Science Distinguished Speaker Series: 2002 – 2003 (peer-elected position)

Graduate student representative, UCSD Department of Cognitive Science: 2001 – 2002 (peer-elected position)

Member of the Local Organizing Committee of Turkish Artificial Intelligence and Neural Networks Conference (TAINN'98), June, 1998, Ankara, Turkey.

Member of the Local Organizing Committee for International Symposium on Computer and Information Science (ISCIS'98), Oct. 1998, Antalya, Turkey.

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Spring, Summer 2005: Datlow, Mitch

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Spring, 2003: Jones, Elizabeth and Fiske, Laurel (with A. Butler)

Spring, Summer, 2002: Schleicher, Eva

Fall 2000, Winter and Spring, 2001: Palacios, Luis (with F. Dick)

Fall 2000: Knowles, Janelle (with F. Dick).

PUBLICATIONS AND PRESENTATIONS

Articles

Arevalo, A., Moineau, S., **Saygin, A.P.**, Ludy, C., & Bates, E. (2005). In search of Noun-Verb dissociations in aphasia across three processing tasks. *Center for Research in Language Newsletter, 17(*1), 3-17.

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Articles Submitted for Publication or in Preparation

Dick, F., **Saygin, A.P.**, Pitzalis, S., Galati, G., Bentrovato, S., D'Amico, S., Wilson, S.M., Bates, E., & Pizzamiglio, L. (submitted). What is involved and what is necessary for complex linguistic and non-linguistic auditory processing.

Hagler, D.J. Jr, **Saygin, A.P.,** & Sereno, M.I. (submitted). Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data.

Saygin, A.P. (in preparation). Biological motion perception in left-hemisphere damaged patients.

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Saygin, A.P. (2005). *Embodied perception: Neuropsychological and neuroimaging studies of language, vision and attention*. Unpublished PhD. Thesis. University of California San Diego, La Jolla, CA.

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Borovsky, A., **Saygin, A.P.**, Dronkers, N.F., & Bates, E. (2005). Lesion mapping of word class deficits in conversational speech production in aphasic stroke patients. *12th Annual Meeting of the Cognitive Neuroscience Society,* April 9-12, 2005, New York, NY.

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Borovsky, A., **Saygin, A.P.**, Wilson, S.M., Dronkers, N.F., & Bates, E. (2004). Lesion mapping of conversational speech production deficits in aphasic patients. *Society for Neuroscience Abstracts* Program No. 595.9.

Cummings, A., **Saygin, A.P.**, Dick, F., Bates, E. (2004). Is there a dissociation between verbal and environmental sound processing in young children? *14th Biennial International Conference on Infant Studies*, May 5-8, 2004, Chicago, Illinois.

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Sereno, M.I., Huang, R., **Saygin, A.P.**, Filimon, F., Hagler, D. (2004). Retinotopy of human cortex using phase-encoded video. *Society for Neuroscience Abstracts* Program No. 709.7.

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Dick, F., Galati, G., Pitzalis, S., Hagberg, G., Bentrovato, S., D'Amico, S., **Saygin, A.P.**, Pizzamiglio, L. & Bates, E. (2002) BOLD fMRI response evoked by processing of environmental sounds and their linguistic equivalents. *Society for Neuroscience Abstracts, Vol 28*, Program No. 583.5

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Saygin, A.P. & Moineau, S. (2002) Auditory agnosia with preserved verbal comprehension after unilateral left hemisphere lesion involving Wernicke's area. *Society for Neuroscience Abstracts, Vol 28*, Program No. 673.7

Saygin, A.P., Dick, F.& Bates, E. (2001) Linguistic and non-linguistic auditory processing in aphasia. *Brain and Language, 79*(1), 143-145.

Saygin, A.P. (2000) Turing Test: 50 years later. *Turing 2000: The Future of the Turing Test*. Jan. 28-30, 2000. Dartmouth College, Hanover, NH. (Invited talk).

Papers in peer-reviewed conference proceedings

Saygin, A.P. & Wilson, S.M. (2002) Paradigm reanalysis and the representation of morphologically complex words in Turkish. *38th Annual Meeting of the Chicago Linguistic Society* (CLS 38).

Saygin, A.P. (2001) Processing figurative language in a multilingual task: Translation, transfer and metaphor. Corpus-Based & Processing Approaches to Figurative Language Workshop, *Corpus Linguistics 2001*. March 29, 2001. Lancaster University, UK.

Wilson, S.M. & **Saygin, A.P.** (2001) Adverbs and functional heads in Turkish: Linear order and scope. Proceedings of *WECOL 2001: Western Conference on Linguistics* Oct 25-28, Seattle, WA.

Saygin, A.P. (1998) Simple feature selection methods that make a difference: An application to text categorization. *Proceedings of the International Computer Symposium* (ICS 98), Dec. 17-19, 1998, Taiwan.

Saygin, A.P. & Yavuz, T. (1998) Query processing in context-oriented retrieval of information. Proceedings of the *Fourth Joint Conferences on Information Science: Computer Science and Informatics* (JCIS: CSI 98), Oct. 23-28, 1998. Research Triangle Park, NC.

Book chapters

Saygin, A.P. (in press). Comments on Turing, 1950. In R. Epstein and G. Beber (Eds). *Turing Test Sourcebook.*

Dick, F., Dronkers, N., Pizzamiglio, L., Saygin, A. P., Small, S. L., & Wilson, S. M. (2005). Language and the brain. In M. Tomasello, & D. I. Slobin (Eds.), *Beyond Nature-Nurture: Essays in Honor of Elizabeth Bates*. Mahwah, NJ: Lawrence Erlbaum, pp. 237-260.

Saygin, A.P., Cicekli, I., & Akman, V. (2000) Turing Test: 50 years later. In J. Moor (Ed.) *The Turing Test : The Elusive Standard of Artificial Intelligence.* Kluwer: Amsterdam.

Reviews

Saygin, A.P. (2001) Review of Horn, R. et al. Mapping Great Debates: Can Computers Think? Seven maps and a handbook. *Minds and Machines, 11*(3): 442-445.

Seminars, Colloquia and Lectures

Sep 2, 2005 – Vision as an embodied process; Cognitive and Cognitive Neuroscience Seminar, Department of Psychology, Vanderbilt University, Nashville, TN.

March 25, 2005 – Using functional MRI as a research methodology in android science; Talk given at ATR, Japan.

Jan 12, 2005 - Understanding others and the theory of “neural simulation”; Guest lecture for CogSci 91: Students for Cognitive and Neurosciences, Department of Cognitive Science, UCSD.

Sept 16, 2004 – Brain areas involved in biological motion perception/Retinotopy in higher cortical areas studied with structured motion; Talk given at Institute for Cognitive Neuroscience, University College London, London, UK.

June 5, 2004 – Human premotor cortex and the perception of point-light biological motion; 2004 Annual Spring Retreat for Cognitive Neuroscience, San Diego.

Dec 1, 2003 – Brain areas involved in the perception of point light biological motion; Colloquium at the Department of Cognitive Science, UCSD.

Oct 15, 2003 – Neuropsychological and neuroimaging studies of biological motion processing. UCLA Brain Mapping Seminars, University of California, Los Angeles.

Oct 14, 2003 – Brain areas involved in the processing of biological motion revealed by voxel-based lesion-symptom mapping (VLSM) and fMRI; Colloquium for the Center for Research in Language, UCSD.

Oct 8, 2003 – Language and the Brain – Guest lecture for the Cogsci 1: Introduction to Cognitive Science, Department of Cognitive Science, UCSD.

May 31, 2003 - Lesion correlates of non-linguistic impairments in left-hemisphere injured patients; 2003 Annual Spring Retreat for Cognitive Neuroscience, Del Mar, CA.

April 15, 2003 - Action comprehension in aphasia: Linguistic and non-linguistic deficits and their lesion correlates. PDPNLP - Colloquium for the Center for Research in Language, UCSD.

Feb 18. 2003 - Neural resources for processing speech and environmental sounds: VLSM and fMRI (with Frederic Dick) PDPNLP - Colloquium for the Center for Research in Language, UCSD.

Jan 14, 2003 - Neural resources for processing speech and environmental sounds: Lesion-symptom mapping of patients with left hemisphere damage and fMRI on normal controls; (with Frederic Dick) Project in Cognitive and Neural Development “Science Series”, UCSD.

May 29, 2001 - Verbal and non-verbal auditory processing in aphasia; PDPNLP - Colloquium for the Center for Research in Language, UCSD.

May 10, 2001 - Turing Test and cognitive science; Guest lecture for CogSci 91: Students for Cognitive and Neurosciences, Department of Cognitive Science, UCSD.

April 30, 2001 - Pragmatics in human-computer conversations; Colloquium at the Dept. of Cognitive Science, UCSD

Oct 1999 - Philosophical aspects of the Turing Test; Guest lecture for Phil 136: Philosophy of Mind, Department of Philosophy, UCSD.

Nov 12, 1998 - Turing Test: 50 years later; METU Cognitive Science Colloquium, Ankara, Turkey.

Sep 29, 1998 - The Turing Test; ACM-SIGART (Association for Computing Machinery - Special Interest Group on Artificial Intelligence) Bilkent Chapter, Ankara, Turkey.

ABSTRACT OF THE DISSERTATION

Embodied Perception: Neuropsychological and Neuroimaging Studies of Language, Vision, and Attention

by

Ayşe Pınar Saygın

Doctor of Philosophy in Cognitive Science

University of California, San Diego, 2005

Professor Martin I. Sereno, Chair

In nature, organisms not only process what is in the environment, but also continuously use the sensory information gathered in planning and acting upon the environment. Thus a theory of perception which regards it as a passive, receptive process is not likely to provide a complete picture. Instead, we can view perception as intimately related to processes and brain areas which were traditionally viewed as motor or executive in nature.

I have studied the neural substrates of human perception in different modalities and at different levels of complexity. There are three main research areas represented in this dissertation: 1) The sensorimotor neural bases of language; 2) Sensory and motor areas involved in biological motion perception; 3) Representations of visual space in higher cortical areas and their response properties.

First, in neuropsychological studies, I have examined the extent to which language comprehension shares processing and neural resources with other complex non-linguistic skills. The results support a view of language as a system which has considerable behavioral and neural links with related non-linguistic skills and sensorimotor substrates. Second, I explored brain areas involved in the visual perception of actions represented with motion cues (point-light biological motion) in both

neuropsychological and neuroimaging (fMRI) experiments. The results suggest that these stimuli are processed in not only posterior, motion-sensitive areas of the brain, but also in premotor areas in frontal cortex. Third, using fMRI, I have aimed to identify retinotopic maps in the human brain and to explore their functional properties. I found significant, well-defined retinotopic maps in multiple areas in the brain, including some which are not traditionally thought to be visual areas. Furthermore, retinotopic responses were affected both by the complexity of stimuli and by attention, with attention as important as visual stimuli in several areas.

These experiments highlight the embodied nature of perception and show that perceptual processes show a great deal of flexibility to subserve a variety of goals, and rely on multiple levels of representations across multiple modalities, often times including significant involvement of motor or executive neural resources.

Introduction to the Dissertation

In this dissertation I report on several experiments designed to study human perception in different modalities, at different levels of complexity. I have used two complementary brain mapping methods to localize the brain areas involved: Lesion mapping using structural MRI (magnetic resonance imaging) scans of patients with brain lesions and functional MRI scans of healthy subjects.

Opinions regarding the localization of sensory, motor and cognitive functions in the brain has been a topic of debate since the early days of neurology. On one end of the spectrum we have "phrenological" theories where each function is subserved by individual regions of cortex (e.g., Fodor, 1983), at the other extreme lie "equipotential" theories where the brain does not have a very clear-cut organization, and a given region of cortex may be involved with multiple functions (e.g., Lashley, 1950). Today, with advances in technologies such as CT (computerized tomography) and MRI we are able to study the localization of functions in the human brain better than ever before and it is no longer interesting to ask whether or not there is any organization in the brain (there is). However much remains to be understood about the nature of this organization and the nature of representations in the brain areas, or networks of areas we identify using these techniques.

I am interested in how humans perceive and understand objects and events in the environment, and how these are represented in the brain in relation to sensory and motor systems. I have had two basic and interrelated approaches which guided my research: 1) What is known about sensory and motor areas, their functional, as well as anatomical properties (preferred stimulus, connectivity, topography) can be used to help "bootstrap" the understanding of processing in domains which are considered more complex or are less-understood; 2) The study of human cognition is interdisciplinary, where the best outcomes are obtained when insights from various disciplines guide studies in others, and results from different methodologies are used to complement one another.

In this endeavor, it may be unexpected, based on a traditional view of sensation and perception, to consider motor areas as well as sensory areas. However, especially in recent years, there

has been accumulating evidence that the study of perception is intimately related to processes (and brain areas) which were previously thought to be motor or executive in nature. As will be detailed below, it appears that the nervous system can link perception and action more directly than envisioned earlier – e.g., motor and somatosensory areas of the brain can be activated by visual and auditory stimuli, and multiple topographic maps of visual space are laid out in temporal, parietal and even frontal cortex subserving spatial processing for attention, saccades, hand and head movements, etc… This dissertation provides various pieces of evidence which support such "embodied" views of perception and cognition, a view which emphasizes the role of the body and its interaction with the environment in the functional organization of the brain.

There are three main research areas represented in this dissertation: 1) The sensorimotor "grounding" of language; 2) Sensory and motor areas involved in action and biological motion perception; 3) Visuospatial maps in higher cortical areas and their response properties. In each of these research areas I have examined the relationship between perception and cognition, and sensory and motor brain areas. I will next give an introduction to each of these topics separately. However, these three areas are not addressed separately in individual chapters of the dissertation; more than one chapter can be relevant to one area, or more than one area can be relevant to a chapter.

The sensorimotor "grounding" of language

The first research area addressed here is the sensorimotor "grounding" of language, more specifically examining the extent to which language shares processing and neural resources with other complex non-linguistic skills.

The neural organization of language has been one of the major domains of discussion regarding localization of functions in the brain. From the very early days of neurology (e.g., Broca's report of Broca's area as "the special faculty of articulated language" in 1861), many researchers have been compelled by the idea of "language areas", regions of the brain dedicated exclusively to carrying out language functions. Many contemporary researchers and linguists also take an explicitly modular

position in which linguistic processes are subserved in specific processing systems and/or brain regions (e.g., Grodzinsky, 2000; Mauner, Fromkin, & Cornell, 1993).

By contrast, especially in recent years, many researchers have moved away from a modular view of language organization without resorting to a theory of equipotentiality. This view of language and cognition, typically known as "embodied cognition" is an approach originally seen in the works of early researchers in affect (James, 1994), perception (Gibson, 1951) and development (Piaget, 1928). Here, the brain is acknowledged to have significant functional and anatomical organization. However, this division of labor is driven not by high-level psychological domains, but by the body that inhabits it. Thus in this view, language and other higher-order skills emerge from, and are intimately linked to, related, more evolutionarily ancient sensory and motor substrates.

There are many ways in which researchers have tested hypotheses from embodied cognition (including some which are mentioned in the next section of this introduction). One particular prediction of embodied cognition would be that we should be able to see neural relationships between linguistic processes and non-linguistic processes which share sensory, motor, attentional and cognitive demands. In my thesis, I have addressed this hypothesis in patients with language disorders due to stroke (aphasia) both by analyzing behavioral outcomes, and by mapping lesion correlates of deficits. The hypotheses were as follows: If language-impaired patients also show systematically related deficits in non-linguistic domains which are comparable in complexity and sensorimotor demands to a language task, then this supports the embodied cognition hypothesis, or at least goes against a domain-specific language impairment in aphasia. If on the other hand language is impaired in isolation in these patients, then this supports a domain-specific view of language disorders, and potentially, language organization in the brain.

Language deficits due to brain damage have traditionally been classified using the following broad categories: 1) non-fluent or Broca's aphasia, characterized by slow and effortful speech, problems with grammatical complexity, and a reduction in overall verbal complexity; 2) fluent or Wernicke's aphasia, characterized by relatively fluent but empty speech, which may be almost jargon in some patients, and poor language comprehension; 3) anomic aphasia, marked by word-finding

problems (which all aphasics exhibit), and mild deficits in other tasks; 4) conduction aphasia, characterized by problems with repetition; and 5) global aphasia, marked by severe deficits in both language production and comprehension. According to classical theories, Broca's aphasia is associated with damage to Broca's area (left inferior frontal gyrus, Brodmann Areas (BA) 44 and 45), Wernicke's aphasia is an outcome of lesions to Wernicke's area (a large region centered around the left posterior superior temporal gyrus; some definitions include the middle temporal gyrus and the temporoparietal junction, or parts of the inferior parietal lobe), and conduction aphasia is caused by the disruption of the arcuate fasciculus, which is the white matter fiber connecting temporal lobe to frontal cortex (i.e, runs between Broca's and Wernicke's areas). However, as mentioned before, the advent of neuroimaging has made lesion localization much easier in the past few decades and a number of studies have now shown that the relations between lesion locus and language deficits are much more variable and complicated than was proposed by classical theories (Bates, Wilson, Saygin, Dick, Sereno, Knight & Dronkers, 2003; Dick, Bates, Wulfeck, Utman, Dronkers, & Gernsbacher, 2001; Dronkers, 1996; Dronkers, Redfern, & Knight, 2001; Kempler, Metter, Curtiss, Jackson, and Hanson (1991), Mohr, Pessin, Finkelstein, Funkenstein, Duncan, & Davis, 1978; Willmes & Poeck, 1993; Wilson & Saygin, 2004).

While the study of language as a special, independent system has been a dominant approach in the cognitive sciences and linguistics, since the early days of neurology, there has also been speculation – and empirical evidence – supporting a more intimate relationship between language processing and other cognitive and sensorimotor domains. To my knowledge, Finkelnburg (1870) was the first to propose that an underlying factor was common to both the language impairments in aphasia and the deficits in nonverbal domains. This idea received some support from subsequent pioneers in neurology (Goldstein, 1948; Head, 1926). More recently, impairments in nonverbal domains in aphasic patients have indeed been demonstrated in experimental settings, in non-linguistic tasks such as gesture (e.g., Duffy & Duffy, 1981) and environmental sound comprehension (e.g., Varney, 1980). However, systematic relations between these impairments and the language deficits have not been established and the lesion correlates of deficits also remain largely unknown.

In this area of my research, my goal was to address domain-specificity of impairments in aphasia as well as lesion correlates of these deficits. In Chapters 1 and 2 of the dissertation, I report on two experiments carried out on groups of aphasic patients and age-matched control subjects. Chapter 1 is a neuropsychological study assessing the relationship between verbal and nonverbal comprehension of complex, meaningful information in the auditory modality by examining aphasic patients' performance in matching environmental sounds (such as the sound of a cow mooing, or a car starting) and corresponding linguistic phrases to associated pictures, using a forced-choice task. Task demands, stimulus characteristics, and semantic features were all carefully controlled; additional details and data provided in (Saygin, Dick & Bates, 2005). Similarly in Chapter 2, I report on an analogous experiment in the visual modality, examining patients' processing of meaningful, transitive actions using corresponding linguistic and non-linguistic stimuli.

The relative merits and problems of group vs. single-case studies has been a long-standing debate in neuropsychology (e.g., Caramazza, 1986; Shallice, 1988). In my neuropsychological experiments, by testing groups of patients I have avoided the pitfalls of the single-case method (lack of generalizability of results to larger populations and the lack of statistical power). On the other hand, group studies can also be criticized for making arbitrary dissections based on classic neuropsychological taxonomies which may have limited validity. Furthermore, there is the potential to lose important information about individual patients. It is possible however to use the strengths of both methods on group data in a multidimensional analysis (Bates, Saygin, Moineau, Marangolo & Pizzamiglio, 2005). Furthermore, dissociations can be studied in a quantified manner such that individual cases of interest can be unveiled (Bates, Appelbaum, Salcedo, Saygin, & Pizzamiglio, 2003). Indeed with such an analysis I have identified a very unusual case of severe non-verbal auditory agnosia following left hemisphere damage, with little effect on language processing and further studied this patient behaviorally and with fMRI (Saygin, Dick, Moineau, Dronkers, Bates, & Sereno, 2005 and in preparation).

In addition to examining behavioral deficits and their relations across domains (linguistic, non-linguistic), for both experiments, I have carried out group-level lesion-mapping results, in Chapter

2 (and 3, see next section) I was able to use the novel method and tool developed by our group: Voxel-based lesion-symptom mapping (VLSM; Bates, Wilson, Saygin, Dick, Sereno, Knight & Dronkers, 2003).

Most previous lesion-symptom mapping work has employed one of two basic approaches: In the "groups defined by behavior" method, a cutoff is stipulated on the behavioral measure(s). Patients who perform below the cutoff are categorized as "impaired", whereas those who perform above it are designated as "intact". An overlay of all the impaired patients lesions can be constructed to determine whether there is an area which is consistently damaged in these patients. (This method has been used in Chapter 1). In the "groups defined by lesion" method, patients are classified based on neuroanatomical criteria. For instance, patients might be divided into groups according to whether or not their lesions involved the parietal lobe. These groups are then compared on the behavioral measures of interest.

Voxel-based lesion-symptom has advantages compared to these methods because it uses both continuous behavioral information (no cutoff) and continuous lesion information (no categorization). The lesion-behavior relationship is inferred on a voxel-by-voxel basis across the group. At each voxel, patients are divided into two groups: Those whose lesion includes that particular voxel, and those whose lesion spares that voxel. The behavioral scores of these two groups are then statistically compared at each voxel (e.g., a t-test) and the results are plotted as color or intensity maps revealing areas associated with behavioral deficits. The statistic which appears to be most appropriate for moderate sample sizes (about 20-30 patients) is d, a standard measure of effect size, which is determined by dividing the difference in group means by the pooled sample standard deviation. The d-maps are smoothed in-plane with a circular filter (usually with a radius of about 7 voxels or approximately 3.5 mm). Voxels where fewer than a set number of patients (e.g., 5) have lesions are typically excluded, as d is a measure of effect size, not an inferential statistic, so values are not reliable if either of the two groups being compared is not well represented. Inferential statistics on regions of interest (ROI) can also be computed. Chapters 2 and 4 use this method and specific details are described therein (the data in Chapter 1 has subsequently been analyzed with this method with no change to the basic results of the study).

Another advantage of VLSM is that it provides a more tangible link than before between lesion and neuroimaging studies because the same graphical formats, coordinate systems (e.g., Talairach or MNI coordinates) and statistics that are currently used to assess fMRI and PET data are being used for lesion-symptom mapping data. Indeed we have used VLSM results from the experiment reported in Chapter 1 in conjunction with an analogous fMRI study of environmental sound and speech processing in healthy controls and integrated localization results from these two different brain mapping methods (Dick, Saygin, Pitzalis, Galati, Bentrovato, D'Amico, Wilson, Bates & Pizzamiglio, in preparation).

As explained in the chapters in detail, the results of both experiments, as well as other research I have been involved with which is not included here (e.g., Dick et al., in prep.; Wilson, Saygin, Sereno & Iacoboni, 2004) are not consistent with the view that language is a domain-specific system, but rather support a view of language as a system which has considerable behavioral and neural links with related non-linguistic skills and with the sensorimotor substrates that allow it to be perceived and produced.

Sensory and motor areas involved in action and biological motion perception

Perceiving and interpreting other individuals' movements and actions is one of the most fundamental processes for many organisms' survival and well-being. Whether the process is one of tracking and hunting prey, detecting and avoiding predators, learning to solve a problem from observation, or inferring and acting in accordance with social cues, in many biologically relevant situations, organisms must be able to observe their conspecifics and understand what their movements and actions mean. However, despite being ubiquitous this process is actually a rather complicated problem for neuroscience and its simplicity is deceptive.

To illustrate, suppose that you are looking at another person raising their arm and waving their hand. You can effortlessly process the signals that enter your visual system, perceive another person's form, identify the body and its parts, process the motion signals and understand which body part is being moved in which manner, and you will likely also be able to infer the person's intention or

goal because you have been raised in a society in which this action has a specific meaning. In this example, your experience of the other individual's action enters your system through the visual sensory modality. However, your experience of your own arm and what it is like to move and wave it around in this manner and what that action may mean about your internal states is rarely perceived visually. That first person knowledge is largely motor, kinesthetic, and also is tied to your own motivational and emotional states. It is thus remarkable that you can so effortlessly and quickly perceive what this *other* person is doing and *know* what kind of action it is even though the representations you are working with are in different modalities. Such a mapping between a third person action (which is most often visually perceived) and a first person action (which is mostly kinesthetically experienced but rarely visually perceived) is not trivial and has indeed been a topic of discussion in the philosophy of mind (see Baressi & Moore, 1996).

At any given time, an organism is likely processing information coming into their sensory system, and using this information, along with data from its own internal states, to plan and guide its actions. In fact, this kind of neural computation underlies a vast range of behavior. The sensory input can be simpler or more complex, relevant or irrelevant to the organism's goals at the time, it can be in different modalities. The planned and/or executed actions also have a wide range such as a freezing or a flight response, an eyeblink, a saccade or just covertly directing attention to a particular location, a limb extension or retraction, a sequence of motor movements, a vocalization, or the articulation of a sentence… Despite large differences in the perceptual, motor, and cognitive processes underlying different sensations and behaviors, processing sensory input in a way that guides planned or executed action is a ubiquitous task for nervous systems of varying properties and complexity.

It is possible for an organism to sense and process the actions of its conspecifics in circuitry completely separate and independent from its own sensorimotor circuitry. For instance, in the jamming avoidance response of the weakly electric fish *eigenmannia*, computations involving the fish's own signal emission and the perception of other fishes' signals are carried out in a sensory pathway which does not make a distinction between the fish's own signal and others' signals and interacts with the signal production circuitry only at the most minimal level (Heiligenberg, 1991). However the range of

behaviors that can be subserved by such systems is limited and indeed in more complex organisms we find more interconnected and interactive sensory and motor/executive systems.

In the primate cortex, roughly speaking, sensory areas lie posterior to the central sulcus, whereas motor planning, actions and executive processes are primarily controlled by areas anterior to the central sulcus. However, since perception and action are so intimately linked, it would be natural to expect this link to be reflected in brain organization. Indeed this is the case and distinct parts of frontal cortex are connected with different posterior regions with several dense fiber pathways or fasciculi.

Of specific relevance to action and biological motion processing are the parieto-frontal connections: The major association pathway between the parietal and frontal cortices is the superior longitudinal fasciculus (SLF), mediating the perception and processing of action and space. The dorsal component of the SLF connects the superior and medial parietal areas (PE, PEc, PGm) which contain neurons that code locations of body parts in a body-centered coordinate system, to the dorsal premotor and supplementary motor regions in frontal cortex (in BA 6, 8ad; or areas F2 and F7). The ventral portion of area F2 (F2vr) is a major target of areas MIP (in the caudal part of the medial bank of the intraparietal sulcus) and V6A (in the dorsal part of the anterior bank of the parietooccipital sulcus). This MIP/V6A–F2vr circuit is thought to be involved with the transformation of somatosensory and visual information for the control of the transport of the hand toward a target (Matelli & Luppino, 2001). F7 on the other hand, has a dorsal portion called the supplementary eye field (SEF), which is richly connected with the frontal eye field (FEF) and may be involved in coding object locations in space for orienting and coordinated actions. The middle component of the SLF runs between the caudal inferior parietal lobule (PG and Opt) and dorsolateral and mid-dorsolateral prefrontal areas (BA 6, 8, 9 and 46, including the FEF). This pathway, especially the LIP (lateral intraparietal area)-FEF circuit, plays a big role in oculomotor aspects of spatial function, which uses eye position and retinotopic information for computing positions in space and programming eye movements. The rostral component of the SLF connects the inferior parietal lobule (area 40 or PF/PFG) to the ventral premotor cortex and the adjacent frontal opercular region (area 6, 44, as well as parts of 9/46; or areas F4 and F5). This pathway is important for goal-directed action processing. In particular, F4 is connected with

area VIP (ventral intraparietal area) and this circuit is thought to be involved with representing peripersonal space and planning actions towards objects in this space. Area F5 on the other hand is connected with area AIP (anterior intraparietal area) and area PF, and is thought to be important for representing properties of objects (such as size and shape) and planning appropriate grasping and handling patterns in interacting with them.

While there are ample connections for perception and action to communicate effectively, there is now a body of evidence showing that the nervous system may sometimes code perceptual and executive/motor processes even more directly. Of particular relevance here is the discovery of the "mirror neuron system": Mirror neurons are a particular class of visuo-motor neurons that were first found in the frontal area F5 in the macaque monkey (Gallese, Fadiga, Fogassi & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). F5 houses motor neurons that code goal-related motor acts (Rizzolatti, Camarda, Fogassi, Gentilucci, Luppino, & Matelli,1988; Murata, Fadiga, Fogassi, Gallese, Raos, & Rizzolatti, 1997) and is heavily connected to parietal areas AIP (anterior intraparietal area) and PF. While some F5 neurons are purely motor neurons, some neurons in area F5 (and later those discovered in parietal area PF) respond not only when the monkey executes a particular goal-directed action, but also when it observes another individual perform the same or a similar action. For instance a mirror neuron that fires as the monkey itself cracks a peanut, will also fire as the monkey observes an experimenter crack a peanut. Indeed some mirror neurons are multisensory – the same neuron will fire when the monkey merely hears a peanut being cracked (Kohler, Keysers, Umilta, Fogassi, Gallese, & Rizzolatti, 2002). Much subsequent work has been carried out to understand the functional properties of these neurons in more detail, as well as their role in larger sensorimotor networks. The existence of a similar "mirror system" in humans has been suggested by a variety of magnetic stimulation (e.g., Hari, Forss, Avikainen, Kirveskari, Salenius, & Rizzolatti, 1998; Fadiga, Fogassi, Pavesi, & Rizzolatti 1995; Strafella & Paus, 2000) and MEG studies (Nishitani & Hari, 2000) and human PET and fMRI studies have revealed activation in premotor and inferior frontal cortical areas (as part of a larger network involving superior temporal and parietal regions) during action observation and imitation (e.g., Rizzolatti, Fadiga, Matelli, Bettinardi, Paulesu, Perani & Fazio, 1996;

Grafton, Arbib, Fadiga & Rizzolatti, 1996; Decety, Grezes, Costes, Perani, Jeannerod, Procyk, Grassi & Fazio, 1997; Iacoboni, Woods, Brass, Bekkering, Mazziotta & Rizzolatti, 1999; Buccino, Binkofski, Fink, Fadiga, Fogassi, Gallese, Seitz, Zilles, Rizzolatti & Freund, 2001), and during viewing of manipulable objects (Chao & Martin, 2000; Gerlach, Law & Poulson, 2002). It also appears that "mirror-like" neuronal responses exist in a variety of human brain areas – e.g., visual observation of pain activates areas of the brain which are responsive when experiencing pain (e.g., Botvinick, Jha, Bylsma, Fabian, Solomon & Prkachin, 2005), visual observation of touch sensation activates somatosensory areas (e.g., Keysers, Wicker, Gazzola, Anton, Fogassi, & Gallese, 2004), etc. In addition to subserving action processing, the current view suggests that the function of mirror and similar neurons may be more general and this system or property may be a basis for forming a connection or empathy between "self" and "other" and thus have implications in emotional and social functioning of organisms. While a thorough treatment of these issues remains outside the scope of this dissertation, it is important to note that perception and action happens in an emotional and social context, and often subserve emotional and social goals.

The discovery of mirror neurons was very exciting for neuroscience and psychology because these neurons constitute direct evidence for perceptual stimuli and motor responses sharing direct neural substrates at some level. This of course does not mean that premotor cortex "sees" or "hears" as well as primary visual and auditory areas – simply that the perceptual stimuli alone can evoke a response in these motor neurons.

. Chapters 2, 3 and 4 of the dissertation address the neural bases of action and biological motion perception in the human brain. There is already a sizable literature on action comprehension, as mentioned above. However, most of this research has been done using neuroimaging on healthy individuals. While there is a large neuropsychological literature accumulated over many decades on action production and comprehension deficits in stroke patients, this research has not been carried out or evaluated within the more contemporary framework of embodied perception and cognition outlined above. In addition, consistent lesion correlates for such impairments have not been identified. I have evaluated some of these older neuropsychological findings in the light of findings from modern studies

of action perception and designed the study reported in Chapter 2. Additionally, I have carried out voxel-based lesion-symptom mapping (VLSM) methods to these data in order to identify lesion correlates of the impairments we observed in the patients (see previous section for details).

Another area that has not received careful attention in the literature on action perception is the relationship between the mirror systems and areas of the brain known to be involved with the visual perception of biological motion – which is the topic of Chapters 3 and 4. In vision research, "point-light" biological motion stimuli have been used for decades in order to study perceptual and neural processes underlying the processing of simplified representations of human body movements (Johansson, 1973). Humans are highly adept at recognizing point-light biological motion; viewers can even infer characteristics such as gender, affect, or identity from such point-light animations (Cutting and Kozlowski, 1977; Kozlowski and Cutting, 1977; Mather and Murdoch, 1994). Children are able to recognize point-light figures from early ages (Fox & McDaniel, 1982; Pavlova, Krageloh-Mann, Sokolov & Birbaumer, 2001). Pigeons can be trained to identify point-light pecking movements (Dittrich, Lea, Barrett & Gurr, 1998) and even newborn chicks appear to have sensitivity to point-light biological motion (but not specifically to chicken biological motion; Vallortigara, Regolin & Marconato, 2005).

Point-light animations have several qualities that make them useful stimuli: They are particularly compelling examples of the form-from-motion effect, evoking very specific percepts even with relatively few dots. They exemplify that despite constituting impoverished visual input (e.g., lacking in contrast, texture or color cues), motion signals of the point-lights alone can carry much information about the action represented. Furthermore, control stimuli for point-light biological motion are readily available since it is easy to temporally or spatially "scramble" the dots – thus in the scrambled animations, local motion signals can be kept the same but without evoking the percept of a coherently moving animate form.

Although point-light motion stimuli have been used to study visual processing of motion, point-light action animations have not typically been used in studies of action perception. Do point-light animations of human actions activate the "mirror neuron" system? Or are these stimuli too

impoverished to activate the embodied network of action comprehension outlined above? I have addressed this question using neuropsychological and neuroimaging methods in Chapters 3 and 4.

Neural correlates of biological motion processing have been suggested by many researchers based on neurophysiological, neuropsychological and neuroimaging studies but the results are not entirely consistent. Areas identified in prior studies include the superior temporal gyrus (STG) and sulcus (STS) (Bonda, Petrides, Ostry & Evans, 1996; Grezes, Fonlupt, Bertenthal, Delon-Martin, Segebarth & Decety, 2001; Vaina, Solomon, Chowdhury, Sinha & Belliveau, 2001; Grossman & Blake, 2002), V5/MT+ (Grezes et al., 2001; Vaina et al., 2001), regions in parietal cortex (Bonda et al., 1996; Grezes et al., 2001; Vaina et al., 2001), and other regions in visual cortex (Vaina et al., 2001; Grossman and Blake 2002; Servos, Osu, Santi & Kawato, 2002) but results are not entirely consistent. The involvement of the STS is perhaps the most robust finding (although not found by Servos et al., 2002), supported also by electrophysiological recordings on the macaque monkey (Oram & Perrett, 1994).

Despite the rich perceptual experience evoked by point-light biological motion, frontal action processing or "mirror neuron" areas have not been reported in the perception of such animations in human functional neuroimaging studies, even when the stimuli comprise meaningful actions. Here I have used both neuropsychological (Chapter 3) and neuroimaging (Chapter 4) approaches in order to examine if the point-light actions activate frontal action comprehension networks or whether they activate only posterior areas of the brain that subserve visual motion processing.

Like parietal cortex, posterior and middle temporal cortex are also connected with frontal regions via white matter fibers. Posterior area Tpt is linked to area 8Ad via the arcuate fasciculus; and the middle region (areas PaAlt, TS3 and TPO) gives rise to a different fiber system which runs in the extreme capsule and connects mainly with area 45 (pars triangularis of the human brain) and also with areas 9, 46, and 8Ad (Petrides & Pandya, 1988). These pathways are thought to transmit auditory spatial and auditory object information to frontal cortex. Whether these connections could also communicate information about biological motion is not known. It appears that areas in parts of STS that respond to action motions and area F5 are not directly connected. However, both of these areas are

linked to the inferior parietal lobule (area PF), which also houses mirror neurons in the macaque and is considered now a part of the mirror neuron system.

In addition to addressing the relationship between biological motion and the mirror neuron system, identifying lesion correlates of impairments in biological motion perception (Chapter 3) was in itself a goal of this dissertation. There have been only a handful of neuropsychological studies concerning biological motion processing deficits after brain damage. Individual patients with deficits in low-level motion analysis who have intact biological motion processing have been reported (Vaina, Lemay, Bienfang, Choi & Nakayama, 2001; McLeod et al., 1996), as have patients with deficiencies in recognizing form-from-motion, including biological motion, in the absence of lower-level visual deficits (Cowey & Vaina, 2000). Despite findings as to its responsiveness to biological motion in electrophysiological and neuroimaging studies, the STS has not been implicated as a lesion site which is uniformly detrimental to the visual perception of such stimuli. In fact, Battelli, Cavanagh and Thornton (2003) reported three patients with parietal lesions, two with right-hemisphere damage (RHD) and one with left-hemisphere damage (LHD) to be severely impaired in a visual search task with point-light biological motion stimuli and they interpret this deficit to be due to attentional processes that may be compromised in parietal patients. Schenk and Zihl (1997) tested a group of stroke patients and found two subjects to be deficient in perceiving biological motion, both with lesions in superior parietal cortex bilaterally. These authors note the discrepancy between this lesion site and the STS findings in the macaque and propose that attentional factors may underlie the deficits of the patients they identified.

On the other hand, as mentioned above, lesions in left posterior parietal regions have long been associated with apraxia and action comprehension. Parietal cortex also is involved with spatial processes and the biological motion tasks in these experiments involved spatial search. Therefore we could hypothesize that point-light biological motion perception may also be compromised in some patients with left parietal damage because these patients have difficulties in processing and representing body movements and/or body part positions in space or due to poor processing of spatial

information. More patient studies would clearly be useful in shedding more light on the nature of deficits in these patients.

Chapter 3 is a neuropsychological study carried out on a group of left hemisphere lesioned patients which tests sensitivity to point-light biological motion perception and explores lesion correlates of poor performance. Chapter 4 reports on an fMRI study on healthy subjects which uses a fairly standard paradigm to localize areas sensitive to biological motion with slight modifications to stimuli, task, fMRI data acquisition and analysis compared with previous studies. Both studies show that in addition to posterior temporal areas, frontal areas suggested to be important for action comprehension are also involved for the processing of point-light biological motion: Patients whose lesions include inferior frontal areas performed worse than patients who don't have lesions to this area, and our fMRI study found more activity in inferior frontal and premotor cortex to point-light biological motion than to scrambled biological motion in the healthy brain.

Representations of visual space outside of visual cortex and their functional properties

In order to seamlessly and efficiently perceive and act upon our environment, we not only need to perceive and understand objects and events, but we also need to be able localize them in space, deploy our attention towards them in the appropriate time and manner, and bring the right objects to our awareness at the right times. In the first two research areas introduced above, I have been primarily concerned with studying how we understand objects and events and with developing brain mapping methods to study the areas in the brain which are important for this process. In my third line of research I have focused on visuospatial maps in human cortex, and the modulation of neural responses in these maps under different conditions of attention or awareness.

To give a simple example, consider the familiar acts of driving or riding a bike, which require our fixation and attention to be on the road in front of us a large percentage of the time. But a peripheral object, such as a cat, a pedestrian, or a biker can always attract our attention and eyes away from the center. It is also possible to keep our eyes on the road but keep our attention on an object which is in the periphery. Even though effortful, we can even be aware of, or "track" multiple objects

in the environment at one time in this manner (such as a biker on one side and a car driving next to us on the other) even while keeping our eyes in front of us. Our nervous system needs to be very flexible in order to allow us to be able to achieve all of these different states and to be able to transition between them as need be. What brain mechanisms are behind such perceptual tasks? Which brain areas allow us to rapidly and effectively shift attention to and from different objects and locations? How are unattended objects and locations (which may at any moment need attention deployed to them) represented? Such questions led to the research reported in Chapter 5 of this dissertation.

There are multiple representations of visual space laid out in topographic "maps" (often called retinotopic maps) in the occipital lobes of primates (e.g. Felleman & Van Essen, 1991). In humans, functional magnetic resonance imaging (fMRI) has been used successfully for over a decade to reveal maps similar to those identified using electrophysiology in non-human primates (Sereno, Dale, Reppas, Kwong, Belliveau, Brady, Rosen & Tootell, 1995). However, little work has been done on identifying retinotopic maps outside of occipital cortex until recently.

Retinotopic mapping protocols typically use flickering checkerboard stimuli optimized to stimulate neurons in early visual cortex. However, in both humans and other primates, higher visual areas are known to respond preferentially to complex higher-order properties of visual stimuli and may show little response to simple stimuli such as checkerboards. Indeed recent work at UCSD and elsewhere is beginning to show that there are maps in areas such as ventral and lateral temporal, parietal, even frontal cortex when more complex stimuli and/or an attentionally demanding tasks are used (Hagler & Sereno, in press; Sereno, Pitzalis & Martinez, 2001; Sereno, Saygin, & Hagler, 2003; Schluppeck, Glimcher & Heeger, 2005; Silver, Rees & Heeger, 2005).

My hypothesis was that some of these maps representing visual space might be actively used in spatial attentional processes.

In order to study this question, I have devised novel variants of retinotopic stimuli and mapping paradigms. I had two specific aims: To establish the presence and functional properties of spatial maps beyond traditional retinotopic visual cortex; and to investigate whether the response in each area is primarily attributable to the stimulus properties or to attention.

The basic phase-encoded retinotopic mapping experiment with fMRI works as follows: Subjects fixate and view a clockwise or counter-clockwise rotating pie-shaped wedge (for polar-angle mapping) or an expanding or contracting ring (for eccentricity mapping). The rotation or expansion or contraction happens at a fixed rate and a certain number of times per scan, which is the stimulus frequency. Then a Fourier analysis is performed on the time series data at each voxel. The amplitude of this Fourier transform at the stimulus frequency will reveal how "retinotopic" the voxel is, and the phase of the Fourier transform corresponds to the polar angle of the stimulus location

I have combined a standard polar-angle retinotopy paradigm with various novel modifications and developed stimuli that are complex enough to drive high-level areas, but have manipulable low-level visual features and are amenable to attentional manipulation: Like in Chapters 3 and 4, I used moving objects defined by point-lights (primarily point-light biological motion, but also non-biologically moving, translating objects composed of point-lights) but this time as parts of phase-encoded polar angle mapping paradigms. There were several reasons for choosing these stimuli: Point-light biological motion is a high-level stimulus on the one hand. It is a salient motion stimulus that is also perceived as a coherent object. On the other hand, it is also simple compared with, for example video. Because these stimuli lack visual cues other than motion (e.g., contours, color), control stimuli are relatively easily available in the form of spatial or phase scrambling of the point-lights and non-biologically moving control stimuli of relatively matched visual complexity are also possible to create. (See previous section for more detail on research on the perception and neural processing of biological motion).

In addition to using a different stimulus, a crucial modification I have made to polar angle mapping is whole-visual field stimulation instead of using a rotating wedge on a uniform background. In the standard paradigm since there is only the retinotopic stimulus on the screen, the responses due to the visual properties of the stimuli and responses due to attention cannot be teased apart. In my experiments there is a retinotopically presented stimulus and the background is also filled with visual stimuli (control stimuli, or identical stimuli). This allowed me to measure, compare and contrast retinotopic responses which are primarily sensitive to stimulus properties (revealed by the contrast

between wedge contents and background contents) and those which are primarily driven by attention (measured when the wedge and the background contain the same kind of stimuli and attention is the retinotopically "rotating" factor). Attention is manipulated by asking participants to perform either a demanding task which requires attention to the moving objects in the wedge while maintaining central fixation, or to perform an attentionally demanding task at central fixation while ignoring all the peripheral stimuli.

The design has an additional aspect which is appropriate for my purposes: the situation where we have full field vision but must select parts of the visual field to attend to is more similar to our natural visual experience than stimulation at only a restricted part of the visual field at different times (classical retinotopic mapping). Of course my stimuli are still extremely simplified and artificial compared to real vision; but they are an appropriate starting point to investigate "retinotopy in use".

My data (reported in Chapter 5) indicate that several areas show responses that "move" on the cortical surface as attention to the objects moves across visual space. With both control stimuli and identical stimuli in the background, well-defined spatiotopic maps were found in parietal, lateral and ventral temporal areas, and even in frontal cortex. When attention is not directed to the stimuli, activations are markedly reduced in both strength and extent although some maps in the vicinity of area MT/MST, V3a and some in the intraparietal sulcus still remain active. Thus retinotopic responses are affected both by the complexity of stimuli and by attention; and attention may be as important as visual stimuli in evoking activity in some areas. It is noteworthy that it is possible to activate well-defined retinotopic maps in higher areas by attention with identical stimulus in all of the visual field. This had been shown in primary visual cortex (Brefczynski & DeYoe, 1999), but here I extended this approach to higher-level stimuli and cortical areas.

Vision and space are inseparable; it is no surprise that the brain has to represent space. But there appear to be numerous maps of visual space replicated on the cortical surface. and increasingly we are finding that visual maps in cortex go well beyond early visual areas. My experiments show that both areas which process visual stimulus properties (motion and form-related cortex) and attentional

control areas (frontal and parietal cortex) are sensitive to attention and stimulus properties in a spatially specific manner. However, their response is modulated by stimulus and attention differently.

As mentioned earlier, effective perception (which is tied to action) requires flexibility and multiple levels of representation. While much remains to be understood about the precise relationships between these maps and their role in perception and action, my results suggest that the ongoing interaction of these maps enables the required flexibility, and are an integral part of the neural substrate for the required representations.

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Chapter 1

Neural Resources for Processing Language and Environmental Sounds

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Neural resources for processing language and environmental sounds
Evidence from aphasia

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Summary
Although aphasia is often characterized as a selective impairment in language function, left hemisphere lesions may cause impairments in semantic processing of auditory information, not only in verbal but also in nonverbal domains. We assessed the 'online' relationship between verbal and nonverbal auditory processing by examining the ability of 30 left hemisphere-damaged aphasic patients to match environmental sounds and linguistic phrases to corresponding pictures. The verbal and nonverbal task components were matched carefully through a norming study; 21 age-matched controls and five right hemisphere-damaged patients were also tested to provide further reference points. We found that, while the aphasic groups were impaired relative to normal controls, they were impaired to the same extent in both domains, with accuracy and reaction time for verbal and nonverbal trials revealing unusually high correlations (r = 0.74 for accuracy, r = 0.95 for reaction time). Severely aphasic patients tended to perform worse in both domains, but lesion size did not correlate with performance. Lesion overlay analysis indicated that damage to posterior regions in the left middle and superior temporal gyri and to the inferior parietal lobe was a predictor of deficits in processing for both speech and environmental sounds. The lesion mapping and further statistical assessments reliably revealed a posterior superior temporal region (Wernicke's area, traditionally considered a language-specific region) as being differentially more important for processing nonverbal sounds compared with verbal sounds. These results suggest that, in most cases, processing of meaningful verbal and nonverbal auditory information break down together in stroke and that subsequent recovery of function applies to both domains. This suggests that language shares neural resources with those used for processing information in other domains.

Keywords: aphasia; auditory agnosia; environmental sounds; Wernicke's area; lesion mapping

Abbreviations: AQ = aphasia quotient; ERD = event-related desynchronization; ERP = event-related potentials; fMRI = functional MRI; IPL = inferior parietal lobule; LHD = left hemisphere-damaged; pMTG = posterior middle temporal gyrus; pSTG = posterior superior temporal gyrus; RHD = right hemisphere-damaged; ROI = region of interest; RT = reaction time; VLSM = Voxel-based lesion-symptom mapping; UCSD = University of California San Diego; WAB = Western Aphasia Battery

Introduction
The relationship between language impairments and deficits in other cognitive and sensorimotor domains has been of interest since the early days of neurology. That aphasia itself may be symptomatic of a more general sensorimotor or cognitive disturbance is an idea with ample historical roots (Head, 1926; Goldstein, 1948). Indeed Jackson (1878), who observed a high incidence of nonverbal impairments in aphasic patients, believed that they suffer from a more general disturbance (sometimes referred to as asymbolia) and may be 'lame in thinking'.

Many studies have provided evidence for a range of nonverbal impairments in aphasic patients (see for example Gainotti and Lemmo, 1976; Ammon, 1979; Chertkow *et al*., 1997). It was noted early on (Jackson, 1878; Head, 1926) as well as more recently (De Renzi *et al*., 1968; Varney, 1978; Duffy and Duffy, 1981; Wang and Goodglass, 1992), that

deficits in comprehension and production of gesture and pantomime are strongly associated with receptive and expressive language disorders. Impairments in nonverbal domains in aphasic patients have been demonstrated in such tasks as associating pictures with corresponding objects (De Renzi *et al*., 1968), colours with pictures (De Renzi *et al*., 1972), gestures with objects (De Renzi *et al*., 1968; Varney, 1978) and sounds with pictures (Spinnler and Vignolo, 1966; Faglioni *et al*., 1969; Varney, 1980). Unfortunately, only a few studies have attempted to test aphasics systematically on nonverbal tasks that are comparable to those that show deficiencies in the language domain (Spinnler and Vignolo, 1966; Varney, 1980; Bates *et al*., 2001).

Of particular interest here is auditory agnosia—a rare neurological disorder characterized by a relatively isolated deficit in auditory comprehension despite normal hearing. When the disorder affects only verbal material, it is often called word deafness; when the deficit is in recognizing environmental sounds, it is often termed nonverbal auditory agnosia. Much of the literature on auditory agnosia consists of case studies. The associated lesions are not particularly consistent and have included unilateral right (Spreen *et al*., 1965; Haguenauer *et al*., 1979; Vignolo, 1982; Eustache *et al*., 1990; Fujii *et al*., 1990), unilateral left (Vignolo, 1982; Haguenauer *et al*., 1979; Eustache *et al*., 1990; Pasquier *et al*., 1991; Clarke *et al*., 2000) and bilateral cortical lesions (Albert *et al*., 1972; Haguenauer *et al*., 1979; Miceli, 1982; Rosati *et al*., 1982; Vignolo, 1982; Lechevalier *et al*., 1984; Motomura *et al*., 1986; Mendez and Geehan, 1988; Buchtel and Stewart, 1989; Lambert *et al*., 1989; Engelien *et al*., 1995; Kaga *et al*., 2000). Subcortical lesions can also cause this deficit (Kazui *et al*., 1990). Auditory agnosia restricted to nonverbal material is a rather rare phenomenon, previously associated with bilateral (Spreen *et al*., 1965; Albert *et al*., 1972; Kazui *et al*., 1990) or right hemisphere (Fujii *et al*., 1990) lesions.

Based on these studies, two forms of auditory agnosia have been proposed: (i) perceptual-discriminative, with patients failing to identify whether two consecutive sounds are identical; and (ii) associative-semantic, with patients being impaired at audio-visual matching or naming. Bilateral lesions appear to be implicated in severe discriminative disorders (Albert *et al*., 1972; Rosati *et al*., 1982; Vignolo, 1982; Lechevalier *et al*., 1984; Motomura *et al*., 1986; Mendez and Geehan, 1988; Buchtel and Stewart, 1989; Kazui *et al*., 1990; Taniwaki *et al*., 2000). Unilateral right hemisphere lesions can lead to normal association with impaired discrimination (Vignolo, 1982; Eustache *et al*., 1990), deficient association with normal discrimination (Spreen *et al*., 1965) or deficient association and deficient discrimination (Fujii *et al*., 1990). Unilateral left hemisphere lesions have been reported to cause deficient association and normal discrimination (Vignolo, 1982); however, in many cases discrimination has not been tested. A clear picture does not emerge from these findings, due in part to the heterogeneity of the tests used. Thorough reviews of the relevant case study literature are provided by Clarke *et al*. (1996, 2000) and Griffiths *et al*. (1999).

Environmental sounds share quite a few perceptual and informational features with language (Gygi, 2001), thus making them useful in exploring possible links between aphasia and (associative) auditory agnosia, and also more broadly between verbal and nonverbal auditory processing. Functional neuroimaging studies of human auditory processing have begun to reveal areas in the temporal lobes that are more activated for certain types of sounds than others. However, it is not yet clear whether these effects reflect divisions based on the type (e.g. music versus speech), semantic content, or spatial and temporal complexity of the sound stimuli used (Belin *et al*., 2000; Binder *et al*., 2000; Zatorre and Belin, 2001). Functional activation related to environmental sounds has been reported in only a few studies (Humphries *et al*., 2001; Lewis *et al*., 2001; Maeder *et al*., 2001; Adams and Janata, 2002; Dick *et al*., 2002*b*). Although contrasts with linguistic sounds were not always carried out or discussed in these studies, environmental sounds were observed to activate some middle and superior temporal areas in the left hemisphere that have been associated with language-related activation in earlier studies (e.g. Wise *et al*., 1991; Démonet *et al*., 1992). These results are consistent with the idea that language shares some neural mechanisms with certain nonverbal processes. In an event-related potentials (ERP) study, Van Petten and Rheinfelder (1995) explored this hypothesis and found that target words were similarly modulated when preceded by contexts consisting of environmental sounds or sentences, suggesting verbal and nonverbal information may influence a common semantic or associative space. Again using ERP, Cycowicz and Friedman (1998) showed that both types of stimuli elicit brain activity with similar characteristics as a function of familiarity and frequency. Looking at event-related desynchronization (ERD), Lebrun *et al*. (1998, 2001) observed left-lateralization for the semantic, but not perceptual processing of environmental sounds. Identifying differences and similarities in the brain mechanisms for processing these different types of auditory input is likely to be a fruitful line of research.

Experimental studies of environmental sound processing in groups of patients with brain lesions have also provided insights. In a series of papers, Vignolo, Spinnler and Faglioni reported disturbances of environmental sound recognition due to unilateral hemispheric damage (Spinnler and Vignolo, 1966; Faglioni *et al*., 1969; Vignolo, 1982). They observed that right hemisphere-damaged (RHD) patients performed significantly worse than controls on perceptual tests involving environmental sounds while left hemisphere-damaged (LHD) patients performed significantly worse on associative tests. Intrigued by the finding that left hemisphere lesions can cause associative auditory agnosia, Varney (1980) used environmental sounds in order to examine verbal and nonverbal comprehension deficits in aphasic patients, an undertaking similar to the present study. He found that defects in

environmental sound recognition were seen only in subjects with impaired verbal comprehension and that all aphasic patients with intact verbal comprehension performed well on sound recognition. There were, however, aphasic patients who were impaired in verbal comprehension, but not in sound recognition. Verbal comprehension was always as impaired as sound recognition, whereas sound recognition performance could be better than verbal comprehension. Interestingly, a similar relationship has been reported between pantomime recognition and reading comprehension (Varney, 1978). More recently, Schnider *et al*. (1994) observed that both LHD and RHD patients performed significantly worse than a group of normal controls on an environmental sound recognition test. They found no significant differences in the performance of the two patient groups; however, the pattern of errors appeared to differ over groups: LHD patients made more semantically-based errors, while RHD patients and control subjects made almost exclusively acoustic errors. For all patients, accuracy in recognizing environmental sounds correlated with language comprehension as measured by the Western Aphasia Battery (WAB) (Kertesz, 1979). Lesion-behaviour correlations showed that LHD patients with impaired environmental sound recognition tended to have damage to the posterior superior temporal gyrus (pSTG) and the inferior parietal lobe. Clarke *et al*. (1996, 2000) also tested patients with brain damage on different aspects of sound recognition. Here, patients who were deficient in the sound recognition task exhibited much variability. In these studies, however, language comprehension was not tested in relation to sound processing; the purpose of some of the experiments was to contrast sound identification and localization, topics that have recently been the focus of much research (e.g. Belin and Zatorre, 2000; Rauschecker and Tian, 2000).

There are several reasons why the above literature tends to provide fragmentary and incomplete answers when addressing the relationship between verbal and nonverbal auditory processes. Many previous studies of environmental sound processing by aphasics did not attempt to make a direct comparison between verbal and nonverbal auditory processing in the same patients. Those that did compare performance between domains used different tasks or tests in the two domains and did not control for factors such as stimulus frequency and identifiability, or the relationship between the auditory and visual stimuli (Varney, 1980; Schnider *et al*., 1994). Such factors are known to have effects on performance in verbal and nonverbal tasks. In addition, all previous studies used four or five picture displays in sound to picture matching tasks, entailing a lengthy visual processing component to the task. Thus, in analysing performance in sound processing, these studies were limited to analysing accuracy data only—losing potentially important information about the time course of processing.

The work we report allows us to address directly the relation between verbal and nonverbal auditory comprehension in chronic aphasic patients, using an 'online' (timed) recognition paradigm, with verbal and nonverbal stimuli that are matched for several factors. First, we briefly describe a norming study on a large set of environmental sound recordings. This study allowed us to test the sound stimuli for recognizability as well as to extract linguistic labels to be used in the verbal trials of the main experiment. Then we report on an online task with aphasic patients and age-matched controls in which stimuli in both domains are matched for identifiability, frequency, and semantic relationship to the visual target. In line with earlier studies by Vignolo, Faglioni and Spinnler (Spinnler and Vignolo, 1966; Faglioni *et al*., 1969), we also address the effect of semantic competition on both domains across our patient groups in order to observe whether processing in the two domains is similarly modulated by higher-level semantic or conceptual constraints.

Methods

Environmental sounds norming study

Participants

Participants were 31 undergraduate and graduate students at University of California San Diego (UCSD), aged 18–31 years with normal vision and hearing. All received class credit for their participation. Prior to the experiment, participants completed a handedness assessment questionnaire and a language history questionnaire. Subjects gave informed consent to participate in the study, which was approved by the UCSD Human Research Protections Program.

Materials

The sound stimuli were taken from digital sound effect libraries including Digifex and BBC®. The sampling rate of the sounds was 44.1 kHz, with 16-bit quantization.

Procedure

Following a procedure used by Ballas (1993), we asked subjects to listen to sounds and to press a button as soon as they believed they had identified the source of each sound. After the sound ended, subjects gave a verbal description, having been instructed to provide both a noun and a verb (e.g. dog barking, engine running). Subjects completed a practice block of eight trials and an experimental block of 236 trials.

Verbal responses were coded by two independent raters. Accuracy was computed using the raters' codes, and response time was computed only for correct trials. More detail about the procedure and results is available in Saygin (2001) and Saygin *et al*. (2002).

Aphasia study

Participants

Patients were voluntary participants recruited from Veterans' Administration Medical Centers from San Diego, CA, USA,

Table 1 *Characteristics of aphasic and RHD patients*

Initials	Age	Patient group	AQ	Site	Lesion site
B.E.	24	Broca's	71.6	SD	Frontal, temporal, parietal, insula, basal ganglia
B.K.	55	Anomic	84.4	M	Basal ganglia, insula
C.H.	66	Anomic	92.2	SD	Basal ganglia
C.W.	72	RHD	–	M	Right hemisphere (not included in group lesion analyses)
D.C.	63	Broca's	74.8	SD	Frontal, insula, basal ganglia
D.D.	56	Broca's	18.9	M	Temporal, parietal, frontal, insula
D.F.	46	Broca's	49.6	M	Temporal, parietal, frontal, insula
E.B.	32	Broca's	68.3	M	Frontal, parietal, insula
E.C.	43	Anomic	91.7	M	Frontal, temporal, parietal, insula
E.R.	81	RHD	–	SD	Right hemisphere (not included in group lesion analyses)
F.N.	58	RHD	–	SD	Right hemisphere parietal (not included in group lesion analysis)
F.Y.	77	Wernicke's	64.1	M	Inferior parietal, small region on superior temporal
G.G.	50	Anomic	90.3	SD	Small, posterior to temporal lobe
H.K.	62	Wernicke's*	47.6	M	Frontal, medial temporal, insula, subcortical
H.M.	72	Broca's	26.7	M	Frontal, temporal, parietal
J.A.	59	Anomic	79.9	M	N/A
J.B.	66	Broca's	13.8	SD	MCA-territory, acute scan shows expanding frontal lesion
J.C.	81	Anomic	91.1	SD	N/A—acute scan shows no lesion boundaries
J.D.	72	Anomic	89.8	M	Frontal, anterior temporal
J.G.	63	Anomic	80.8	M	Basal ganglia
J.H.	62	Anomic	92.4	SD	Frontal, tip of anterior temporal
J.Q.	76	Broca's	11.2	SD	Frontal, temporal, parietal, insula
J.S.	51	Broca's	48.8	SD	Frontal, temporal, parietal
J.W.	72	Anomic	90.9	SD	Temporal, parietal
K.W.	64	Anomic	98.0	SD	Frontal
L.L.	76	Anomic	78.9	M	Excluded from all analyses—possibility of multiple infarcts
L.R.	56	Anomic	79.2	SD	Frontal, temporal, parietal
M.B.	50	Broca's	31.0	SD	Frontal, insular and subcortical extension, parietal
P.B.	75	Anomic	98.0	SD	Medial frontal
P.P.	50	Wernicke's	78.0	SD	Frontal, temporal, parietal, insula
R.K.	52	RHD	–	SD	Right hemisphere (not included in group lesion analyses)
R.S.	74	Wernicke's	33.3	M	Temporal
RS	55	RHD	–	M	Right hemisphere temporal, parietal (not included in group lesion analyses)
V.H.	71	Wernicke's	78.6	SD	Frontal, anterior temporal
W.G.	82	Wernicke's	51.5	M	Temporal, parietal

*Criteria for classification for Wernicke's aphasia based on WAB subscores are as follows: fluency = 5–10; comprehension = 0–6.9; repetition = 0–7.9; naming = 0–9. Criteria for transcortical sensory aphasia are identical except for repetition (8–10). Since repetition is not a component of the task here, we found it appropriate to analyse this subject's data in the Wernicke's aphasia group. M = Martinez, CA, USA; SD = San Diego, CA, USA. Lesion summaries are based on CT or MRI scans or medical records.

or Martinez, CA, USA, and were paid $25.00 for their participation. Thirty LHD patients with varying types and severity of aphasia and five RHD patients with no measurable aphasia participated in the experiment. CT or MRI scans and the medical records of all patients were evaluated by a neurologist; only patients with unilateral lesions due to a single cerebrovascular accident were included. Exclusionary criteria included diagnosed or suspected hearing difficulties, dementia, head trauma, tumours or multiple infarcts. Aphasic patients were classified using the WAB (Kertesz, 1979) as anomic (n = 14), Broca's (n = 10) or Wernicke's aphasics (n = 6). Details are provided in Table 1.

Age-matched controls were 21 adults aged 53–78 years, with no history of audiological, neurological or psychiatric disorders; all had normal or corrected-to-normal vision, and were tested for hearing impairment with a standard questionnaire and/or with an audiometer. All were paid $25.00 for their participation. Informed consent was obtained from all subjects in accordance with guidelines of the UCSD Human Research Protections Program.

Data from two control subjects were excluded (one talked to the experimenter throughout the testing session and one reported low-frequency hearing loss afterwards). Data from one patient (L.L., anomic) were excluded due to a possibility of multiple infarcts.

Experimental design and materials

A 2-within- × 1-between-subjects design was used, with domain (verbal versus nonverbal) and semantic competition (visual target related to distracter versus visual target unrelated to distracter) as within-subject factors, and patient

group (control, RHD, Broca's, Wernicke's, anomic in the main analysis; LHD, RHD, control in a supplementary analysis) as the between-subjects factor.

Stimuli were black-and-white line drawings, nonverbal sounds and speech sounds. Visual stimuli were 10.6 cm × 10.6 cm digitized drawings culled from extensively normed picture databases. Naming norms for these pictures have been reported elsewhere (Bates *et al*., 2003). Forty-five nonverbal sound stimuli were selected from the set normed in the preliminary study explained above. Selection criteria included identifiability (moderate to high), inter-rater reliability for identifiability, imageability (identifiability/availability of picture) and recognition time. Selected sounds included animal cries ($n = 10$; e.g. cow mooing, bird chirping), human sounds ($n = 6$; e.g. sneezing, laughing), vehicle noises ($n = 5$; e.g. train, car, tractor noises), tool/machinery sounds ($n = 4$; e.g. drill, lawnmower noises), alarms/bells ($n = 5$; e.g. telephone ringing, bells tolling), water sounds ($n = 6$; e.g. dripping, pouring), sports ($n = 4$; e.g. bowling, golf) and music ($n = 5$; e.g. piano, violin). A full list of sounds used, as well as norming results on these sounds, are reported in Saygin *et al*. (2002). Speech stimuli were phrases based on the most common labels provided by the subjects in the preliminary experiment. Grammatical complexity was kept constant by putting together commonly reported nouns and verbs in 'noun phrase + verbing (+ object)' constructions. Examples of phrases used were 'cow mooing', 'water boiling' and 'someone eating an apple'. All phrases were read by a 38-year-old male speaker of American English and were digitally recorded at a sampling rate of 44.1 kHz with 16-bit quantization.

Three line drawings were matched to each sound pair: a target, a related distracter and an unrelated distracter. For example, for the sound of a cow 'mooing' or its verbal description, the target drawing was 'cow', the semantically related distracter was 'sheep', and the unrelated distracter was 'violin' (see Fig. 1). In order to ensure that the semantically related and unrelated distracters were appropriately assigned, we made use of the semantic relatedness measure latent semantic analysis (Landauer *et al*., 1998). The average latent semantic analysis index for semantically related pairs was 0.36; for unrelated pairs it was 0.04.

Over the course of the experiment, each picture appeared eight times in a fully counterbalanced fashion: picture type (target/distracter) × domain (verbal/nonverbal) × distracter type (related/unrelated to the target). Each of the 45 sound 'types' (e.g. 'cow') was also crossed with domain (verbal/nonverbal) and distracter type (related/unrelated). A full list of items used is reported in Saygin *et al*. (2002).

Procedure

The experiment was run on Apple Macintosh PowerBook 3400c computers using the PsyScope experimental driver (Cohen *et al*., 1993). Participants sat in front of a VGA monitor, Yamaha YST-M7 speakers were placed on each side, and a standard PsyScope button box was used to collect responses. The experimenter read a set of instructions to each participant and asked him or her to complete a practice session of six trials.

The experimental block consisted of 180 experimenter-advanced trials. In each trial, subjects were presented with a two-picture display on the screen. After 1000 ms, the sound stimulus (either verbal or nonverbal) was presented through the speakers. This delay allowed subjects enough time to process the visual stimuli, thus mitigating visual processing contributions to reaction time data. Subjects pushed the button under the picture they believed matched the sound. Reaction time and accuracy were recorded for each trial. Subjects were continuously monitored for attention to the task, and were asked at intervals whether they needed a break. The nature of errors was noted, as were any comments made during or after the experiment. Special care was taken to note whether or not the subject was immediately aware of the error (as indicated by an overt verbal or physical response). Motivational feedback (e.g. 'you are doing great so far') was provided as often as considered necessary to keep participants engaged in the task (for aphasic patients, this was approximately once every 20 trials); however, this feedback did not relate any information about the subject's accuracy in a particular trial.

Lesion analysis

As noted above, head CT or MRI images were obtained for all of the patients. For 20 of our LHD patients, computerized lesion reconstructions to be used in lesion overlay analyses were available. For another six patients, we had MRI or CT scans showing lesion boundaries, which were used in some analyses but not for the lesion overlays. Only acute scans were available for the remaining three LHD subjects; chronic scans showing distinct lesion boundaries could not be obtained. Lesion reconstructions were available only for two of the RHD patients who participated in this study, so we did not include this group in our lesion analyses.

Lesion reconstructions were based on CT or MRI scans at least 3 weeks post-onset and were hand-drawn onto 11 axial slice templates based on the atlas of DeArmond *et al*. (1976), They were then entered into a Macintosh computer via electronic bitpad using software developed at the VA Medical Center in Martinez, California (Frey *et al*., 1987). All reconstructions were completed by a board-certified neurologist, experienced in neuroradiology, but blind to the behavioural deficits of the patients. Individual variations in gyral patterns and any differences in imaging angles were compensated for by using subcortical structures as landmarks.

To determine common areas of infarction in patients who exhibit similar behavioural profiles, we overlapped their lesions using the voxel-based lesion symptom mapping (VLSM) software developed by our group (Wilson *et al*., 2002).

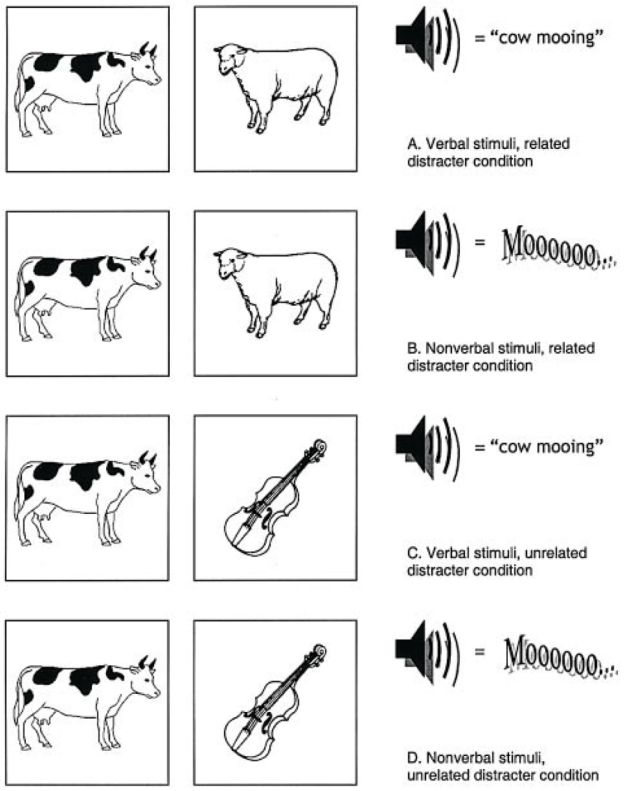

Fig. 1 Summary of the experimental design. Domain (verbal/nonverbal) and distracter type (related to target/unrelated to target) were within-subject factors, and subject group was the between-subjects factor. The target 'cow' appeared four times, twice with verbal sound stimuli (the phrase 'cow mooing'), twice with non-verbal stimuli (the sound of a cow mooing), twice with 'sheep' as the distracter (related condition), and twice with 'violin' as the distracter (unrelated condition). All these trial types with the target 'cow' are depicted in the pictures. Forty-five pictures and sounds were used as targets and related and unrelated foils, giving rise to 45 triplets such as 'cow–sheep–violin'. A total of 180 trials was administered. Twenty quasi-random orders of the list were rotated among the subjects.

Statistical analysis

Performance across groups was compared using repeated measures analysis of variance (ANOVA). Regression and correlation analyses were performed to examine the relationships between performance in the two domains. We also conducted outlier analyses to identify any dissociations in performance. All analyses were performed using JMP and StatView statistical packages (Sall *et al*., 2001).

Results

Here we examine differences in accuracy and reaction time between patient and control groups, the correlation in performance across verbal and nonverbal domains and the relationship between lesion site and processing deficits.

Is nonverbal processing spared in aphasic patients?

We examined accuracy and reaction time (RT) for the aphasic (LHD) and RHD subjects, and their age-matched controls. LHD subjects were grouped according to aphasia subtype (as determined by the WAB) into Broca's, Wernicke's and anomic groups. RTs were analysed only for correct responses. We analysed RT data in several different ways (e.g. patients' RT measured as the difference from the normal controls' RT, or converted into standardized scores) with no change in the pattern of results. Therefore, we report results for the simple case of RTs measured from the onset of sound.

As depicted in Fig. 2, groups differed in their overall accuracy [$F(4,48) = 8.533$, $P < 0.0001$]; planned comparisons showed that control, anomic and RHD groups did not differ significantly from each other (all making very few errors),

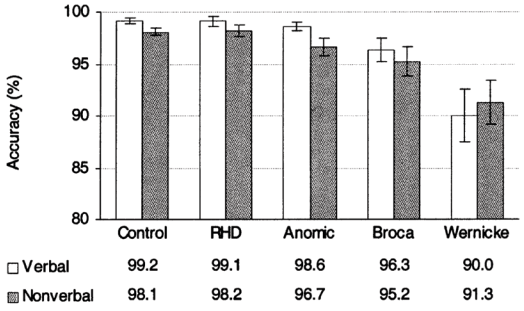

Fig. 2 Accuracy depicted across verbal and nonverbal domains for all subject groups. Groups differed in their overall accuracy ($P < 0.0001$) with control = RHD = anomic > Broca's > Wernicke's (all comparisons corrected $P < 0.01$).

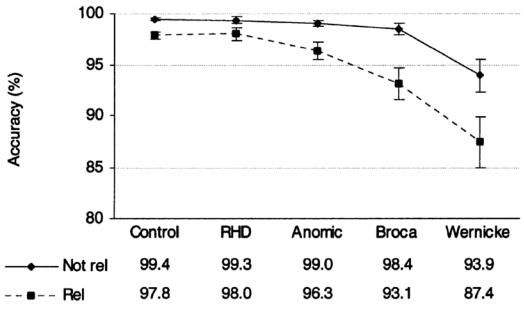

Fig. 3 Accuracy depicted across related and unrelated distracter conditions for all subject groups. There was a main effect of distracter type ($P < 0.0001$). There was also an interaction of distracter type with group ($P < 0.01$), driven mainly by the Broca's and Wernicke's aphasics.

whereas Broca's aphasics and Wernicke's aphasics were less accurate than all other groups and, furthermore, differed significantly from each other, with Broca's more accurate than Wernicke's ($P < 0.01$ for all significant differences, with correction for multiple comparisons).

Distracter type had an effect on accuracy, such that subjects were less accurate when the distracter picture was semantically related to the target picture [$F(1,48) = 62.920$, $P < 0.0001$]. The effect of distracter type was also modulated by group [$F(4,48) = 5.612$, $P = 0.0009$]. Patient groups were more adversely affected when the distracter was related to the target (see Fig. 3). This interaction appears to be driven mainly by the Broca's and Wernicke's aphasics. When both of these severely affected groups were excluded from the analyses, the distracter type by group interaction was no longer significant [$F(2,34) = 1.458$, $P = 0.25$]; conversely, ANOVA comparisons between either Broca's or Wernicke's patients and normal controls revealed significant distracter type by group interactions [$F(1,27) = 10.730$, $P = 0.0029$ and $F(1,23) = 57.816$, $P < 0.0001$, respectively].

There was no main effect of domain; accuracy in verbal and nonverbal conditions did not differ significantly [$F(1,48) = 2.895$, $P = 0.095$]. Domain did not interact with distracter type [$F < 1$], nor was there an interaction of group by domain [$F(4,48) = 1.333$, $P = 0.27$] or a three-way interaction of group, domain and distracter type [$F(4,48) = 1.397$, $P = 0.25$].

The fact that the group by domain interaction did not reach significance is especially notable, as we might expect aphasic groups to commit more errors in verbal trials compared both with normals and with patients with RHD. In fact, the (non-significant) numerical results were in the opposite direction (verbal accuracy > nonverbal) for all groups except for Wernicke's aphasics, the most impaired group. To determine whether the anticipated interaction would hold if we restricted our attention only to these patients, the ANOVA was repeated for Wernicke's and controls only. In this case, the group by domain interaction reached significance [$F(1,23) = 4.442$, $P = 0.046$]. Comparable re-analysis comparing each of the other patient groups with normals did not reveal any evidence for a group by domain interaction (see Fig. 2).

RT was analysed for the accurate trials only. We found significant differences in RT over patient group, as plotted in Fig. 4 [$F(4,48) = 9.891$, $P < 0.0001$]. Pairwise comparisons showed the following ordering of RT (from slowest to fastest, $P < 0.0001$ for all differences): Wernicke's = Broca's > anomic = RHD > control patients. As with accuracy, there were significant effects of distracter type on RT [$F(1,48) = 254.849$, $P < 0.0001$], where RTs to semantically related target and distracter pairs were higher than those to unrelated ones. The distracter type interaction with patient group just reached significance [$F(4,48) = 2.605$, $P = 0.047$]. Here, control subjects were slightly less affected in their response latencies by the distracters compared with all groups except RHD (Ps < 0.05); none of the other groups differed from one another.

There was no main effect of domain on reaction times [$F < 1$], but contrasts were carried out to examine whether there was a differential effect of domain across patient groups. Comparing each patient group with controls revealed that anomic patients [$F(1,30) = 4.485$, $P = 0.042$] and, to a lesser extent, the RHD patients [$F(1,22) = 4.118$, $P = 0.055$] tended to respond slower relative to controls on the nonverbal material. For anomics, this is the opposite to what might be predicted in a traditional account of aphasia. There were no significant interactions between controls and Broca's [$F(1,27) = 0.242$, $P = 0.63$] or Wernicke's [$F(1,23) = 2.771$, $P = 0.11$] patients.

In summary, our analyses did not reveal a sparing of nonverbal processing in aphasic patients; in particular, LHD patients performed poorly in the nonverbal domain at levels comparable to their performance in the verbal domain.

Analyses over hemisphere of lesion

Although the analyses reported above examine the effects of lesion side on performance in the experiment, we also report

results of analyses in which aphasic subjects were considered as a single LHD group. This is mainly to enable comparison with previous studies that used side of lesion as the grouping variable across subjects and did not form groups based on aphasia type.

For accuracy, there were main effects of group (LHD, RHD, controls) [$F(2,50) = 4.625$, $P < 0.014$] and of distracter type [$F(1,50) = 18.864$, $P < 0.0001$]. Controls and RHD patients performed better than LHD patients. The group by distracter type interaction reached significance, with the LHD group making more errors when related distracters were presented [$F(2,50) = 5.872$, $P = 0.0051$]. Once again, the group by domain interaction was not significant [$F < 1$]. The RT data closely parallel the accuracy data and previous analyses: The main effects of group [$F(2,50) = 12.563$, $P < 0.0001$] and distracter type [$F(1,50) = 160.925$, $P < 0.0001$] are significant. The LHD group was the slowest; the RHD group was faster than the LHD group, but slower than the control subjects. The group by distracter type interaction reached significance, with the LHD group more adversely affected by related distracters [$F(2,50) = 5.307$, $P = 0.0081$]. The group by domain interaction was again not significant [$F(2,50) = 1.311$, $P = 0.28$].

To summarize, hemisphere of lesion did not significantly affect the relative impairment on the verbal and nonverbal conditions in this experiment. There was, however, a reliable effect of semantically related distracters: LHD patients found them harder to process than RHD and control subjects.

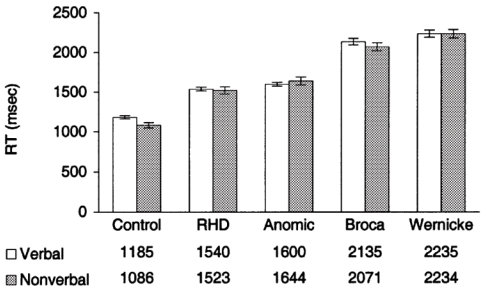

Fig. 4 Reaction time for correct responses depicted across verbal and nonverbal domains for all subject groups. Groups differed in their response latencies ($P < 0.0001$) with control < RHD = anomic < Broca's = Wernicke's (all comparisons corrected $P < 0.01$)

Associations between task performance across domains and outlier analyses

Within the LHD group, accuracy in verbal and nonverbal domains was very tightly correlated ($r = 0.74$, $P < 0.0001$), with reaction time data demonstrating an even closer relationship, approaching an identity function ($r = 0.95$, $P < 0.0001$). Impairments in verbal and nonverbal domains go hand in hand in our data. Fig. 5A and B show correlation scatter plots and linear fits for accuracy and RT in LHD subjects over the two domains.

We also assessed the relationship between patients' WAB-derived aphasia quotient (AQ), a measure of overall aphasia severity, and performance in our task. Note that AQ is a task-external measure of language impairment. Overall, accuracy was correlated with AQ ($r = 0.526$, $P = 0.0033$); when split by domain, both verbal and nonverbal performance were correlated with severity of aphasia (verbal: $r = 0.539$,

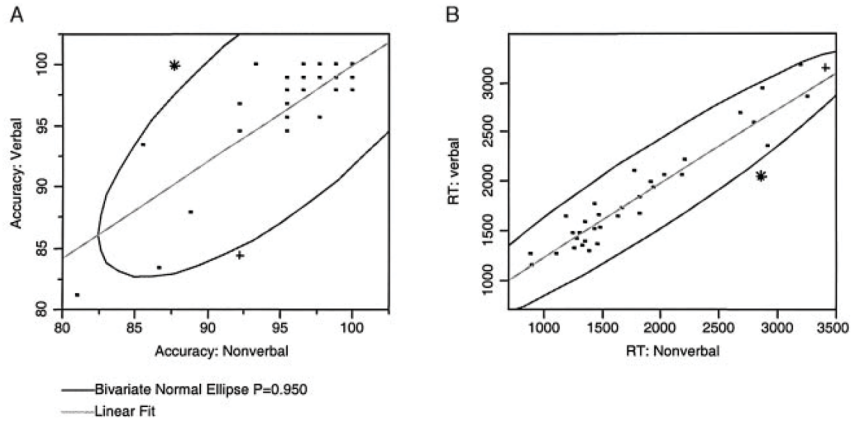

Fig. 5 Correlation of performance in the verbal and nonverbal domains within the aphasic group for (**A**) accuracy and (**B**) reaction time. Linear fits and density ellipses using a confidence interval of 95% are shown. Correlations are significant ($P < 0.0001$ for both) and high ($r = 0.74$ and 0.95, respectively). Data points outside the ellipses are outliers based in Mahalanobis distances. + denotes patient R.S. and * denotes patient J.W; the two patients who show signs of possible dissociations between the two domains.

$P = 0.0025$; nonverbal: $r = 0.440$, $P = 0.017$). RT measures also correlated with AQ ($r = 0.619$, $P = 0.0003$); when split by domain, both the verbal performance ($r = 0.689$, $P < 0.0001$) and the nonverbal performance ($r = 0.546$, $P = 0.0022$) showed significant relationships to aphasia severity. Very similar results have been reported by Schnider *et al*. (1994).

In order to explore the outliers in the dataset, we calculated density ellipses using a confidence interval of 95% using the outlier analysis tool of the JMP statistical software package. These ellipses are based on Mahalanobis distances and, assuming a bivariate normal distribution, show where a given percentage of the data is expected to lie. The Mahalanobis distance takes into account the correlation structure of the data as well as the individual scales (Appelbaum *et al*., 1999; Sall *et al*., 2001). We used a 95% confidence ellipse for both of our measures. These outlier analyses report only the aphasic (LHD) population; we also carried out the analysis including RHD subjects and found very similar results.

For accuracy, three subjects remained outside the ellipse and were identified as outliers, (as shown in Fig. 5A). For RT, we identified only one outlier—as can be seen in Fig. 5B. In order to compare these results with what would be expected by chance, we carried out a small-scale randomization test. The verbal and nonverbal accuracy scores were shuffled 50 times and outlier analysis was performed each time. The mean number of outliers obtained was 2.9 (range 2–4). This demonstrates that the procedure identifies roughly the same number of outliers regardless of the correlation structure of the data; thus, no special significance should be attached to the number of patients identified. Rather, the advantage of outlier analysis is that it provides a quantitative method of identifying patients who may potentially exhibit dissociations.

The actual process of identifying genuine dissociations is more qualitative. Based on Fig. 5A, we saw that patient J.W. (*) showed a striking dissociation with 100% accuracy on verbal (better than healthy controls) and 87.7% accuracy on nonverbal trials. Patient R.S. (+) showed some dissociation with 92.2% accuracy on nonverbal and 84.4% accuracy on verbal trials. Patient W.G. was an outlier by virtue of the fact that he was severely impaired with 81% accuracy in both domains. RT analyses pinpointed J.W. as the sole outlier, shown in Fig. 5B.

R.S. and W.G. are both severe Wernicke's aphasics, with large lesions involving temporal and parietal regions. In order to further investigate R.S. as a patient exhibiting a potential dissociation, we re-tested him on the same task after a six-month delay. His performance was better, with 95% accuracy on nonverbal and 90.2% accuracy on verbal trials. At the time of re-testing, he had made more gains in the nonverbal domain and, with these scores, he would no longer be an outlier with respect to the rest of the sample. However, a relatively low score in the verbal domain remains in his profile; we conclude that his dissociation should be noted but interpreted with care.

For J.W. on the other hand, who showed a striking dissociation in a rather unexpected direction (worse nonverbal processing in an aphasic patient) which was also reflected in his RT scores, follow-up testing revealed that the dissociation was persistent and reliable. J.W. has an unusual neurological profile: despite a large temporoparietal lesion, he presents with a very mild aphasia (anomic) with almost completely intact verbal auditory comprehension. We carried out several additional tests on this patient after a nine-month delay and verified that he has severe auditory agnosia for nonverbal sounds (Saygin and Moineau, 2002).

Lesion location analyses

We performed a lesion analysis to investigate further the neural correlates of auditory comprehension. First, we overlapped the computer-reconstructed lesions of the patients who exhibited behavioural profiles of interest (e.g. poor performance in nonverbal sounds) to determine if they shared a common area of infarction. Next, we used these shared areas of injury as regions of interest (ROIs) to determine statistical differences between groups of patients whose lesions either spared or involved these particular areas.

For the lesion overlays, the 20 LHD patients for whom we had lesion reconstructions were grouped together based on their performance in the task, regardless of aphasia classification. We used accuracy and RT values, respectively; both converted into *z*-scores with respect to normal controls as a measure of patients' degree of impairment. The VLSM software (Wilson *et al*., 2002) was used to assess the degree of spatial overlap in lesions shared by patients with similar behavioural deficits. Patients who performed $\geqslant$2 SDs below the normal controls were considered deficient and their lesions overlapped to determine if a common area of infarction could be found.

For accuracy, overlays are provided in the top panel of Fig. 6, broken down by stimulus domain. Here, we show the results on three axial slices that pass through the middle temporal (slice 1), superior temporal (slice 2) and inferior parietal regions (slice 3). Based on the criteria used here, eight patients were deficient in nonverbal sounds and 10 were deficient in verbal sounds. As can be seen, the overlays are very similar across these two domains. Consistent with Schnider *et al*. (1994) and recent neuroimaging studies of environmental sound processing (e.g. Adams and Janata, 2002), the areas of maximal overlap for patients impaired in the nonverbal domain are centred in the posterior superior temporal gyrus (pSTG, in slice 2) extending into some middle temporal (in slice 1) and inferior parietal (in slice 3) regions. The implicated areas for verbal sound processing are strikingly similar, though a slightly smaller fraction of patients overlap on these regions, i.e. not all patients with poor verbal comprehension have damage to the areas of maximal overlap.

For reaction time, overlays for patients who were identified as deficient based on slow response latencies appear to be

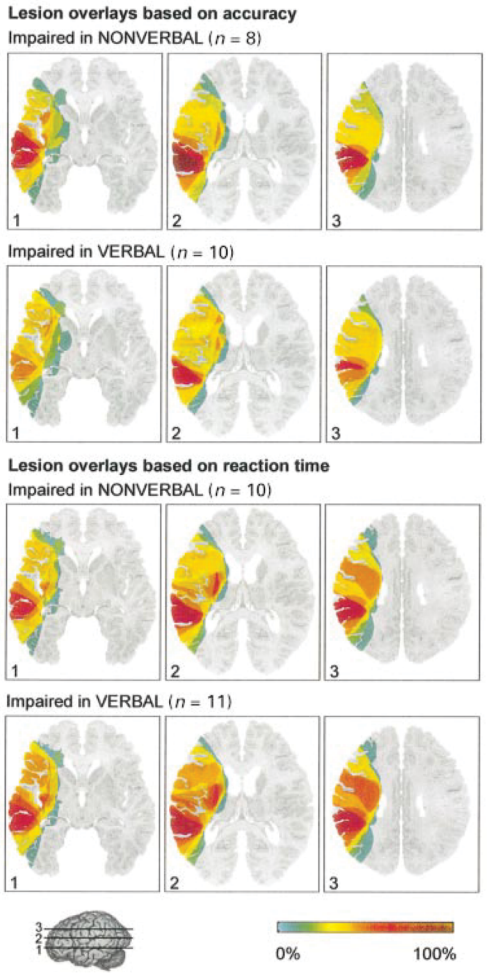

Fig. 6 Lesion overlays for LHD patients who performed poorly in the nonverbal and verbal domains based on accuracy and reaction time. The overlays consist of lesions from patients who performed ⩾2 SDs below the age-matched controls in the corresponding measure in each condition. Lesions are depicted on three axial slices that go through middle temporal, superior temporal and inferior parietal lobes. The colour maps indicate the percentage of patients whose lesions involve that particular region.

almost identical for the two domains (verbal versus nonverbal). The lower panel of Fig. 6 shows that the same pSTG region identified for accuracy is once again the focal point for patients with slow RT (Fig. 6). The pattern of results looks very similar to that revealed by the overlays based on accuracy, although for RT, there seems to be a stronger overlap in the insula.

The analyses above selected patients based on behavioural deficits and identified the common areas of infarction. Another possible method is to examine the behavioural profiles associated with the ROIs previously discussed. This type of analysis enables us to see how general the localization results are and allows us to assess quantitatively which areas are differentially implicated in verbal versus nonverbal processing. For the analyses below, we identified as ROIs the maximal areas of infarction for each slice in the lesion overlays. Then we divided the patients into groups consisting of those who had a lesion in that ROI and those whose lesions spared that area. This permitted us to compare and contrast performance in relation to the ROIs and the two domains quantitatively. Only patients whose lesion reconstructions (or scans, for the six patients for whom we did not have digital reconstructions) clearly involved or spared the ROIs were included in the groups.

Patients were first divided into two groups consisting of those who had a lesion in the region with the darkest colour in Fig. 6, slice 2 (pSTG) and those whose lesions did not involve this region [n(lesioned) = 11, n(intact) = 14]. For accuracy, there was a significant main effect of pSTG lesion [$F(1,23) = 5.714$, $P = 0.025$]; patients who had lesions in this location had significantly lower accuracy scores than patients who did not have a lesion here [mean(lesioned) = 92.8%, mean(intact) = 97.2%]. There was also an interaction of pSTG lesion with domain [$F(1,23) = 4.349$, $P = 0.048$], mainly driven by the nonverbal errors (see Fig. 7). The difference between patients with pSTG lesions versus those without was larger in the nonverbal domain than in the verbal domain. Furthermore, the difference between verbal and nonverbal domains was larger in the pSTG-lesioned patients than the difference between domains in those without lesions to this area. Additionally, pSTG-lesioned patients were significantly slower than the patients whose lesions spared this region [mean(lesioned) = 2223 ms, mean(intact) = 1649 ms, $F(1,23) = 5.338$, $P = 0.030$]. However, there was no interaction of domain and pSTG lesion for RT [$F(1,23) = 1.529$, $P = 0.23$], consistent with the great similarity of the overlays for the two domains in Fig. 6.

For the posterior middle temple gyrus (pMTG) region that is identified as possibly important for sound processing in slice 1, a similar analysis with eight lesioned patients and 16 non-lesioned patients revealed a main effect of pMTG on accuracy [$F(1,22) = 7.582$, $P = 0.012$]. Patients with lesions here were significantly less accurate than patients whose lesions spared this region [mean(lesioned) = 91.6%, mean(intact) = 96.9%]. However, this region did not make a differential contribution to the two domains: the interaction of pMTG lesion and domain was not significant [$F < 1$]. In a separate analysis on reaction times, patients with pMTG lesions were significantly slower than those without lesions here [mean(lesioned) = 2450 ms, mean(intact) = 1613 ms, $F(1,22) = 11.767$, $P = 0.0024$], but again the pMTG lesion and domain interaction did not reach significance [$F(1,23) = 2.214$, $P = 0.15$], as was also the case for RT for the pSTG.

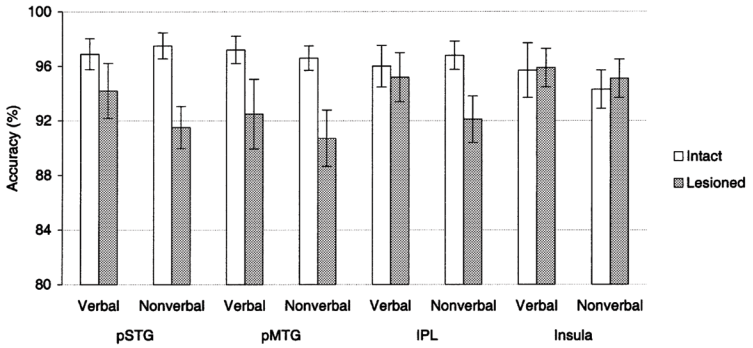

Fig. 7 Summary of statistics on the regions of interest based on Fig. 6: pSTG, pMTG, IPL and insula. There is a significant main effect of pSTG and pMTG on accuracy. We also found significant interactions indicating the involvement of the pSTG and IPL in nonverbal deficits above and beyond verbal deficits. As can be seen, there is no clear implication to the portion of the insula that we examined on accuracy in either of the domains.

For the inferior parietal lobule (IPL) region in slice 3, we carried out the analogous analyses [n(lesioned) = 11, n(intact) = 13]. Here, although there was no main effect of group on accuracy [F(1,22) = 1.827, P = 0.19] or RT [F(1,22) = 2.680, P = 0.12], the IPL lesion by domain interaction was significant for accuracy [F(1,22) = 6.695, P = 0.017], largely due to the fact that those patients whose lesions included this region were significantly less accurate for the nonverbal trials [mean(lesioned,verbal) = 95.2%, mean(lesioned, nonverbal) = 92.1%]. These latter findings suggest that the IPL region may be especially important for processing nonverbal sounds; however, the absence of a main effect demands caution in drawing strong conclusions.

Recall that on slice 2, there was some evidence from the RT data for insula involvement. However when we examined all the LHD patients [n(lesioned) = 14, n(intact) = 7], damage involving this portion of the insula was not significantly associated with accuracy or RT in either domain [all Fs < 1].

Although we observed extremely high correlations between performance in the two domains, for exploratory purposes we also performed lesion overlay analysis for patients who performed relatively better in one domain compared with the other (Fig. 8). First, we identified patients whose accuracy in one domain was ⩾1 SD different from their performance in the other domain. We then constructed an overlay of lesions for those patients who performed more poorly in the nonverbal domain (n = 10) and those who performed more poorly in the verbal domain (n = 5). As can be seen, the patients who were relatively more impaired in the nonverbal domain have lesions along the middle and posterior portions of the superior temporal gyrus and in the IPL. Notice that these are the same areas already identified as being important in Fig. 6 and showed some significant quantitative effects after lesion-location-based group analyses. We see now that these regions (especially the pSTG) are implicated even when the patients whose deficits are comparable in the verbal and nonverbal domains are excluded from this highly correlated dataset. This lends further support to the importance of these regions for environmental sound processing. On the other hand, once the patients whose deficits also equally involve the nonverbal domain are excluded, the lesion overlay for the patients with verbal deficits becomes less focal and has a visibly more anterior and medial focus moving towards the anterior insula, basal ganglia and caudate nucleus.

Turning to results for reaction time, we regrouped the patients into those whose performance was slower in the nonverbal than the verbal domain (n = 10) and compared them with those whose verbal performance was slower in the verbal compared with the nonverbal domain (n = 11). Here a similar anterior focus for relatively slow response times in the verbal domain can be seen, whereas the focus for relatively slow response times in the nonverbal domain does not change.

However, unlike the posterior foci analysed above, this anterior area which is implicated in patients who perform relatively poorly in the verbal domain is not significantly associated with our behavioural measures. When analogous statistics are computed between groups of patients with (n = 10) and without (n = 11) lesions to the region of maximal overlap for worse performance in the verbal domain in Fig. 8, no differences can be found between these patients in accuracy or RT. Nor are there any interactions or tendencies towards selective involvement in one domain versus the other [all Fs < 1]. Note that this common lesion location in patients with poorer performance in the verbal domain may reflect the participation of aphasic patients with haemorrhagic stroke who tend to have more subcortical involvement.

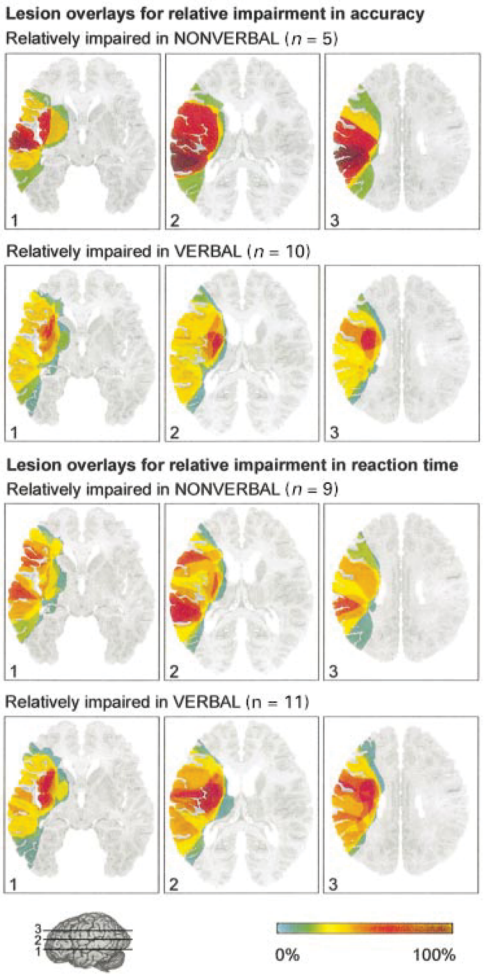

Fig. 8 Lesion overlays for patients whose performance in one domain was worse compared with the other domain. For accuracy, the overlays consist of lesions from patients whose accuracy z-scores were ⩾1 SD apart between the two domains. For reaction time, the scores were too tightly correlated and very few patients had scores that were 1 SD apart. The overlays for this measure were thus computed based on positive or negative *z*-score differences. Patients whose lesions are overlapped in the top panel for the RT overlays were thus relatively slower in responding to nonverbal trials than they were to verbal trials. Conversely, lesion overlays in the bottom panel depicts patients who were slower in responding to the verbal trials.

Thus, the results for the relative impairment overlays corroborate prior results that point to the pSTG as a critical region for nonverbal sound processing. This area is also important for verbal comprehension. However, despite obtaining a different pattern of lesions for patients who are more deficient in the verbal domain, based on the present

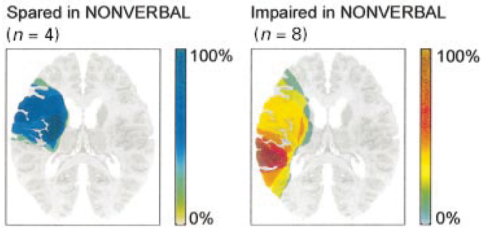

Fig. 9 Lesion overlay on slice 2 depicting patients who are 'spared' in the nonverbal domain along with an overlay depicting patients who are impaired. Note that the latter overlay is the same as slice 2 of the top panel in Fig. 6, replicated for easy contrast.

data, we cannot identify a specific region that is differentially and specifically implicated for verbal processing.

We performed one more lesion overlay to determine whether the pSTG region that is significantly implicated in nonverbal processing in prior analyses is essential for performing well in this domain. Four patients in our sample were 100% accurate on nonverbal trials, thus performing better than normal controls. Fig. 9 depicts the lesion overlays on slice 2 for these patients (on a blue colour scale to emphasize that this is a map of sparing) along with an overlay for patients who were deficient in the nonverbal domain (2 SDs below the controls; same as the overlay in Fig. 6). As can be seen, all of the patients who performed well in the nonverbal domain have lesions that spare the pSTG region (as well as the pMTG region, data not shown). Thus, based on our sample, it appears that the pSTG region may be crucial for normal nonverbal auditory processing.

Discussion

Aphasic patients do not have spared nonverbal processing

The data revealed no clear evidence of an advantage for nonverbal auditory processing in these aphasic patients. We did not find a consistent interaction of stimulus domain (verbal versus nonverbal) by patient group in the direction of spared performance on the nonverbal domain by the clinically language-impaired subjects. We did find differences between patient groups that were reliable and systematic: Broca's and Wernicke's aphasics performed similarly in the task, with the latter group faring slightly worse, while anomic and RHD patients performed similarly to each other. All patient groups were impaired relative to normal control subjects. However, impairment in the verbal condition tended to go hand-in-hand with impairment in the nonverbal condition for all patient groups. In the single instance where processing of language stimuli was less accurate than nonverbal stimuli (in latter patients), the result was not mirrored in the RT data. In fact, the latter measure showed that anomic and RHD patients had longer reaction times for nonverbal than verbal stimuli,

thus implying that our nonverbal stimuli were even more challenging for these groups than were the verbal stimuli. In short, there was little evidence for a specific deficit in language processing in our group of patients.

Impairments in the two domains go hand-in-hand

That our aphasic patients are not selectively deficient in linguistic processes is an interesting result, but the lack of a statistically significant difference between verbal and nonverbal processing does not necessarily imply a similarity or contiguity in processing. However, additional results and analyses strengthen our contention that these two domains may draw on some of the same processing resources. Similar to findings by Schnider *et al*. (1994) and Varney (1980), but unlike findings of Clarke *et al*. (1996), we observed correlated patterns between behavioural deficits of our patients across the two domains. First, aphasia severity was correlated strongly not only with performance on the verbal condition of our task, but almost equally as well with performance on the nonverbal condition. This is consistent with results reported by Schnider *et al*. (1994). That a significant amount of the variance in our nonverbal task was predicted by a separate measure of aphasic patients' language competence is suggestive of an association between processing of verbal and nonverbal auditory information. Secondly, within the LHD group, high cross-domain correlations over both RT and accuracy (Fig. 5) demonstrate that the severity of language deficit goes hand-in-hand with the severity of the deficit in environmental sound recognition.

A potential alternative explanation for the associations we show here may be that subjects are engaging in verbal/sub-vocal mediation in the processing of environmental sounds. However, there is some evidence against this explanation. First, both younger controls (Saygin, 2001) and the elderly control subjects reported here were significantly faster in processing the environmental sounds stimuli than the verbal stimuli (see Fig. 4). If subjects were using verbal mediation for both tasks, then we could expect reaction times for environmental sounds to be at least equal to, if not longer than, those for verbal material. Secondly, we made an explicit test of this sub-vocal rehearsal hypothesis (Dick *et al*., 2002*a*). We asked subjects to perform the nonverbal portion of the task with and without sub-vocal naming of the sounds. The results were clear; while using the verbal mediation strategy, subjects responded an average of 20% more slowly than when using no linguistic mediation. Given the pattern of reaction times we have obtained in these experiments, it seems unlikely that sub-vocalization or naming is the root of the close relationships observed here.

Another hypothesis to entertain is that the behavioural correlations we see in the patients are not due to a systematic neural relationship between the processing of nonverbal and verbal sounds, but are simply due to lesion size. It could be that patients with larger lesions perform poorly in both domains because they are likely to have damage to both verbal and nonverbal processing systems that may actually have separate neural substrates. Similarly, patients with smaller lesions would be less likely to have damage to either system and hence have relatively spared processing in both domains.

To explore this possibility, we examined the effect of lesion size on performance in the verbal and non-verbal domains. For the 20 patients with reconstructed lesions, we computed lesion volume (in cm^3) on standardized space. While we had a range of lesion volumes in this group (ranging from 6.4 cm^3 to 162.6 cm^3 with mean volume of 66.7 cm^3), the correlation of lesion size with overall accuracy ($r = 0.04$) or RT ($r = 0.21$) did not approach significance (Fs < 1), nor were there any significant correlations of lesion size within the verbal or the nonverbal domains (Fs < 1). This suggests that it is unlikely that lesion size alone could suffice to explain the high degree of correlation we observed on performance across the two domains.

Furthermore, if lesion size were a crucial factor, it might be expected that similarly high correlations would be observed between any two behavioural measures. To investigate this possibility, we examined correlations between different WAB subscale scores in a larger set of 97 LHD patients (including most of the LHD patients included in this study). Significant correlations with effect sizes comparable to the verbal/nonverbal correlations reported above ($r = 0.75$ for accuracy, $r = 0.95$ for RT) are only found within the respective verbal and nonverbal domains on the WAB. Table 2 summarizes some examples of within- and across-domain correlations for three verbal subscales and three nonverbal subscales. The three verbal scales reported here are 'auditory word comprehension' (AudComp; a word-to-picture matching task), 'object naming' (ObjName; a cued picture-naming task) and 'fluency' (a performance rating of speech output, incorporating factors such as phrase length, word-finding, and grammatical complexity). The nonverbal subscales are 'Raven's coloured progressive matrices' (Raven; assesses visuospatial perception and processing), 'block design' (Block; is a subtest derived from a performance IQ test), and 'calculation' (Calc.; tests arithmetical ability utilizing one or two digit numbers controlling for any comprehension or reading deficits). While correlations between pairs of verbal measures are generally high, as are correlations between pairs of nonverbal measures, correlations between verbal and nonverbal measures tend to be low—sometimes even non-significant. In other words, the correlation between performance on environmental sounds and their matched linguistic descriptors 'looks like' a correlation between two closely related language tasks on the WAB.

In summary, these analyses indicate that higher correlations in patient datasets are not merely due to covariates such as lesion size, but are likely caused by further perceptual, neural and cognitive commonalities between behaviourally

Table 2 *Within- and between-domain correlations among aphasic patients' WAB subscale scores*

WAB subscale	Verbal			Nonverbal		
	AudComp	ObjName	Fluency	Raven	Block	Calc.
AudComp	1	0.87**	0.63**	0.32**	0.22*	0.37**
ObjName		1	0.77**	0.26**	0.17 (n.s.)	0.29**
Fluency			1	0.21 (n.s.)	0.19 (n.s.)	0.27*
Raven				1	0.77**	0.78**
Block					1	0.81**
Calc.						1

Verbal measures depicted here are auditory word comprehension (AudComp), object naming (ObjName) and fluency of speech production. The nonverbal measures are Raven's progressive matrices (Raven), block design (Block) and calculation (Calc.) tests. **Correlation significant at $P < 0.01$ level; *Correlation significant at $P < 0.05$ level; n.s = correlation not significant.

correlated processes. These commonalities in turn may be direct (e.g. some common brain areas are involved in the processes of interest) or indirect (e.g. the processes have some more basic components in common), or a combination. It is not possible from such data alone to determine whether the associations between correlated measures are direct or indirect, but it is possible to say that for the present data, the high correlations are indicative of shared neural resources and processes.

Hemisphere of lesion and distracter effects

Like some previous studies (e.g. Spinnler and Vignolo, 1966; Faglioni *et al*., 1969), but unlike Schnider *et al*. (1994), we observed significant differences between LHD and RHD groups in our task. The RHD group (all non-aphasic) performed overall at a very similar level to the mildest aphasic group (anomics), but faster and more accurately than either the Broca's or the Wernicke's patients. However, LHD patients were significantly more affected by the semantic distracter manipulation. On closer inspection, this effect is seen to be driven by the two more severely language impaired LHD groups (Broca's and Wernicke's; see Fig. 3). Interestingly, this distracter effect did not interact with domain. Thus, not only did performance levels go hand-in-hand in the verbal and nonverbal domains, but the two domains also display similar effects of semantic distance. Furthermore, while there is some evidence that deficits in semantic processing follow posterior lesions of the left hemisphere (Cappa *et al*., 1981; Hart and Gordon, 1990; Chertkow *et al*., 1997), a differential impairment in dealing with semantic competition was not seen in this study even on the subset of our patients with posterior lesions (see Saygin, 2001). That a semantic manipulation affected performance more in the aphasic subjects but did not differentially affect language processing is an outcome that agrees with several prior studies (e.g. De Renzi *et al*., 1972; Duffy and Duffy, 1981). Such results may support the more general hypothesis advanced by earlier pioneers in neurology (e.g. Jackson, 1878; Head, 1926) that aphasia is correlated with or is itself a more general symbolic or conceptual deficit rather than being restricted only to the linguistic domain. However, these hemispheric findings should be interpreted with some caution because of the disparity in sample sizes in the present study.

On dissociations

In an earlier study, Varney (1980) reported deficits in nonverbal comprehension only in patients who also exhibited deficits in verbal comprehension. However, he did find dissociations in the opposite direction, i.e. aphasic patients who were impaired in verbal comprehension but not in sound recognition. In contrast, Clarke *et al*. (1996) did find one patient who was deficient in the nonverbal auditory domain but had no diagnosed verbal comprehension deficits. Clarke *et al*. (1996, 2000) also report on subjects with impaired language comprehension who performed well on nonverbal sounds, implying that there could be dissociations of verbal and nonverbal comprehension in aphasic subjects, in both directions.

In our experiment, both task and items were closely matched across domains, response latencies as well as accuracy were recorded, and outliers were analysed quantitatively taking correlations at the group level into account. Under these conditions, we saw that deficits in the two domains largely went hand-in-hand. Three outliers for accuracy (patients J.W., R.S., W.G.) and one for RT (patient J.W.) were identified. Subsequent testing confirmed that J.W. has a persistent and reliable nonverbal auditory agnosia. Patient R.S. exhibits some evidence for a weaker dissociation in the opposite direction. W.G. was classified as an outlier based on very low scores in both domains and thus does not represent a theoretically interesting dissociation. R.S. and J.W. both have extensive lesions that are largely overlapping and thus we cannot make any localization inference based simply on the dissociations we identified.

We believe that the differences between our results and others' are due primarily to task differences, to differences in experimental design and, perhaps, partially to the random distribution of patients studied. Note that previous dissociations suggested by Varney (1980) and Clarke *et al*. (1996) were both based on a classification of impaired performance

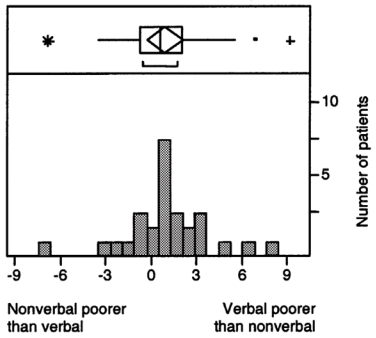

Fig. 10 Histogram depicting the distribution of *z*-score differences between subjects' accuracy scores in the two domains. Confirming previous findings by others and as expected given the clinical diagnosis of the population, we found aphasic patients whose performance in the verbal domain was worse than their performance in the nonverbal domain. However, we also identified several patients who exhibited the opposite pattern despite having diagnosed language disorders. Note that the histogram's outlier scale depicts the three patients identified earlier in Fig. 5A, patients J.W. (*), R.S. (+) and W.G. (·).

as performing below the level of the worst control subject. While we advocate quantifying dissociations in neuropsychology using more quantitative methods such as outlier analyses, we can compare our results to these prior studies by using the same criteria. According to these criteria, nine patients in the current study performed worse than the poorest performing control subject in the verbal domain and eight patients did so in the nonverbal domain. Furthermore, with these criteria, five of our patients would be considered to show dissociations: three impaired in verbal processing but not in nonverbal processing (M.B., P.P., C.H.) and two deficient in the nonverbal domain but not in the verbal domain (J.W., F.Y.). Note that according to this analysis, R.S.'s performance was deficient in both domains.

While Clarke *et al.* (1996, 2000) did not focus upon comparing performance in verbal and nonverbal domains and did not test or report language processing in much detail, Varney's study featured verbal versus nonverbal processing as an experimental condition (Varney, 1980). Varney also examined processing in the two domains without stipulating performance cut-offs by using standardized score differences in verbal and nonverbal tests, and found that deficits in nonverbal recognition were consistently associated with deficits in verbal recognition of equal or larger severity. We examined the distribution of standardized score differences in our sample in a similar fashion (see Fig. 10) and saw that, while the distribution is skewed in the direction Varney observed, several patients in our sample had worse impairments in the nonverbal domain. Once again, the difference between Varney's results (Varney, 1980) and ours may well be due to the fact that we used the same controlled online task across both conditions.

In summary, our data indicate that, while performance in the verbal and nonverbal domains is highly correlated, it is possible to identify not only patients who perform worse in the verbal domain (i.e. the expected result based on an aphasic sample), but we can also identify reliably patients who perform worse in the nonverbal domain—an unexpected and rarely reported outcome. However, we did not observe any systematic pattern in the lesion locations or behavioural profiles of the few patients who exhibited dissociations. It is possible that these dissociations are due to variation between individuals' pre-morbid brain organization for these functions, as well as non-uniform post-stroke recovery patterns across patients and across domains.

Localization

The strong behavioural correlations elicited by our verbal and nonverbal stimuli suggest that these two domains may utilize common brain regions and/or processes. In an effort to understand where in the brain those directly or indirectly shared resources may reside, we used lesion–symptom correlation analyses.

We performed lesion overlays on patients who exhibited specific behavioural deficits and identified some posterior regions in the middle temporal gyrus, superior temporal gyrus and IPL that were associated with impairments in our task. These regions most likely correspond to Brodmann's areas 41 and 42, posterior portions of areas 21 and 22, the superior portion of area 37, and inferior portions of areas 39 and 40. There was some indication that the insula may also be involved. The overlay maps were similar for both the verbal and the nonverbal domains. The regions of maximum overlap were more clearly defined for the nonverbal domain, whereas for the verbal condition the foci were less strong. We then reanalysed the behavioural data based on these regions to see how general the results were and to quantify any domain differences that might arise. We found that the pMTG and pSTG regions contributed significantly to performance in both domains, while the IPL region showed a tendency linked primarily to non-verbal processing. In addition, the pSTG region was significantly implicated as important for nonverbal processing above and beyond its importance for the verbal domain. Patients who performed well in the nonverbal domain all had lesions sparing the posterior areas we identified with lesion overlays, specifically the pSTG focus. We did not identify any areas for which verbal processing had quantifiably more impact compared with nonverbal processing.

Interestingly, the left-hemisphere regions we identified using overlays and further verified with quantitative analyses are typically considered to be language-specific areas of the human brain. Indeed the pSTG region we identified in the current study (the posterior portion of Brodmann's area 22) corresponds to the original Wernicke's area held since the early days of neurology to be crucial for language comprehension. We now see that Wernicke's area and the surround-

ing mid-temporal and parietal regions are implicated strongly in environmental sound processing as well. What is rather surprising is the finding that Wernicke's area itself, while it is significantly associated with deficits in both domains, is identified to be significantly more associated with deficits in the nonverbal domain above and beyond the deficits in the verbal domain. Our claim is not that Wernicke's area is selectively involved in environmental sound processing; but it is reliably and significantly implicated in our data in relation to deficits in the processing of familiar environmental sounds.

The finding that environmental sound processing relies on the same areas that are known to be important for linguistic comprehension is difficult to reconcile with very strong views on domain-specific brain regions for language. However, it is consistent with recent research on the superior temporal region. Mammalian temporal lobes contain multiple auditory areas that respond to different types and complexities of auditory stimuli (Rauschecker and Tian, 2000). Human imaging studies are revealing that different kinds of auditory stimuli are processed in various regions of the brain (e.g. Belin *et al*., 2000). In fact, a recent functional MRI (fMRI) study by Binder *et al*. (2000) concludes that the human superior temporal region consists primarily of auditory sensory cortex. Considering the fact that speech sounds and environmental sounds are both complex auditory signals that have rich semantic associations, they could indeed be expected to share neural representations and resources. Indeed, language-related areas in the left hemisphere have recently also been implicated in the processing of environmental sounds in other lesion studies (Schnider *et al*., 1994) and fMRI studies (e.g. Lewis *et al*., 2001; Adams and Janata, 2002; Dick *et al*., 2002*b*).

Note that we did not find a specific region that was clearly more important for performance in the verbal domain in this task. Instead, we saw that verbal deficits are associated with similar lesion locations to nonverbal deficits but less uniformly and less focally. Again, this finding is perhaps not surprising given that language is a complex phenomenon, relying perhaps upon more diverse and diffuse neural and cognitive resources. Thus following brain damage, there may be more ways for language processes to break down compared with environmental sound processing.

Conclusion

Although aphasia is often characterized as a selective impairment to language, we found that patients typically have nonverbal auditory comprehension deficits as well. In a carefully normed and controlled task involving the matching of environmental sounds and corresponding phrases to pictures, Broca's and Wernicke's aphasics were the most impaired, while anomic and right hemisphere-damaged patients showed less severe deficits. Interestingly, we found no sparing of nonverbal processing in the aphasic patients; instead, impairments in verbal and nonverbal domains went hand-in-hand. Lesion analysis revealed that the patients with pMTG, pSTG and IPL lesions were especially impaired, suggesting a role for these regions in the processing of not only verbal but also nonverbal sounds. Furthermore, we identified the posterior part of the left superior temporal gyrus (corresponding to Wernicke's area) to be important for nonverbal sound processing above and beyond verbal sound processing. Our results and others suggest that aphasia is not a circumscribed linguistic deficit and that language may share neural resources utilized for the processing of meaningful information across cognitive domains.

Further investigation will expand on the current results, exploring for instance whether they reflect general impairments in auditory comprehension, deficits in associating auditory and visual information, or problems in accessing from memory the semantic associations of auditory input. It would also be ideal to test more patients with right hemisphere damage to gain more insight on hemispheric differences as well as to study patients with left-hemisphere damage without a diagnosis of aphasia to examine verbal and nonverbal auditory processing in a sample without a priori language disorders. We are currently carrying out related fMRI experiments with normal controls in order to shed more light on the nature of the interactions between verbal and nonverbal processes in the human brain (Dick *et al*., 2002*b*).

Author note

The experimental stimuli and norms can be made available to researchers who wish to study or contrast verbal and nonverbal auditory processing in different subject populations (Saygin *et al*., 2002). For more information on running this test on new populations, please contact the corresponding author.

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Chapter 2

Action Comprehension in Aphasia:
Linguistic and Non-linguistic Deficits and their Lesion Correlates

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Action comprehension in aphasia: linguistic and non-linguistic deficits and their lesion correlates

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Abstract

We tested aphasic patients' comprehension of actions to examine processing deficits in the linguistic and non-linguistic domains and their lesion correlates. Twenty-nine left-hemisphere injured patients and 18 age-matched control subjects matched pictured actions (with the objects missing) or their linguistic equivalents (printed sentences with the object missing) to one of two visually-presented pictures of objects. Aphasic patients performed poorly not only in the linguistic domain but also in the non-linguistic domain. A subset of the patients, largely consisting of severe and non-ıent aphasics, showed a greater de□cit in the linguistic domain compared with the non-linguistic domain and across the patient group, de□cits in the linguistic and non-linguistic domains were not tightly correlated. Poor performance in pantomime interpretation was associated with lesions in the inferior frontal, premotor and motor cortex, a portion of somatosensory cortex, and the caudate, while poor reading comprehension of actions was associated with lesions around the anterior superior temporal lobe, the anterior insula and the anterior portion of the inferior parietal lobe. Lesion size did not correlate with deficits. The lesion results for pantomime interpretation deficits demonstrate that lesions in the frontal component of the human analog of the 'mirror neuron system' are associated with deficits in non-linguistic action understanding. For reading comprehension deficits, the lesion correlates are brain areas known to be involved in linguistic tasks including sentence processing and speech articulation; the parietal lesion site may also correspond to a subpart of the human mirror neuron system. These results indicate that brain areas important for the production of language and action are also recruited in their comprehension. Similar findings have been reported in electrophysiological and neuroimaging studies. Our findings now also lend neuropsychological support to an embodied view of brain organization for action processing.

Keywords: Pantomime; Reading; Mirror neurons; Action understanding; Lesion-symptom mapping; Embodiment

1. Introduction

While aphasia is primarily characterized by disturbance of language functions following brain injury, patients have been observed to also exhibit impairments in nonverbal domains, revealed by tasks such as associating pictures with corresponding objects (De Renzi, Pieczuro, & Vignolo, 1968), colors with pictures (De Renzi, Faglioni, Scotti, & Spinnler, 1972), and environmental sounds with pictures (e.g., Saygin, Dick, Wilson, Dronkers, & Bates, 2003a; Spinnler & Vignolo, 1966). In particular, aphasic patients' deficits in using and recognizing signs, gestures and pantomime have been examined in numerous studies (e.g., Bell, 1994; Duffy & Duffy, 1981; Gainotti & Lemmo, 1976; Goodglass & Kaplan, 1963; Pickett, 1974; Varney, 1978; Wang & Goodglass, 1992).

In the present study, we examined aphasic patients' comprehension of visually presented action stimuli in both linguistic and non-linguistic domains. We used a variant of a classical neuropsychological paradigm commonly used to test comprehension in aphasic patients: an object selection task. We had a two-alternative forced-choice (2AFC) design and asked patients to choose the object that best matched visually presented stimuli containing action information. In both the linguistic and the non-linguistic domains, the associated objects upon which the actions should be carried out were removed from the stimuli; thus subjects matched either a sentence missing its object (such as "he is licking the ..."), or a picture missing its object (such as a picture of a

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boy licking an invisible ice-cream cone) to the corresponding object (in this case, the ice-cream cone). We used static black and white drawings of pantomimed actions in our design (like Seron, van der Kaa, Remitz, & van der Linden, 1979) because they are more appropriate visual matches to written text stimuli which are also static in nature.

We had two main goals in this study: (1) to test linguistic and non-linguistic action comprehension at the same time, using the same task, on the same patients, and with stimuli as closely matched as possible, (2) to conduct lesion-symptom mapping analyses using voxel-based lesion symptom mapping (VLSM; Bates et al., 2003b) to identify the lesion correlates of action comprehension deficits.

Regarding the first goal, relationships between linguistic and non-linguistic deficits in aphasic patients are important to examine because they shed light on whether aphasia is a domain-specific disorder which affects only language, or is part of a larger deficit which affects other domains as well. Such questions have been asked since the early days of neurology. Finkelnburg (1870) was the first to propose what is known as the "asymbolia" hypothesis: he suggested that a single underlying factor was common to both the language impairments in aphasia and the deficits in nonverbal domains that these patients exhibit. This idea received some support from subsequent pioneers in neurology as well (e.g., Goldstein, 1948; Head, 1926). On the other hand, it does not seem plausible that aphasia is completely reducible to a strong version of asymbolia, especially given that dissociations in performance between linguistic and non-linguistic domains can be encountered in individual patients.

Even though nonverbal deficits in aphasia have been of interest to researchers for a long time, it has been difficult to assess whether the linguistic and the non-linguistic deficits patients exhibit are related to each other. First, performance on language processing and on non-linguistic tasks must be explored in the same patients. Furthermore, task and stimulus-level factors should be as closely matched as possible. Considerations such as these motivate the first goal of the present study: to contrast linguistic and non-linguistic comprehension of action information in aphasia by comparing performance in the two domains in the same patients more directly than in previous studies. Previous studies seeking correlations between patientsí performance in various language tests and various action comprehension tests do exist, although stimuli and tasks have often not been closely matched across the two domains. While some of these studies found correlations between language impairments and non-linguistic action processing impairments in aphasic patients (e.g., Duffy & Duffy, 1981; Pickett, 1974; Seron et al., 1979; Varney, 1978, 1982), others found largely uncorrelated performance (e.g., Bell, 1994; Goodglass & Kaplan, 1963; Kimura, 1977).

With regards to the second goal, although it has been known since the early days of neurology that left-hemisphere lesions can often cause receptive and/or expressive disorders in both language and action domains (i.e., aphasic and apraxic disorders) and that patients with right hemisphere injury will rarely exhibit such impairments, the precise lesion sites leading to aphasic and apraxic deficits remain quite unclear. Specifically, results on lesion correlates of impairments in action, pantomime and gesture *comprehension* deficits are few, and not entirely consistent. Heilman and colleagues have reported that apraxic patients with posterior lesions have more trouble in comprehending the meaning of pantomimes (Heilman, Rothi, & Valenstein, 1982; Rothi, Heilman, & Watson, 1985) and have suggested that posterior parietal regions of the cortex may mediate the production and comprehension of purposeful movements (see also De Renzi, Faglioni, Scarpa, & Crisi, 1986; Kertesz, Ferro & Shewan, 1984). On the other hand, Ferro, Martins, Mariano, and Castro Caldas (1983) reported that while gesture recognition impairments were most commonly associated with parietal lesions in chronic stages of brain damage, in acute stages it was the patients with left frontal and basal ganglia damage who showed deficiencies, but unfortunately this study had a rather small sample size. Other studies failed to find reliable lesion sites associated with deficits (e.g., Schnider, Hanlon, Alexander, & Benson, 1997; Wang & Goodglass, 1992). Recently, Tranel, Kemmerer, Adolphs, Damasio, and Damasio (2003) used more novel lesion-mapping methods and reported that lesions in the left premotor/prefrontal and parietal cortex and in the white matter underlying the left posterior middle temporal cortex are implicated in deficits in tasks which were designed to tap into conceptual knowledge for actions.

There is also a substantial literature on the related question of brain areas differentially involved in the naming of actions versus objects, and/or the processing of verbs versus nouns. Many researchers have argued that left frontal areas are differentially involved in the processing of actions or verbs. For example, in a PET study using a lexical decision task, Perani, Cappa, Schnur, and Tettamanti (1999) found that verbs activated left dorsolateral frontal cortex more than nouns. However, other studies have failed to find significant differences; for instance, Tyler, Russell, Fadili, and Moss (2001), using carefully matched stimuli, did not find any regions differentially involved in the lexical decision or semantic processing of nouns versus verbs. Hillis, Tuffiash, Wityk, and Barker (2002) reported that damage or hypoperfusion in precentral and middle temporal gyri were associated with action naming deficits in patients with acute left hemisphere injury, while for object naming, middle temporal and superior temporal gyri were associated with impairment. However, for comprehension of action and object words, they did not find separate sites; impairments were associated with superior temporal lesions. Hillis et al. suggested in light of this finding that only the naming of actions, rather than semantic knowledge, may be localized to left frontal cortex.

Given the diverse results which have been reported in the literature, we wanted to use VLSM, a quantitative lesion-symptom mapping technique, to contribute to identifying

lesion correlates of action comprehension in aphasia in linguistic and non-linguistic domains.

In addition to these two major goals, we had some other points in mind in our design: In line with earlier studies (e.g., Varney, 1978), we also addressed the effect of semantic competition in both domains in order to see if processing in the two domains is similarly modulated by higher-level conceptual constraints. In addition, following Seron et al. (1979), Wang and Goodglass (1992) and Bell (1994), we also used distracters that were related to the targets in the way they may be handled, to see if there are differential effects of this kind of competition (previous researchers termed these morphological, perceptual or motoric distracters; here we refer to these as "affordance-based" distracters; see Gibson, 1977).

2. Methods

2.1. Participants

Patients were voluntary participants recruited from the community in San Diego, CA or the VA Northern California Health Care System (VANCHCS) in Martinez, CA, and were paid US$ 25.00 for their participation. Twenty-nine left-hemisphere injured patients with varying types and severity of aphasia participated in the experiment. All aphasic patients were administered the Western Aphasia Battery (WAB; Kertesz, 1979) and were diagnosed as Anomic (N = 9), Broca's (N =12), or Wernicke's aphasics (N = 8). In this sample, we did not have patients with other types of aphasia (e.g., global, conduction). More detail is provided in Table 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and medical records of all patients were evaluated by a neurologist at the time of enrolment into our program, and only patients with unilateral lesions due to a single cerebrovascular accident were included. Exclusionary criteria included non-native English pro□ciency, as well as a diagnosis or suspicion of hearing dif□culties, dementia, head trauma, tumors, multiple infarcts or other neurological conditions. We carefully monitored for patients with any diagnosed or suspected visual problems, including agnosia. No patients were excluded on this basis. Subjects with corrected-to-normal vision were allowed to participate. For this particular study, patients were also administered a subtest of the Minnesota Test for Differential Diagnosis of Aphasia (MTDDA; Schuell, 1965) in order to assess their ability to match single words to pictures, so as to exclude patients with severe single word reading de□cits. It was planned that patients who scored below 75% in this 2AFC task would not be allowed to participate, but

Table 1
Characteristics of aphasic patients

Initials	Age	Aphasia type	AQ	Lesion site
B.E.	25	Broca's	71.6	Frontal, temporal, parietal, insula, basal ganglia
B.K.	56	Anomic	84.4	Basal ganglia, insula
C.H.	67	Anomic	92.2	Basal ganglia
D.C.	64	Broca's	74.8	Frontal, insula, basal ganglia
D.D.	57	Broca's	18.9	Temporal, parietal, frontal, insula
D.F.	47	Broca's	49.6	Temporal, parietal, frontal, insula
F.Y.	78	Wernicke's	64.1	Inferior parietal, small region on superior temporal
H.K.	63	Wernicke's	47.6	Frontal, medial temporal, insula, subcortical
H.K.	75	Broca's	n/a	Frontal, temporal, parietal, head of caudate
H.M.	73	Broca's	26.7	Frontal, temporal, parietal
J.B.	67	Broca's	13.8	MCA-territory, acute scan shows expanding frontal lesion
J.C.	82	Anomic	91.1	N/Aóacute scan, shows no lesion boundaries
J.H.	63	Anomic	92.4	Frontal, tip of anterior temporal
J.Q.	77	Broca's	11.2	Frontal, temporal, parietal, insula
J.S.	52	Broca's	48.8	Frontal, temporal, parietal
J.T.	78	Wernicke's	31.7	Temporal
J.W.	73	Anomic	90.9	Temporal, parietal
K.W.	65	Anomic	98.0	Frontal
L.R.	57	Anomic	79.2	Frontal, temporal, parietal
M.B.	51	Broca's	31.0	Frontal, insular and subcortical extension, parietal
P.B.	76	Anomic	98.0	Medial frontal
P.P.	51	Wernicke's	78.0	Frontal, temporal, parietal, insula
R.S.	75	Wernicke's	48.7	Temporal, inferior parietal
S.A.	77	Anomic	66.7	Frontal, anterior temporal
S.S.	78	Broca's	22.6	Frontal, anterior temporal
V.H.	72	Wernicke's	78.6	Frontal, anterior temporal
W.G.	83	Wernicke's	51.5	Temporal, parietal
W.R.	59	Broca's	72.8	Frontal, anterior temporal
W.T.	67	Wernicke's	73.6	Frontal, posterior temporal

Patient group determined using the Western Aphasia Battery (WAB), AQ: aphasia quotient, a measure of aphasia severity, based on the WAB. Lesion summaries are based on CT or MRI scans or medical records.

we did not encounter any such patients; indeed over 90% of our patients scored over 90% on this task, with many performing perfectly.

Age-matched controls were 18 adults aged 50-80 years, with no history of neurological, or psychiatric disorders; all had normal or corrected-to-normal vision and hearing. All were paid US$ 25.00 for their participation. There were an additional 20 participants from UCSD, aged 18-35, who took part in two preliminary norming studies in exchange for course credit. All had normal or corrected-to-normal vision and hearing.

The study was approved by the University of California, San Diego (UCSD) and VANCHCS Human Research Protection Programs, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants gave informed consent prior to participation.

2.2. Experimental design and materials

A 2-within- x 1-between-subjects design was used, with Domain (linguistic versus non-linguistic) and Distracter Type (semantic, affordance-based, unrelated distracters) as within-subject factors, and Subject Group (Control, Aphasic) as the between-subjects factor. In further analyses, we also included aphasia severity (AQ) and aphasia type (Anomic, Broca's, Wernicke's) as between-subjects factors.

Stimuli were black-and-white line drawings of pantomimed actions and objects, and written text. The drawings of pantomimed actions depicted people carrying out transitive actions, but with the objects removed. These stimuli were created by the first author (APS) in collaboration with an artist. Eighteen such pictures, along with three practice items, were selected from an initial set of 30 in a preliminary norming study. In the norming study, 12 subjects were shown each of the 30 pictures. They were instructed to explain the action in each picture by providing a sentence that describes the picture, and they were required to provide a verb and a noun. They were allowed to write as many as three sentences for each picture. These responses were used to select the most identifiable actions, to determine the target objects, and to determine the linguistic labels to be used in the main experiment. A list of items is provided in Table 2 along with corresponding distracters in each of the conditions.

Linguistic stimuli were (incomplete) sentences based on the most common labels provided by the subjects in the norming study. Since the target objects were missing from the picture stimuli, the objects were missing from the sentence stimuli as well. Thus sentences were of the form "He is licking the … " or "She is sweeping with the … ". Grammatical complexity was kept constant by putting together commonly reported nouns and verbs in "He/she is verb-ing [preposition] the …" constructions.

The object stimuli were digitized drawings culled from extensively normed picture databases. Naming norms for these pictures have been reported elsewhere (Szekely et al., 2004). Four line drawings of objects were matched to each action: a target, a semantically related distracter, an affordance-based distracter and an unrelated distracter. For example, depicted in Fig. 1 are the stimuli for the action *licking ice-cream cone*: The non-linguistic stimulus was a drawing of a person holding and licking an invisible ice-cream cone and the linguistic stimulus was the sentence fragment "he is licking the … ". The target item in each case was *ice-cream cone*. The semantically related distracter was the picture of a *cake*, an object one would eat, but normally not 'lick' as depicted in the sentence (so that it was not a better fit than the target), and not hold and lick in the manner depicted in the action picture. The affordance-based distracter was a *bouquet*

Table 2
List of items used, along with target and distracter objects

Action	Target	Semantic distracter	Affordance-based distracter	Unrelated distracter
Blowing out a candle	Candle	Lamp	Cigarette	Football
Brushing hair	Hair brush	Bow (for hair)	Knife	Boat
Brushing teeth	Toothbrush	Dentures	Paintbrush	Pig
Digging with a shovel	Shovel	Wheelbarrow	Guitar	Light bulb
Drinking water from a glass	Glass	Faucet	Telescope	Cat
Eating a burger	Burger	Salt	Football	Helicopter
Eating an ice-cream cone	Ice-cream cone	Cake	Bouquet of ө wers	Rooster
Fencing	Foil	Mask	Umbrella	Penguin
Playing the guitar	Guitar	Flamenco dancer	Rie	Horse
Playing the piano	Piano	Ballet shoes	Desk	Fish
Raking	Rake	Leaf	Flag	Book
Shooting with a bow and arrow	Bow and arrow	Target	Violin	Bus
Singing into a microphone	Microphone	Television	Wrench	Onion
Sweeping with a broom	Broom	Bucket	Double bass	Spaghetti
Swinging a baseball bat	Baseball bat	Baseball	Frying pan	Sheep
Talking on the telephone	Telephone	Alarm clock	Drill	Barrel
Throwing a baseball	Baseball	Net	Light bulb	Tree
Typing	Typewriter	Envelope	Knitting	Skateboard

Fig. 1. Summary of the experimental design. Here, the Domain and Distracter conditions are illustrated using the action stimulus licking ice-cream cone. The left panel shows the non-linguistic (pantomime) and linguistic (text) stimuli. The linguistic stimuli were based on the most common label provided for the picture stimuli in our preliminary norming study. On the right panel, the three pairs of pictures show the target (ice cream-cone), along with the semantic (cake), affordance-based (bouquet of flowers), and unrelated (rooster) distracters for this item. In the experiment, only one of the three pairs was presented during each trial, and the two object pictures were displayed below the pantomime or text stimulus (see Section 2).

of flowers, an object one would typically hold in a manner similar to an ice-cream cone, but normally not manipulate with the mouth in the manner depicted in the picture (so that it was not a better fit than the target), and would not 48'lick'as depicted in the sentence. The unrelated distracter was a *rooster*, an object one would manipulate neither in the manner depicted in the picture, nor in the sentence.

In order to ensure that semantic relatedness was assigned appropriately across the conditions, we made use of the semantic relatedness measure *latent semantic analysis* (LSA; Landauer, Foltz, & Laham, 1998). Higher LSA indices indicate higher relatedness. The average LSA index for the semantically related pairs was 0.40, for affordance-based pairs it was 0.09, and for unrelated pairs it was 0.006.

To verify the affordance-based distracter assignments, we carried out another norming study in the form of a questionnaire. Eight participants were provided with pictures of target objects (objects matching the action stimuli we selected) and three other objects (the semantic, affordance-based, and unrelated distracters we assigned based on LSA). They were given detailed written instructions to rank order the three latter pictures as to how well they ful□lled the following statement in relation to the target object: *this object may be held, manipulated, acted upon or interacted with in a way that is similar to the way one could hold, manipulate, act upon or interact with the target object*. They were encouraged to reply based on physical properties of the objects rather than on conceptual relationships. The results of the study confirmed our choices of affordance-based distracters: these were ranked first (mean rank = 1.06; median rank = 1). Semantically-related distracters were ranked second (mean rank = 2.08; median rank = 2), and unrelated distracters third (mean rank = 2.83; median rank = 3).

Over the course of the experiment, trials appeared in pseudorandomized order. Each stimulus appeared in the linguistic and non-linguistic conditions as well as with three distracter types (Fig. 1). Three separate pictures of the target object were used for each action stimulus to avoid repetition of the exact same target pictures.

2.3. Experimental procedure

The experiment was run on Apple iBook computers using the PsyScope experimental driver (Cohen, MacWhinney, Flatt, & Provost, 1993). Participants sat in front of the monitor and a standard PsyScope button box was used to collect responses. The experimenter read a set of instructions to the participant, and asked him or her to complete a practice session of six trials.

The experimental design was analogous to a previous study (Saygin et al., 2003a). There were 108 experimenter-advanced trials. In each trial, subjects were presented with a two-picture display on the screen. These pictures were presented on the lower half of the screen, one on each side. After 1000 ms, the pantomime or text stimulus was presented centrally on the upper half of the screen, above the two object pictures. This delay allowed participants enough time to process the object stimuli prior to being presented with the action stimuli. Participants pushed the button under the picture they believed matched the pantomime or sentence. Reaction time (RT) and accuracy were recorded for each trial. Participants were continuously monitored for attention to the task, and were asked at intervals whether they needed a break. The nature of each error was noted, as were any comments made during or after the experiment. Care was taken to note whether or not the participant was immediately aware of the error (as indicated by an overt verbal or physical response). Motivational feedback (e.g., 'you are doing great so far', 'going good') was given as often as considered necessary to keep participants engaged in the task (for aphasic patients, approximately once every 20 trials); however, this feedback did not relate any information about accuracy in a particular trial.

2.4. Behavioral analysis

Performance across groups was compared using repeated measures analysis of variance (ANOVA) and analysis of covariance (ANCOVA). Regression and correlation analyses were performed in order to examine the relationships between performance in the two domains. We also conducted outlier analyses (Bates, Appelbaum, Salcedo, Saygin, & Pizzamiglio, 2003a) and cluster analyses (Sokal & Sneath, 1973). Results were Geisser-Greenhouse corrected, where appropriate.

2.5. Lesion analysis

Lesion analysis was carried out using voxel-based lesion-symptom mapping (VLSM) techniques recently developed by our group, described in Bates et al. (2003b). VLSM involves carrying out statistical analyses of the relationship between tissue damage and behavior on a voxel-by-voxel basis, and plotting the resultant statistics as color maps which depict the degree of behavioral involvement for each voxel. VLSM analyzes the relationship between behavioral data and lesion location and extent without requiring any cutoffs or grouping to be stipulated based on behavior or lesion site.

There are also limitations inherent in this kind of lesion analysis which should be noted. Firstly, the lesions of the patients in our sample do not cover the entire brain. Because all patientsí lesions were restricted to the left hemisphere, we are unable to examine any hemispheric effects on action comprehension, of the sort discussed, for example, by Goldenberg (1999) in the domain of gesture perception, production and imitation. Moreover, most of the lesions in our sample resulted from infarcts of the middle cerebral artery (MCA), and hence only in MCA territory do we have sufficient sample sizes to make inferences.

Secondly, lesions almost invariably affect multiple brain areas. In lesion-symptom mapping, damage to an area may correlate with behavior because the area genuinely supports the cognitive function in question, or because the area is frequently lesioned along with some other area which is actually crucial for the function. Bates et al. (2003b) discussed the use of analyses of covariance to examine multiple areas which may potentially underlie behavioral deficits, but in the present study our sample size is not sufficient to perform such analyses. However, the lesion maps obtained by Bates et al. (2003b) for two WAB subscales do confirm that VLSM yields results which broadly conform to established locations for major linguistic functions, supporting the validity of the method.

As noted above, head CT or MRI images were obtained for each patient. For 21 of our patients, computerized lesion reconstructions to be used in lesion overlay analyses were available; the remaining lesion information reported in Table 1 was obtained from CT or MRI scans or neuroradiological reports. Lesion reconstructions were based on CT or MRI scans at least 3 weeks post-onset and were hand-drawn onto 11 axial slice templates based on the atlas of DeArmond, Fusco, and Dewey (1976). The reconstructions were then entered into a Macintosh computer via electronic bitpad using in-house software. The reconstructions were performed by a board-certified neurologist with experience in neuroradiology who was blind to the behavioral deficits of the patients. Voxels were 0.5 mm x 0.5 mm in-plane, with approximately 6 mm between slices.

At each voxel, patients were divided into two groups according to whether they did or did not have a lesion affecting that voxel. Behavioral scores were then compared for these two groups, yielding a statistic for each voxel, which was then plotted. The statistic computed in the present study was *d*, a standard measure of effect size determined by dividing the difference in group means by the pooled sample standard deviation. The *d*-maps were smoothed in-plane with a circular filter with a radius of 3.5 mm. Voxels where fewer than five patients had lesions were excluded, as *d* is a measure of effect size, not an inferential statistic, so values are not reliable if either of the two groups being compared is not well represented. Software to perform VLSM operates on lesion files in the popular ANALYZE image format, and is freely available online at http://crl.ucsd.edu/vlsm.

3. Results

Here, we report differences in accuracy and reaction time between patient and control groups, the correlation in performance across verbal and nonverbal domains, and the relationship between lesion site and processing deficits.

3.1. Behavioral results

We examined accuracy and reaction time (RT) for the aphasic subjects and their age-matched controls. RTs were analyzed only for correct responses and were measured from the onset of the action stimulus.

As depicted in Fig. 2a, groups differed in their overall accuracy [$F(1, 45) = 13.47$, $P = 0.0006$]; aphasic patients were significantly less accurate than control subjects. There was no main effect of Domain, but a tendency for accuracy to be higher in the nonverbal (pictured) action comprehension trials [$F(1, 45) = 3.31$, $P = 0.076$]. The interaction of Domain by Group [$F(1, 45) = 6.26$, $P = 0.016$] reached significance, revealing that patients made comparatively more linguistic errors than controls, as would be expected based on the fact that all patients were clinically diagnosed with aphasia.

Distracter Type had an effect on accuracy [$F(2, 90) = 9.66$, $P = 0.0006$] reecting that overall, subjects made more errors when the distracters were related to the target object, compared with when they were unrelated. The effect of Distracter Type was modulated by Group [$F(2, 90) = 9.75$, $P = 0.0006$], showing that patients were disproportionately affected by the distracter manipulations. The data are shown in Fig. 2b. This interaction was driven by the following effects (all Bonferroni corrected): Patients were significantly less accurate in trials with semantic distracters compared with unrelated distracters ($P = 0.0001$)and also compared with affordance-based distracters ($P = 0.05$);the effect of affordance-based distractors did not reach significance compared with unrelated distracters after correction ($P = 0.16$). For controls, the only significant effect was when affordance-based distracters were compared to unrelated distracters ($P = 0.012$). These distracter effects showed no differentiation between the linguistic and non-linguistic conditions: The interaction of Distracter Type and Domain as well as the three-way interaction of Group, Domain, and Distracter Type were

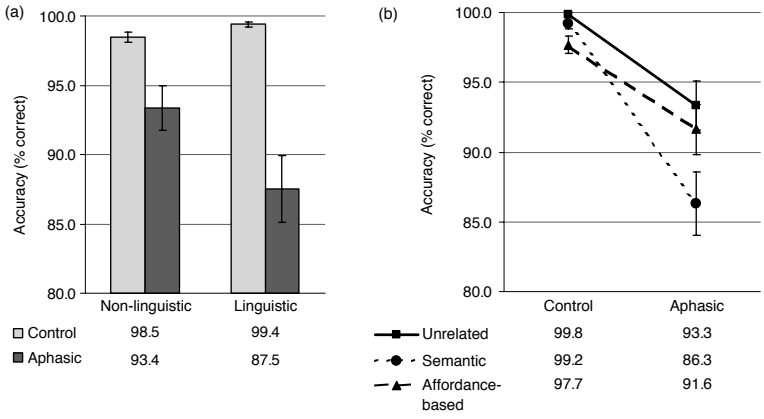

Fig. 2. Accuracy data shown across the linguistic and non-linguistic domains for the two subject groups (a). Error bars represent the standard error of the mean, in this and subsequent figures. Aphasic patients were significantly less accurate than control subjects in both linguistic and non-linguistic domains. The group by domain interaction was also significant. Accuracy data is also depicted across related and unrelated distracter conditions for the two groups (b). There was a main effect of Distracter Type and also an interaction of Distracter Type by Group, indicating that aphasic patients were disproportionately affected by the semantically related distracters.

not significant [$F(2, 90) = 1.12$, $P = 0.32$; $F(2, 90) = 0.26$, $P = 0.74$].

We found signi□cant differences in RT by subject group, as plotted in Fig. 3 [$F(1, 45) = 23.40$, $P = 0.0001$]; patients responded slower than controls. There was a main effect of Domain on reaction time [$F(1, 45) = 13.72$, $P = 0.0006$] where subjects were slower to respond on the linguistic trials. There was an interaction of Domain and Group [$F(1, 45) = 11.83$, $P = 0.0013$]; as can be seen in Fig. 3a, patients responded especially slowly in the linguistic domain.

There was a significant main effect of Distracter Type [$F(2, 90) = 8.90$, $P = 0.0003$], shown in Fig. 3b. Overall the slowest response was to semantic distracters and this was signi□cant compared with unrelated distracters ($P = 0.0001$, all comparisons corrected) as well as affordance-based distracters ($P = 0.017$). Affordance-based distracters led to slower reaction times compared to unrelated distracters, but this reached significance only in the control group ($P = 0.0018$). Overall, Distracter Type did not interact with Group [$F(2, 90) = 1.15$, $P = 0.22$]. The interaction of

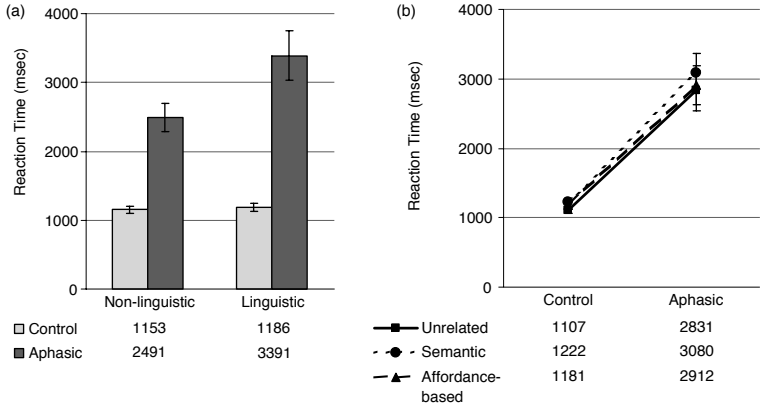

Fig. 3. Reaction time (RT) for correct responses depicted across linguistic and non-linguistic domains for the two subject groups (a). Patients with aphasia were significantly slower than controls in both domains but the RT discrepancy was larger in the linguistic domain. RT data is also shown for related and unrelated distracter conditions for the two groups (b). There was a main effect of Distracter Type; semantic distracters had the largest effect.

Distracter and Domain as well as the three-way interaction of Group, Domain, and Distracter Type were not signi□cant for RT [Fs < 1].

We next conducted analyses based only on the patients' data to see how the experimental scores were related to aphasia severity, by including aphasia quotient (AQ, a measure of aphasia severity, derived from the patientsí WAB scores) as a continuous variable in our analysis. Low quotients are associated with severe aphasia and higher quotients are associated with relatively mild aphasia. Mean AQ in this sample was 61.5 (S.D. = 25.2, range: 11.2-98.0). Table 1 reports AQ for each of our patients.

There were main effects of AQ [$F(1, 26) = 15.92$, $P = 0.0005$] and Domain [$F(1, 26) = 18.24$, $P = 0.0002$], and an interaction of Domain by AQ [$F(2, 52) = 10.76$, $P = 0.003$]. There was a main effect of Distracter Type [$F(2, 52) = 14.35$, $P = 0.0001$] and an interaction of Distracter by AQ [$F(2, 52) = 5.67$, $P = 0.011$]. The interaction of Distracter and Domain and the three-way interaction were not signi□cant [Fs < 1]. The significant interactions of Domain by AQ and Distracter Type by AQ reveal that the patient groupís performance is related to aphasia severity; more severely affected patients were responsible for both the Domain and the Distracter Type effects. Several effects were also mirrored in the RT data: There was a main effect of AQ [$F(1, 26) = 12.37$, $P = 0.0016$], a main effect of Domain [$F(1, 26) = 24.53$, $P = 0.0001$], and an interaction with Domain and AQ [$F(1, 26) = 10.06$, $P = 0.0039$]. To summarize, the severity of aphasia was seen to be a signi□cant correlate of the relatively severe impairment the patient group exhibited in the linguistic domain and also to the relatively difficult time they had with semantic distracters.

We next added the grouping variable aphasia type (Anomic, Broca's, Wernicke's, based on the WAB) to the model. In these analyses, aphasia type had no significant main effects or interactions for either accuracy or RT, but the effects reported above remained significant.

3.2. Associations between task performance across domains, cluster and outlier analyses

So far we saw that aphasic patients have significant deficits in both linguistic and non-linguistic action comprehension. However, this does not necessarily imply that the de□cits have a common substrate.

We examined if the deficits were correlated in the two domains and at a first glance it appeared that accuracy in the linguistic and non-linguistic domains were significantly correlated in our action recognition test [$r = 0.53$; $P = 0.03$]. However, a closer inspection showed that this correlation was pulled by patient JB (marked with * in Fig. 4a), whose performance was at chance for both domains. This patient was reliably identified as an outlier by our analyses and was singled out in cluster analyses (see below). When the correlation analysis was repeated without JB in the dataset, we found that the correlation between accuracy in linguistic and non-linguistic domains was no longer significant [$r = 0.12$; $P = 0.53$].

On the other hand, a high correlation between the two domains was found for the RT data [$r = 0.91$; $P = 0.0001$, see Fig. 4b]. This correlation, unlike the one for accuracy, was robust and still held when the outliers were excluded from analyses [$r = 0.90$; $P = 0.0001$]. In the absence of a correlation in accuracy scores, we can only interpret the RT

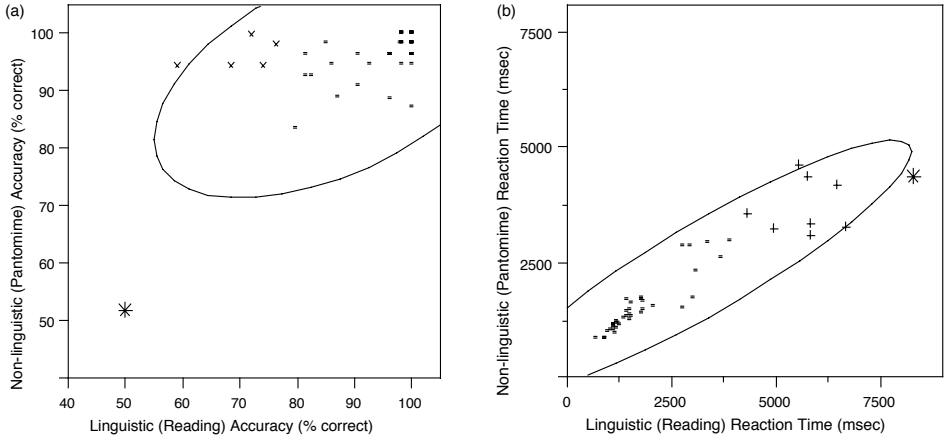

Fig. 4. Correlation of performance in the verbal and nonverbal domains within the aphasic group for (a) accuracy and (b) reaction time. Density ellipses using a confidence interval of 95% are shown. Data points outside the ellipses are outliers based in Mahalanobis distances. Cluster analysis results are also depicted with the different markers. In Fig. 5a, * denotes patient JB, + and • denote the second and third clusters. In Fig. 5b * denotes patient RS, + and • denote the second and third clusters.

correlations as being due to common factors in the task such as motor planning and execution, orienting and attention, rather than being reflective of an association between the linguistic and non-linguistic domains.

In order to further explore the relative impairments in the two domains, we performed cluster analyses on the data. We first performed hierarchical clustering with cluster size 3 with the accuracy in the two domains (linguistic, non-linguistic) as variables, a process that transforms data points into a sequence of nested partitions (Sokal & Sneath, 1973). The clusters are plotted using different markers in Fig. 4a. Cluster 1 consists of patient JB and represents a severely impaired pattern in both domains. Cluster 2 emerges from the patients who had a pronounced deficit in linguistic processing but less of an impairment in the non-linguistic domain. Five severely aphasic patients fell into this cluster; four are Broca's aphasics, and one is a Wernicke's aphasic. Cluster 3 contains the majority of the patients and contains patients who had milder impairments in either domain. Patients in Cluster 2 were marginally significantly more severely impaired (mean AQ = 40.8, S.E.M. = 5.2) and significantly less fluent (mean WAB fluency score = 2.6, S.E.M. = 0.6) compared with patients in Cluster 3 (mean AQ = 68.4, S.E.M. = 9.8; mean fluency score = 6.5, S.E.M. = 1.3; $P = 0.06$ and $P = 0.02$, respectively). Within Cluster 3, accuracy scores in linguistic and non-linguistic trials were significantly correlated [$r = 0.42$; $P = 0.05$].

Note that we already reported above that aphasia severity has a significant interaction with Domain - consistent with this, the cluster analysis reveals a subset of relatively severely affected individuals who show a disproportionate impairment in the linguistic compared with the and non-linguistic domain. The remaining patients show correlated deficits.

An analogous cluster analysis on RT data did not reveal theoretically interesting clusters. Cluster 1 consists of Wernicke's aphasic patient RS (marked by * in Fig. 4b, see below for outlier analysis) who was very slow to respond, especially on the linguistic trials. Cluster 2 (marked by + in Fig. 4b) contains eight patients who were relatively slow to respond in general. This group contains five Broca's aphasics, two Wernicke's aphasics and one Anomic patient. Cluster 3 contains the remaining patients.

We carried out outlier analyses in an attempt to identify any individual subjects who may exhibit dissociations between the linguistic and non-linguistic domains. We followed the procedure outlined by Bates et al. (2003a) in order to pick out the outliers and calculated density ellipses using a confidence interval of 95% (the ellipses shown in Fig. 4). This procedure uses the Mahalanobis distance and takes into account the correlation structure of the data as well as the individual scales (Bates et al., 2003a).

For accuracy, two subjects remained outside the ellipse and were identified as outliers as shown in Fig. 4a. Patient JB performed at chance in both linguistic and non-linguistic domains and was the poorest-performing subject in the sample. The second outlier was patient MB who was disproportionately affected in the linguistic domain - his accuracy in action comprehension in the non-linguistic domain was 94.4% while he managed to answer correctly in only 59.3% of the linguistic trials. For RT, we identified two outliers, as can be seen in Fig. 4b. These were patient RS and patient DC. Both patients were slower to respond to the linguistic trials with RS's discrepancy being much more pronounced. In summary, outlier analyses revealed a few potential dissociations in this sample of aphasic patients: JB was at chance in both domains and did not exhibit a dissociation. On the other hand, patient MB's performance in action comprehension through reading was severely compromised while he performed much better in action comprehension in the non-linguistic domain. The outliers identified for RT data also showed more impairment in the linguistic domain, although these should be interpreted with caution since they are not mirrored in the accuracy data and also because longer response latencies for reading comprehension was characteristic of the behavior of severe aphasics in general. No outliers were identified who were markedly more impaired in the non-linguistic action condition, and thus we have no evidence here for a double dissociation.

In a series of papers, Varney proposed a theory of impairments following left-hemisphere strokes that result from two determinants: a supralinguistic impairment which also affects nonverbal abilities, and specific disturbances in processing semantic information from a sensory modality (Varney, 1978, 1980, 1982; Varney & Benton, 1982). In particular, Varney (1978) reported that patients who were deficient in pantomime recognition were also impaired in reading comprehension. Conversely, all patients who were intact in reading were also intact in processing pantomime. As mentioned above, reading comprehension was relatively more impaired compared with pantomime interpretation across our population as well: 21 patients' z-scores differed by more than one in the direction of more impairment in the linguistic domain. There were five patients who showed the reverse pattern and three for whom the z-score differences were less than one. Note that this distributional information is reported for ease of comparison with previous results and is not considered to be evidence for dissociations (which have already been discussed above with more appropriate analysis techniques which take cross-domain correlations in the data into account).

3.3. Lesion location analyses

We performed a lesion analysis to investigate the neural correlates of linguistic and non-linguistic action processing using VLSM. Here, we constructed VLSM d-maps. Three axial slices for pantomime and reading comprehension are shown in Fig. 5. The color of each voxel reects the magnitude of the difference between the scores of patients whose lesions included that voxel and those whose lesions did not include that voxel, which suggests the extent to

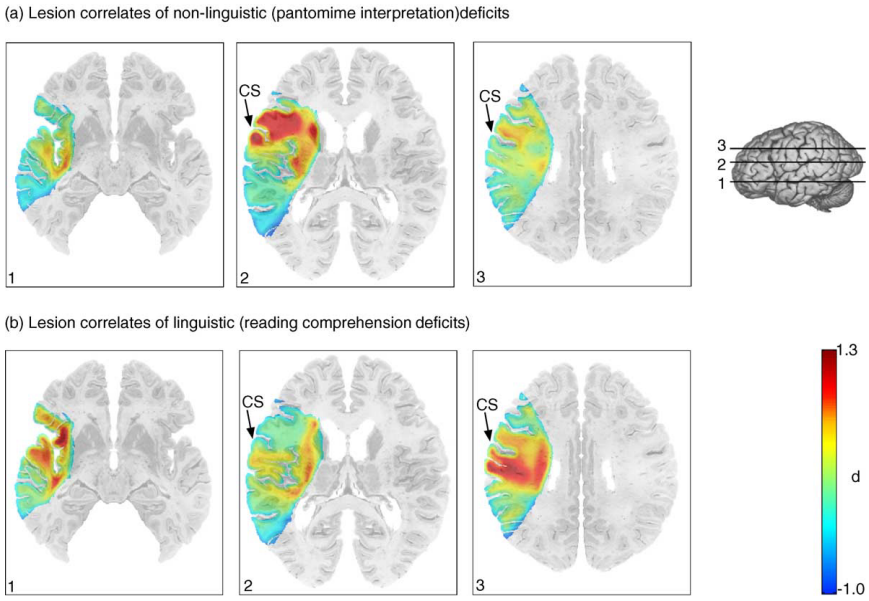

Fig. 5. Axial VLSM displays showing the relationship between tissue damage and behavioral deficits. The values displayed at each voxel are *d*-statistics comparing the patients lesioned at that voxel to the patients intact at that voxel. High *d* values top the scale in red, indicating areas where damage led to significant deficits in task performance. Voxels denoted in blue reflect negative *d* values, which arise when patients with lesions to those voxels performed better than those who had lesions elsewhere. Voxels that are not color-coded were damaged in less than 5 of the patients in our sample. The behavioral measures displayed are (a) non-linguistic action processing (pantomime interpretation), and (b) linguistic action processing (reading comprehension). The central sulcus (CS) is marked on slices 2 and 3, based on DeArmond et al.'s (1976) labeling in the atlas. The lateral view shows the approximate locations of the axial slices.

which damage to the voxel is associated with performance deficits.

The VLSM *d*-map for the accuracy measure in the non-linguistic domain (Fig. 5a) revealed a large focal region including parts of the posterior inferior frontal gyrus (IFG) and ventral pre- and primary motor cortex (vPMC), extending medial to the frontal ventral-dorsal fibers of the superior longitudinal fasciculus (SLF), to be reliably associated with performance deficits when lesioned, as can be seen in slice 2. Also shown in red, just posterior and lateral to this area on the same slice, is part of the primary somatosensory cortex (PSC) in the postcentral gyrus. The head of the caudate nucleus is implicated, here visible again on slice 2. Finally, the most posterior focus shown in red on slice 2 includes white matter as well as part of the claustrum and possibly part of the insula, but the resolution does not permit us to distinguish between these structures. We will interpret these findings in more detail in the discussion.

The VLSM *d*-map for the accuracy measure in the linguistic domain (Fig. 5b) revealed several distinct areas where lesions were predictive of deficits in reading comprehension of actions. Deficits were associated with damage to the anterior superior temporal gyrus (aSTG) extending back to the temporal isthmus, depicted on slice 1, the inferior anterior insula (aINS), also depicted on slice 1, and in the anterior inferior parietal lobe (aIPL) including parts of the postcentral and supramarginal gyri, as seen on slice 3. Lesions affecting white matter were also associated with deficits: the internal capsule in slice 2 and the SLF in slice 3. These anatomical localizations were based largely on the sulcal and gyral labels in the DeArmond, Fusco, and Dewey (1976) atlas on which all patients' lesions were mapped.

Note that the lesion maps for linguistic versus non-linguistic action comprehension deficits are quite distinct from one another, suggesting that different brain regions are important for these two tasks.

To analyze the lesion-symptom relationships in more detail, we chose six regions of interest (ROIs) based on these *d*-maps - points corresponding to maximal *d*-values in each of the 'hot spots' in Fig. 5. The accuracy scores in the linguistic and non-linguistic domains of patients who have damage in these ROIs were compared to those whose lesions spared that ROI. This enabled us to quantitatively assess whether the areas we found in the *d*-maps are differentially impli-

Table 3
Summary of region of interest (ROI) analyses

ROI	Brodmann areas	Talairach coordinates			Linguistic		Non-linguistic	
		x	*y*	*z*	*F*	*P*	*F*	*P*
IFG/vPMC	6, 44, 4	48	10	16	0.04	0.42	5.09	**0.018**
PSC	43, 3, 1, 2	60	10	16	0.13	0.36	7.83	**0.006**
CAU	-	12	12	16	0.00	0.99	3.827	**0.033**
aSTG	22, 38	50	15	12	5.00	**0.018**	0.21	0.33
aINS	(13)	37	10	6	7.54	**0.006**	0.00	0.50
aIPL	40, 3, 1, 2	56	30	26	10.5	**0.002**	0.09	0.38

Bold values indicate significant comparisons ($P < 0.05$).

cated in linguistic versus non-linguistic processing. Our six ROIs were the posterior part of the inferior frontal gyrus and pre- and primary motor cortex (IFG/vPMC), the portion of primary somatosensory cortex just posterior to IFG/vPMC (PSC), and the caudate head (CAU, all three ROIs based on Fig. 5a, slice 2), the anterior superior temporal gyrus (aSTG; based on Fig. 5b, slice 1), the inferior anterior insula (aINS; based on Fig. 5b, slice 1), the supramarginal gyrus and surrounding sensory cortex (aIPL; based on Fig. 5b, slice 3). Note that the aIPL and IFG/vPMC ROIs likely contain more than one anatomical region as it was not possible to obtain higher resolution inside these areas in this sample of patients given the distribution of their lesions. Table 3 depicts each ROI, associated Brodmann areas and approximate Talairach coordinates, here reported for comparison with other lesion or functional neuroimaging studies.

As could be expected based on the VLSM *d*-maps, lesions in the IFG/vPMC, PSC, CAU regions were associated with significant deficits in pantomime interpretation. In these regions, there were no effects on reading comprehension (Fig. 6 and Table 3). We see the opposite pattern in the aSTG, aINS, aIPL: Lesions in these ROIs significantly affected reading comprehension of action information but did not have any effect in the non-linguistic domain (Fig. 6 and Table 3). Thus, the regions identified by our VLSM analyses and depicted in Fig. 5a and b are distinct areas and when damaged, have detrimental effects in performance in one domain but not the other.

Finally we examined the correlations between lesion volume and accuracy in the linguistic and non-linguistic action comprehension tasks. In our patient set, lesion volume varied greatly, from 6.4 to 162.6 cc, with a mean of 63.6 cc. However, lesion volume did not predict task performance in either of the two domains [$r = \ 0.03$, $P = 0.90$ for accuracy in pantomime interpretation and $r = \ 0.26$, $P = 0.25$ for reading comprehension].

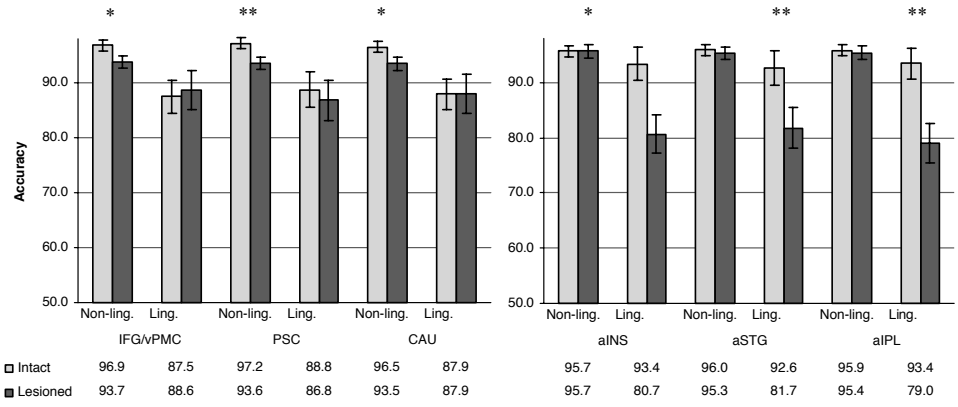

Fig. 6. Summary of statistics on the regions of interest: IFG/vPMC, PSC and CAU on the left graph and aSTG, aINS, and aIPL on the right. The IFG/vPMC and PSC foci were associated with significant deficits in the non-linguistic domain but not in the linguistic domain; conversely the aSTG, aINS and aIPL foci lesions caused significant impairments in linguistic, but not non-linguistic processing.* $P < 0.05$; ** $P < 0.01$ one-tailed - see Table 3 for more detail. Note that the absolute differences between scores of lesioned patients and intact patients are greater for the linguistic condition, but so are the associated error bars, reflecting higher variance in the sample for linguistic scores compared to non-linguistic scores.

4. Discussion

4.1. Action processing impairments in aphasia and their relation to language deficits

Aphasic patients were significantly impaired in our action-to-picture matching task compared with control subjects. Performance was compromised in both linguistic and non-linguistic domains. However, patients tended to show deficits that were more pronounced in the linguistic domain and the severity of aphasia was strongly related to the relative disparity between performance in linguistic and non-linguistic domains. There was no overall correlation between patients' deficits in the two domains, suggesting that the deficits observed in comprehension of pantomimed actions and comprehension of actions through reading are not tightly coupled processes.

Although global correlations in the dataset were not found, we have to refrain from concluding that action understanding in linguistic and non-linguistic domains are completely independent because we also found several pieces of evidence pointing to some shared substrates between linguistic and non-linguistic action understanding, which may help explain correlations observed in prior studies. Firstly, a large cluster of patients with relatively mild and relatively fluent aphasia did show correlated impairments in the two domains indicating perhaps there is some underlying relationship between these two tasks which does not hold for severely impaired subjects. Secondly, our outlier analyses taking correlation structure of the dataset into account did not lead to the identification of a significant number of individual patients exhibiting dissociations between the two domains and no double dissociations. Thirdly, the distracter manipulation showed no difference between the two domains, indicating common underlying processes, most likely of conceptual nature (see below).

What kind of conclusions can be drawn on the nature of non-linguistic deficits accompanying aphasia based on these results? We must reject a strong version of asymbolia, because pantomime comprehension impairments were not tightly correlated with linguistic deficits. On the other hand, we cannot hold that aphasia is a domain-specific disorder, because non-linguistic impairments *are* found in aphasia, and sometimes these are correlated with language deficits. Even in the present study, we see some evidence for some common substrates between linguistic and non-linguistic processing of action information. We must conclude then that the nature of the relationship between linguistic and non-linguistic tasks or processes in question can be variable. Our view is that the more the non-linguistic task has in common with the linguistic task (e.g., in terms of perceptual similarity, conceptual networks involved, developmental stages the skills are acquired), the more likely they will be to have common brain areas subserving them, leading to correlated deficits in aphasic populations.

4.2. Effects of semantically related and affordance-based distracters

Three classes of distracters were employed in this study: semantic, affordance-based, and unrelated. Patients with aphasia were affected dramatically by semantic distracters, indicating that conceptual/semantic processes were especially compromised. Both patients and controls also made more errors when affordance-based distracters were present compared with unrelated distractors, although this did not reach significance for the patient group.

Semantic distracters are well known to affect aphasic patients' performance in non-linguistic domains, specifically in gesture and pantomime comprehension (Duffy & Watkins, 1984; Seron et al., 1979; Varney, 1978; Varney & Benton, 1982), consistent with our findings. Prior results for affordance-based distracters are less consistent: some studies have found that aphasic patients make more semantic and affordance-based errors compared with neutral errors in pantomime interpretation (Seron et al., 1979; Wang & Goodglass, 1992); in another study more affordance-based than semantic errors were observed (Bell, 1994). We observed both kinds of errors, but semantic errors were considerably more frequent.

A few aspects of the distracter effects obtained in the present study were unexpected. First, even for the task of matching an object to a pictured action, semantic relatedness was a more potent distracter than affordance-based relatedness. We also collected data from college-age control subjects and verified the strong effect of semantic distracters (data not shown). We can conclude that associative or conceptual processes must be engaged in the comprehension of the action stimuli in both domains, at least in the context of this task. Thus both modality-specific and conceptual processes must be engaged in our task (see Glaser, 1992 for an argument that this is typical for conceptual tasks involving either words or pictures). The relatively small effect of affordance-based distracters remains more elusive and may need to be explored in further studies. Importantly, distracter-related effects did not differ across the verbal and nonverbal domains, suggesting that underlying processing deficits in aphasia have semantic/conceptual and affordance-based components that are not domain-specific.

4.3. Lesion correlates of impairments in the non-linguistic domain

We found that action processing deficits in the linguistic and non-linguistic domains have distinct lesion correlates. This section and the next discuss brain areas where lesions were predictive of non-linguistic and linguistic action comprehension deficits, respectively.

Deficits in non-linguistic action comprehension were associated with lesions in the inferior frontal and precentral gyri, in the primary somatosensory cortex in the postcentral gyrus, and in the head of the caudate. It is interesting that

premotor and motor regions in the IFG/vPMC, known to be important for motor action production, were found also to be important for visual action comprehension. There was also involvement of the basal ganglia, specifically the caudate, which is another region involved in motor planning and control (see Caplan et al., 1990). The PSC area implicated is densely interconnected with pre- and primary motor cortex.

We believe these findings lend support to an embodied cognition view of action processing as they point to an underlying *analysis-by-synthesis* system. According to this view, an individual can understand others' actions by mapping the visual representation of the observed action onto his/her motor representation of the same action, thus using his/her own embodied experience of the world. In other words, 'an action is understood when its observation causes the motor system of the observer to "resonate" '(Rizzolatti, Fogassi, & Gallese, 2001; p. 661; see also Jeannerod, 1995, 2001).

Recently, the discovery of the "mirror neuron system" has added a new dimension to research concerning the neural representation of action. Mirror neurons are a particular class of visuo-motor neurons that were first found in area F5 in the ventral premotor cortex of the macaque (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996a). The main functional characteristic of these neurons is that they fire not only when an animal executes a particular action, but also when the animal observes another individual performing the same or a similar action. The existence of a similar mirror system in humans has been demonstrated by a variety of neurophysiological and neuroimaging studies, revealing neural activity in premotor and inferior frontal cortical areas (as part of a larger network involving superior temporal and parietal regions) during action observation and imitation (e.g., Buccino et al., 2004; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Grezes, Armony, Rowe, & Passingham, 2003; Iacoboni et al., 1999; Rizzolatti et al., 1996b), and even during viewing of manipulable objects (e.g., Chao & Martin, 2000). Another interesting aspect of the human mirror neuron system is that the responses in frontal cortex during action observation have been fairly consistently left-lateralized in different studies (e.g., Grafton et al., 1996; Grezes et al., 2003; Iacoboni et al., 1999; Rizzolatti et al., 1996b), consistent with findings from the neuropsychological literature on the dominance of this hemisphere for action processing.

These findings are in agreement with our analysis of the lesion correlates of non-linguistic action processing. Indeed, embodied action representation theories may help explain the roles of not only the IFG/vPMC regions, but also the other areas which were predictive of de□cits: there is evidence that this kind of embodied perception may also involve somatosensory regions of the brain (see Avikainen, Forss, & Hari, 2002; Keysers et al., 2004). Another fMRI study has also found that the caudate is active during imagery of hand motions (Gerardin et al., 2000). Thus, we argue that lesions to the IFG/vPMC, PSC and CAU were associated with poor performance in our non-linguistic action comprehension task because processing in this embodied network was disrupted in our patients by damage to parts of this analysis-by-synthesis system.

One potentially relevant role of left frontal areas in action comprehension is the view that these regions may be important for action naming and/or verb processing (e.g. Perani et al., 1999). However, as noted above, some studies have not found differences between verb and noun processing (e.g. Tyler et al., 2001), and Hillis et al.'s (2002) study with neuropsychological patients found evidence for left frontal involvement only for the naming of actions, but not for their comprehension.

There have been relatively few prior neuropsychological studies of action comprehension which have attempted to identify relevant brain areas. This is partly because deficits in movement production (apraxia) have been more studied than deficits in action comprehension. An important focus of the literature on apraxia is the role of the parietal lobe. In a recent review, Koski, Iacoboni, and Mazziotta (2002) concluded that "the left parietal cortex subserves a particularly important component of the praxis system, especially concerned with the knowledge or representation of overlearned actions" (p. 75). As mentioned in the introduction, apraxic patients with posterior lesions have been reported to have more trouble not only in action production, but also in comprehending the meaning of pantomimes (Heilman et al., 1982; Rothi et al., 1985). There is also evidence that parietal lesions may be detrimental to the perception of biological motion (Battelli, Cavanagh, & Thornton, 2003; Saygin, Wilson, Hagler, Bates, & Sereno, 2003b).

In contrast to these findings of the importance of parietal areas for action understanding, Halsband et al. (2001) examined parietal and premotor-lesioned patients and found that while patients with left parietal damage were most impaired in imitation of pantomimes, they did not show differential comprehension deficits. Likewise we did not observe parietal lesions (except for the small locus in the PSC) to be associated with pantomime interpretation deficits. A possible reason for this could be the stationary nature of our stimuli, as parietal areas are known to be involved in visuo-motor transformations. Although stationary images with implied motion or action can activate motion-sensitive areas in functional neuroimaging studies (e.g., Kourtzi & Kanwisher, 2000), these activations are usually in the occipital and temporal regions.

A parallel finding to ours from the neuropsychological literature has very recently been reported by Tranel et al. (2003): Their lesion-symptom mapping procedure identified very similar left inferior frontal areas (along with parietal and temporal regions) to be associated with deficits in conceptual knowledge of actions in a group of patients. It is not unexpected for our study to have some different lesion findings with Tranel et al.'s as the tasks administered were different in the two studies. However, the common frontal lesion finding probably reflects the neural regions subserv-

ing shared processes involved in action understanding and retrieving conceptual knowledge for actions. We believe both Tranel's results and ours are beginning to show that these frontal regions may be important lesion correlates for action processing in the nonverbal domain.

4.4. Lesion correlates of impairments in the linguistic domain

We found three regions that are associated with impairments in the linguistic domain in our task (but not in the non-linguistic domain): aSTG, aINS, and aIPL.

The anterior temporal lobe has been implicated as an area that is important for sentence processing in previous neuropsychological work (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). Neuroimaging studies have also pointed to the role of this region in sentence processing in both auditory (see Staab, 2002 for a review) and visual (Stowe et al., 1999; Vandenberghe, Nobre, & Price, 2002) modalities. These results are consistent with our findings because the linguistic stimuli along with the completion task would be expected to rely upon sentence-level processing.

The superior anterior insula in the left hemisphere has also been identified by Dronkers (1996) as a crucial area for language processing: Lesions in this part of the brain are associated with impairments in speech production. This finding has received further support from subsequent neuropsychological (Bates et al., 2003b) and neuroimaging studies (e.g., Blank, Scott, Murphy, Warburton, & Wise, 2002). The region we found in the present study is slightly inferior to the part of the insula reported in Dronkers (1996). In a recent fMRI study, the insula was among the regions that showed increased activity for "tongue-twister" sentences, even though the task was reading comprehension and did not involve articulation (Keller, Carpenter, & Just, 2003). We believe the involvement of this region in deficits in the linguistic domain in our experiment is most likely due to a recoding of read material into phonological and/or articulatory representations (e.g., Coltheart et al., 1993; Plaut et al., 1996).

The aIPL area identified for linguistic action comprehension deficits may reflect the involvement of either linguistic or sensorimotor systems. This region overlaps partially with the supramarginal gyrus which is known to be important for a number of linguistic functions including phonological (Fujimaki et al., 1999) and semantic processing (Bullmore et al., 1996; Metter et al., 1990). A large group study of aphasic patients found that the supramarginal gyrus (along with the posterior middle and superior temporal gyri) were most often damaged in patients with reading comprehension de□cits (Hojo, Watanabe, Tasaki, Sato, & Metoki, 1985). This region could also be important for the conversion of orthography to phonology (Booth et al., 2002; Moore & Price, 1999) and may be part of the "articulatory loop" for verbal working memory (Paulesu, Frith, & Frackowiak, 1993).

On the other hand, this region of parietal cortex is also known to contain mirror neurons in the macaque (see Rizzolatti et al., 2001) and recent human studies have provided evidence that it is a component of the human mirror neuron system as well (Buccino et al., 2004), showing activation in areas very close to the ones found in our VLSM maps. Thus the involvement of the aIPL focus in our lesion map for reading comprehension may also reflect embodied action comprehension processes. Indeed, based on the relatively anterior location of this lesion focus, it may be more likely that this lesion site reflects the involvement of the mirror neuron system, rather than the linguistic systems discussed above, which tend to be associated with more posterior portions of the inferior parietal lobule. In this latter interpretation, however, it is interesting that action comprehension in the linguistic modality may rely selectively upon the parietal component of the mirror neuron circuitry, while in the non-linguistic modality we see the selective involvement of the frontal component (see Fig. 6). Further studies, perhaps with neuroimaging, may shed more light on why our pantomime interpretation task requires access to the frontal subpart of the mirror neuron system while the linguistic action comprehension task may require access to the parietal subpart.

The fact that we found multiple lesion foci to be associated with deficits in reading comprehension of actions is perhaps not unexpected given that in this task, there could be different components to the impairment in the linguistic domain - i.e., there may be potentially independent factors at play such as an inability to understand written sentences, or deficits in matching the actions described in text to corresponding objects, or a difficulty with processing the action information itself. But the effects of these different factors would be compounded in the behavioral scores and associated lesion sites. Thus, it is possible that the different ROIs we found are associated with different aspects of the task. Based on prior work however, we propose that the aSTG involvement reflects sentence-level linguistic processing aspects of the task, while the aINS (and perhaps aIPL) is involved in translating between different code systems during reading comprehension (orthographic, phonological, articulatory) and aIPL may additionally be involved in action understanding due to being part of the mirror neuron system.

4.5. Theoretical discussion: neuropsychological evidence for embodied representations in action perception

We propose that the lesion sites we identified in the present study support a view which is sometimes called *embodied cognition*, and here we discuss the lesion as well as the behavioral results from this theoretical perspective. The embodied cognition view emphasizes that the brain functions in a body, which in turn, develops and functions in an environment - both physical and social. Proponents of this view hold that this needs to be taken into account in order to understand the functional organization of the brain for different sensory, motor and cognitive domains and tasks. While similar ideas have been put forth by several pioneers

in psychology (see Gibson, 1996, 1977; Werner & Kaplan, 1967), most work in embodied cognition is relatively recent. Researchers working in this paradigm argue that seemingly abstract concepts in language and higher cognitive domains can be grounded onto a body-based framework (see, Barsalou, 1999; Lakoff & Johnson, 1980) and a number of studies have reported behavioral evidence in support of this view (e.g., Gernsbacher, Varner, & Faust, 1990; Glenberg & Kaschak, 2002).

The discovery of mirror neurons in the macaque, and findings suggesting a homologous system in humans, have been exciting developments for embodied cognition. This research has shown that areas of the brain which subserve motor action production are also involved in action perception and comprehension. Thus one's own body and action representations are used as templates and simulations in order to understand those of others. The present experiment now adds neuropsychological evidence to this body of literature, by showing that lesions in these premotor and motor areas can lead to deficits in the comprehension of information representing actions.

The lesion sites we identified which are not part of the mirror neuron network can also be understood within the framework of embodied cognition. Here, we argue that lesion sites we observed are related to the task components, rather than the semantics of the actions in the sentences (with the possible exception of the anterior parietal focus). The lesion sites which led to deficits in reading comprehension of actions are areas which are involved in sentence comprehension, phonological processing, and interestingly, speech planning and articulation. Note crucially that the embodiment view always takes development into account. By the time people learn how to read, spoken language has already been acquired, and there is already in place a rich multisensory, semantic representation of the world. Reading skills would thus be overlaid upon already existing neural circuitry for carrying out related linguistic and non-linguistic operations, rather than having its own domain-specific neural regions. Our results are in agreement with this kind of model.

Finally, note that an embodied cognition view is not at odds with the lack of correlation between domains observed in the behavioral results of the present study. A strong asymbolia view would expect such an outcome, but embodiment does not imply complete overlap of related processes. In this particular case, even though task and stimulus level factors were controlled for across the two modalities, there were other varying factors between the two domains. According to the embodied cognition view, the non-linguistic action comprehension system would be overlaid very early in development on the body's own motor, sensory and proprioceptive representational systems, whereas reading, being a later-acquired skill, would be overlaid on a more distributed linguistic and conceptual network. If the systems are acquired and related skills are honed at such different stages in development, the resulting brain networks subserving processing in the two domains will also be rather different, and patients with brain injury will not show tightly correlated deficits. In contrast, in a very similar study we conducted in the auditory modality, where the linguistic and nonlinguistic stimuli are both perceptually similar and are acquired at similar stages in development (Cummings, Saygin, Dick, & Bates, 2004), we did find tightly correlated deficits in aphasic patients' performance, along with shared lesion sites (Saygin et al., 2003a).

To summarize, patients with aphasia had globally uncorrelated deficits in the comprehension of action information through pantomime interpretation and reading comprehension. On the other hand, we also found evidence for some shared underlying processes. Patients had impairments in both pantomime interpretation and comprehension of actions through reading but their deficits were more pronounced in the linguistic domain, especially for the more severe aphasics. Pantomime interpretation deficits were associated with lesions in anterior brain areas known to be involved in motor planning and execution, demonstrating that lesions in the frontal component of the human mirror neuron system are associated with deficits in action understanding in left hemisphere injured patients. Reading comprehension deficits followed from damage to brain areas known to be involved in linguistic processes including sentence processing, speech articulation and phonological processing, and potentially also the parietal component of the human mirror neuron system.

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Chapter 3

Biological Motion Perception in Left Hemisphere-Damaged Patients

Biological motion perception in left hemisphere-damaged patients *

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Abstract

Left hemisphere lesions are known to cause impairments in action perception. On the other hand, little is known about biological motion perception in left hemisphere-damaged (LHD) patients. Here, point-light biological motion perception was tested in two experiments on 25 unilateral LHD subjects with unselected lesion loci. Patients were significantly impaired compared to age-matched control subjects. Deficits did not correlate with patients' age, gender, lesion size, or behavioral deficits in other domains. Voxel-based lesion-symptom mapping revealed two sites associated with deficits in perception of biological motion: an anterior region in the inferior frontal lobe involving Broca's area (pars opercularis), and a large posterior region involving the superior temporal and inferior parietal lobes. The same areas have recently been identified as neural substrates of action perception in humans and macaques. We argue that patients' deficient performance is due to impaired processing of the biological motion stimuli in this fronto-temporo-parietal action processing network.

Introduction

We are highly adept at recognizing biological motion, i.e. the movement of humans or other animate entities. Image sequences constructed from only a dozen point-lights attached to the limbs of a human actor can be easily identified by observers (Johansson, 1973). Viewers can even infer characteristics such as gender, affect or identity from these simplified point-light animations (Cutting & Kozlowski, 1977; Kozlowski & Cutting, 1977).

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Recently a number of functional neuroimaging studies have examined the neural correlates of the perception of point-light biological motion in the human brain. Areas identified in these studies include the superior temporal gyrus (STG) and sulcus (STS), parietal cortex, and regions in visual cortex and motion sensitive area V5/MT+ (Bonda et al., 1996; Grèzes et al., 2001; Grossman et al., 2000; Grossman & Blake, 2002; Servos et al., 2002; Vaina et al., 2001), but results are not entirely consistent. The involvement of the STG/STS is perhaps the most robust finding (see Beauchamp et al., 2002; Pelphrey et al., 2003; Puce & Perrett, 2003, Saygin et al., 2004; although see also Servos et al., 2002), supported also by electrophysiological recordings in the macaque monkey (Oram & Perrett, 1994). The STS in humans is also known to be responsive to moving or static body parts and is in general held to be an area that is important for the comprehension of others' acts and intentions (see Allison, et al., 2000; Blakemore & Decety, 2000; Puce & Perrett, 2003 for reviews).

There have been only a few neuropsychological studies concerning biological motion processing deficits. Case reports of patients with deficits in low-level motion analysis who have intact biological motion processing have been reported (McLeod et al., 1996; Vaina et al., 1990), as have patients with deficiencies in recognizing form-from-motion, including biological motion, in the absence of early visual deficits (Cowey & Vaina, 2000). However, patients with such profound deficits in recognizing biological motion are very rarely encountered. Despite robust findings as to the responsiveness of the STG/STS to biological motion in electrophysiological and neuroimaging studies, this region has not been implicated as a lesion site which is detrimental to the visual perception of such stimuli. Schenk and Zihl (1997) tested a group of stroke patients and found two subjects to be deficient in perceiving biological motion, both with bilateral lesions in parietal cortex. Battelli et al. (in press) recently reported tested patients with parietal lesions, two with right hemisphere damage and one with left hemisphere damage and found them to be impaired in point-light biological motion processing. Note that both Battelli et al. and Schenk and Zihl's patients (as opposed to patient AL, reported in Cowey and Vaina, 2000) were able to "see" the point-light biological motion when the stimuli were presented without any occlusion with noise dots; it was when the patients had to perform a search tasks among noise dots that their deficits were identified. Therefore the perceptual deficits are likely due to

higher-level and/or attentional problems rather than due to a pure inability to process and bind the motion information conveyed by the point-lights into a coherent visual form.

It has long been known that lesions in the left hemisphere are associated with apraxia. For instance, Jackson, one of the early pioneers of neurology, noted "pantomime impairment" as one of the primary characteristics he observed in his left-lesioned patients (1878). These impairments often affect the comprehension domain as well: Deficits in gesture or pantomime understanding are quite common among LHD patients, but are very rare among RHD patients (e.g., Duffy & Duffy, 1981; Gainotti & Lemmo, 1976). Lesion correlates of these impairments are not clear-cut, but in general posterior sites have been implicated (Varney & Damasio, 1987). More specifically, based on a series of studies, Heilman, Rothi and colleagues have advanced the view that parietal regions of the left hemisphere store visuokinesthethic motor engrams of actions that mediate the processing of purposeful movements (e.g., Heilman et al., 1982; Rothi et al., 1985). Therefore we could hypothesize that because they comprise body actions, point-light biological motion perception may also be compromised in some patients with left parietal damage.

Electrophysiological and functional neuroimaging studies in both macaques and humans have recently revealed a network of brain areas that subserve the understanding of other individuals' actions: In addition to parietal and superior temporal cortex, more anterior areas in premotor and inferior frontal cortex have also been revealed to be involved in the perception and understanding of other individuals' actions (for review see Rizzolatti, et al., 2001). Based on these findings, again since the point-light animations comprise actions, we may also hypothesize that patients with lesions in these areas could show impairments.

In the present study we examined biological motion perception in 25 unilateral LHD patients (unselected for lesion location), and age-matched controls. Experiment 1 tested basic recognition and discrimination of point-light animations when they were displayed on a uniform dark background. Experiment 2 estimated the ability to search for and identify the point-light stimuli among masking noise dots: participants were presented with two moving dot displays and had to point to the one which

"contained the man"; the other display contained a scrambled version of the same point-light animation presented among the same noise dots. 82% accuracy thresholds were estimated using an adaptive method. We then explored lesion correlates of poor performance in this sample using voxel-based lesion-symptom mapping (VLSM), a method which analyzes the relationship between continuous behavioral data and continuous lesion extents (Bates et al., 2003).

Our goal was to investigate the behavioral and lesion correlates of biological motion deficits in LHD patients. Do patients with unilateral lesions in the left hemisphere exhibit deficits in point-light biological motion processing, as they do in gesture and pantomime understanding? If so, are these deficits correlated with deficits in other domains? Which lesions lead to significant impairments in biological motion perception? Are lesions to the areas identified above—STG/STS, the inferior parietal lobe, and inferior frontal cortex—associated with deficits in biological motion perception?

Results

Group comparisons

In experiment 1, all neurologically normal controls performed perfectly in identifying the point light actions and distinguishing them from scrambled animations. All LHD patients except one (discussed below) were also able to identify the non-noise-masked displays and discriminate them from scrambled animations.

The results for experiment 2 are summarized in Figure 1. The 82% thresholds were quite variable both for LHD patients and for normal controls. The mean threshold for LHD patients was 10.0 (s.d. 4.7; range 3.3 – 25.2), and for control subjects the mean threshold was 16.0 (s.d. 6.8; range 8.6 – 31.5). This difference was significant ($p = 0.0013$, one-tailed *t*-test).

<FIGURE 1 ABOUT HERE>

It has long been known that LHD can cause gesture and pantomime comprehension deficits. While LHD patients can have many such high-level or symbolic deficits, these may have significant perceptual or attentional components, as our present results indicate that unilateral LHD is associated

with poor biological motion processing, even when tested with this low level detection task. However we argue that deficits are not due to very low-level visual impairments, based on the lesion sites identified (see below).

Correlation analyses

We sought correlations between patients' 82% accuracy thresholds in the present study with their gender, age, and lesion volume. None of these correlated significantly with accuracy threshold ($p = 0.28$; $p = 0.38$ and $r^2 = 0.04$; $p = 0.08$ and $r^2 = 0.13$; $p = 0.08$ respectively). We also examined whether any linguistic or cognitive measures administered as part of the Western Aphasia Battery (WAB, (Kertesz, 1979)) were correlated with biological motion perception. None of the these measures significantly predicted accuracy thresholds either (speech fluency: $p = 0.27$, $r^2 = 0.06$; language comprehension: $p = 0.17$, $r^2 = 0.08$; word and sentence repetition: $p = 0.82$; $r^2 = 0.04$; object naming $p = 0.74$, $r^2 = 0.04$; construction (a composite test that contains calculation, drawing and visuospatial tasks): $p = 0.70$, $r^2 = 0.03$). While the lack of a correlation between biological motion perception scores with some of these scores is perhaps not unexpected, it has previously been observed that some nonverbal measures do correlate highly with neuropsychological and linguistic assessment scores in LHD patients (Duffy & Duffy, 1981; Saygin et al., 2003).

Group lesion analyses

Lesion analysis was carried out using voxel-based lesion-symptom mapping (VLSM). We constructed maps of the *d* statistic reflecting standardized difference between scores of lesioned and intact patients at each voxel (see Experimental Procedures). Representative slices for 82% accuracy thresholds in Experiment 2 are shown in Figure 2: Two distinct regions emerge as especially important lesion correlates of impairments. The smaller, anterior spot seen in slice 1 is in the inferior frontal gyrus (IFG) and corresponds to Brodmann areas 6 and 44. The larger, posterior region visible in slices 2 and 3 extends inferiorly into the posterior STG and includes the posterior STS and the superiormost portion of the posterior MTG, and extends superiorly into the inferior parietal lobe (IPL), including both the

supramarginal gyrus (SMG) and the angular gyrus (AG). The posterior region contains portions of Brodmann areas 22, 37, 39 and 40.

<FIGURE 2 ABOUT HERE>

We next carried out a region of interest (ROI) analysis in which we tested the significance of behavioral deficits resulting from lesions to regions of interest arising from prior studies. The ROIs investigated were: STG and STS (based on prior findings in neuroimaging studies of biological motion perception), IPL (based on neuropsychological and neuroimaging studies of biological motion and action perception, as well as its role in apraxia), IFG (due to its involvement in action perception) and the anterior insula (aINS), which served as a control point, since it is involved in fluent speech articulation (Bates, et al., 2003; Blank et al., 2002), which is impaired in many of these patients, but not in biological motion perception.

<FIGURE 3 AND TABLE 1 ABOUT HERE>

For the STG, STS, IPL and IFG ROIs, patients with lesions performed significantly worse than patients without lesions, whereas lesions to the aINS had no effect on biological motion perception (Table 1, Figure 3). Note that the Talairach coordinates of these "lesion hot spots" correspond closely to previously published sites of activation in neuroimaging studies: the STS point is less than 2 mm from the peak voxel reported by Grossman et al. (2000); the IPL point is 19 mm from the peak IPL voxel in Grezes, et al. (2001), and the IFG point is 13 mm from the peak IFG voxel in Iacoboni, et al. (1999). Although lesion mapping is inherently limited in its localizing power, these correspondences with neuroimaging studies provide further support for the roles of the areas identified in our patient population as most relevant to the task.

Individual case reports

It is common practice in neuropsychological research to focus on patients that perform below a certain behavioral criterion; often the score of the worst performing normal control is used as a cutoff point. While we advocate analyzing neuropsychological data using continuous behavioral scores and

lesion information without behavioral cutoffs or classifications based on lesion site, we also believe case studies can sometimes help shed light on research questions or constrain theories. We thus wanted to focus briefly on the most severely impaired patients in the present study.

In this study, too many patients (14) performed below the level of the worst performing control subject in Experiment 2 for this cutoff to be informative. Thus we performed cluster analyses on the patient group to identify the worst-performing subset. Using three different cluster methods, we found that the same four patients were identified in the worst performing cluster using all three methods: KH, WJ, PP and TW.

Patient WJ was the only patient in our sample who failed in recognizing unmasked point-light biological motion. WJ is a 73 year old male who has a rather large temporoparietal lesion extending superiorly into the superior parietal lobe and inferiorly into the middle temporal gyrus. Despite this large lesion, he has only a very mild language disorder and has occasional word-finding problems (anomia) and self-reported difficulty in reading (but has normal performance in our assessment). In the current study, WJ was initially unable to see the point-light animations as comprising actions (Experiment 1a). When asked verbally (e.g., "Does that look like someone kicking?"), he replied that he was not sure. When the experimenter (author APS) got up and performed the action depicted in the point-light stimulus (e.g., throwing a side kick), he was able to see that the actions matched. In the following two trials, he was able to name walking and jogging point-light figures without prompt. For the rest of the animations, he had initial trouble identifying the actions and reported "it's not really working for me", but eventually either answered comprehension questions successfully or verified the action after actual performance by the experimenter.

Interestingly, WJ had little trouble with the discrimination task (Experiment 1b) and responded successfully in all trials. In Experiment 2 however, in the presence of noise dots, he once again performed at a severely impaired level: During the QUEST procedure, he initially made few errors but before reaching the middle of the experiment however, he once again started acting hesitant and taking a long time to respond. In the latter half of the experiment his responses were random guesses even

though he was clearly attempting to perform the task, and his overall performance was severely deficient with an eventual estimated threshold of 3.43 noise dots. The fact that he was able to perform at a level better than this estimated threshold for a short period of time may suggest a deficit that may be due to an inability to engage attention effectively to biological motion.

Patient KH's threshold in experiment 2 was estimated at 3.25 noise dots, a clearly impaired level of performance. This patient is a 63 year old male and has a lesion with several small cortical and subcortical foci including the anterior insula, basal ganglia, Broca's area and in the white matter underlying temporal and parietal lobes. He has restricted speech output, moderately impaired speech comprehension, severe hemiplegia and apraxia. KH performed badly throughout the experiment and was unaware of this impaired functioning.

Patient PP's threshold was 4.39 noise dots. This patient is a 51 year old female and has a very large lesion covering most of frontal, temporal and parietal cortex, extending into the superior parietal lobe from the inferior temporal lobe. Her speech is fluent but she has mild to moderate auditory comprehension difficulties. She has no observable motor or apraxic difficulties, a surprising outcome given the extent of her lesion. However, PP is left-handed which is often associated with more bilateral brain organization for some linguistic and motor functions. PP found the task difficult and performed badly despite trying hard.

Patient TW's threshold was estimated at 5.17 noise dots. TW is a 67 year old male and has Wernicke's aphasia; he presents with fluent speech with some jargon and has impairments in language comprehension. The patient has a lesion that has two separate foci: one in the frontal lobe, including the inferior and middle frontal gyri and the precentral gyrus, the other extending from the superior temporal gyrus into the parietal lobe. TW was unaware of his impaired performance.

As can be seen from these brief case reports, patients who are very severely deficient in biological motion perception varied in lesion size, age, gender and handedness. These patients were also varied in the nature and extent of their language and motor deficits, as patients range from intact to severely impaired on different dimensions. However there were some patterns in the regions damaged.

All patients except KH have lesions covering inferior and superior parietal lobe and also a clear involvement of the STG and STS. All patients except WJ have inferior frontal gyrus involvement in their lesion, consistent with group level lesion analyses. Note that KH's lesion has a small focus that involves a portion of the STS as well as multiple foci in the parietal lobe, mostly restricted to the white matter. It must also be borne in mind that small lesions in subcortical structures and white matter tracts can sometimes lead to impairments that are qualitatively similar to impairments that are due to much larger lesions because they may cause disconnection syndromes between different cortical areas.

Discussion and Conclusion

We found that lesions in superior temporal, inferior parietal and inferior frontal areas have the greatest effect on biological motion perception. Our results indicate that Schenk and Zihl's (1997) findings about the adverse effects of bilateral parietal lesions on biological motion processing apply also to unilateral left hemisphere lesions. Unilateral parietal lesions that lead to impairments in biological motion processing have been reported recently also by Battelli et al. (in press). Our findings now extend these results to a larger group of patients.

As mentioned above, this lesion site is consistent with lesions that are associated with ideomotor apraxia. In a recent review, Koski, et al. (2002) have concluded that "the left parietal cortex subserves a particularly important component of the praxis system, especially concerned with the knowledge or representation of overlearned actions" (p. 75). Our patients' deficits could be due to an inability to engage this system effectively to recognize the point-light actions.

In addition to this, note that biological motion perception is natural and effortless for the intact visual system under normal conditions but attention is required when more complex motion processing is required or when there is masking (Cavanagh et al., 2001; Thornton et al., 2002). Could our patients be performing deficiently because of attentional problems? A role for attention is indicated in the present study since most patients were able to identify and discriminate biological motion, but were impaired compared with normal controls in identifying the motion when the stimuli were presented with masking elements. However, while parietal areas are known to be important for spatial attention,

we believe a simple explanation along those lines will not be sufficient to account for the present findings. First, purely spatial deficits are often seen after RHD rather than LHD (Mesulam, 1981). Second, there was no indication of spatial neglect in our data; patients did not fail to recognize point-light motion selectively on one side of the visual field (data not shown). The role of attention in biological motion perception must be complex, likely in modulating the integration of visual motion information across space and also the interactions with motor cortex in preparation for action on the perceived space. In terms of neuropsychological populations, future studies may tease apart deficits that stem from impairments in these visuomotor transformations from those that result from ineffective attentional modulation of such processes.

As mentioned above, several recent fMRI studies have examined biological motion processing in healthy human subjects. Our VLSM results are in close agreement with these studies. Notably, similar parietal areas have been associated with biological motion processing in some of these studies (Bonda et al., 1996; Grèzes et al., 2001; Vaina et al., 2001). Most importantly, as mentioned above, STG/STS activation is one of the most uniform findings across the various neuroimaging studies. Our results now corroborate these STG/STS findings with neuropsychological data.

Finally, it must be noted that in our sample of patients, we did not have any patients with lesions extending posteriorly into occipital cortex or into motion-sensitive area V5/MT+, so we cannot make inferences about the role of lesions in these areas based on the results of the present study. We would hypothesize that unilateral lesions in higher areas such as those found here (and also Battelli et al, in press), but not in areas which subserve lower stages of visual processing, would affect performance in our task. Patients with unilateral occipital lesions are rare due to brain vasculature and in our knowledge have not been reported to present with full-visual-field biological motion processing deficits (although pantomime comprehension problems have been observed in a few cases, see Rothi et al., 1986) . On the other hand, unilateral left hemisphere damage can cause disturbances in action comprehension, and as we have shown here, biological motion perception. A compelling model of biological motion processing in the ventral and dorsal visual pathways and their relation to each other

and regions such as the STS has been proposed by Giese and Poggio (2003). Temporal and parietal areas such as those we identified may have a complex relation to the perception of biological motion, perhaps in modulating top-down and embodied aspects of processing, thus far not incorporated into such models.

While most research on biological motion processing has been carried out within the framework of vision science, there is a related, but largely independent body of literature concerning the so-called "mirror neuron system" which could shed more light on the mechanisms and neural resources used for processing point-light biological motion (Rizzolatti et al, 2001). Mirror neurons are a particular class of visuo-motor neurons that were first found in area F5 in the ventral premotor cortex of the monkey (Gallese et al., 1996; Rizzolatti et al., 1996a). These neurons fire not only when an animal performs a particular motor behavior, but also when the animal observes another individual execute the same action. Subsequently, the existence of a similar "analysis by synthesis system" in humans has been suggested by a number of electrophysiological (Fadiga et al., 1995; Nishitani & Hari, 2000; Strafella & Paus, 2000) and functional neuroimaging studies concerned with action observation and imitation (Binkofski et al., 1999; Buccino et al., 2001; Decety et al., 1997; Grafton et al., 1996; Grezes et al., 2003; Iacoboni et al., 1999; Rizzolatti et al., 1996b). This body of literature has revealed that regions in the human frontal cortex (including an inferior frontal region thought to be the human homolog of monkey area F5 – see Petrides & Pandya, 1994) constitute part of a fronto-temporo-parietal system for action perception and execution. This network is held to constitute an embodied action recognition system. According to this view, an individual can understand others' actions by mapping the visual representation of the observed action onto his/her motor representation of the same action, thus using his/her own embodied experience in the world (see Jeannerod, 2001; Rizzolatti et al, 2001).

Point-light animations, even though they provide rather impoverished visual input compared with real actions, constitute vivid impressions of human figures and can even carry information about gender, identity or affective states (Cutting & Kozlowski, 1977; Kozlowski & Cutting, 1977). Could point-light biological motion also recruit neuronal resources that may be part of the human mirror

neuron system? Our VLSM results indicate that this is a distinct possibility. Our lesion findings are highly overlapping with the fronto-temporo-parietal network identified in several prior studies (see above) despite the fact that we are working with a technique which affords lower resolution in most cases.

More specifically, IFG involvement in point-light biological motion processing is a relatively new finding. F5 neurons in the monkey have not typically been tested with point-light action stimuli; in general, these neurons have been known to respond to real actions performed in front of the monkey, but not to artificial or even video stimuli (as opposed to STS neurons). Previous functional neuroimaging studies on humans have not reported selective activation in frontal regions for point-light stimuli either, except perhaps in relation to a fixation baseline for one individual subject in Vaina et al. (2001). Servos et al. note that a failure to find an involvement of the human mirror neuron system in their study may be due to distortions in the signal in these regions due to the magnetic field and air in the ear canal (2002). On the other hand, recently we have observed robust and reproducible activity in inferior frontal cortex with fMRI at 4T during point-light biological motion perception (Saygin et al., 2004).

Unilateral left hemisphere lesions can cause deficits in biological motion processing. The lesion sites most strongly associated with deficits in our patient group were the STG/STS, the IPL and the IFG. Since this network has been implicated in the perception of action stimuli in many studies, patients' deficits may reflect an inability to effectively engage this "analysis by synthesis" system. Our results indicate that this system may be involved with (Saygin et al, 2004) and required (present study) for the processing of point-light biological motion perception as well as actions defined by other cues.

Methods

Participants

Patients were voluntary participants recruited from the community or the Veterans' Administration Medical Centers in Martinez, CA. 25 unilateral LHD patients aged 51-83 participated in

the experiment. Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans and medical records of all patients were evaluated by a neurologist at the time of enrollment into our program, and only patients with unilateral lesions due to a single cerebrovascular accident (CVA) were included. Exclusionary criteria included diagnosed or suspected vision or hearing loss, dementia, head trauma, tumors, or multiple infarcts. Motor and language impairments ranged from very mild to severe in the sample, but all patients were able to understand and carry out the task. None of the patients had clinically diagnosed spatial neglect or other attentional disorders. Age-matched controls were 13 adults aged 51-80, with no history of audiological, neurological, or psychiatric disorders; all had normal or corrected-to-normal vision and audition. All participants were paid for their participation. Informed consent was obtained from all subjects in accordance with guidelines of the UCSD and VA Northern California Health Care System Human Research Protections Programs.

Stimuli

Stimuli were presented using a Dell 610C PC computer running Matlab (Mathworks, Natick, MA) and the Psychophysics Toolbox (Brainard, 1997). Point-light biological motion sequences were based on a subset of those used by Grossman et al. (2000), and were created by these authors by videotaping an actor performing various activities and then encoding the joint positions in the digitized videos. 7 actions were used: walking, jogging, throwing, underarm throwing (bowling), stepping up, a high kick into the air, and a lower kick. Each animation consisted of 20 frames which were displayed at a rate of 25 Hz for a total animation duration of 0.8 seconds. The final frame then remained visible for 0.3 seconds. The animation was continuously repeated in this manner until a response was recorded. The joints were represented by 12 small white dots each subtending approximately 13 arc min of visual angle against a black background. Scrambled animations were created by randomizing the starting positions of the dots while keeping the trajectories intact, except that they were randomly rotated in 90 degree increments and/or mirror-inverted. The starting positions were chosen randomly within a region such that the total area encompassed by the figure was similar to that of the real figures. Masking dots in experiment 2 were generated in the same way except that they were dispersed over a wider area.

Procedure

Experiment 1a aimed to determine if participants could "see" the point-light biological motion stimuli. It also served as a familiarization step for Experiments 1b and 2. Each of the 7 point-light animations was presented one at a time on a uniform dark background. Participants were asked to identify the action represented in each point-light animation. Patients were not placed under any time pressure to respond, as some of them had word-finding problems. Five patients who had significantly reduced speech output were tested via "yes/no" comprehension questions.

Experiment 1b aimed to test discrimination of point-light biological motion animations from scrambled versions of the same animations. In each trial, participants were presented with the point-light motion and its scrambled equivalent on either side of the screen and were asked to point to the set of the dots that "contains the man". The side of presentation was randomly determined.

In Experiment 2, stimuli were the same as those used in Experiment 1. An adaptive procedure (QUEST) was used to estimate participants' ability to discern point-light biological motion presented among masking noise dots (Watson and Pelli, 1983). We used a 2-alternative-forced-choice task where two displays of dots were presented on either side of the screen, one containing a biological motion animation, the other its scrambled counterpart, as in Experiment 1b. Participants had to search for the moving figure among the noise dots. A total of 65 trials were administered in each run. While healthy participants were administered two QUEST runs of 65 trials each in parallel, and the two thresholds then averaged, stroke patients were tested with just a single QUEST run in order to keep testing time to a minimum. 82% accuracy thresholds were estimated for all participants using the mean of the posterior probability density function.

Lesion-symptom mapping

Voxel-based lesion-symptom mapping (VLSM) was used to quantify the relationship between lesion sites and behavioral deficits (Bates et al., 2003). Software to perform VLSM is freely available online at http://crl.ucsd.edu/vlsm. For 18 of our LHD patients, computerized lesion reconstructions to

be used in VLSM analyses were available; the remaining lesion information was obtained from CT or MRI scans or neurological reports at time of enrollment. Reconstructions were based on scans at least 3-weeks-post-onset of stroke and were hand-drawn onto 11 axial slice templates based on a photographic atlas of the human brain (DeArmond et al., 1989). The reconstructions were then entered into a computer with an electronic bitpad. These reconstructions were performed by a board-certified neurologist with experience in neuroradiology who was blind to the behavioral deficits of the patients and the goals of the current experiment.

At each voxel, patients were divided into two groups according to whether they did or did not have a lesion involving that voxel. Behavioral scores were then compared for these two groups. The statistic computed in the present study was d, a standard measure of effect size (determined by dividing the difference in group means by the pooled sample standard deviation). The d-maps were then smoothed in-plane with a circular filter with a radius of 7 voxels or approximately 3.5 mm. Voxels where fewer than 5 patients had lesions were excluded as d is a measure of effect size, not an inferential statistic, so values are not reliable if either of the two groups being compared is not well represented.

ROIs were defined anatomically based on the hypotheses of the study, except for the insula, which was chosen as a control point. The insula ROI was defined as that part of the anterior insula important for speech fluency according to prior studies. Within each anatomical ROI, the peak lesion point was used, i.e. the voxel with the greatest difference between the scores of lesioned and intact patients.

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Table 1 *Summary of region of interest (ROI) analyses*

ROI	**Brodmann areas**	**Talairach coordinates**			**Effect of lesion on biological motion perception**	
		x	y	z	*t*	*p*
STG	22	-60	-25	18	3.09	0.0035
STS	22, 39	-44	-61	18	1.86	0.040
IPL	39, 40	-38	-49	35	2.66	0.0085
IFG	6, 44	-52	14	4	2.01	0.031
aINS	(13)	-36	10	8	0.26	0.40

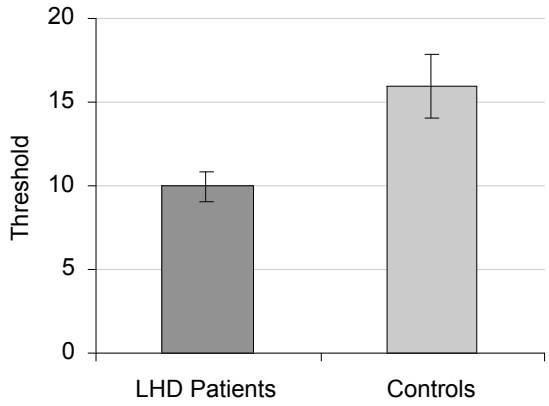


Figure 1: *Thresholds for biological motion perception for patients and controls.* Thresholds were determined with an adaptive procedure for the perception of biological motion in noise. Error bars show standard error of the mean.

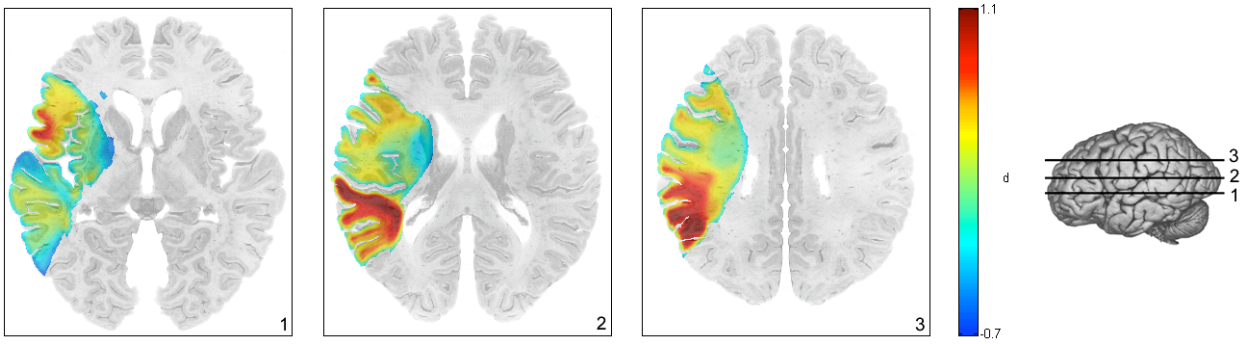
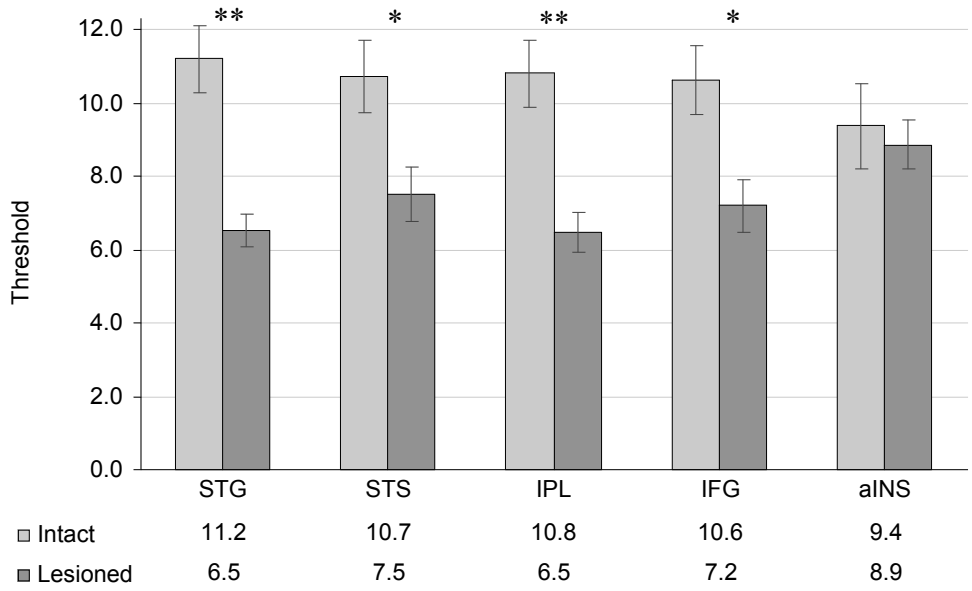


Figure 2: *Axial VLSM displays showing the relationship between tissue damage and behavioral deficits.* The values displayed at each voxel are d statistics comparing the patients lesioned at that voxel to the patients intact at that voxel. High d values top the scale in red, indicating areas where damage led to significant deficits in task performance. Voxels denoted in blue reflect negative d values, which arise when patients with lesions to those voxels performed better than those who had lesions elsewhere. Voxels that are not color-coded were damaged in less than 5 of the patients in our sample. The lateral view shows the locations of the axial slices, however this is only approximate since this is not the same brain as shown in the slices.



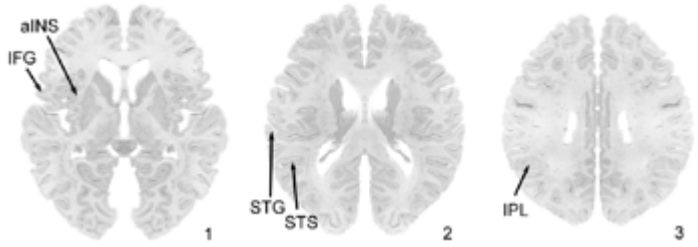


Figure 3: *Effects of lesions to regions of interest (ROI):* STG, STS, IPL and IFG were associated with significant deficits in biological motion perception; lesions in aINS did not have an effect. *: $p<0.05$; **: $p<0.01$ one-tailed – see Table 1 for more detail.

Chapter 4

Point-light Biological Motion Perception Activates Human Premotor Cortex

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Behavioral/Systems/Cognitive

Point-Light Biological Motion Perception Activates Human Premotor Cortex

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Motion cues can be surprisingly powerful in defining objects and events. Specifically, a handful of point-lights attached to the joints of a human actor will evoke a vivid percept of action when the body is in motion. The perception of point-light biological motion activates posterior cortical areas of the brain. On the other hand, observation of others' actions is known to also evoke activity in motor and premotor areas in frontal cortex. In the present study, we investigated whether point-light biological motion animations would lead to activity in frontal cortex as well. We performed a human functional magnetic resonance imaging study on a high-field-strength magnet and used a number of methods to increase signal, as well as cortical surface-based analysis methods. Areas that responded selectively to point-light biological motion were found in lateral and inferior temporal cortex and in inferior frontal cortex. The robust responses we observed in frontal areas indicate that these stimuli can also recruit action observation networks, although they are very simplified and characterize actions by motion cues alone. The finding that even point-light animations evoke activity in frontal regions suggests that the motor system of the observer may be recruited to "fill in" these simplified displays.

Key words: **biological motion; premotor cortex; functional MRI; action observation; motion; frontal**

Introduction

The perception of other individuals' movements and actions is important for tracking and hunting prey, detecting and avoiding predators, and, in many species, social interaction. In humans and at least some other primates, premotor areas are involved in the perception of others' actions. Recent research has shown that there are "mirror neurons" in the macaque frontal cortex in area F5 that fire during both action production and action perception (Gallese et al., 1996; Rizzolatti et al., 1996a, 2001; Ferrari et al., 2003). Studies on humans have also demonstrated the involvement of motor and premotor areas in action observation, indicating that humans may use information from their own body representations in understanding the actions of others (Fadiga et al., 1995; Grafton et al., 1996; Rizzolatti et al., 1996b; Decety et al., 1997; Iacoboni et al., 1999; Buccino et al., 2001; Grèzes et al., 2003).

Besides the visual perception of actions, other components of actions also drive neurons in premotor areas. Auditory mirror neurons respond to the sound of actions (such as the sound of a peanut cracking) (Kohler et al., 2002), and "canonical neurons" respond to the target objects of actions (such as a visually presented peanut) (Murata et al., 1997). The present study investigates whether premotor areas can be driven solely by motion cues of actions. It is possible to define actions by motion cues alone using "point-light biological motion." Image sequences constructed from point-lights attached to the limbs of a human actor can readily be identified as depicting actions, although they do not define a form when stationary (Johansson, 1973). These animations convey surprisingly detailed information about movements of the human body, despite using motion signals almost exclusively and lacking other visual cues such as color, shading, and contours. Given that point-light biological motion figures depict actions, could their perception also recruit frontal cortex? Or are these stimuli too simplified to drive the neural activity in frontal action observation areas?

Previous neurophysiological and neuroimaging studies of point-light biological motion perception have not typically reported activations in frontal regions. Instead, areas identified in these studies include the superior temporal gyrus and superior temporal sulcus (STS) (Grossman et al., 2000; Grèzes et al., 2001; Vaina et al., 2001; Beauchamp et al., 2003; Puce and Perrett, 2003), the motion-sensitive region MT (middle temporal visual area) and surrounding areas (MT+) (Grèzes et al., 2001; Vaina et al., 2001), the parietal cortex (Bonda et al., 1996; Grèzes et al., 2001; Vaina et al., 2001), and other regions in visual cortex (Vaina et al., 2001; Servos et al., 2002).

In the present study, using functional magnetic resonance imaging (fMRI), we investigated whether frontal action observation areas are involved in the perception of whole-body biological motion. Our approach was to use a relatively standard paradigm to identify regions in the brain that are responsive to biological

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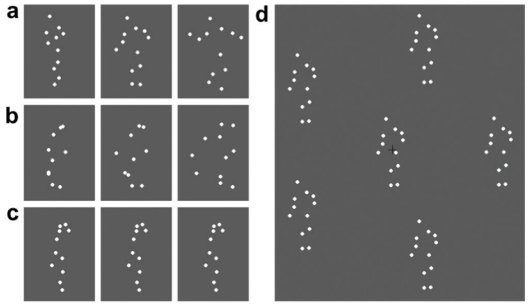

Figure 1. Example frames for the three stimulus conditions. Three (of 20) frames are shown from one animation each for biological motion (*a*), scrambled biological motion (*b*), and static point-lights (*c*) (baseline) conditions in the experiment. The biological motion animation in this example depicts frames from an actor throwing an object (e.g., a ball). The static point-lights condition does not have any motion, and hence all frames are the same. In *d*, an example screenshot from the actual experiment (biological motion condition) is shown. All six copies of the figure executed the same motion.

motion. However, we used a combination of methods in our experimental design, fMRI acquisition, image processing, and data analysis to maximize signal in frontal cortex.

Materials and Methods

Participants. Twelve participants with no known visual or neurological abnormalities (seven females, aged 22–34) participated in this study. Eleven participants were unaware of the main hypothesis of the study, and one participant was an author. Subjects gave informed consent, according to procedures approved by the Institutional Review Board of the University of California.

Experimental design and procedure. Participants were scanned as they viewed point-light biological motion animations, scrambled versions of the same animations, and stationary point-light figures. Scrambled animations, which contain the same local motion cues but not the form defined by biological motion, have been used as control stimuli in some previous studies of biological motion processing (Grossman et al., 2000; Servos et al., 2002). Because scrambled animations do not constitute actions, we would predict that an area that responds to the action information would respond significantly more to biological motion compared with the scrambled motion. We used a stationary point-light baseline condition so that activity during biological and scrambled motion could both be measured.

A blocked design was chosen to maximize statistical detection power (Liu et al., 2001), in which the blocks consisted of biological motion, scrambled biological motion, and baseline (stationary point-light images). Figure 1 depicts several individual frames from each of these kinds of stimuli. During the scan, the three block types were presented in pseudo-randomized order and lasted 24 sec each. There were three runs, with 21 blocks in each run.

Point-light biological motion sequences were a subset of those used by Ahlstrom et al. (1997) and were created by videotaping an actor performing various activities and then encoding the joint positions in the digitized videos. Ten point-light actions were used in the present study, depicting walking, walking up stairs, jogging, jumping jacks, throwing, underarm throwing, skipping, stepping up, a high kick into the air, and a lower kick. Six identical point-light figures were displayed at all times to maximize coverage of the visual field. The total area covered by the stimuli was ~16–18° of visual angle in diameter (Fig. 1*d*). The animations were presented at 20 frames/sec. Each animation was presented for 1 sec, with a delay of 250 msec between animations and an extra 250 msec interval between blocks. The joints of each point-light actor were represented by 12 small dots, each subtending ~17 arcmin of visual angle against a uniform dark background. For all point-light animations, the visual spatial locations stimulated were maintained approximately the same. To achieve this, for the biological motion animations, when the action depicted motion that would normally result in the figure moving in space (e.g., walking), the point-light figure was adjusted such that the figure did not leave the region in which the animations were presented (e.g., the figure walked in place, as if on a treadmill). There was a small, dark red cross hair at the center of the visual field to help subjects maintain central fixation and to minimize eye movements.

Scrambled animations were created by randomizing the starting positions of the point-lights while keeping the trajectories intact, except that each point-light could be randomly rotated in 90° increments and/or mirror inverted. The rotation and mirror inversion of dots during scrambling additionally disrupts local form information that may remain after spatial scrambling. The starting positions were chosen randomly within a region such that the total area encompassed by the figure was similar to that of the real figures. Ten scrambled animations and 10 static frames were used.

The experiment was programmed and run using Matlab (MathWorks, Natick, MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Stimuli were projected onto a screen that was suspended above the subject's torso, using an XGA video projector through a custom lens (Buhl Optical, Rochester, NY), and were viewed through a mirror that was placed inside the head coil. We used an adjustable bite bar to minimize head movements during the scan.

To control for differences in attention across conditions as much as possible, subjects were asked to perform a simple task of judging whether the color of the point-lights in each trial were green or not; the task was the same regardless of stimulus type. Responses were collected with a Lumitouch button box (Photon Control, Burnaby, Canada).

Pilot data were acquired from individual subjects using alternate tasks or with no task before the present design was finalized; activation patterns observed in these pilot scans resembled those found in the results of the analyses reported here (see below). However, during passive observation scans, pilot subjects often reported feeling inattentive, so we used the color-monitoring task to keep subjects alert. The point-lights were presented only in white, green, or yellow, and the task was "green or not." The green and yellow colors were similar enough that sustained attention was required to avoid false alarms. This task was chosen because performance does not depend on the form of different visual stimuli, so the subject's attention is focused on a feature of the stimulus (color) that can be varied in the same manner across the three conditions (biological, scrambled, and static). Finally, the task does not vary in difficulty across the different types of stimuli (confirmed in behavioral data, with accuracy in the task as follows: biological motion, 98.2%; scrambled motion, 98.4%; static point-lights, 97.8%) ($p > 0.05$ for all comparisons).

Many visual fMRI studies use one-back working memory tasks to engage subjects' attention, which means that subjects monitor for repetitions of the visual stimuli as they are presented (Kanwisher et al., 1997). However, our pilot investigations and post-study subject interviews revealed that this task may not be ideal here because the difficulty of the working memory task varies by condition. To measure this more precisely, we asked 12 subjects to perform a one-back working memory task with our three stimulus types outside the scanner. The results confirmed that indeed the one-back task varies in difficulty for these stimuli. Accuracy was found to vary significantly by condition as follows: biological motion, 91.9%; scrambled motion, 87.0%; and static point lights, 96.1% ($p < 0.05$ for all comparisons). Compared with biological motion, the task is harder with scrambled motion as a result of the unfamiliarity of the stimuli and easier with static point-lights because the final and initial frames of successive matching stimuli are identical. Because working memory tasks often activate frontal areas (Smith and Jonides, 1999), such variation in task difficulty across conditions would complicate the interpretation of activity in frontal action observation areas.

Image acquisition. Scanning was performed on a 4 tesla Varian (Palo Alto, CA) scanner, equipped with a TEM (transverse electromagnetic resonator) transmit/receive head coil (Nova Medical, Wakefield, MA), at the University of California San Diego Center for fMRI (La Jolla, CA). We acquired three runs of functional data (509 sec each) using a whole-head echo-planar imaging (EPI) sequence [repetition time (TR), 2400 msec; echo time (TE), 26.3 msec; flip angle, 90°; 32 axial slices with

interleaved acquisition; in-plane resolution of 3.75 × 3.75 mm; and through-plane resolution of 3.8 mm with 0 mm gap]. Experimental stimuli began after three TRs to allow the magnetization to reach steady state.

Given that this study was performed on a high-field-strength magnet, magnetic susceptibility-induced artifacts were a significant concern. To help minimize these, we used a careful manual shimming routine and adjusted both linear ($n = 3$) and higher-order ($n = 5$) shims. In addition, a per-voxel equilibrium longitudinal magnetization (B0) field map (estimated from a set of multiecho EPI images) was at the beginning of each scan session, after shimming, and was used to estimate the residual nonflatness of the B0 field. These data were then used to correct for magnetic field inhomogeneities, which cause displacements in the phase-encode direction (Reber et al., 1998).

After functional scanning, a single structural volume for each subject was acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR, 10.5 msec; TE, 4.8 msec; flip angle, 11°; 1 × 1 × 1.5 mm voxels). This structural scan was used as an intermediate step in spatially aligning the functional images to high-resolution (1 × 1 × 1 mm) T1-weighted MPRAGE scans previously obtained on a 3 tesla Varian scanner or a 1.5 tesla Siemens Vision (Erlangen, Germany) clinical scanner. These previously obtained high-resolution scans were used to reconstruct the cortical surface of each subject, as described previously (Dale et al., 1999; Fischl et al., 1999a).

Image processing and analysis. Image preprocessing and statistical analysis were performed using Analysis of Functional Neuroimages (AFNI) (Cox, 1996), FreeSurfer (Dale et al., 1999; Fischl et al., 1999a), and Matlab (MathWorks, Natick, MA) software packages.

For each individual subject, the B0 field maps were used to correct for distortions in the phase-encode direction using in-house software developed at the University of California San Diego fMRI center by L. Frank. The three runs were concatenated (yielding 630 volumes) and spatially registered in three-dimensional space for motion correction using AFNI programs. Estimates of the three translation and three rotation parameters were computed during this registration and saved. The AFNI program 3dDeconvolve was used to fit a general linear model at each voxel. The model contained four parameters for each of the two nonbaseline conditions, modeling hemodynamic responses at different lag times (0–3 TRs), three parameters for each run to account for slow drifts, and the six motion vectors as determined during motion correction. For individual subject analyses, the contrast between the two conditions (biological vs scrambled motion) was performed by using *F* tests to compare the sums of the four parameters (i.e., the areas under the fitted hemodynamic response functions).

The group data were analyzed using cortical surface-based methods (Dale et al., 1999; Fischl et al., 1999a,b). Each subject's cortical surface was reconstructed and was then morphed to an average spherical representation of the cerebral hemispheres that optimally aligns the sulcal and gyral features across subjects, through a procedure that aims to match these features across subjects while minimizing metric distortion (Fischl et al., 1999b). To perform functional analysis on the sphere, each subject's volume-based individual statistical maps of coefficients were first interpolated onto the spherical representation of their hemispheres using FreeSurfer. Then these maps were morphed and resampled into the common spherical space. At this stage, 50 steps of spatial smoothing on the spherical surface were applied. We performed simulations with a set of surfaces and a set of points on the cortex and found this to correspond approximately to a Gaussian filter with a full-width at half-maximum of 7 mm, along the cortical surface (A. P. Saygin and D. J. Hagler, unpublished simulations). A two-factor ANOVA was performed on the spherical surface using a mixed-effects model, with condition as the fixed effect and subjects as the random effect. The resulting statistics were then transferred onto the inflated cortical surface of a single subject for display.

To examine responses to biological motion and scrambled biological motion more closely, we also defined regions of interest (ROIs) and examined the responses in these areas. We selected inferior frontal (IF) and premotor (Prem) cortical regions as our main regions of interest on the basis of previously known involvement of these areas in action observation. We also studied the posterior superior temporal sulcal (pSTS) region because it is an area known to respond to point-light biological motion. These ROIs were drawn on the cortical surface of each hemisphere of each individual subject using FreeSurfer and saved as surface patches. Anatomical criteria were as follows. The IF ROI contained the inferior frontal gyrus (IFG) and the inferior frontal sulcus (IFS) and was bounded by (but did not contain any cortex from) the middle frontal gyrus, precentral sulcus, lateral orbital sulcus, and the Sylvian fissure. The Prem ROI was drawn on the lateral cortical surface and consisted of the precentral gyrus and the posterior bank of the precentral sulcus but did not extend into the middle and superior frontal gyri or the central or inferior frontal sulci. Although most action observation studies have observed responses in ventral portions of premotor cortex, it is also known that responses in premotor cortex during observation of body actions may be somatotopically specific (Buccino et al., 2001). Because our stimuli contain actions of the whole body, we found it appropriate to include the whole lateral extent of the precentral region to cover a large extent of human premotor cortex rather than only the more ventral portions that correspond mostly to the arm and hand representations. This ROI did not extend into the medial surface of the precentral gyrus. Finally, the pSTS ROI was drawn to include the posterior half of the superior temporal sulcal cortex.

For these three anatomical ROIs, time courses were extracted based on voxels that were responsive to motion, either biological or scrambled, at $p < 10^{-3}$. Because the design of the experiment was a mixed-block design (to maximize signal), biological motion and scrambled motion blocks could follow each other, and thus the hemodynamic responses to each kind of stimulus could overlap. Thus, to extract the blood oxygen level-dependent (BOLD) responses corresponding to each condition in our experiment, we used the AFNI program 3dDeconvolve. The mean time course from each ROI of each hemisphere was averaged and deconvolved with a model containing 16 parameters each for the biological motion and the scrambled motion conditions, corresponding to stimulus time points throughout the experiment (10 stimulus TRs per block, the two TRs preceding each block and the four TRs after each block). The extracted BOLD responses for biological motion and scrambled biological motion across the 16 time points were then averaged across subjects for each ROI and hemisphere, resulting in average estimated BOLD responses for biological motion and scrambled biological motion blocks.

Results

The group results for the 12 subjects are depicted in Figure 2. We first discuss responses to biological motion and scrambled biological motion compared with the static baseline (Fig. 2*a*,*b*) before moving to the main comparison of interest, which is the contrast between biological motion and scrambled motion (Fig. 2*c*). The activations against baseline are important because they illustrate the areas that respond to both biological and scrambled motion, which cannot be inferred from a difference image.

When biological motion observation was compared with the static point-light observation baseline (Fig. 2*a*), we found a robustly responsive region along the inferior frontal and precentral sulci bilaterally, indicating that point-light animations indeed recruit frontal areas known to be involved in action observation. This activation followed inferior frontal and precentral sulci in a fairly continuous manner, but Talairach coordinates of the most significantly responsive points in the inferior frontal, inferior precentral, and superior precentral sulci are reported online in supplemental Table 1 (available at www.jneurosci.org).

In posterior brain regions, compared with the static baseline condition, biological motion led to extensive activation in occipital, temporal, and parietal cortex, extending along both the ventral and dorsal visual streams. Because many of these regions were also responsive to scrambled motion (see below), motion processing may account for much of this activity. The peak of this continuous response was in the lateral temporal cortex, inferior to the STS, near anatomical areas that are known to respond strongly to motion stimuli (human MT, medial superior tempo-

ral area MST, and surrounding regions; henceforth MT+). Peak coordinates here and in the pSTS, intraparietal sulcus, inferotemporal cortex, and the posterior insular cortex (which has been considered the putative human analog of the monkey parietoinsular vestibular cortex, or PIVC) (for review, see Güldin and Grusser, 1998) are reported in supplemental Table 1 (available at www.jneurosci.org).

Scrambled biological motion, relative to the static point-light baseline, activated many of the same regions as biological motion in occipital, temporal, parietal, and posterior insular cortex, although the activation was noticeably less extensive (Fig. 2*b*) (for coordinates of activation peaks, see supplemental Table 1, available at www.jneurosci.org). The most significant responses were once again in posterior lateral temporal cortex around MT+, reflecting motion processing. On the other hand, scrambled biological motion did not evoke much activation in frontal cortex, even when compared with baseline and even at low thresholds. Indeed, no difference was visible between scrambled motion and the static baseline in the left hemisphere (LH). In the right hemisphere (RH), a small area of activation in the precentral sulcus associated with scrambled motion against baseline was found, but this was weaker and less extensive than the activation seen for biological motion.

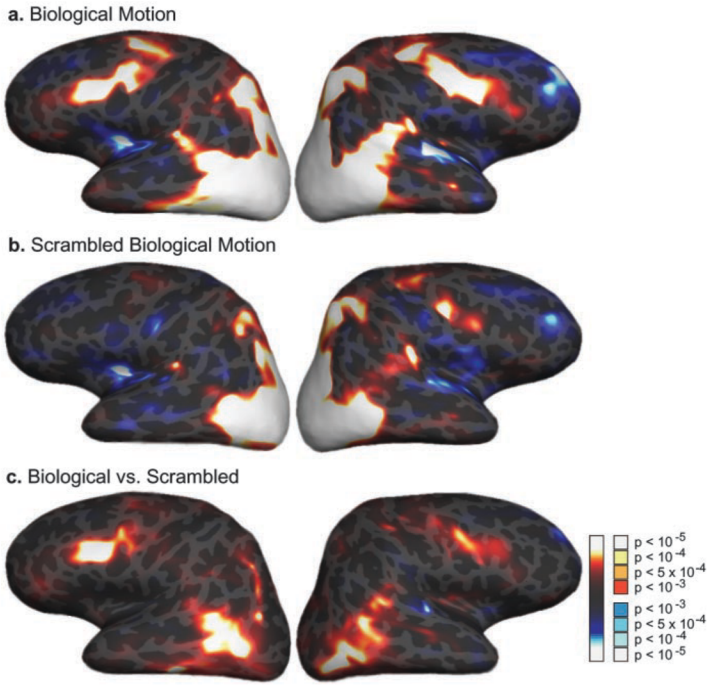

Figure 2. Results of group analyses. Surface-averaged group ANOVA results are displayed on the lateral views of the inflated cortical hemispheres of a single subject for biological motion (*a*) (vs baseline), scrambled biological motion (*b*) (vs baseline), and biological motion versus scrambled biological motion contrast (*c*). The color bar displays the colors in the images, and the discrete swatches mark colors that correspond to *p* values smaller than 10^{-3}, 5×10^{-4}, 10^{-4}, and 10^{-5}, or $t > 4.4$, $t > 4.8$, $t > 5.9$, and $t > 7.6$, respectively. Note that the same color scale is used to depict the results for the activations against baseline (*a*, *b*) and the activation differences between the two motion stimuli (*c*). For coordinates of peak activations, see supplemental Table 1 (available at www.jneurosci.org).

When biological motion and scrambled biological motion responses were compared directly, we found that a region in the left IFS, at its junction with and partially extending into the precentral sulcus, responded significantly more to biological motion (Fig. 3*c*). In fact, this was the most significantly responsive area for this contrast in the whole brain [peak Talairach coordinates (−41, 14, 18) with $t = 9.8$]. There were less significant peaks in the inferior precentral sulci bilaterally [left hemisphere peak at (−37, 5, 25) with $t = 5.5$ and right hemisphere peak at (34, 7, 27) with $t = 5.2$]. Thus, we found support for the hypothesis that motion information in body actions can drive neural activity in frontal cortical regions.

In line with previous work, we also found lateral temporal regions that responded more strongly to biological motion than to scrambled motion. Although the peak voxels were in rather similar locations in the two hemispheres (see supplemental Table 1, available at www.jneurosci.org), the region that was significantly responsive to the contrast extended more anteriorly and superiorly toward the STS in the left hemisphere, and, although these areas were responsive in the right hemisphere as well, the strongest responses lay more posteriorly in this hemisphere. Finally, a region in left ventrolateral inferotemporal cortex (most anterior activation in temporal cortex seen in Fig. 2*c*) also showed significant responses to biological motion compared with scrambled biological motion. We did not find brain areas that preferred scrambled motion over biological motion.

Note that the large activated regions in temporal cortex likely contain multiple functional visual areas because they are very close to or partially overlapping with areas that have been reported in previous studies to be responsive to simple motion (Tootell et al., 1995), visual form of objects (Grill-Spector et al., 1999), human bodies (Downing et al., 2001), and shape-from-motion (Murray et al., 2003). In fact, we verified this by examination of several individual subjects' biological motion-responsive regions identified in this study in relation to results from localizer scans performed in our laboratory and found that, at the individual subject level, brain areas that have a preference for biological motion have considerable overlap with areas that respond to simple motion, object form, human faces, and, especially, human body form (data not shown). Additionally, although a large area in lateral temporal is cortex responsive to biological motion, it has also been observed that different portions of human temporal cortex have relative preferences for different kinds of motion stimuli, such as biological versus artifact motions (Beauchamp et al., 2003; Pelphrey et al., 2003).

We next examined the average hemodynamic responses to the biological motion and scrambled biological motion blocks across the 12 subjects for two anatomical regions in frontal cortex that are known to respond during action observation: IF and Prem cortex. We also studied the pSTS because it is known to respond more to biological motion than to scrambled biological motion (for anatomical boundaries of these ROIs, see Materials and

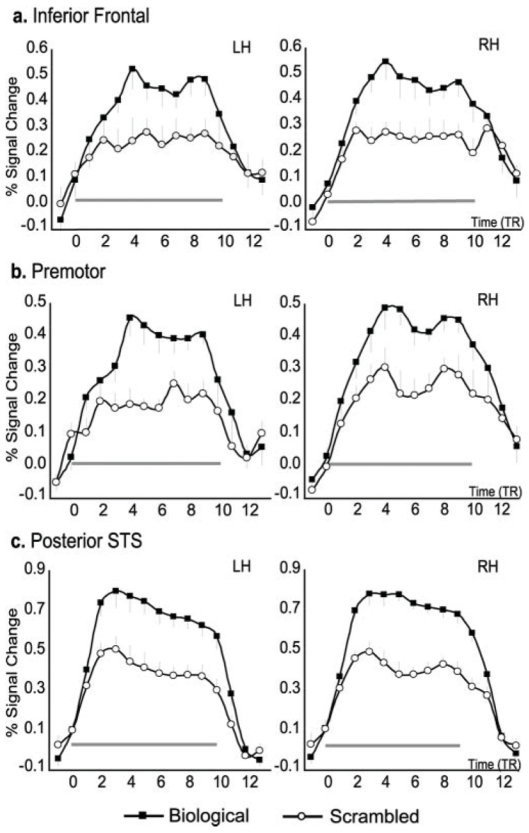

Figure 3. Percent MR signal change across time for the biological motion and scrambled biological motion blocks in the IF, Prem, and pSTS regions of interest. The filled squares depict the signal for biological motion, and the open circles depict the signal for scrambled motion. The error bars show SE across the 12 subjects. In IF, the mean number of voxels included in the ROI analyses across the 12 subjects was 53 in LH, 58 in RH; in Prem, the mean number was 64 in LH, 80 in RH; and in pSTS, the mean number was 108 in LH, 98 in RH. The horizontal gray line marks the actual duration of stimuli (10 TRs or 24 sec).

Methods). Figure 3 depicts the percent signal change for each of these ROIs in each of the two hemispheres.

In contrast to most previous studies, the addition of a baseline condition in our experiment (stationary point-light observation while executing the color-monitoring task) allowed us to examine responses to both biological and scrambled motion. In all ROIs in both hemispheres, responses to biological motion were much larger than the responses to scrambled motion, although scrambled motion can also be seen to give rise to responses significantly above baseline in all regions. The amplitude of the signal change in pSTS was greatest, which is not unexpected because this is a posterior brain area known to be involved in the visual perception of biological motion. Signal change in pSTS for scrambled motion was also quite high, but the area showed a stronger response to the biological motion stimuli, as has been previously observed (Grossman et al., 2000). Responses in frontal cortex were also strong. We found very similar response patterns to those in pSTS in both the IF and the Prem ROIs; the percent signal change in these regions for biological motion was much greater than that for scrambled biological motion. Moreover, the difference in the responses to the two stimulus types in frontal cortex was similar in magnitude to the difference observed in the pSTS. To quantify this, we calculated the area under the estimated hemodynamic response curves for the biological and scrambled motion conditions, and we found that the size of the response in the scrambled motion condition as a fraction of the response in the biological motion condition was very similar across ROIs: IF, 56.3%; Prem, 55.7%; and pSTS, 58.6%. This suggests that the frontal regions are just as selective for biological motion as the pSTS.

As with most fMRI studies, group analyses show the strongest and most reliable responses to biological motion across a group of subjects, whereas for individual subjects there is some variability in the activation patterns obtained. In Figure 4, we show biological versus scrambled motion contrasts for three individual subjects. There were some subjects who showed significant responses to biological motion compared with scrambled biological motion in parietal cortex (e.g., subjects 2 and 3), consistent with some previous results [Bonda et al., 1996 (only for hand actions); Grèzes et al., 2001; Vaina et al., 2001]. In some individual subjects, the response extended ventrally toward inferotemporal cortex (e.g., subject 3 and in the left hemisphere of subject 2; the extension is partially visible in the lateral view; ventral view not shown), which has also been reported in some previous studies (Vaina et al., 2001; Grossman and Blake, 2002). The frontal response, which is the focus of this study, also showed some variability. Most notably, several subjects' frontal activation extended dorsally along the precentral sulcus, beyond the IFS focus, which emerged from the group average as the most responsive region to biological motion (subjects 1, 2, and 3). Other subjects had activation in slightly more anterior or inferior regions of the IFS (subject 2 and a smaller focus seen in the left hemisphere of subject 1). For some subjects, the response in the posterior insula (or human PIVC) showed a significant difference between biological and scrambled motion (e.g., seen bilaterally in subjects 2 and 3).

Finally, overlaid on the activation maps for subject 3 are the areas activated in a separate scanning session for biological versus scrambled motion, in which this subject performed a one-back working memory task instead of the color-monitoring task. As noted above, behavioral data indicate that the one-back task is more difficult for scrambled motion, presumably because the items to be compared are unfamiliar. However, the areas activated were very similar across the two tasks; in particular, the IFS and premotor cortex responded significantly more strongly to biological motion during the one-back task. Also shown is average percent signal change in each of the three ROIs (IF, Prem, and pSTS, right and left hemispheres averaged) for each task. In each ROI, the response pattern (biological motion > scrambled motion) was the same regardless of the task. These results suggest that the activated frontal areas are unlikely to reflect general attentional differences between the conditions because the one-back task is more challenging for the scrambled condition and hence presumably places greater demands on working memory, executive systems, and attentional systems, yet even in this case the IFS and premotor regions respond more strongly to biological motion.

Discussion

This study aimed to investigate whether frontal areas known to be activated by action observation would also respond to actions characterized solely by motion cues. We used point-light biolog-

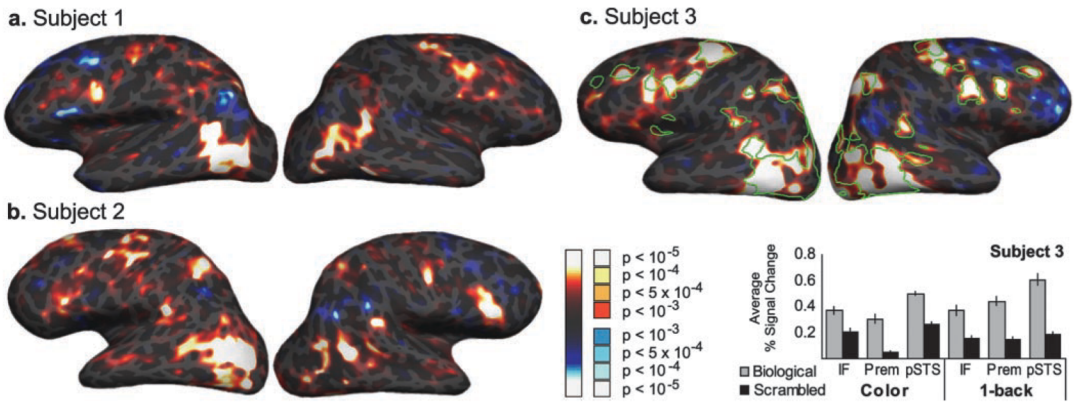

Figure 4. Example individual subject results. Results for the biological motion versus scrambled biological motion contrast is shown on inflated lateral views of three subjects' hemispheres. The color bar shows the colors in the images, and the discrete swatches mark colors that correspond to p values smaller than 10^{-3}, 5×10^{-4}, 10^{-4}, and 10^{-5}, or $t > 3.3$, $t > 3.5$, $t > 3.9$, and $t > 4.5$, respectively. In *a*, subject 1 can be seen to show a pattern similar to the frontal and temporal response pattern found in the group study, with more extension into precentral sulcus. In *b* and *c*, subject 2 and subject 3 are depicted showing strong activity in inferior frontal and premotor areas in frontal cortex, in addition to superior temporal, parietal, posterior insular, and inferotemporal cortex (left-lateralized for subject 2; bilateral for subject 3 with extension into ventral cortex, which is not visible). In *c*, additional data for subject 3 is shown from a separate scan in which the same stimuli were presented in a one-back working-memory task with different attentional requirements. To show precise alignment of activated regions in the two different tasks, regions responsive to the biological motion versus scrambled biological motion contrast during the one-back task at $p < 10^{-3}$ are outlined in green and superimposed onto the surface on which the data from the main experiment (color-monitoring task) was rendered. Also shown in *c* is a graph of the average percent signal change in our three ROIs (IF, Prem, pSTS; data from left and right hemispheres combined) for these two scanning conditions, which revealed that all of these areas were more responsive to biological motion than scrambled motion under both task conditions.

ical motion animations of whole-body actions that have consistently activated superior temporal cortical areas in most previous human neuroimaging studies (Bonda et al., 1996; Grossman et al., 2000; Grèzes et al., 2001; Vaina et al., 2001; Beauchamp et al., 2003) (but see Servos et al., 2002). Our approach was to keep the experimental design straightforward (block design with two motion conditions and one static baseline, using a simple task) but to use a combination of methods to increase the signal from frontal cortex.

We found that frontal cortex showed a robust response to point-light biological motion. Compared with static point-lights, there was activation that followed the precentral and inferior frontal sulci bilaterally. Frontal areas also showed selective responsivity to biological motion compared with scrambled biological motion. These results support the view that perception of the motion information in body actions can drive inferior frontal and premotor areas involved in action perception.

When we investigated the MR signal in IF, Prem, and pSTS ROIs, we saw that the BOLD response in frontal areas showed a very similar pattern to that in pSTS, an area whose importance in biological motion processing is already established. More precisely, IF and Prem were as selective as pSTS to the contrast between biological and scrambled motion, as revealed by both the surface-based group analysis and the ROI analyses.

Frontal cortical areas (as well as sensory areas in other parts of the brain) are known to be modulated by attention (for review, see Pessoa et al., 2003). However, the frontal areas observed in our study are unlikely to primarily reflect differences in attention across the conditions. A one-back working-memory task, which is more attentionally demanding for the scrambled condition, revealed the same pattern of responses (biological > scrambled) in the inferior frontal and precentral areas activated with the "neutral" color-monitoring task. Another consideration is that the areas activated in this study overlap only partially with areas thought to be important for attentional control. The very dorsal extent of the premotor activity we observed likely overlaps with the location of the frontal eye fields near the junction of the superior frontal sulcus and superior precentral sulcus (Paus, 1996), and attention shifts have also been reported to activate an area in the inferior precentral sulcus (Beauchamp et al., 2001). However, the IFS, in which we saw the largest differences between biological and scrambled motion in the surface-based group analysis, is not thought to be involved in these spatial attentional processes.

The present study is the first study that shows a clear response to point-light biological motion animations in frontal areas known to be involved in action observation. There are a few related results from previous studies. First, we found inferior frontal lesion sites (as well as superior temporal and parietal sites) to be implicated in biological motion perception deficits in a group of unilateral stroke patients (A. P. Saygin and S. M. Wilson, unpublished observations). Second, right lateralized frontal activation in Brodmann area (BA) 47 and extending into BA 45 was found in a previous fMRI study of biological motion processing (Vaina et al., 2001). However, in that study, subjects were viewing both biological and scrambled biological motion stimuli within a single condition and performing a discrimination task between the two kinds of motion, which makes the interpretation of this activation difficult. Santi et al. (2003) also reported activation in BA 47 in the right hemisphere during biological motion perception. Note that BA 47 is inferior and anterior to regions typically active during action observation. In the same study, a large region of frontal activation, overlapping with known action observation networks in the left hemisphere, was found to be responsive to point-light biological motion. However, this area was responsive only to visible speech biological motion as subjects were trying to lip-read and did not respond during observation of whole-body biological motion actions. On the basis of these results, the authors suggested that the activation in these premotor and motor regions was linguistically specific. The present study, however,

shows that body actions also evoke activity in these frontal regions. Perhaps the linguistic task they used (lip-reading) may have led to the relative differences they observed between speech and nonspeech biological motion observation.

In summary, although frontal cortical involvement has sometimes been observed in previous studies involving biological motion, no previous imaging study has shown responses specific to point-light biological motion actions in frontal areas known to be involved in action observation. Methodological differences between previous neuroimaging studies that examined biological motion perception and our experiment may account for the different results we obtained. First, we used a color-detection task as opposed to passive viewing or a working-memory task. Second, we presented multiple point-light animations at any given time. Finally, and probably most importantly, we took additional steps to maximize signal in our fMRI design, acquisition, and analysis methods (e.g., used a 4 tesla scanner, B0 field map correction, linear and higher-order shimming, and surface-based intersubject averaging methods).

Where do the frontal regions activated in our study lie in relation to areas identified in previous studies of action observation? Many action observation and imitation studies have pointed to the posterior IFG as being a particularly important area and a possible homolog for macaque area F5, which contains mirror neurons (Rizzolatti et al., 2001). Several action observation and imagery studies have found responses in premotor areas, as well (for review, see Jeannerod, 2001). We plotted on the cortical surface several reported peak activation coordinates from previously published studies that had action observation conditions and that found responses in inferior frontal cortex (Grafton et al., 1996; Rizzolatti et al., 1996b; Decety et al., 1997; Iacoboni et al., 1999; Grèzes et al., 2003). Several of these foci fell on the IFG, a few millimeters to a centimeter inferior to our activation (Grafton et al., 1996; Rizzolatti et al., 1996b; Iacoboni et al., 1999); one was a few millimeters anterior to our focus, again on the IFG (Decety et al., 1997); and one study reported a focus that is overlapping with our biological motion responses (Grèzes et al., 2003). However, because the reported peaks are points in the center of an activated region, they may still overlap with our responses.

Does this localization in the present study to the IFS rather than to the IFG have any significance? We suggest three possible reasons for the differences in precise localization. First, there are methodological differences between studies. The present study used surface-based group registration, which aims to optimally align particular sulci and gyri. The localization to the sulcus in the group results follows from the fact that the activation was generally localized to the sulcus for each individual subject. Second, the difference might depend on the fact that the actions in the present study were defined by motion alone, whereas previous action observation studies have used videotaped actions that contain many other visual cues such as form, contour, and color. It may be that slightly different frontal areas are engaged by different aspects of action perception. Third, and perhaps most likely, most previous studies have used hand-action stimuli (e.g., grasping), whereas in the present study whole-body actions were used to maintain contiguity with the previous literature on point-light biological motion processing. It has been shown that action observation activates premotor areas in a somatotopic manner (Buccino et al., 2001); therefore, it may be expected that actions involving different body parts would activate different regions. Because hand motor representations are ventral to representations for many body parts, such as the arms, shoulders, trunk, and legs (Preuss et al., 1996), the more superior focus that we observed could be attributable to the fact that our stimuli contained whole-body movements.

Finally, it is noteworthy that, in the macaque, mirror neurons in premotor cortex respond only to real actions performed in front of the monkey and not even to videotaped actions (Ferrari et al., 2003), whereas human premotor cortex responds even to point-light biological motion representing actions. This contrast between humans and macaques suggests that the human mirror neuron system may be more capable of processing abstract visual representations of actions.

Whereas others' actions are most often experienced through the visual system, an organism's own experience of performing the same action will involve motor, sensory, and proprioceptive representations (Barresi and Moore, 1996). A unified representation of action requires that perceived actions and performed actions be related to each other in the brain, although they are often experienced through different sensory modalities. In this context, the discovery that perception of actions can engage neural systems involved in production of actions has been an exciting development. The present study showed that human premotor cortex responds during the perception of actions defined by motion cues alone. Our findings suggest that we may be filling in these simplified animations using information from our own motor system, lending support to an analysis-by-synthesis view of action perception.

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Chapter 5

Stimulus and Attention-Driven Retinotopic Responses in Occipital, Parietal, Temporal and Frontal Cortex

Stimulus and Attention-Driven Retinotopic Responses in Occipital, Parietal, Temporal and Frontal Cortex [*]

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We explored the role of high-level stimulus properties and attention on driving neural activity in retinotopic areas in the human brain. We used structured motion stimuli (e.g., point-light biological motion) in phase-encoded polar angle mapping paradigms. In contrast to standard mapping, we also filled the background with either scrambled versions of the structured motion (a subtle stimulus contrast), or with additional copies of the structured motion (no stimulus contrast). Additionally subjects either attended to the rotating wedge (task performed on wedge contents) or centrally (unrelated attentionally demanding foveal task). Each subject was scanned in three experimental conditions which represent the retinotopically varying factors: Attention+Stimulus, Stimulus, Attention. Significant retinotopic maps were found in a number of regions in primary visual, lateral and ventral temporal, parietal, and frontal cortex. In lateral temporal cortex retinotopic activity covered MT and surrounding areas and extended into the STS. Dorsally, there was a continuous band of activation including V3a, V7, LIP, another area anterior to LIP, extending anteriorly to the postcentral sulcus. There was clear retinotopy in the frontal eye fields and in smaller regions in the precentral sulcus. Retinotopic responses were affected both by the complexity of stimuli and by attention. Attention strenghtened retinotopy in most areas, most strongly in parietal and frontal cortex. In fact, attention alone could drive neural activity in all areas identified except in primary visual cortex where retinotopy appeared to require a stimulus contrast. In some lower-level areas retinotopic activity could

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be evoked also without attention (Stimulus condition). These stimulus-driven maps were strongest in lower areas such as primary visual cortex.

Introduction

There are multiple representations of visual space laid out in topographic "maps" (often called retinotopic maps) in the occipital lobes of primates (e.g. Felleman & Van Essen, 1991). In humans, functional magnetic resonance imaging (fMRI) has been used successfully for over a decade to reveal maps similar to those identified using electrophysiology in non-human primates (Sereno, Dale, Reppas, Kwong, Belliveau, Brady, Rosen & Tootell, 1995). While there are uncertainties about the exact layout and human-monkey analogies, the existence and borders of multiple visual areas (such as V1, V2, V3, V4v, and V3a) representing all or part of the contralateral visual hemifield is well-established (Sereno & Tootell, 2005). However, until recently, very little work had been done on identifying retinotopic maps outside of these areas. There are reasons to expect spatial representations outside of early visual areas: First, spatially-lateralized attentional deficits can follow unilateral parietal or frontal lesions (Driver & Mattingley, 1998), suggesting that at least some dorsal stream areas (which are often viewed as sources of top-down attentional control signals, Pessoa, Kastner & Ungerleider, 2003) may possess spatiotopic organization. Secondly, at least some higher cortical areas have retinotopic representations in the monkey brain (Heider, Jando, & Siegel, 2004; Sereno & Tootell, 2005; Schall, Morel, King, & Bullier, 1995). Thirdly, we would expect there to be organized representations of visual space in areas of the brain which are involved in coordinate transformations required for an organism to plan and execute behaviors on space, such as eye, hand, or body movements, (e.g. transformations between retinotopic and egocentric reference frames). Indeed regions in which some of these transformations take place are already known, e.g. in parietal cortex (Andersen, Essick, & Siegel, 1985; Read & Siegel, 1997; Snyder, Grieve, Brotchie & Andersen, 1998).

Early neuroimaging studies examining human retinotopy either did not study areas outside of early visual cortex (e.g, Sereno et al., 1995), or did not find retinotopy in higher visual areas (e.g., Halgren, Dale, Sereno, Tootell, Marinkovic & Rosen, 1999; Portin & Hari, 1999). However, with rapid

methodological advances (e.g., higher field strength imaging, advanced hardware and software development) and the increased signal-to-noise, more recent studies have identified retinotopy in at least some motion and form sensitive visual areas (Brewer, Liu, Wade, & Wandell, 2005; Hasson, Harel, Levy & Malach, 2003; Huk, Dougherty & Heeger, 2002). Secondly, retinotopic mapping protocols typically use flickering checkerboard stimuli optimized to stimulate neurons in early visual cortex. However, in both humans and other primates, higher visual areas are known to respond preferentially to complex higher-order properties of visual stimuli and may show little response to simple stimuli such as checkerboards. Recent work is beginning to show that there are retinotopic maps in areas such as ventral and lateral temporal, parietal, even frontal cortex but that more complex stimuli and/or an attentionally demanding tasks may be required to reveal them (Hagler & Sereno, in press; Sereno, Pitzalis & Martinez, 2001; Sereno, Saygin, & Hagler, 2003; Schluppeck, Glimcher & Heeger, 2005; Silver, Rees & Heeger, 2005).

A summary of higher retinotopic areas identified recently by our lab and others are as follows: In ventral temporal cortex while there is much debate about the exact organization of visual areas (see Sereno & Tootell, 2005), it is becoming apparent that retinotopy here extends further than envisioned before, anteriorly and laterally into inferior temporal areas which are known to be sensitive for higher-level stimuli such as objects and faces (Sereno et al., 2003). In lateral temporal cortex, a large region of cortex extending into the STS shows retinotopic responses which is composed of multiple areas including LOC, MT and other motion-sensitive areas (henceforth MT+; this region likely contains human analogues of monkey MT, MST, FST, V4t and possibly other areas, see Sereno & Tootell, 2005). There is also a retinotopic region in the precuneus. Dorsally, we find a continuous band of retinotopic areas which covers areas V3a, V7, LIP or ‘posterior LIP’, (which is the area originally mapped in the human with delayed saccades, Sereno et al., 2001), another area in front of that, or ‘anterior LIP’ (which corresponds to IPS2 reported by Silver et al. 2005), and then further extends anteriorly towards the postcentral sulcus (possibly including area VIP). It appears that there are several distinct visual areas in this dorsal region which remain to be further subdivided.

The functional properties of these maps is now an important area to explore. What stimuli are these maps driven by? How might they be used in vision and spatial processing?

We hypothesize that at least some maps in cortex representing visual space would be actively used during tasks that organisms carry out in space, e.g., spatial attentional processes. Other maps might respond to higher-order stimulus properties (e.g., form, motion).

While some previous studies have studied the relationship between retinotopy and spatial attention (especially in regions along the intraparietal sulcus, e.g. Sereno et al, 2001; Silver et al. 2005), or used complex stimuli such as faces or video rather than checkerboards (Sereno et al., 2003), it is not possible to infer from these studies whether the retinotopic response in a particular area is primarily driven by the properties of the visual stimulus, or to attention directed to the visual stimulus (either via an explicit task, or simply because nothing else in the visual field is competing for the subjects' attention). The present study thus aims to explore stimulus-driven and attention-driven retinotopy in higher cortical areas by contrasting these conditions in an experimental design.

In order to study this question, we devised novel variants retinotopic stimuli and mapping paradigms. In the basic phase-encoded retinotopic mapping experiment subjects fixate and view flickering checkerboard stimuli in a continuously moving portion of the visual field: either inside a clockwise or counter-clockwise rotating pie-shaped wedge (for polar-angle mapping), or inside an expanding or contracting ring (for eccentricity mapping). In the present study we used only polar angle mapping. The movement of the rotating wedge has a fixed frequency, the stimulus frequency. A Fourier analysis is performed on the fMRI time series at each voxel: The amplitude of this Fourier transform at the stimulus frequency reveals how "retinotopic" the voxel is, and the phase corresponds to the polar angle of the preferred stimulus location (see Materials and Methods).

We made some modifications to this basic polar angle paradigm. First, we used complex stimuli so that we can study effects of higher-level stimulus features on retinotopic maps. We used moving objects defined by point-lights, more specifically, point-light biological motion (Johansson, 1973) in this experiment, although other stimuli were used in pilot scans. There were several reasons

for choosing this stimuli: On the one hand, point-light biological motion is a high-level stimulus: It is a salient motion stimulus that is also perceived as a coherent (indeed, meaningful) object. Multiple visual features can thus be studied with these stimuli (motion, form, structure from motion). On the other hand, these stimuli are also simple in comparison to some other high-level stimuli, for example video. Because point-light motion lacks many other visual cues (e.g., contours, color, contrast), control stimuli are relatively easily available in the form of spatial or phase scrambling of the point-lights and static or non-biologically moving stimuli of relatively matched visual complexity are also possible to create.

The stimulus contrast in this experiment is thus rather subtle compared to prior studies which typically present the stimuli on a blank background. We instead look at the contrast between biological motion and scrambled biological motion control stimuli. This comparison in a block design leads to activations in multiple cortical areas including MT+, the superior temporal sulcus (STS), inferotemporal cortex, and premotor cortex (Grossman, Donnely, Price, Pickens, Morgan, Neighbor & Blake, 2000; Grossman & Blake, 2002; Saygin, Wilson, Hagler, Bates & Sereno, 2005).

In addition, we used attention as a factor. In the Attention+Stimulus condition of the experiment, the stimulus contrast was present (biological motion in wedge, scrambled version in background) and the subjects' attention was explicitly directed to the wedge as they were asked to do an attentionally-demanding task with the contents of the wedge (see Materials and Methods). In this condition any retinotopic brain response could reflect either a response to the stimulus properties (structured motion, form, biological motion), or attention, or a combination of the two. In the Stimulus condition, the visual stimuli were completely identical to the Attention+Stimulus condition. This time, subjects were asked to ignore the rotating motion stimuli in the periphery while they performed a very difficult task at fovea. The goal of using this task is to subtract attention away from the exact same retinotopic stimulus as in the Stimulus + Attention condition. Thus we can study which maps require attention to be activated and which maps respond even when attention is directed elsewhere. Since subjects carry out the task continuously there will be no task-specific (i.e. related to working memory)

activity at the stimulus frequency. A task which alters the stimuli minimally and is sufficiently difficult was chosen (see Materials and Methods). Finally in the Attention condition, only attention rotates across visual space and the same type of stimuli are presented in the retinotopic wedge and the background. The goal was to observe whether attention alone can lead to retinotopy and if so, to identify regions in which this can be observed. Several years ago, Brefczynski and DeYoe (1999) reported directing attention to different locations in space leads to activity in the cortical representation of those locations in early visual areas. Recently, Silver et al reported a related result in the intraparietal sulcus (2005). Our Attention condition asks a similar question. Additionally, using the same attention task in the Stimulus+Attention condition here, we can find out which maps in that condition are primarily driven by the subtle stimulus contrast (biological motion vs. scrambled).

We only performed polar angle mapping because it was not feasible to use eccentricity mapping in a similar experiment as attention becomes a confound while doing an "attend to the retinotopic stimuli" task because it is much easier to attend to the fovea than to the periphery.

Materials and Methods

Participants: 9 adults (age 25-35) participated in this study (5 women). All participants had normal or corrected to normal vision. All were moderately to highly experienced with behavioral and with functional MRI experiments, including retinotopy scans. One subject was an author (APS), the remaining participants were not told about the general hypotheses of the experiments until after all scan sessions were completed. The experimental protocol was approved by the UCSD internal review board, and informed consent was obtained from each participant.

Imaging Protocol: Each subject was scanned in 4-6 runs of each of three conditions: Stimulus+Attention, Stimulus, Attention. Some subjects participated in additional sessions (pilot scans or additional control conditions). Scans were conducted on separate sessions on different days. Scanning and analysis parameters were the same for all scans and were as follows: Imaging was conducted with a 3T GE scanner with an 8 channel head coil. 31 axial slices were acquired with 3.5

mm thickness (0 mm gap) and 3.125 mm x 3.125 mm in plane-resolution using a standard single pulse echo-planar sequence (TR=2000 ms, TE=30 ms, flip angle=90 degrees, bandwidth 125 kHz, 64 x 64 matrix). After allowing magnetization to reach steady-state, 256 repetitions were acquired in each run, corresponding to 8 full rotations of the retinotopic stimuli and 8 min 32 sec of scan time. When possible, a per-voxel equilibrium longitudinal magnetization (B0) field map was collected at each session and subsequently used in reducing distortions in the images (Reber, Wong, Buxton & Frank, 1998). During each session A T1-weighted anatomical scan (TR = 10.5 ms, TE = 4.8 ms, flip angle = 11 degrees, bandwidth = 50 kHz, 256x256 matrix,1x1x1.5 mm voxels) was also acquired in order to aid the spatial alignment of the functional images to a previously obtained (on 1.5, 3, or 4 Tesla scanners) high resolution (1x1x1 mm) T1-weighted anatomical scan of each subject.

Stimuli and Procedure: Subjects directly viewed the stimuli on a screen which was suspended inside the magnet bore above their chest. Stimuli were projected onto this screen using a standard XGA video projector and a 7.38-12.3" focal length Xtra Bright Zoom lens (Buhl Optical, USA). This setup allowed a large field of view (on average 55 degrees in diameter). The experiments were programmed and presented using MATLAB (Mathworks, Natick, MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) on a laptop computer (Dell, Round Rock, TX) running Windows 2000 (Microsoft, Redmond, WA).

Subjects maintained fixation on a fixation cross around which 18 figures each composed of 12 moving point lights were presented, arranged in a circular fashion, increasing in size with eccentricity (see Fig 1). The movements of the dots were either “structured”, i.e. the moving dots led to a coherent form/object percept, or they were scrambled versions of these structured animations. In the experiment, biological motion was used – so the point-lights depicted a human actor carrying out full body motions. Non-biologically moving (translating) objects were also used in pilot scans (data not shown).

Point-light biological motion sequences were a subset of those used in Ahlstrom, Blake & Ahlstrom (1997), and were created by videotaping an actor performing various activities and then encoding the joint positions in the digitized videos. Scrambled biological motion animations were

created by randomizing the starting positions of the biological motion point-lights while keeping each dot's trajectory intact. The starting positions of the dots were chosen randomly within a region such that the total area encompassed by the figure was similar to that of the structured motion figures. 11 biological motion animations and 11 corresponding scrambled animations were used in the experiment. The actions depicted walking, walking up stairs, jogging, jumping jacks, throwing, underarm throwing, skipping, stepping up, a high kick into the air, a lower kick and jumping rope.

The whole display of moving dots rotated around the fixation cross, refreshing once per second. At each refresh of the display both the content and the color of the each individual animation changed. 11 isoluminant colors were used randomly except in the Attention condition as described below. The rotation always started at the horizontal meridian of the right hemifield (i.e., 3 o'clock) but in half of the scans was counterclockwise, in the other half clockwise. The rotation direction is varied so that any phase-spread we find cannot simply be due to differences in hemodynamic delay (Sereno et al., 1995; 2001).

Subjects maintained fixation throughout each run and used a button box (Photon Control Inc, Barnaby, B.C. Canada) to report matches in the task, which varied between the conditions as described below.

Conditions and Tasks: All conditions feature a polar angle retinotopy experiment. Subjects fixate and view a clockwise or counter-clockwise rotating pie-shaped wedge for which the response is analyzed in a Fourier analysis. A crucial modification in the present study is whole-visual field stimulation instead of presenting the rotating wedge on a uniform background.

The wedge and background content varies between the conditions as described below. Additionally, in each run, the subjects are engaged in an attentionally demanding task which varies between the conditions.

There are three conditions corresponding to the main factors rotating with the wedge: Attention + Stimulus, Stimulus and Attention.

Attention + Stimulus condition: In this condition, different kinds of stimuli were presented in the retinotopic polar angle wedge and the background. The wedge contained structured (biological) point-light motion while the background contained "scrambled" version of the same motion (Figure 1a). Note that this is a rather subtle stimulus contrast – compared to standard retinotopy which has no stimuli in the background, or even compared to a non-motion control stimuli such as stationary dots.

In addition to a stimulus contrast, the subjects' attention was actively directed to the wedge stimuli with an attentionally demanding task. While fixating on a white fixation cross, subjects were asked to keep their attention on the rotating wedge and monitor for trials in which the three figures in the wedge were not identical (e.g., for biological motion, all three point-light actors not carrying out the same action). This is a difficult and attention-demanding task to perform at the rate our stimuli refresh and with the large field of view we used.

Stimulus condition: In this condition, the visual stimuli presented were identical to the Stimulus + Attention condition with structured motion in the wedge and scrambled motion in the background. The only difference was the fixation cross: In addition to each point-light animation color randomly changing at every refresh, the fixation cross also changed color (Figure 1b). The task was as follows: Subjects were asked to ignore all peripheral stimuli and carry out a 2-back working memory task with the color of the fixation cross (respond when a trial matches the trial before the previous trial, e.g., red, blue, red). This task is very difficult to perform at the refresh rate of these stimuli and requires sustained attention. Subjectively subjects reported the central task being very attentionally engaging, not being aware of the details of the peripheral stimuli, and in some cases "not even seeing anything other than the fixation cross". The 2-back color task was chosen because it alters the stimulus only minimally and in a non-periodic manner and is sufficiently difficult.

Attention condition: Here subjects saw the same type of point-light figures in the wedge and background (biological motion) and were asked to attend to the wedge. However, given that the visual field now contained the same stimuli everywhere "the wedge" had to be defined. Experienced subjects could track a wedge only defined by attention simply by monitoring it carefully from the start of a

session – but we wanted to provide an additional cue because if one's attention lapses for a moment it often becomes impossible to "find" the retinotopic wedge and a whole run of data would be useless. In order to allow subjects to know which part of the stimulus to attend to, a color cue was used. Instead of using randomized colors for each animation at every refresh, the wedge was separated from the background either by presenting the wedge in a uniform color and the background in randomly refreshing colors, or by presenting the wedge in randomly refreshing colors and the background in uniform color (Figure 1c) – these color conditions were varied in order to ascertain that the retinotopy obtained could not be due to color or color uniformity. As in the Stimulus + Attention condition, subjects kept their eyes on the white fixation cross and attended to the wedge (defined by uniform color of foreground or background) and responded whenever the three figures in the wedge were not identical (i.e., point-light actors not carrying out the same action).

Data analysis: The data were analyzed using cortical surface-based methods (Dale, Fischl & Sereno, 1999; Fischl, Dale & Sereno 1999, Fischl, Sereno, Tootell & Dale, 1999) using the Freesurfer software package, and the Analysis of Functional Neuroimages (AFNI) (Cox, 1996) package, as well as in-house software.

Each subject's cortical surface was reconstructed (Dale, Fischl & Sereno, 1999), inflated, resampled to a sphere, and then morphed to an average spherical representation of the cerebral hemispheres (derived from 40 spherical surfaces) through a procedure that aims to optimally align sulcal and gyral features across subjects while minimizing metric distortion (Fischl et al., 1999b). Group level statistics are carried out on this common spherical coordinate system and the results are transferred onto the inflated cortical surface of a single subject for display.

Each subject's phase-encoded data were analyzed using Fourier-based methods: The Fourier transform of the fMRI time series at a voxel at the stimulus frequency (here 8 cycles/run) yields a vector with real and imaginary components, or the amplitude and the phase. For a polar angle mapping scan, the phase of this vector corresponds to the polar angle of the preferred stimulus location and the

amplitude reflects the strength of the retinotopic response and is equal to -log10 of the p-value (e.g. -log10(0.001) = 3). The significance is estimated by dividing the squared amplitude of the signal at the stimulus frequency by the sum of squared amplitudes at all other frequencies ("noise" frequencies), excluding low frequencies, and harmonics of the stimulus frequency (Sereno et al., 1995). This is a ratio of two chi-squared statistics and has an F-distribution (Larsen & Marx, 1986) and a corresponding statistical p-value can be obtained, degrees of freedom being the number of time points. (Note that this significance estimate is not completely accurate and tends to be conservative because the "noise" we are dividing by is not evenly distributed across frequencies).

For each subject, within each condition, multiple scans are averaged in the Fourier domain in a manner which uses both amplitude and phase in maximizing signal-to-noise. The real and imaginary components are averaged across scans independently so a vector average can be obtained. If the phases of the Fourier transform at a frequency is varying randomly, the amplitude of the vector average will tend towards zero. Thus voxels at which the Fourier transform has high amplitude and consistent phase across runs will have the maximal ratio between stimulus and noise frequencies.

For each condition, where possible subjects were scanned with equal numbers of scans with stimuli rotating counterclockwise or clockwise. Before averaging, phases for the clockwise scans were reversed. At this point, 0.05 cycles of phase (~3 seconds) were subtracted from the data before averaging to account for hemodynamic delay.

After each subject's data was processed, two kinds of group analyses were conducted. First the real and imaginary components from each subject are averaged directly to make a "group retinotopic map". Any cortical patch with a phase spread representing the contralateral visual field emerging in this average means that these vertices not only have significant response to the stimulus frequency, but also consistent phase across subjects, and thus indicates a very strong and consistent retinotopic representation. However, with this method, smaller areas which contain phase spreads in individual subjects may not show as clear-cut maps, and even in larger areas the phase map may blur due to averaging. The phase of a patch of cortex can vary between subjects even though there is strong

retinotopic response in the area across subjects. So in a second analysis, at each voxel, the Fourier data was converted to a "signed amplitude". Here the Fourier amplitude is used to find areas which have a reliable representation of contralateral space regardless of phase. The amplitude is "signed" positive or negative depending on whether the phase corresponds to contralateral or ipsilateral space. This signed amplitude is used not only to identify areas with reliable contralateral preference in each condition, but also to quantitatively compare spatiotopic responses in the different conditions of the experiment (Attention+Stimulus VS Stimulus; Attention+Stimulus VS Attention) by running analyses of variance (ANOVA) with subjects as random effects.

Results and Discussion

Attention+Stimulus Condition: Significant retinotopic regions were found in extensive regions of early visual cortex, temporal, parietal and frontal cortex bilaterally; many of these regions contained clear phase spreads indicating full or partial field representation. In primary visual cortex (see Figure 2d) retinotopic maps have the expected phase (with only slight blurring of boundaries), indicating the surface-based group average method is reliable and also shows that subjects did not make significant eye movements during the scans. Also in this view significant V6 activation is seen (the upper field representation in the posterior bank of the parietooccipital sulcus, then extends dorsally with a meridian and lower field representation). Further dorsally, there is also bilateral activity in the precuneus although phase spread is less clear, especially in the left hemisphere. In ventral temporal cortex (Figure 2c) retinotopic responses extends anteriorly and laterally covering V2, VP, V4, V8 (as originally defined Sereno et al., 1995) and extending into posterior inferotemporal cortex. Laterally (Figure 2a) retinotopic response covers a continuous region of occipital and temporal cortex including areas LOC, MT+, and reaches into the STS. Multiple areas along the dorsal surface of both hemispheres (Figure 2b) along the intraparietal sulcus are strongly activated and show phase reversals. Going anteriorly areas which can be seen clearly are V3a, V7, 'posterior LIP' and 'anterior LIP'. Retinotopic activity extends further towards the postcentral sulcus and here may include area VIP and additional intraparietal areas which remain to be subdivided. Finally we saw that even frontal cortex

exhibits significant retinotopy with clear phase spread: Bilaterally the frontal eye fields (FEF) are strongly activated and even more anterior retinotopic areas are activated in the precentral sulcus (see Hagler & Sereno, in press for more frontal maps).

Stimulus condition: When subjects did not attend the same stimuli as in the Stimulus+Attention condition, in most areas retinotopic activation was reduced, both in extent and in strength. However, many strong retinotopic maps were still activated by the subtle stimulus contrast, even though subjects reported not even being aware of the stimuli as they were engaged in the unrelated working-memory task at fixation. Primary visual areas (Figure 3d) showed clear retinotopy indicating the activation there may be primarily stimulus-driven and may not require attention. (See discussion below). While present, the responses in V6 and precuneus were diminished. Motion-sensitive areas in lateral temporal cortex and V3a also showed strong retinotopy even without attention (Figure 3a and 3b). Ventrally retinotopic activity was visibly reduced in extent (Figure 3c); the more anterior and lateral areas were no longer activated indicating these form-related areas may require attention to respond. As expected, frontal and parietal areas were no longer strongly responsive when attention was not directed to the retinotopic stimuli. However, some retinotopic maps in the dorsal stream including LIP, responded even in the absence of attention (only in the left hemisphere; Figure 3b)., We may interpret this response as residual attention still being directed towards the retinotopic stimuli. A more precise interpretation could be that this response is driven by the salience of the biological motion stimuli: LIP neurons can represent objects of immediate behavioral importance not just because of task demands but also due to an intrinsic property such as an abrupt onset or the meaning of the stimuli (see Gottlieb, Kusunoki & Goldberg, 1998, 2005) thus it may be the latter kind of activation we are seeing in this condition as subjects are not actively attending the retinotopic stimuli.

Attention Condition: When only attention moved retinotopically, the results looked very similar to the Attention+Stimulus condition with strong maps all along parietal, lateral and ventral

temporal cortex and in FEF and precentral sulcus (Figure 4a, 4b, 4c). Thus attention alone can drive strong retinotopic neural activity in these areas. However, primary visual cortex no longer responded retinotopically when there was no stimulus contrast (Figure 4d). V6 and precuneus remained responsive.

Attention effect (ANOVA): We converted the complex Fourier data to signed amplitude and used this in an ANOVA for the Attention + Stimulus condition and the Stimulus condition in order to identify more quantiatively brain areas which showed attentional modulation retinotopically (see Materials and Methods for details). Attention increased retinotopic activity in most areas in which retinotopic responses were found in ventral and lateral temporal, parietal and frontal cortex (Figure 5a, 5b, 5c). Overall attention effects were stronger in the right hemisphere – but note that this is due to the retinotopic responses being more diminished in the right hemisphere compared with the left hemisphere in the absence of attention. Some of the areas in which attention had a significant effect were areas in which the Stimulus condition also revealed significant retinotopy – but attention increased the strength of these responses (e.g., lateral temporal areas including LOC, MT+, V3a, V7). Other areas in which attention effects were found were regions such as FEF and the intraparietal areas (especially in the right hemisphere), where the Stimulus condition did not reveal significant retinotopy. In contrast to the significant differences found in higher areas, primary visual areas (V1 and most of V2) did not show a strong attention effect (Figure 5d). Higher along the visual processing stream (e.g., parts of V2, mostly corresponding to the periphery, V4/V8 (Figure 5c) and in V6 (Figure 5d) and V3a, V7 as mentioned above (Figure 5b) we can see clear attention effects. These results are consistent with neurophysiological results from non-human primates (Cook & Maunsell, 2002; McAdams & Maunsell, 1999). On the other hand, human fMRI studies were repeatedly able to show attentional effects in V1, and often these are similar in magnitude to those in higher areas (e.g., Brefczynski & DeYoe, 1999; Gandhi, Heeger & Boynton, 1999; Martinez, et al., 1999; Somers, Dale, Seiffert & Tootell, 1999). In our data, at reduced thresholds, the attention contrast can be seen in V1 and V2 in the right hemisphere and most of V2 and a portion of V1 in the left hemisphere – thus it is possible that

there was not enough power to in this experiment to measure attentional modulation of neural activity in V1. However the present data at least suggests that attention effects in V1 with the present stimuli are much more modest compared to those found in higher areas.

Stimulus effect (ANOVA): A similar analysis comparing Attention+Stimulus and Attention conditions will reveal retinotopic responses driven by the stimulus contrast (structured motion vs. scrambled control). We had hypothesized that complex stimuli may drive some retinotopic maps in some areas because neurons in higher areas may respond to complex higher-order properties of such stimuli (as opposed to flickering checkerboard stimuli). However, we did not find many higher areas to be driven mainly by the stimulus contrast in this experiment; instead frontal, temporal and parietal maps seemed to be activated regardless of the stimuli in the background as long as attention was directed to the rotating wedge. The stimulus contrast made a difference in V3a (Figure 6b), which is sensitive to coherent motion and 3D structure from motion (see Paradis et al. 2000), V6 (Figure 6d), which is thought to be important for flow field perception and self motion (Galletti, Fattori, Gamberini & Kutz, 1999), in the ventral stream (Figure 6c), perhaps reflecting the processing of the "form" information coming from the structured motion, and interestingly in early visual areas including V1 (Figure 6d). The latter result (and in general the activation of retinotopy in V1 with the stimulus contrast in this experiment) is surprising because V1 neurons are not known to differentially respond to motion coherence or structure from motion – and may in fact have a preference for unstructured motion (Braddick, O'Brien, Wattam-Bell, Atkinson, Hartley & Turner, 2001). More specifically, V1 has not been among the areas to show a reliable response to the biological motion vs. scrambled biological motion comparison in non-retinotopic fMRI experiments (Grossman et al., 2000; Saygin et al, 2004). When presented in a phase-encoded design however the same stimulus contrast (with or without attention) evokes a retinotopic response in V1. This discrepancy may be because the phase-encoded presentation differentially activates or suppresses possible surround mechanisms in V1. Or it may be non-specific to biological motion and may reflect activity which reflects adaptation of the neurons with receptive fields corresponding to the stimuli in the rotating wedge.

Additional results: Additional scans were run on a small number of individual subjects as pilot studies or as additional control experiments. First, point-light biological motion was presented in a polar angle paradigm with no background stimulation and no active task and with the task used in the Attention conditions here. This was a pilot experiment to ascertain that these stimuli were strong enough to reveal retinotopy in areas which we identified to be retinotopic using video – which contains many additional cues and features such as color, form, contours, faces, objects, bodies etc (Sereno et al, 2003).

Secondly on a small number of subjects, we ran a variant of the Attention+Stimulus condition in which non-biological motion was used. The task and basic design was the same as the Attention+Stimulus condition described above. Instead of biological motion, inside the wedge we presented 3 copies of a shape consisting of 12 point lights moving non-biologically (translating motion achieved by all dots moving uniformly in one of 8 directions). This point-light object is also an example of structure from motion but does not have any immediate meaning and the motion is not biological. In the background, we presented scrambled versions of the same dots. Subjects had to fixate and keep their attention on the wedge. They responded when all three shapes did not move in the same direction. This task is also difficult and requires attention to perform successfully. While we did not acquire enough data to make a definitive comparison, for the subjects who participated, maps activated by this variant of the experiment were very similar to the ones found with biological motion. It appears that the maps identified are not specific to biological motion. We chose to continue with the biological motion stimuli because subjects reported this stimuli was more engaging and easier to attend to over long periods of time compared to the non-biological, meaningless objects.

Finally, we ran a single subject on the condition which logically completes the possibilities in our experimental design: No Attention + No Stimulus, i.e, the condition where the wedge and the background contain the same kind of stimuli (biological motion everywhere) and subjects' attention is not directed to the wedge but is at the fovea (2-back task on the color of the fixation cross). We ran this condition to ascertain that something in the stimuli other than the experimental factors was not causing

any retinotopic activity (e.g., a perceived contour of the wedge, color). Since there is nothing varying periodically, there should be no retinotopy, which is exactly what we found.

Conclusion

Our nervous system needs to be very flexible in order to allow us to achieve various different perceptual and attentional states and to be able to transition between them as needed. For example we need to be able to pay attention to an object or location but at the same time we must represent unattended locations so that if a sudden event occurs, we can react quickly and appropriately. On the other hand, sometimes we need to keep our attention on an object which is not currently at our center of gaze (e.g., cars in traffic). The present study aims to study the functional properties of retinotopic maps in higher cortical areas, e.g., whether they are driven by certain stimuli, whether attention is necessary to evoke retinotopic responses. At the same time it is also a first step towards examining how retinotopic maps may be used in active vision and how they may serve the organism's goals in active visuospatial processes. Our results show that both areas which process visual stimulus properties (motion and form-related cortex for the present stimuli) and attentional control areas (frontal and parietal cortex) are sensitive to attention and stimulus properties in a spatially specific manner. However, their response is modulated by stimulus and attention differentially. While much remains to be understood about the precise relationships between these maps and their effect on perception, their ongoing interaction likely enables flexibility required for perception and attention, and are part of the required neural representations.

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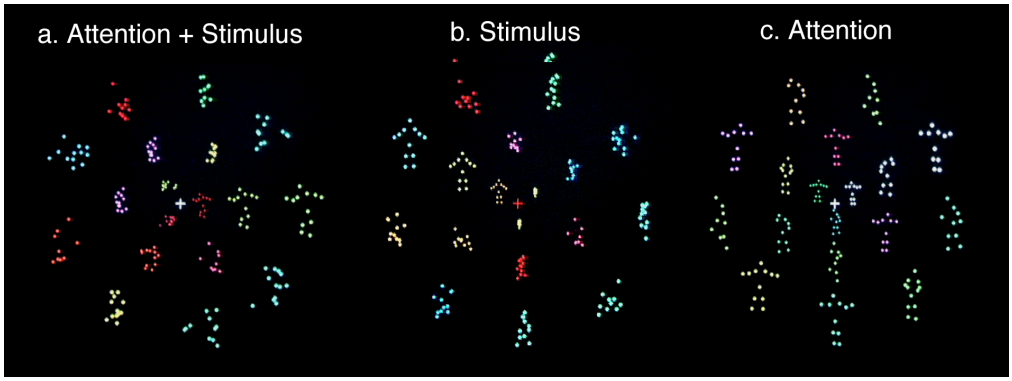

Figure 1. Still frames from the animations depicting the experimental stimuli. In all conditions subjects fixated and the whole display of stimuli rotated counterclockwise or clockwise around the fixation cross. The diameter of the entire region in which stimuli was presented subtended 55 degrees of visual angle on average. There were 18 point-light animations presented. Each animation took 1 second to complete its motion and then the whole display refreshed (after a 150 ms delay). The display continued its rotation as the point-lights within each figure moved such that the percept was more like an uninterrupted rotation with the objects inside the animation locations changing rapidly. a) In the Attention + Stimulus condition the retinotopic wedge contained point-light biological motion and the background contained scrambled biological motion, therefore there was a subtle stimulus contrast. In this particular still frame, the wedge containing biological motion can be seen at the horizontal meridian of the right hemifield. b) The visual stimuli in the Stimulus condition was identical to the Attention + Stimulus condition, except at each refresh of the display, the fixation cross also changed color. This was done in order to have subjects perform a task which pulls attention away from the wedge (see Materials and Methods). The color of the fixation cross constitutes a minimal change to the stimuli and did not correlate with the stimulus frequency and for the purposes of a phase-encoded design, the visual input in the Attention + Stimulus condition and the Stimulus condition can be considered identical. c) In the Attention condition, biological motion was displayed in the wedge and the background. The wedge was defined by a color cue either by presenting the wedge in a uniform color, or by presenting the background in a uniform color. Here in the example frame, the point-lights in the wedge to be attended (just above the horizontal meridian of the right hemifield) are white in color (see Materials and Methods).

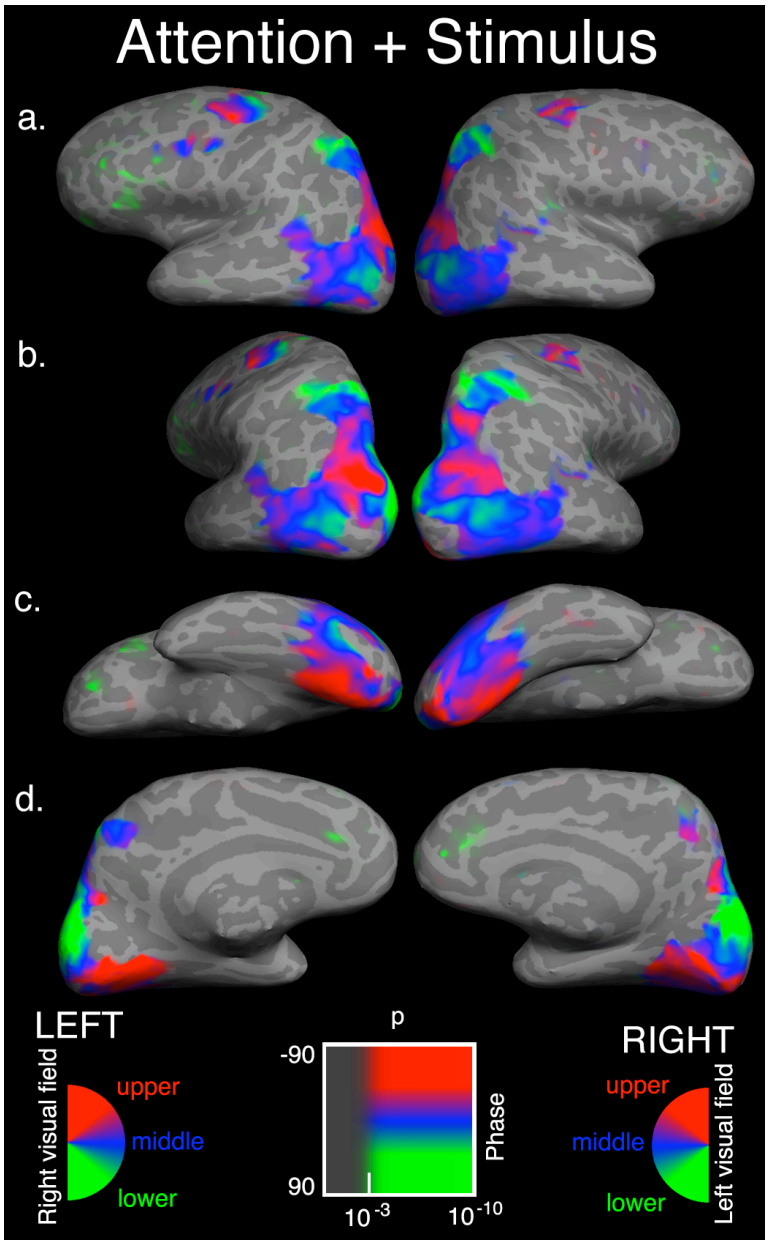

Figure 2. Surface-based group average retinotopy: Attention + Stimulus condition. In this condition retinotopy could be due to either the stimulus contrast and/or attention. Complex data (phase, amplitude of Fourier transform) have been averaged across 9 subjects using spherical surface-based methods (Fischl et al., 1999b) and are then displayed on the lateral (a), dorsolateral (b), ventral (c) and medial (d) views of a single subject's inflated cortical hemispheres. Red, blue, and green areas are colored depending on the phase of the Fourier transform at stimulus frequency and represent preference for upper, middle, and lower portions of the contralateral visual field, respectively. The intensity of the color plotted reflects the significance of the correlation between the BOLD signal and stimulus frequency, and is derived from the amplitude of the Fourier transform (see Materials and Methods).

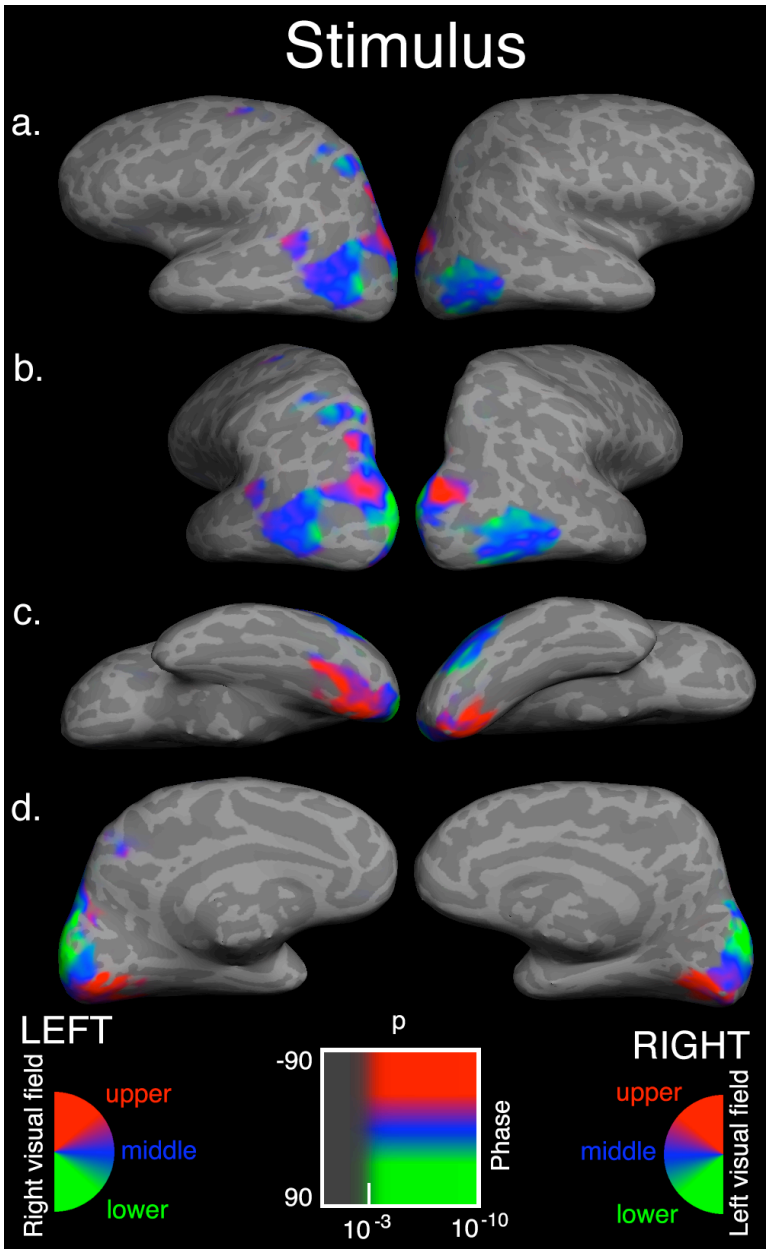

Figure 3. Surface-based group average retinotopy: Stimulus condition. In this condition subjects are not attending to the retinotopic stimuli, thus the retinotopy revealed should primarily be due to the stimulus contrast. Complex data (phase, amplitude of Fourier transform) have been averaged across 9 subjects using spherical surface-based methods (Fischl et al., 1999b) and are then displayed on the lateral (a), dorsolateral (b), ventral (c) and medial (d) views of a single subject's inflated cortical hemispheres. Red, blue, and green areas are colored depending on the phase of the Fourier transform at stimulus frequency and represent preference for upper, middle, and lower portions of the contralateral visual field, respectively. The intensity of the color plotted reflects the significance of the correlation between the BOLD signal and stimulus frequency, and is derived from the amplitude of the Fourier transform (see Materials and Methods).

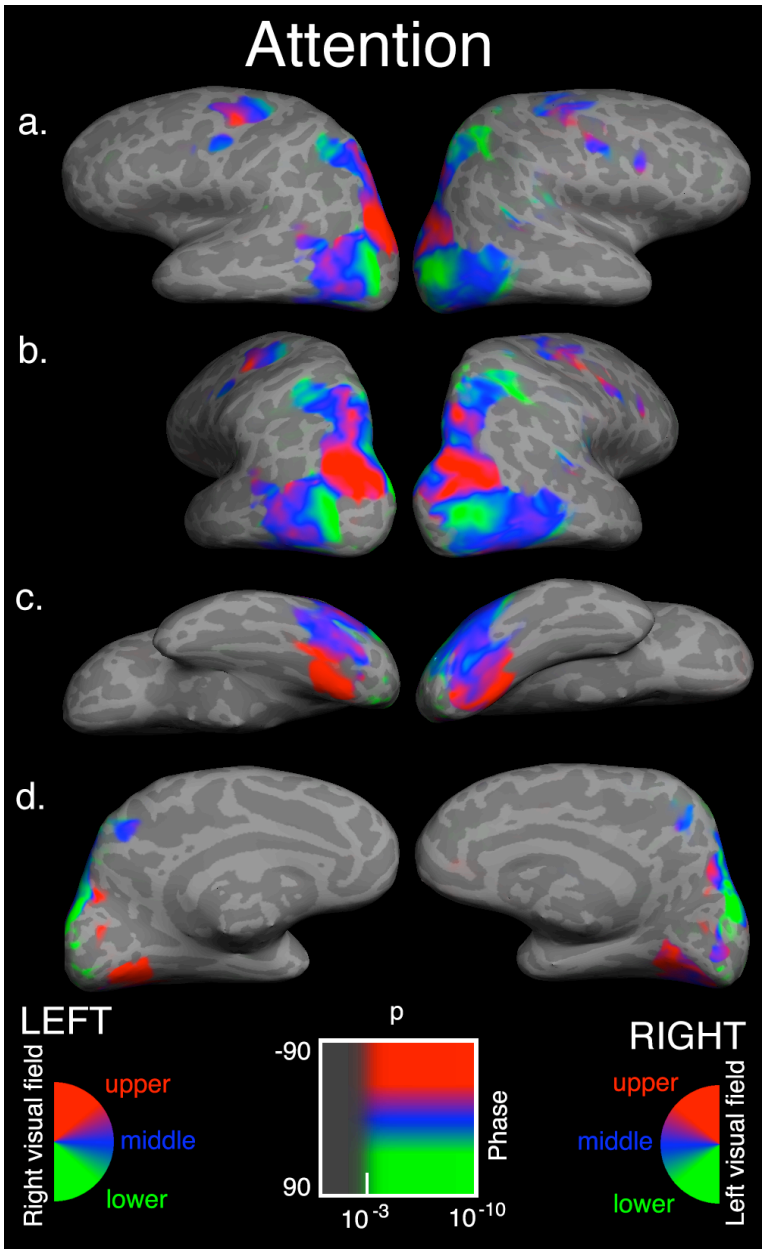

Figure 4. Surface-based group average retinotopy: Attention condition. Here there is no stimulus contrast and attention is rotating across space; thus the retinotopy revealed should be due to attention-related neural activity. Complex data (phase, amplitude of Fourier transform) have been averaged across 9 subjects using spherical surface-based methods (Fischl et al., 1999b) and are then displayed on the lateral (a), dorsolateral (b), ventral (c) and medial (d) views of a single subject's inflated cortical hemispheres. Red, blue, and green areas are colored depending on the phase of the Fourier transform at stimulus frequency and represent preference for upper, middle, and lower portions of the contralateral visual field, respectively. The intensity of the color plotted reflects the significance of the correlation between the BOLD signal and stimulus frequency, and is derived from the amplitude of the Fourier transform (see Materials and Methods).

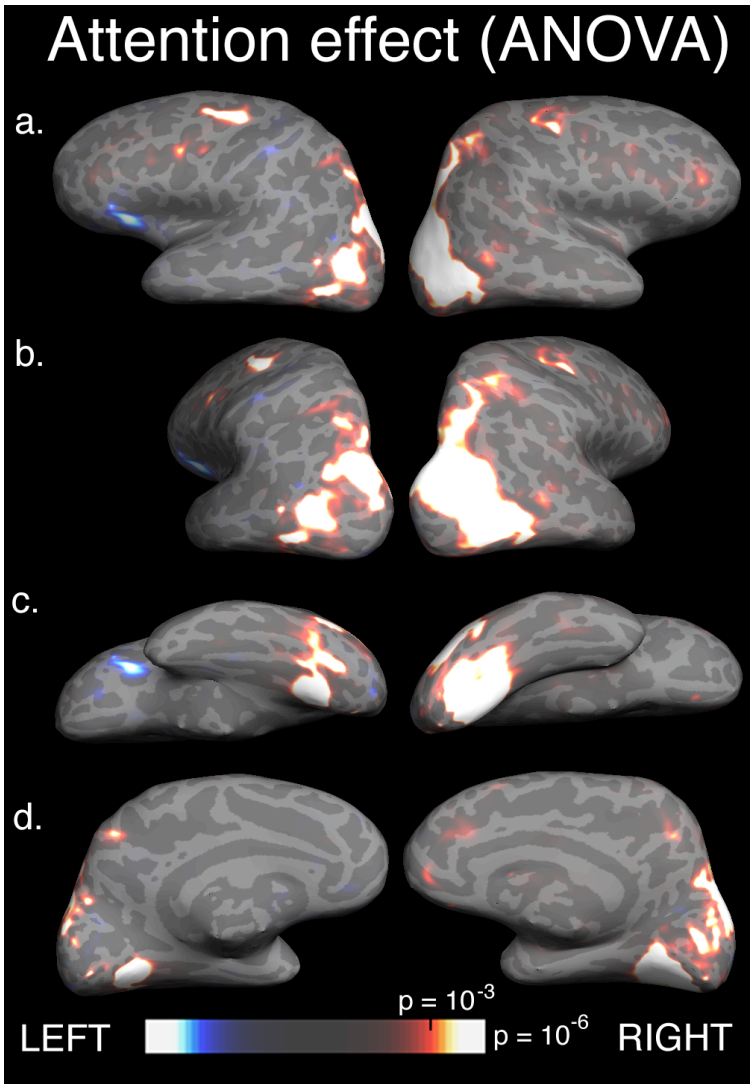

Figure 5. Surface-based group average: Attention effect. Here we contrast the Attention + Stimulus condition and the Stimulus conditions to quantitatively study areas which show significant attentional modulation. At each voxel, the contralateral preference is denoted with signed amplitude and an ANOVA is carried out on the spherical surface with subjects (N=9) as random effect. Results are then displayed on the lateral (a), dorsolateral (b), ventral (c) and medial (d) views of a single subject's inflated cortical hemispheres. This figure shows the Attention + Stimulus vs. Stimulus contrast.

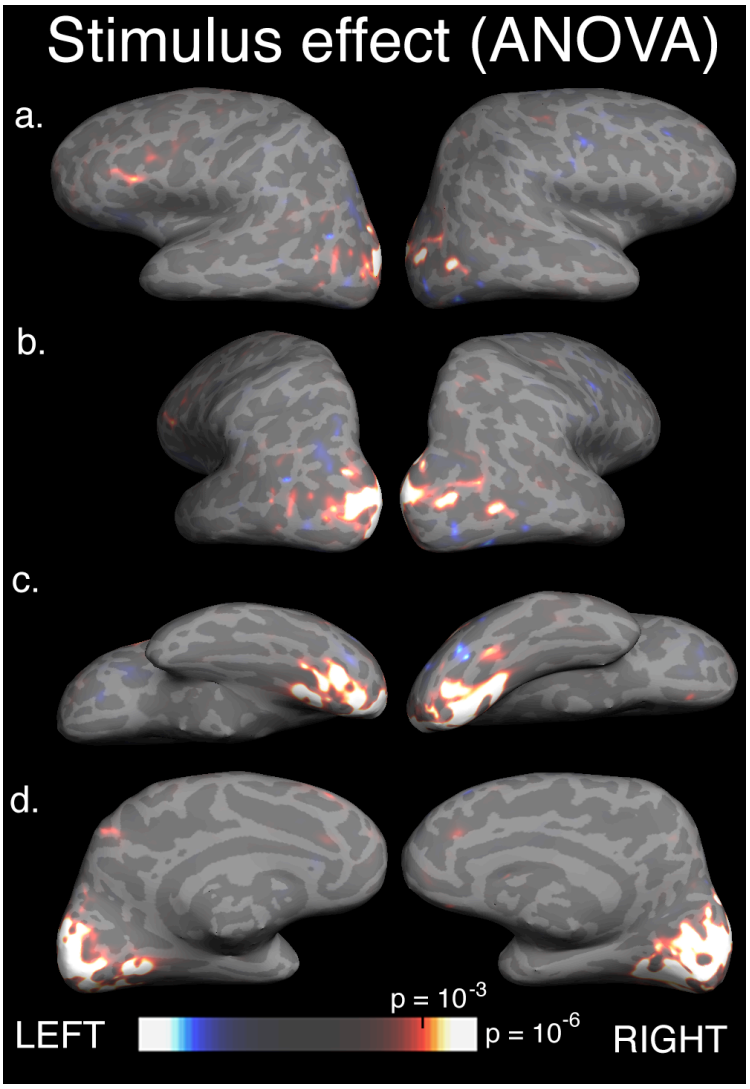

Figure 6. Surface-based group average: Stimulus effect. Here we contrast the Attention + Stimulus condition and the Attention condition to quantitatively study areas which show stimulus-driven retinotopy. At each voxel, the contralateral preference is denoted with signed amplitude and an ANOVA is carried out on the spherical surface with subjects (N=9) as random effect. Results are then displayed on the lateral (a), dorsolateral (b), ventral (c) and medial (d) views of a single subject's inflated cortical hemispheres. This figure shows the Attention + Stimulus vs. Attention contrast.