Seeking the Neural Basis of Grammar: English Noun and Verb Morphological Processing Investigated with Rapid Event-Related fMRI and Intracortical Electrophysiology

by

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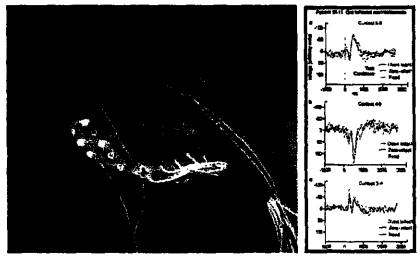
fMRI group activation data



Direct electrical recording from brain

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Submitted to the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology on May 25th, 2003 in partial fulfillment of the requirements for the degree of Masters of Science in the Brain and Cognitive Sciences.

1 ABSTRACT

Inflectional morphology is the component of language concerned with changing a word's form to reflect context-specific meaning, such as the affixing of "-ed" for English verbs in the past tense, or adding "-s" in order to signal a noun's plural form. Although it is but one part of language, morphology may be useful as a *model system* for larger issues in language and cognition. Morphological processing touches on: the manipulation of memorized items (the vocabulary of words, and maybe word endings), the application and power of combinatorial rules (to generate correct forms, even of unknown words), and the binding of units of information into meaning. Morphology's relationship with other more traditional facets of language such as syntax (sentence structure) and semantics (meanings of individual words) is debated, as is the objective reality of grammatical categories (e.g. noun / verb) as well as combinatorial rules.

Functional Magnetic Resonance Imaging (fMRI) is an exciting technique for peering into the brain and answering questions about its function. However, the technique has limited temporal and spatial resolution, and indexes the brain basis of cognition only indirectly, via blood response to cellular metabolism.

In this thesis I propose a task for manipulating morphological production, embedded in a 2*2*3 design simultaneously varying grammatical class (nouns versus verbs), regularity of inflection (e.g. words like "walk" which take the stereotyped or regular ending "-ed", versus those like "bring" and "sing" which have idiosyncratic past tense forms), and three types of morphological task aimed to separate the assignment of grammatical features (e.g. present/past tense) from changes in word sound. I introduce and utilize software to extend the functionality of the fMRI data analysis and visualization tools used at Massachusetts General Hospital. I analyze and interpret an 18-subject fMRI experiment I ran using the new task design and software tools. Finally, I present preliminary findings on linguistic questions as well as the nature of fMRI signal, using direct Electrophysiological data recorded from electrodes implanted in the brains of two Epilepsy patients. These patients had electrodes implanted through or near classical language areas of their brains, as a necessary clinical step in locating and surgically removing the seizure-causing tissue.

The main findings of this thesis are: 1.) Morphology alone can activate Broca's area, 2.) Other areas are involved, including BA47, anterior insula, and SMA, 3.) Broca's area and BA47 respond to application of abstract grammatical features, even without phonological manipulations, 4.) Morphophonological manipulation additionally recruits insula and SMA, 5.) While simply accessing nouns versus verbs may involve separable brain regions, inflectional processing of the two categories may be done by the same process, 6.) Regularly and Irregularly inflected verbs show a double dissociation of activation in frontal and medial regions, 7.) Processing of English noun more than verb morphology may rely on some contribution from number processing brain systems, 8.) Simple reading may draw on a special set of processes in the brain, not strictly a subset of the processes for more linguistically complex tasks, 9.) The electrical signals associated with morphological processing may involve major components around 250, 400, and 500-600 milliseconds after stimulus presentation, and 10.) Depth electrophysiology validated our fMRI interpretations by confirming that most electrical activity in some task-responsive regions came from processing the target word, not reading the cueing frames.

Overall, fusing metabolic and electrical data yielded strong clues to the neural processing of morphology.

Thesis Supervisor: Steven Pinker

Title: Peter de Florez Professor of Psychology

2 ACKNOWLEDGEMENTS

It is my honor and pleasure to begin by acknowledging and thanking my PhD Advisor, Steven Pinker. Steve has been a support, an inspiration, and a steady guiding hand since I began my graduate work. He has allowed me to explore and to grow intellectually – striking the elusive balance between magnanimously allowing freedom and flexibility, and yet delivering the requisite direct guidance as well as coaxing to focus on practical tasks rather than the myriad digressions my mind wishes to follow! He has had endless patience with me, especially in the preparation of this very document! He was supportive of my desire to do neuroimaging research even though the difficulties of setting up a one-man fMRI operation meant I spent most of my time at MGH receiving training, especially for the first stage of the project. It is a tribute, I think, to how close our collaboration has become that I am writing this thesis to complete my work at MIT, and move with him to Harvard.

Steve's immitigable and surprising delight with life is infectious! I think one of the reasons he has a quip or joke or hilarious and affectionate turn of phrase for almost every concept that filters through his mind, is that he is deeply entertained with life – and because his mind works so quickly he has spare time while waiting for his speech apparatus to utter his words in which to work in those flourishes!

Steve and I share a work schedule that stretches deep into every night, and a love for technology. I have been continually impressed and grateful that my e-mails to him at 1:00 am are usually answered by 2:00 or 3:00 am – transparent to whether he is currently traveling and e-mailing from a phone or other device, or just at home! Moreover, he has not complained about the barrage of long and detailed e-mails I have sent (592 to date, containing 140,000 words). In fact he has responded in kind (with 508 e-mails)!

Steve has been overwhelmingly generous in providing me with computers and equipment I have needed and used for this research. It has been extremely useful and of course quite an honor to have this equipment at my disposal, and to be supported in all the expenses of fMRI research.

The intellectual environment Steve has created around himself and in which I am included inspires and fosters scientific curiosity. A man who tackles some of the biggest questions that ever occupy the mind – the tenets of human nature; the interconnections among

all facets of psychology and sociology, and the evolutionary dynamics that have led to them; and of course the human ability to communicate with language – he is nonetheless one of the most detail-oriented people I know and he is ever eager to dive into a new methodology or discourse and quickly drink in and work through its technical details and scientific implications.

It will be a pleasure to continue to learn from and collaborate with Steve.

Figure 1: Steve and Ned in the fMRI control room at MGH.
The BBC was filming a special on Steve's work, and Ned arranged to have the camera crews allowed into this 3T fMRI lab.

The fMRI scanning at the core of the thesis would not have been possible, nor would much of my ability to analyze the resulting data, if not for the mentorship of Dr. Eric Halgren. Eric has been my advisor, business partner, political advocate, intellectual colleague, and above all else friend in the last 4 years. I have been affiliated with MGH and the Neuroimaging center (once the NMR Center, and now the MGH/HMS/MIT Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging) since my first summer internship in 1995, as a freshman in college. Over the years I have gotten to know many people and worked into more

serious roles at MGH. In 2000, when I began MIT, I approached several investigators to see where I might have common interests. Eric took me under his wing and has been a devoted mentor ever since. Scanning at MGH requires MGH IRB (ethics board) aproval, and a collaborating investigator with an appointment at Partners Healthcare – Eric allowed me to use his name and lab infrastructure to set myself up as basically equivalent to a collaborating principle investigator. While this was crucial, Eric's help has gone way beyond the bureaucratic. Our discussions have always been fervent, productive, and deeply intellectual. We have concocted and refined experiments. I have built on his direction to seek out and coalesce wisdom and technical information necessary to choose the right sequences and parameters for scanning. Another very important aspect of Eric's aegis has been his affording me with space to do my work. Much of my time has been spent not at MIT but at MGH. fMRI research is by nature highly collaborative and the MGH software tools for data analysis are experimental and sometimes quirky. For these reasons, as well as pure raw data transfer and processing speed, it is highly advantageous to be onsite and online at MGH to do my work. It has been especially important since I would otherwise have had no milieu for discussing the daily technicalities of running an fMRI experiment. Eric has been a large influence in my ability to have a full cubicle at MGH for the last 3+ years, even while post-docs and faculty are without work spaces around me or share tiny spaces. Finally, Eric handed me the opportunity to do Depth Electrophysiological recordings! Such work requires a network of collaborating neurosurgeons, neurologists, and clinical electrophysiologists and I am extremely grateful to have been given access to such a system he had built up in the Boston area. My continuing collaborations with Eric, on projects relating to language morphology and beyond, are very exciting and rewarding.

I would like to thank also Dr. Anders Dale, one of the founders of the MGH Martinos imaging center, and a friend and mentor. Anders has helped me refine the task paradigm presented here, and has continually tempted me with new techniques for the fMRI research, such as multi-echo sequences, automatic brain alignment, and sequences for eventually combining my fMRI with MEG data. Anders and Eric have been friends and colleagues and have invited me behind the scenes as to how many things operate at MGH, which will be endlessly instructive as I build my career.

Dr. Doug Greve, who wrote nearly all the FS-FAST software used for fMRI data analysis, was a great help at many stages of this project and an irreplaceable resource.

I owe endless gratitude to Paul Raines, the system administrator for all of the Martinos Center, and undoubtedly the highest-bandwidth technical infrastructure professional I have had any contact with in academia or in industry. Paul has supported my computers, Linux and Windows, and has helped with countless technical matters. He single-handedly has set up and supported probably 500 cutting-edge Linux workstations at MGH where each person has custom hardware and software configurations, quirky usage patterns, and complex setups of data volumes, user groups, and file permissions for their collaborating workgroups. There is never global downtime, and selective outages are almost always dictated by infrastructure concerns such as power reallocations and outages.

Thanks goes to Andre van der Kouwe, a pulse sequence programmer and general developer who has helped me on untold occasions, to find and use the right sequence or to understand more and more about the physics involved in MRI. On the subject of physics, I must thank our head physicist Dr. Larry Wald, who has helped me choose my scanning parameters as well as the head coil arrays.

Thanks also to Brian T. Quinn and Evelina Busa who did substantial work on this project by running the reconstruction algorithms to create "inflated" electronic versions of my subjects' brains, necessary for averaging them into a group map of common activations.

Along the way I received a lot of general guidance and morale boosting from Chris Moore and Moshe Bar. Chris was a friend at MIT and MGH, and has helped me think about building a multi-disciplinary career much as he has. Moshe is the head of the Cognitive Neuroscience group at MGH, and has had regular meetings with me to keep me on track and discuss ideas. He also has looked out for my work space, and has been very supportive of my various political and organizational initiatives at MGH.

My deep and infinite thanks go to Koral Marinković, who has been so supportive and ultimately crucial to my even attempting and then actually working through this document. The close monitoring and motivation from Koral will live on in all my memories of this process.

I would like to extend deep thanks to Nathan Wilson, my entering classmate at MIT, with whom I have continued to have close work sessions and neurophilosophical discussions, even though our actual research interests are so far apart.

There were truly many people who helped me with my many questions as I put together this paradigm and protocol. I just want to highlight two who guided my understanding of fMRI and its data interpretation: Drs. Randy Bucker and Russ Poldrack.

Finally I would like to thank my family for standing by me during the research and this writing phase. I especially thank my father, a former academic and business man, who has continued to believe in me and to try to point me to role models who are highly productive. In the final stages of this project his guidance and pressure were critical.

Thanks to all others who have helped make this document possible!

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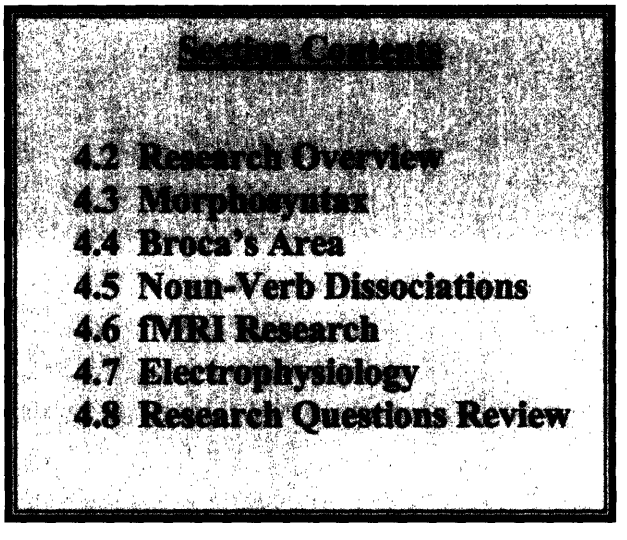
4 INTRODUCTION

4.1 Chapter Abstract

An introduction and motivation for this thesis is given. General background is discussed, and the primary motivating literature. Since this document has several chapters for specific and fairly independent findings following the general fMRI methods and results sections, a refresher of the appropriate specific literature is included in each of those chapters. This chapter concerns the general overview of morphosyntax, Broca's area, noun-verb dissociations, Regularity of grammatical inflection, and dual-route reading. Furthermore, general descriptions of fMRI and depth electrophysiology preview the results and motivate the types of data collected.



4.2 Research Overview

This project aimed to unravel the neural circuits underlying grammar by studying morphology, the combination of elements to form complex words. This complements the study of syntax, the combination of words to form phrases and sentences. English inflectional morphology embraces the pluralization of nouns and the conjugation of verbs, which both attach word endings, or inflectional morphemes, to signify the context-appropriate grammatical information content of words. An advantage of studying grammar through morphology rather than syntax (e.g. comparing complex sentences) is that it can reduce working memory demands, selection demands, and computation of semantics. Also, a morphological task likely avoids varying integration across multiple words, sentential moved elements, and involves only a single word for which to control low-level features such as frequency, syllables, and pronounceability. Using fMRI, we assessed the contributions of the classical language areas in frontal and temporal lobes to processing grammatical features (tense, number, etc.), phonology (word sound form), grammatical category (e.g. noun vs. verb), and regularity (predictability of the inflected form). The same paradigm was also performed on two epilepsy patients before and after depth electrodes were implanted directly through the language areas of their brains. Before implantation, fMRI data were collected and afterward direct electrical recordings from 32 cortical and sub-cortical areas were collected.

Language is one of the most complex and socially-relevant abilities we possess. Characterizing the neural organization of language is fundamental to unlocking how our brain gives rise to our mind. Specifically, uncovering how the morphological tasks studied here segregate in their neural response will inform models of both the lexicon (the mental dictionary of words) and the application of combinatorial rules of grammar. Since these aspects of Language explain much of its capacity to handle complex cognitive information, understanding the neural correlates of our morphological processing tasks may allow us to comment more generally on the brain basis of some cognitive principles and impairments that go beyond Language.

From a clinical point of view, revealing the organization of language is important toward the goals of assisting children who fail to develop normal language at a time or speed commensurate with their chronological age, and assisting adults who lose parts of their ability to

communicate with their loved ones and other members of society - after a stroke or physical accident.

Specific results from this program of study may also help settle two debates: 1.) whether a single or multiple brain systems are utilized in morphologically inflecting English words, and 2.) whether the linguistic categories of Nouns and Verbs echo real divisions in the brain-based organization of information storage and access.

4.3 Morphosyntax

As with many complex systems, we need a constrained but representative *model system* with which to study the larger system of Language. Every language is considered to have a *grammar*. This is not the set of "prescriptive" rules we learned in school such as not splitting infinitives, ending on prepositions, nor beginning a sentence with "because." This is the description of how languages actually do work, and interestingly so much is shared across all languages that there is considered to be a Universal Grammar underlying them all.

Traditionally, grammar can be broken down into Syntax, Morphology, and Phonology. Phonology addresses the patterns of sound in a language but does not comment on their meanings. Syntax conveys meaning but is very complex: the collection of rules for combining words into phrases and sentences with all their inter-relations.

Morphology is the combination of words and smaller elements into complex words. For instance *inflectional* morphology addresses conjugation of verbs and pluralization of nouns, in English. Combining "talk" and "-ed" to get the past-tense form "talked" is an example of morphological processing. Morphology provides us with a system where elements are one word long. This allows for a great deal of control over incidental features of potential stimuli – for instance we can easily control the frequency of usage of words in a given experiment's word list so this factor is not a nuisance variable in our studies.

Morphology bears resemblance to syntax since it controls rules of combination, and encodes meaning from structural context, for instance changing the information about when an action was performed and by whom, but not changing the core meaning of the action-naming word. Morphology can be considered a separate category of information and processes from Semantics (word meaning) and Syntax. However, the status is debated. More important than what

(linguistic) hat Morphology gets to wear home, though, is the fact that as our model system it forms a convenient nexus among all other categories of linguistic information.

Morphology interfaces with Syntax, as already discussed, in that in many parts of most languages the morphological markings on a word are what unambiguously label it for its role in the discourse. The 'geographical' location (position) in a sentence may give strong clues as to what role must be played by a word there, but it is often the morphology that makes the final determination. In a language that morphologically marks all these features, it would be the morphology that determines the word is, for instance, a verb, in the past tense, indicative mood, imperfective aspect, 3rd person, with plural number. In fact, the more a given language allows to be marked by morphology, the more free the word ordering can be in sentences – exactly because responsibility for conveying that information is shifted into the morphology system from the sentence-level syntax system. The interface between morphology and syntax is sometimes called "morphosyntax" and refers to the system of structural meaning conveyed in affixed morphemes.

Our versatile model system Morphology also interfaces with phonology, and where it does the system can be designated with the term "morphophonology." Morphophonological differences between words must by nature concern the word sounds, such as for instance how the regular past tense morpheme in English can be represented "*-ed*" but has the phonology "-t" or "-d" or "-id" depending on the final sound of the word stem. Furthermore, the fact that past tense is marked only on some words with an ending at all and on others with an internal vowel change (fare/fared versus wear/wore) falls under the rubric of morphonological description, even if the underlying mechanism may be of an entirely different category. Finally, while morphosyntax and morphophonology usually go hand in hand (if a word feature is marked at all, morphologically, you can usually hear the difference), there is perhaps a case where these two dissociate. English has no overt morphemes for mood, and very impoverished marking of verb number. However, according to some linguistic theories, the phrases "I walk..." "You walk..." "They walk..." and "He walks..." all differ not just in syntax but in morphology. In English all we can *hear* is the third-person plural verb ending "-s" because that morphosyntactic role is played by a morpheme with overt morphophonology. These theories, though, posit that all the above instances of "walk" and indeed all spoken/produced forms are morphologically marked. The morphemes in the other cases, are thought to fulfill their responsibilities very discretely: they are silent. The existence of so-called "zero affixes" that are unspoken but which have morphosyntactic content is debated. If

they do exist, that would provide a very nice dissociation or decoupling between the phonological and syntactic status of morphology at a given state of a language's evolution. The English language, currently so impoverished in (overt) morphology, may be the perfect context in which to study this phenomenon exactly for this reason. The research presented here specifically adds a middle condition to the morphological task dimension in order to be sensitive to this distinction. As discussed below, one possible comparison between task sets in our study should vary morphosyntactic information alone by requiring the assignment of abstract grammatical features without any overt phonology (going from a raw form of the noun or verb to its singular or present-tense form). Another possible comparison takes us all the way to noun singular or verb past-tense, and thus additionally adds phonologically apparent morphemes.

Neuroimaging of this distinction stands to reveal not just the neural computation of morphology, but to isolate such processing from any added demands on articulation, and to address the objective reality of the zero affix.

4.4 Broca's Area

Broca's area may be the most well-known region of the brain, outside of this field of study, and its role in language the most famous example of brain structural to functional correlation. Indeed the history of Broca's area goes back to 1861, when physician Paul Broca described a case of aphasia (loss of functional language ability) resulting from lesions determined upon autopsy to be located in the left inferior frontal gyrus.

Nearly 150 years later, it is not clear what Broca's area does. It has not been settled if Broca's area has any special role in language processing, neither in the form of a special part of language processing that can only be supported by Broca's area nor in any role of Broca's area that is only applicable to Language. Furthermore there has not been consent as to where "Broca's area" is located or how it can be stably defined, even to the point that the joke has been made that "Broca's area is where you have a lesion if you have Broca's aphasia, and Broca's aphasia is what you have if you have a lesion in Broca's area." Thus we have three questions open: 1.) Is there some part of language that is only supported by Broca's area (perhaps some core facet of syntax), 2.) Is there something that Broca's area does that is only for Language (a refutation could be, for

instance, that the role Broca's plays in language is working memory and that this is a domain-general function), and 3.) Where is Broca's area?

One of the reasons the literature in this area is somewhat messy is of course because all these questions that are open simultaneous are highly inter-dependent. For instance it is hard to nail down a single area responsible for a type of information processing when it hasn't been decided what exactly that type of processing should be!

Another reason for inconsistencies in the literature is the fundamental inconsistency of the methods that have been employed and the questions they can entertain. This is not an inconsistency due to uneven adoption of methodological specifics by the field – though that is the case as well – but rather a matter of fundamentally but knowingly different methods. Broca's original study and indeed much neurological study to this day, are examples of the lesion-deficit correlation approach to language research. Also termed aphasiology, the basic paradigm is that a patient with some sort of injury or lesion to the brain is tested on a fine-grained battery of language tests. Any patterns of language deficits are then *correlated* with patterns of the underlying brain damage. The interpretations are in the form of what brain area must have served the language function observed to be missing. The methods have evolved greatly over the last century and a half, in terms of better language tests tuned to new theoretical developments, and in terms of MRI scanning that allows characterization of the brain damage before autopsy and at high resolution.

However, the logical core of the methodology remains the same. The question that can be asked is of the form "If not B, then not which A?"

For instance, one might ask of an appropriate patient, if he cannot produce nouns with relation to verbs, then which part of the brain was lost. With a series of patients one can start accumulating sets of these correlations and look for meta-patterns in the results. For instance, if patients have overlapping deficits, specifically in some language ability B, then if they have similarly overlapping lesions one can deduce that brain region A is the common denominator in the pattern. Note that the goal may be to have predictive power, to go from A to B and to say that lesions in A will most likely produce aphasiological phenotype B. However, one can only proceed inductively and cannot directly ask the question of "If not A, then not which B" with aphasiological research. This is because we cannot experimentally manipulate where and to what extent people have their brain injuries.

One actually can ask this question, though, in another way. Transcranial Magnetic Stimulation (TMS) can use a strong local magnetic field to disrupt subjacent cortical function. This provides a temporary and reversible lesion, and importantly it is a "forward" lesion model in that one does in fact experimentally manipulate the lesion location and one can use the subject as his/her own control. TMS will not be discussed extensively here, but it is important to note that while it falls generally into the category of lesion-based research it does address different questions, as a forward not inductive model, compared to classical aphasiological research.

Whichever logical direction we proceed, lesion-based research is still has some fundamental logical characteristics. First of all, the negations ("not A" and "not B") remind us that this research is only about what can go wrong: what is preserved and what is destroyed in a non-normal state of the brain. We don't get direct data about how the brain functions normally, we can only deduce this from what we can learn about how it can malfunction. There is no doubt that this can be informative in telling us what categories of information there at least must be. For instance if we take a simple desktop computer, if the image on-screen suddenly goes out but any sounds being made or played continue, you do know that the sound and image systems of the computers are separate at some level. However you don't know if there are further sub-categories that are relevant, nor do you know if the two systems are actually unified somewhere up or downstream of whatever "lesion" cause the computer screen to go blank. Perhaps you can poll the system further by typing or clicking the mouse: if the system responds with sounds you can know that something about the input system is spared, while the output system is impaired. The metaphor can be pushed but perhaps the first important parallel is already made: that we can learn some but not all by studying the non-normal system.

Secondly, an important feature of aphasiological work is that it tests logical necessity. If a lesion in region A causes impairment in B, we know that A was necessary to produce B. We do not know how much A actually contributes to B, however. In the case of our blacked-out computer we can see this plainly. If we are looking to understand the graphics subsystem of computers, we might study 100 computers in a similar state to the one described. What we would really want would be computers where the GPU (graphics processing unit) chip on the actual graphics card was fried or video RAM was corrupted, or the port controller chips for the slot that houses the graphics card were destroyed. Investigating such lesions would, by good luck, take us right upstream to the core of the graphics system. However, it turns out that it is unlikely that such

lesions would occur, and amongst our 100 computer most of the deficits in the behavior B (correctly displaying image on screen) there would be many simpler downstream causes. For instance the identical B deficits could result from the monitor coming unplugged from the electrical outlet. Similarly, the video cable could come loose or be cut. These are not just idle metaphors: information to any output system is most vulnerable in its transmission or conduction and usually less vulnerable at its source, exactly because the source is usually more complicated, spread out, and often times redundantly specified.

It would make sense, therefore, that since aphasiological research focuses only on necessity, and on situations where a behavior has been obliterated entirely, that this would select for brain regions that are the final common output path for many signal types or which conduct widely derived information through tightly organized circuits. The emphasis would also be on situations where no redundant system can take over the function. In any case, aphasiological research definitely focuses on the not-B to not-A correlation, in terms of necessity.

This all stands in contrast to "functional" studies, for instance using modern neuroimaging methodologies. Briefly, neuroimaging studies can investigate normal subjects with intact behavior, and address the positive A to B correlation. They can look in the B to A direction ("when we process verbs, what areas of the brain are active?") or the A to B direction ("On trials where area X is more active, do subjects perform better on subsequent memory tests?"). As opposed to necessity, they assay functional contribution. This makes functional studies more likely to focus on or at least strongly include the primary processing centers in the brain for the given behavior, and not just the final common and crucial pathways. In this way it is should be expected that functional studies will give more complicated pictures of a behavior's neural correlates, and results should be interpreted in such a light. It only requires a single cut pathway to disable a behavior, but it may require many types and regions of processing to enable it. (Note that the pure subtraction methodology used to analyze and interpret functional data ultimately limits and simplifies the types of information that can be extracted, but that is for another discussion.) Therefore it is intrinsically difficult to compare Broca's aphasiological studies to functional imaging studies of any of the components meant to comprise the processing ability lost in Broca's aphasia.

Aside from the main reasons for incompatibility of major sets of studies focusing on Broca's area, there is also a history of reinterpretation of the functional role of this region. The

original view, for instance, was that Broca's area controlled pretty much all of speech. With the addition of patients described by Wernicke who could perform the act of speech (if unintelligibly) but could not understand what was being spoken to them, the model matured. The language ability was broken into expressive (speech) and receptive (comprehension) language abilities. Broca's was then implicated in the expressive half because Broca's aphasics were effectively mute but could respond to instructions and fairly complex questions. A crucial observation changed this view, namely that while Broca's aphasics responded to simple sentences, they performed at chance on sentences containing reversible passive constructions. These sentences, such as "the boy was hit by the girl" or "the dog was attacked by the man" require sentence-level syntax to disambiguate. If we go simply by the semantics and canonical role of the words, or simply by straight word order (a simple syntactic cue), then it would be the boy and the dog we would assume to be doing the attacking and the biting, respectively. This is generally how Broca's aphasics responded. However, the true syntax of the sentence reveals the opposite to be true. Broca's area then became implicated in syntax.

Note, in line with the above discussion on morphology, that these reversible passive constructions are somewhat a product of the English language having so little overt morphology. Nouns are not marked for case so the nouns themselves give no disambiguating information as to their thematic role. This must be assigned by the argument structure of the verb. In many other languages some of this responsibility would be shifted to the morphological system. It is just worth keeping this in mind for our later discussions of morphology and Broca's area.

In a 2002 review paper, Edith Kaan and Tamara Swaab carefully review all the literature on Broca's area and syntactic processing (Kaan & Swaab, 2002). They basically take on all three questions: whether a process (namely syntax) is computed only in Broca's, whether whatever Broca's does is language-specific, and where Broca's area is, if it exists. In fact they also take on the stronger and perhaps more obviously straw-man claim that the only thing Broca's does is syntax.

The standard physical location of Broca's area is not precisely defined but its core is generally agreed to be in Brodmann's area 44 and usually 45: respectively the *pars opercularis* and *par triangularis* of the inferior frontal gyrus.

Kaan and Swaab come down against the privileged status of Broca's area in all accounts. First of all they dispense with the idea that the only thing Broca's area computes is syntax:

> "Are these areas uniquely activated for syntactic processing? The answer is no. Each of these areas has been shown to be activated for tasks involving lists of syntactically unconnected words and, in some cases even for tasks using non-linguistic materials. Broca's area (BA 44/45) is involved in a wide variety of tasks using lists of words or syllables, including semantic tasks, phonological tasks, and memory tasks, and is also active during music perception."

It is probably not a widely-held notion that Broca's would only compute syntax, given that there are a few hundred million neurons in question, the region is on the border of a standard motor area, Language is evolutionarily recent (thus needing to rely heavily on previous underlying skills), and other reasons.

They furthermore give a negative answer to the first question, namely that syntax is not computed solely in Broca's:

> "Broca's area is also not the only area involved in syntax: other areas include the anterior temporal lobe (BA 38, and anterior parts of BA 21 and 22) and the middle and posterior parts of the superior and middle temporal gyri (BA 22,21). Interestingly, activations are not restricted to the left hemisphere."

Finally, they further conclude against the second question above, namely saying that whatever Broca's area is doing it is not specific to language. They point the finger strongly at working-memory demands:

> "Broca's area is only systematically activated when processing demands increase due to working memory demands or task requirements."

They also seem to implicate what can be described as the storage and integration costs in sentence processing (Gibson, 1998) or the demands of processing moved elements in a sentence (Grodzinsky, 1986a, 2000):

> "Broca's area might be involved in storing non-integrated material when processing load increases."

Many of the issues Kaan and Swaab point to in the literature stem from the complexity of full-sentence syntactic tasks, and other factors necessarily confounded in the studies. For instance, one of their main suggestions is that modulation of Broca's area by many syntactic tasks has to do with tightly correlated but incidental varying of the working memory load. For instance, comparing

the syntactic features of a sentence with 4 nested clauses to one with none or with 4 clauses that are not nested drastically changes the demands on memory. Therefore they do not rule out that Broca's area could be fairly uninterestingly a center for working memory and not a specialized syntax area.

It should be noted that our model system of morphosyntactic processing does not in general involve the sort of working memory that goes into full sentences production or comprehension. Furthermore, it removes that working memory component that may be a real confound, while retaining much of the types of operations that are the hallmarks of syntactic manipulations. Namely, morphosyntax requires combination of elements that have meaning into larger forms that have meaning related to but often different from the sum of component meanings. These operations require rules for proper combination, and must draw on memory stores of the words and endings. The relationships between words, such as number, person, and gender agreement, thematic role, etc. are clued by morphosyntactic markings.

Our study sought to find the neural underpinnings of morphosyntactic processing, and specifically to see if morphological processing alone could activate Broca's Area.

4.5 Noun-Verb Dissociations

Do we use fundamentally different regions or neural assemblies in the brain for words of different grammatical categories, such as Nouns and Verbs? What is the nature of category representations? What do we mean in any case – storage of nouns/verbs, retrieval, morphological processing of them?

Neuroimaging studies have claimed neural differences for grammatical categories for some time. One early study in this domain (Goodglass, 1966) showed that Broca's aphasics were more impaired at naming actions and fluent aphasics (Wernicke's) were more impaired at naming objects. This was early evidence that frontal areas such as the Inferior Frontal Gyrus might be involved in verbs, and posterior areas more involved in representing nouns.

However this work also began two trends that have run through the reports in this domain until today. The first is the ambiguity as to whether the neural differences have to do with the actual abstract grammatical category of the words investigated, or rather perhaps the semantics of these words. That is, is it the meanings of the words or the grammatical facts of how they are used that leads to whatever neural dissociation is observed? The second is a confounding of what aspect

of words or word processing and production is actually addressed: is it storage, access, morphological processing, or other facets that is assumed to separate by grammatical category, or semantics? Could they vary independently? This is to say, is it the mental dictionary (the "lexicon") that is spread over the cortex with some sort of geographical specialization, and/or is the neural processing related to actually using these words in sentences somehow geographically separated?

The idea that features of the individual words determine the brain region activated is championed for instance by Friedmann Pülvermüller and colleagues (Pulvermuller, Mohr, & Schleichert, 1999). They used ERPs to investigate whether the specificity of brain response to groups of words had to do purely with their grammatical category, or with semantic features intrinsic to the particular words.

For instance, could a dissociation between verbs like "run" and nouns like "apple" be related to the fact that "run" names and activates motor representations related to running, while "apple" activates many more visual representations? This would account for neural separation data without invoking grammatical categories as such. The question then might be how would more visuable verbs like "to paint" assort relative to more abstract nouns such as "fate" or nouns with more action-oriented semantics such as "hammer". Pulvermüller and colleagues (Pulvermuller et al., 1999) showed that the response for action-semantic nouns patterned with that for action-related verbs, and not with visual nouns.

Luzzatti, *et a.l*, (Luzzatti et al., 2002) showed both semantic and syntactic-category effects, in a large population of aphasiological case studies. Selective impairment of verbs was more frequent, at 34%, than nouns, at 10% (n=58). The selective impairment, however, was removed in 80% of cases when the factors of word frequency and imageability were factored out of the data. Nonetheless in the 20% the category effects remained. These results suggested category as well as semantic effects in different cases.

Alfonso Caramazza and colleagues have reported patient case studies that form a double dissociation between nouns and verbs categorically. These patients are tested on their ability to name and produce nouns and verbs. One patient, SJD, was selectively impaired at producing verbs relative to nouns (Caramazza & Hillis, 1991). Further control was imposed by having the subject produce the same word as either noun or verbs, for instance "he judges..." versus "the judges..." which had the effect of equalizing semantics. However the semantics of stimuli chosen could still

bias the results. To eliminate this concern, they also used pseudo-words: word-like items that are phonologically valid but non-existent. For instance the patient would be asked to produce "he *wugs..." versus "the *wugs..." and was selectively impaired on the verb tasks. The idea was to remove the dimension of semantics entirely (with its accompanying motor or visuability parameters) by using stimuli devoid of semantics.

There is still a potential confound here, which can be understood upon inspecting non-sense words such as those in Lewis Carroll's famous collection of pseudo-words "Jabberwocky". *All mimsy were the borogroves* states the 'poem' famously, and goes on to conjure in most readers a strong sense that a story is being told, even if the specifics are not accessible. It is possible that the framing 'meaning' comes purely from the syntactic structure such as word order and placement of function words. However it is also possible that hints of semantics linger in the phonology, perhaps by analogy to known words. This idea gains some credulity, also, when considering the common and fairly widely accepted perception of "onomatopoeia" – the sense that a word (such as "zap" or "gurgle") actually "sounds like" what it means. This again suggests that phonology can somehow encode primitive meanings, even if for the most part it does not. The concept is not entirely ludicrous if some words evolved as descriptions not purely arbitrary labels for their respective meanings. This is a subtle confound, but still may erode the ability to take the strong stance that their manipulations are devoid of semantics.

Furthermore, their study relies on a feature that is particularly notable in English – namely that many words can be used as both nouns and verbs. In fact the ratio of noun-usage to verb-usage of each English word is an important lurking variable. Below is a simple plot of numbers of words falling into each bin from most often used as Noun (e.g. surface, table, and side) to most often used at verb (e.g. find, say, and buy). Similarly, plotting V-N ratio against raw frequency score for either category shows no interaction but some local trends, indicating that this important factor is likely to be stochastically distributed through any data set that does not control for it explicitly. (Data from (Francis, 1982).)

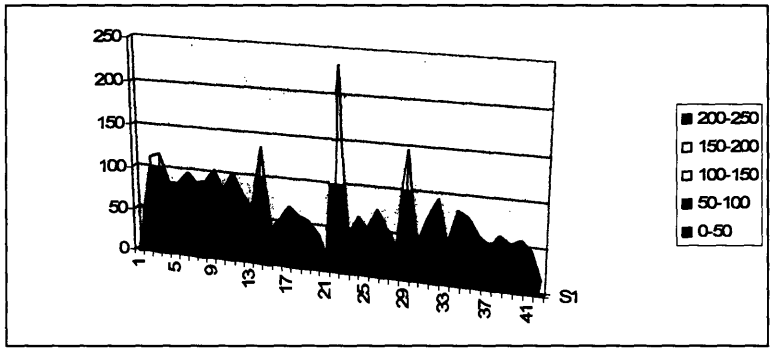


Figure 2: V-N Class ambiguity distribution as function of raw token frequency.

Moreover, this distinction seems to have much less random consequences behaviorally. Federmeier and colleagues (Federmeier, Segal, Lombrozo, & Kutas, 2000) used ERPs to show that there were interactions with ERP components for lexical access for both the likelihood a given word is used as given grammatical class, and for whether it is used thus at the time. The noun-verb distinction was least clear amongst words that are class-ambiguous or can be used as both. While the English language contains many words that purely or nearly purely a single grammatical category, the Caramazza studies by nature use only ambiguous words.

In any case, notwithstanding these caveats, the Caramazza studies do show functional dissociations across grammatical category boundaries. These distinctions were robust in their patients. They use their data to further the older claim that there is distinction based on grammatical category itself. This they position in opposition to what they call the "Sensorimotor Account" of distinctions based on their intrinsic sensorimotor semantic associations.

Patients with lesions, however, often have fairly large lesions with fairly large resulting deficits. Furthermore, cognitive abilities, especially those in higher, more widely distributed, and more plastic brain regions, may reorganize following brain injury. The Caramazza group extended their studies, led by Kevin Shapiro, into a methodology called Transcranial Magnetic Stimulation (TMS). TMS involves pulsing a small area of the cortex with a strong magnetic field, via a coil placed outside the skull. This field in turn induces currents in the underlying neurons. If the pulses are given in bursts of frequent repetition, the net effect is a temporary lesion of the neural function. Shapiro and Caramazza (Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza, 2001) applied rTMS to a PFC area slightly anterior and superior to Broca's area. Using this paradigm they replicated in normals a selective deficit on natural verbs versus nouns, as well as on verb versus noun usages of pseudo-words.

Finally, direct functional imaging data for Noun-Verb neural dissociation have been shown, such as in a PET study by Perani, *et al.* (Perani et al., 1999). While they found an interaction with their semantic variable, concreteness, after partialling this out they still found a set of left-hemisphere regions selectively more responsive to verb versus noun reading in a lexical decision task. These included an anterior temporal area, a dorsolateral PFC area, an inferior PFC area, and some minor parietal activation. As with other studies, there was no noun-selective activation found. These results motivate my own imaging investigation of Noun-Verb dissociations, and as we will see converge well with one contrast that was run.

All of these studies employ tasks that may focus the subjects on the low-level and semantic features of the word stimuli employed. These tasks, such as lexical access, word naming, and word reading, require processing of the meanings of the words, and perhaps attention to low-level features. Morphological processing would be minimal because in most cases only one (default) morphological form is expected in all the responses, and in English this form is not overtly marked. With the attention drawn away from morphology (no task manipulation) and drawn to semantics (necessary for many of the tasks), the amount of activation the morphological system should receive is minimal, and crucially would not vary among task conditions. These studies simply did not focus directly on morphology, and because of the factors above even trying to pull out the morphological component at meta-analysis is difficult. The fact that they did focus if anything on semantics makes the various results implicating semantic groupings among the stimuli in a large proportion of the observed variance a little less surprising, and quite a bit harder to interpret in setting hypotheses for the current study.

The present study aimed to vary and investigate morphological processing specifically. My focus is not on differential *storage* locations for words in the brain. This research focuses on the morphological processing of the words, specifically inflectional morphology. If nouns are stored in one place and verbs in another, the question here is whether nouns are inflected in the noun area and verbs inflected in the verb area; or if words of both categories are inflected in the same area, for instance a central location separate from either noun or verb storage areas. Note that storage and access need to be disambiguated, and discussions in the relevant chapter will show that only access is likely to be empirically testable with imaging methods in adults. Also of note is that regardless of what is found in terms of geographic segregation or overlap in the fMRI signal, there

are many assumptions involved in inducing that the organization of information follows the same pattern.

While storage and access of lexical items seem likely to be distributed across large areas of the cortex, it is possible that the extra areas for morphosyntactic processing could be more focal and task-related. We sought to find this out, as well as whether there are multiple sites or one for the computation of inflectional morphology.

4.6 fMRI Research

fMRI is becoming fairly commonplace, at least in leading research environments, but it is worth noting how miraculous it really is to be able to look into people's brains/minds and read their thoughts. The task here does not even involve overt speech but only thinking to oneself the correct word. For instance, with fMRI we are able to read the subtle differences, within every little piece of the brain, between what it takes to think of "dogs" and a few other plural words and what it takes to think of "dog" and the respective singulars!

fMRI caps a history of methods for investigating the brain basis of cognition that includes studies of cognitive deficits that correlated with brain damage. fMRI has a great many advantages since it can image a reflection of actual activity in normal undamaged living brains.

Yet it is also important to note that while fMRI is a brain imaging technology, it images changes in blood oxygenation level. It does not image, for instance, neuronal electrical activity nor chemical nor transcriptional changes. It relies on a loose, time-lagged and ill-understood coupling between the blood effects and nearby neuronal activity. For this reason, fMRI in comparison to Electrophysiology may be affectionately termed "The Ghost of Brain Blood Past."

4.7 Electrophysiology

After completing the fMRI project, an exciting opportunity presented itself that was irresistible: recording electrically from a living human brain during the identical task performed for fMRI!

A patient about to undergo surgery to resect the portions of her brain causing her epilepsy was clinically implanted with depth electrodes, according to normal procedure for localization of intractable seizure focus.

I was able to scan her in fMRI before the implantation, as she completed the identical task that the group of 18 normals carried out. Then, about 1.5 weeks following the implantation, she performed the same task again for an hour, with electrodes containing 32 good contacts passing right through classic language areas of her left perisylvian cortex. The patient also had a 64-channel grid of surface electrodes implanted over the perisylvian cortical surface. Finally, inserted through the depth macroelectrodes were microscopic "laminar" electrodes. Each of four had 24 contacts each – spaced at 150-micrometer intervals.

The opportunity to record directly was impossible to turn down. While more patients and more careful analyses of these data stand to be extremely fruitful, the current data confirm and extend the fMRI results!

Since this work combines fMRI with direct electrical measures of activity deep within the living, behaving, human brain it is possible to gain greater information about the neural nature of task-related processing and also uncover more about the coupling of fMRI and electrical activity.

4.8 Research Questions Review

The current study simultaneously varied grammatical class and regularity. This allowed for individual questions about N-V dissociations and regularity effects on inflection, as well as comparisons of any regularity effects across classes. Furthermore, inflectional morphology was simultaneously manipulated. This allowed us to investigate the neural signature of inflectional processing, and also to compare this across nouns and verbs to see if they were processed similarly as well as comparing regularity effects to see affects based on how much of that regular or irregular inflection must be accessed. Finally, the inflectional manipulation was in 3 not 2 degrees so effects could be measured with 3 different baselines: the task involving overt inflection (e.g. verb past tense) could be compared against a condition requiring unambiguous selection of the correct but unmarked form (the verb present or noun singular), or against a simple repetition/reading of the word, or ultimately against the passive fixation time between task trials.

The basic questions we were able to ask based on this are listed below..

Can morphology, in isolation of working memory and other domain-general manipulations, activate Broca's area?

What is the neural signature of inflectional morphological processing in Verbs?

What is the neural signature of inflectional morphological processing in Nouns?

How do these two compare?

How do the neural processing correlates of processing in general for Nouns and Verbs compare?

Is storage/retrieval of nouns neurally distinct from that of verbs?

Are nouns processed morphologically by circuits near those for noun storage/retrieval, and verbs processed near verb storage/retrieval, or are both perhaps processed in one central region?

What is nature of irregular versus regular processing for verbs?

What is the nature of irregular versus regular processing for nouns?

How do these compare? Is there a common difference or similarity that binds processing of irregular forms, across grammatical categories?

5 COGNITIVE TASK AND FMRI METHODS

5.1 Chapter Summary

This chapter details the core methodological basis of this thesis. Experiment 1 of the thesis is an fMRI experiment, with 18 subjects, which was designed to and did yield multiple streams of results. Experiment 2 includes two patient case studies in which *in-vivo* electrophysiological methods were employed. The cognitive task paradigm was identical across these studies, and it was developed specifically for the constraints and strengths of fMRI methodologies, in an interactive process. Therefore, the cognitive task paradigm and all the fMRI methods are described here together. This chapter, accordingly, comprises the main methodological explication for this thesis. Individual chapters that report on fMRI findings will point out elements of task design and imaging methods that are particularly relevant to their treatments of the data. Chapter 7 of the thesis will detail the methods for in-vivo electrophysiological recordings.

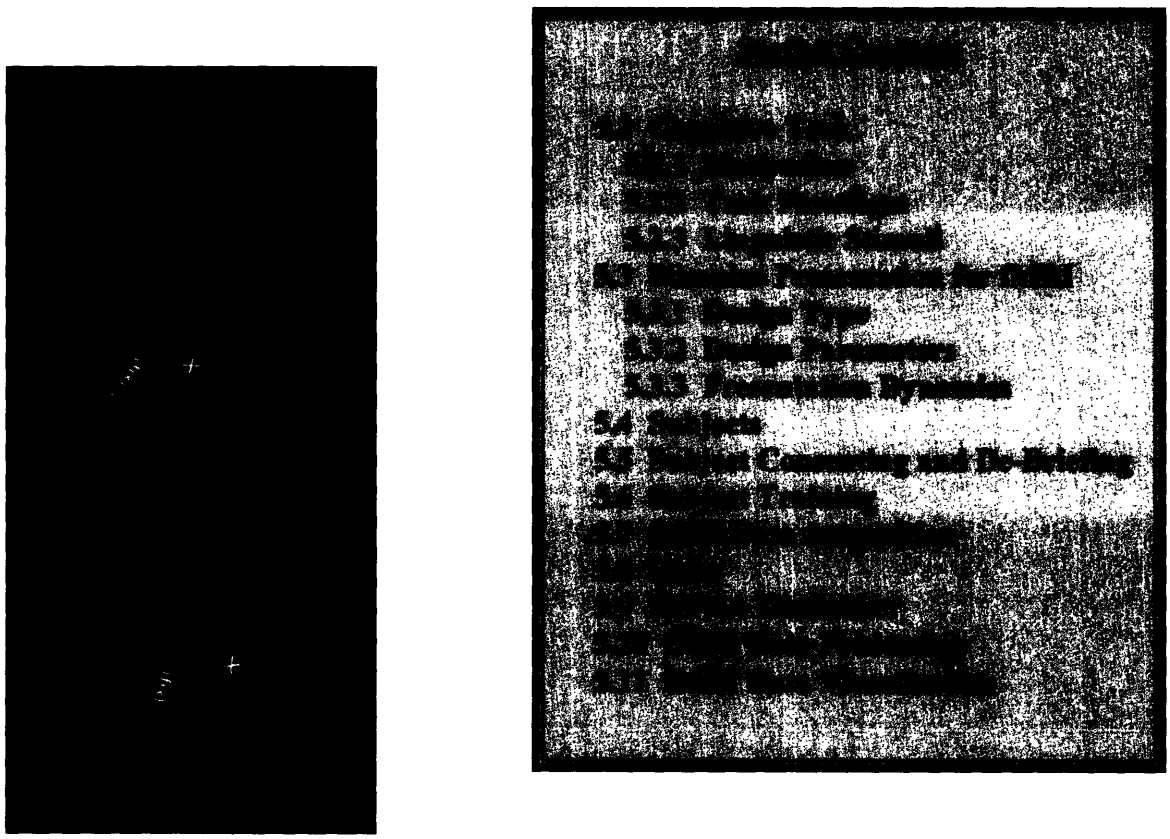


Figure 3: Schematic of one trial of the cognitive task, progressing downward through time.

5.2 Cognitive Task

5.2.1 MOTIVATION

An overall goal of the present research was to survey broadly the neural processing of language morphology, with a single task and in the same set of subjects. This was intended to launch a program of investigations of individual components of morphology while keeping their interdependencies and commonalities in view. The challenge was to design a task as simple as possible that would isolate morphological processing, and simultaneously probe grammatical class differences, regularities of inflection, and a few of the steps involved in producing a grammatically inflected word. A further challenge was to have the morphological inflection cued in a "natural" way – by familiar linguistic context – yet without having to compare complex, differently constructed sentences.

5.2.2 TASK PARADIGM

5.2.2.1 Summary

Subjects saw short incomplete sentence-like "frames" with a blank in the final position. The frames unambiguously dictated both the grammatical class and grammatical inflection necessary to fill in the blank. Next the subjects briefly saw the target words, and the subject's task was to produce covertly (think) the correct form that would go into the blank, and then press a response button. For instance the frame "Yesterday they ____." cued a verb, in the past tense, so if the target was "walk" the subject would think "walked" then press a button to signal completion, and if the target was "eat" the correct response was "ate."

5.2.2.2 Factorial Design

The study task had a 2x2x3 factorial design, with independent variables of Grammatical Class (2 levels: Noun, Verb), Inflectional Regularity (2 levels: Regular, Irregular) and Inflectional Task (3 levels: Overt-Inflect, Zero-Inflect, and Read). Table 1 below summarizes the design, including features to be discussed in further sections.

	Verb Trials	Noun Trials	Time	Subject Task
Overt-Inflect	Yesterday they ___.	Those are the ___.	650ms	read, extract task
	+	+	1100ms	fix
	to lead	a house	250ms	read, extract target word
	+	+	1500ms	covert prod, button press
Zero-Inflect	Every day they ___.	That is the ___.	650ms	read, extract task
	+	+	1100ms	fix
	to walk	a man	250ms	read, extract target word
	+	+	1500ms	covert prod, button press
Read	repeat word: ___	repeat word: ___	650ms	read, extract task
	+	+	1100ms	fix
	to refuse	an elf	250ms	read, extract target word
	+	+	1500ms	covert prod, button press
NULL	+	+	3500ms	Fixation (NULL)

Table 1: Summary of task factorial design.
Shows the frames used to cue each of the 3 inflectional tasks (Overt-Inflect, Zero-Inflect, Read) across each of the two grammatical categories (Nouns and Verbs). Timings for each part of the trials are also given, along with a brief categorization of the subject's task at each epoch.

The Inflectional Task factor determined in what form the subject was supposed to produce the target word. In the *Read* condition subject would simply read back the word presented, ostensibly with no grammatical inflection, or no more than the baseline for all produced words. This condition was intended to form our (lowest) cognitive baseline for fMRI subtractions. In the *Overt-Inflect* condition, the subject would produce a form that demanded the addition of an overt inflectional morpheme (it would change the sound of the word). For instance the verb "hone" would be produced in the past tense, adding the "-(e)d" morpheme to yield "honed." For nouns, the cued form was the plural. Since there is only this one available inflectional morphological manipulation for English nouns (excepting possessive), the verb task was also kept to only one tense (past). The *Zero-Inflect* condition capitalized on the impoverishment of English morphology, specifically that many forms show no overt morphology. These are grammatically determined forms, such as a present tense verb or singular noun, but there is no morphological change with respect to what is sometimes called the dictionary form of the word. Our design uses unambiguous context to cue production of present tense verbs or singular-number nouns. The responses for *Read*

condition and *Zero-Inflect* condition are identical in overt form, therefore, but the *Zero-Inflect* responses may involve a "null affix" that marks the morphosyntactic status of the word in context. This is not assumed in the present study, rather is rendered empirically testable by including this "middle" task condition.

The Regularity factor in this factorial design draws on a quirk of English and indeed many languages: that many words are grammatically inflected according to highly stereotyped patterns (walk→walk*ed*, hone→hon*ed*; dog→dog*s*, bone→bone*s*), while some words (usually the most frequently used) take idiosyncratic inflections. Examples of these *irregularly* inflected words include: sing→sang, think→thought, cling→clung, eat→ate, sleep→slept; sheep→sheep, man→men, child→children. This phenomenon is described elsewhere in this document, but here it is noted that our design included equal numbers of trials where subjects had to operate on *Regular* and *Irregular* words. Note that this 1:1 ratio was chosen mostly for design simplicity, however even though there many fewer irregular than regular words (type frequency) their usage numbers (token frequencies) are so high that such a ratio is not out of the normal range for regular speech.

Grammatical Class was manipulated in that all inflectional tasks were carried out for both *Nouns* and *Verbs*.

It is of value to note that while Inflectional Task is clearly a factor of the overt cognitive task, the other two factors are more dimensions of the target word stimuli. Grammatical Class of course interacts with Inflectional Task in that no natural cue frames could unambiguously signal the inflectional task across nouns and verbs. However, for the most part this was a manipulation of the stimuli presented to the subjects. Subjects reported being unaware or only vaguely aware that experiment consisted simply and purely of nouns and verbs as target words. Moreover, the Regularity dimension was completely or nearly transparent for the subjects. Upon debrief, only a few reported noticing this divide, and only after prodding. It is possible that any other divide, such as single vs. multiple syllables or man-made vs. natural objects might have been as salient, though this was not addressed. The net result is that the Regularity manipulation comes "for free" in this design: in that subjects do not need to keep another set of instructions or examples in mind that they learned specially for the task, and the setup of the study does not need to add a true task type

to incorporate this dimension. Rather, the study design allows the subjects to utilize (and thus mentally compute in a "natural" way) the facts of their language they have over-learned over most of their lives. Grammatical Class does necessitate design and instruction additions, in that the frames and instructions are different for nouns and verbs.

It is important to consider which factors are transparent or "collapsible" from the point of view of the subject or from the point of view of the experimental design, especially because this is a complex factorial design. Since it is a 2x2x3 design, there are 12 fundamental conditions. fMRI generally yields a low signal to noise ratio, especially for cognitive experiments (as opposed to motor or low-level visual experiments). In many fMRI comparisons, or contrasts, it is desirable to collapse across conditions to ask superordinate questions (e.g. the global differences between noun and verb processing, or regular and irregular) before drilling down and asking subordinate questions (such as whether the production of verbs, in the past tense, when the inflection is irregular differs from the production of regular past-tense verbs). The appropriateness of collapsing along a given dimension relates to how overt or transparent that dimension is, and for instance if there is a strong attentional or cognitive load gradient. Furthermore, in fashioning this design, care was taken to assure that from the subject's point of view the task would seem as simple as possible. The transparency of the manipulations is an indication of this, and the use of already-learned linguistic cues in the frames was an important part of keeping the study manageable.

5.2.2.3 Frames

The frames presented in the first part of each trial cued the grammatical class and inflection required for the correct response in the second part of the trial. Frames for a given condition did not vary across the experiment – subjects were cued in the identical way for each trial of a given type. All frames can be seen in Table 1 above.

The frames provided a natural context to prescribe morphological processing of the target words – preferable over, for instance, a paired-associate task where prompts would have to be learned, such as "blue-square means past tense and orange-circle means present." On the other hand, these frames formed highly reduced phrases without the complexity of most sentences and indeed without any variance across examples within a condition. This was intended to allow any

neural differences between conditions to be interpreted largely in terms of the morphological processing of the target word.

The *Read* condition was identically cued, across grammatical class, with the frame "repeat word: ___". This zero-variance cueing meant that even very subtle differences between nouns and verbs could be reliably attributed the stimulus differences. Also, since one of the primary reasons for this condition was to allow replication of noun-verb differences, it was useful that the absence of demand on morphological processing meant this condition could draw relatively more on the semantics of the words. More precisely, subtractions within this condition (*Verb-Read* minus *Noun-Read*) should be more related to semantic differences than subtractions between this and other conditions (e.g. *Verb-Overt-Inflect* minus *Verb-Read*). Most existing noun-verb studies use tasks that focus on semantics, as discussed in a later chapter.

The noun frames (Those are the ___. / That is the ___.) varied only in the number of the pronoun and the linking verb, and they cued a difference in number of the noun. Therefore the total unit of the frame and target could be seen as tightly focusing on number assignment.

Likewise, verb frames (Yesterday they ___. / Every day they ___.) differed only in the time information in the adverb, and phonologically only on the first two syllables.

Across all frames, the first word in the frame was the disambiguating word, so the subject could know right away what task to perform, and the most salient part of the frame was furthest upstream from processing of the target. This first word was diagnostic not just within category but across all conditions. The disambiguating words were of the same type within pairs of overt-inflect and zero-inflect frames (time adverbs for verbs, number-marked pronouns for nouns). Complementarily, the words immediately preceding the blank were identical within grammatical category ("the" for nouns and "they" for verbs), and were phonologically similar all around.

Within each grammatical class therefore (or indeed collapsed across them), the comparison of *Zero-Inflect* to *Read* held the phonological output identical while adding context that determined the morphological status and features of the word. Comparison of *Overt-Inflect* to *Zero-Inflect* kept

the context frames and task very nearly constant, but changed which features we required of the output form and added overt phonological change. Comparison of *Overt-Inflect* to *Read* varied features, phonology, and task context all at once.

The chosen frames were neutral in meaning – empty shells of canonical syntax into which any respective noun or verb token could fit regardless of its semantics. It was important that the frames accommodate target words equally, so effects of the frame would not be confused with effects of the stimulus words. This would be especially important in applying this task to ERP or depth electrophysiological measures. If the frames were skewed toward expecting, say, more visuable nouns (e.g. frames such as "John saw one ___." / "John saw three ___.") then words that violated the expectation would show the strong electrical components characteristic of general anomaly (N400), semantic violation (N400), and maybe syntactic violation/re-analysis (P600). These components, or their fMRI equivalent, might drown out the more interesting signals due to the variables under study. At the least, this would make it difficult to address the question of whether observed noun-verb differences are due to grammatical category *per se* rather than semantics.

All frames were presented as digital image files, not actual screen font text, so that the image files could be proportionately scaled to take up the identical space on screen. Within each grammatical class, the frames had the identical number and distribution of syllables.

It should be noted that there was some ambiguity in the frame "Every day they ___." because it could accommodate both present (imperfective) constructions as well as past tense. Future studies will use "Today they ___." but for the present work, subjects were explicitly trained to use exclusively the present tense for these trials, and they demonstrated very quick learning.

Also note that what is referred to here as the *Read* condition is cued by the word "repeat." In future experiments the frame will be "read word: ____" and for the purposes of this document the condition will be referred to as *Read*. "Repeat" can be confusing to other researchers because there many studies that vary words that have been previously presented in the study ("repeats") versus ones that have not ("novel"). Furthermore, the word "repeat" consistently confused subjects

for the first trial or two of practice – they thought they were supposed to repeat whatever word they had produced for the previous trial. This was corrected with training but any extra source of inhibiting one action over another should be eliminated from the signal, ideally, so in the future this will be changed. Finally, "read" is more true to the current task: translating a visually presented word into a spoken (or covert pre-spoken) output form. "Repeat" would be a more applicable condition name if the target words were presented in spoken form.

5.2.2.4 Word Targets

In the second part of each trial, the target word was shown briefly on screen, then replaced by a fixation point. As soon as the target word appeared the subject would prepare and produce the correctly inflected form, covertly. **Table 1** above gives examples of the targets and the way and timing in which they were presented, for the 3 inflectional tasks crossed with the two grammatical classes. **Table 2** below lists of each of the 12 conditions, with examples of the correct forms the subjects would produce.

Condition	Code	Example		Condition	Code	Example
Verb-Reg-OvertInflect	VRO	*faded*		Noun-Reg-OvertInflect	NRO	*forts*
Verb-Irreg-OvertInflect	VIO	*fought*		Noun-Irreg-OvertInflect	NIO	*feet*
Verb-Reg-ZeroInflect	VRZ	*fade*		Noun-Reg-ZeroInflect	NRZ	*fort*
Verb-Irreg-ZeroInflect	VIZ	*fight*		Noun-Irreg-ZeroInflect	NIZ	*foot*
Verb-Reg-Read	VRR	*fade*		Noun-Reg-Read	NRR	*fort*
Verb-Irreg-Read	VIR	*fight*		Noun-Irreg-Read	NIR	*foot*
NULL	FIX	+				

Table 2: The 12 condition types, their 3-letter codes, and examples of each

Table 1 also shows that word targets were presented not alone but in a minimal phrase that included a "particle." The noun particle was the determiner "a/an", and the verb particle was "to." The primary reasons for presenting the words in this way were to signify that the targets were in a raw "dictionary" form, and to equalize the task demands and strategies across conditions.

English lacks an enclitic morpheme to signify the infinitive form, and furthermore it shows no overt morpheme for most grammatical forms. Therefore, it is often impossible to show with a single word form what inflectional status it has, or even if it has any determinate inflection at all. Specifically here, a single word presented without an affix would be inflectionally ambiguous.

Since one objective of this study was to probe for neural computation related to a zero affix, it is important to make it clear that the presented form lacks at least that particular zero affix. Ideally we want the target word to be in as close to a "base" or "raw" form, lacking all inflectional morphology, as possible. This was one reason for presenting the word with the particle. There was, however, no suitable match for the "to" within nouns in that "a/an" would likely require the same zero affix, if any, as would the *Zero-Inflect* task condition.

The second reason for the particle was an attempt to equalize task difficulty and strategy over conditions. If only the target word itself were presented, say "dog," then the strategy for 2/3 of the trials could be simply to repeat the word or simply to tack it on to the frame: subject sees the frame, such as "That is the___." (*Zero-Inflect*) and then sees the word, and simply adds the word right into the open sentence fragment and sends it to the output speech stream. However, if in these cases the word is simply shunted to the output, then in the Overt-Inflect condition where the word does not fit ("Those are the___." ... "dog*") this strategy will fail. This could cause an anomaly signal for the grammatical mismatch on these trials. Similar situations are known to cause either a "P600" or a "mismatch negativity" component in the Event-Related evoked Potentials (ERP) electrophysiological signal, the correlates of which are often strong but not fully characterized in fMRI. This would be a large confound in the *Overt-Inflect* minus *Zero-Inflect* subtraction. Also, the *Overt-Inflect* task may be that much harder because of the necessity to override a pattern that is both simple and most common in the task items. Resulting signal differences could therefore stem less from processing specific to linguistic operations and more from generalized cognitive set and task switching costs.

Having the particle universally bound to the presented target words meant that the simple concatenation strategy was blocked universally for all conditions. For instance, the subject could not grammatically say "Yesterday they ... to walk" nor "That is the ... a dog." Note that this second example also shows why the noun particle could not be "the" (because the two "the"s might more easily be combined in a concatenation strategy), and so it was necessary to use "a/an" even notwithstanding its inconsistency across words beginning with vowels versus consonants. Since the simple concatenation was blocked, the universally presented particle had to be stripped from the phrase or ignored in order to proceed with the task. This putative particle-stripping

operation was intended to help equalize task difficulty somewhat across all tasks, and provide a common level of processing of the target in order to make the contrasts more interpretable. That is to say, the subjects in all cases had to make an effort to extract the stem of the target word, and then build the correct output form by determining, assigning, binding, and producing any required inflectional morpheme. Thus the conditions should be somewhat more parallel and equivalently composed than for instance a situation in which the subjects never had to perform grammatical work on the target stimuli. There is the possible confound, however, that some of the activity assumed to be related to the grammatical processing of inflectional morphemes could stem simply from particle stripping. Future experiments will compare the task without any particles.

5.2.2.5 Timing

Each trial lasted 3.5 seconds, and was broken down into 2 parts, 1.75 seconds each. In the first part of the trial, the frame was presented for 650ms and replaced by a fixation cross in the center of the screen for 1100ms. In the second part of the trial, the target word was presented for 250ms then replaced by fixation for 1500ms. These timings can be seen in Table 1 above and are illustrated below in Figure 4. The inter-trial interval (ITI) was variable because there were variable amounts of fixation time inserted between trials. This was necessary for the purposes of fMRI data analysis, as explained below in the description of Design Parameters.

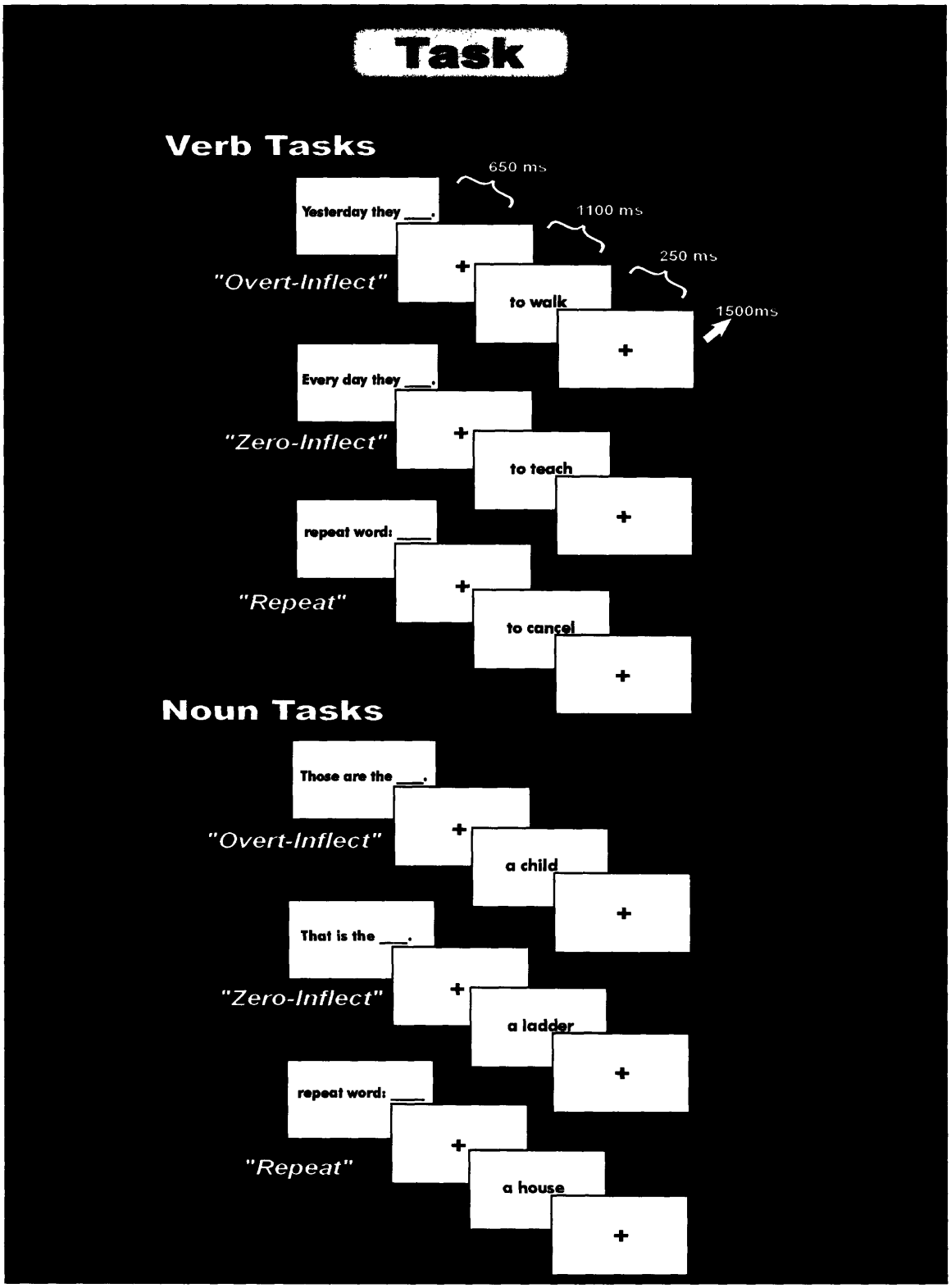


Figure 4: Depiction of cognitive task, based on what subject sees on screen.
Includes timings, condition names, and examples for all conditions. Each white rectangle depicts what is seen on the stimulus presentation screen at a given time, and the overlapping rectangles each depict the progress of a given trial type over time

5.2.2.6 Covert Production

This study was concerned with Production, the active *expressing* of words and phrases, as opposed to pure comprehension. This distinction may be more blurry when we look closely, for at instance at subvocalizing during reading or reanalysis during speech, and indeed in normal speech the two must proceed in synchrony and in parallel. However, in the laboratory, every object of study must be pulled apart and pulled apart until only chunks deemed manageable remain. Under such conditions the blessing and the curse is that one often can isolate these chunks from their natural interdependencies and context. The overall direction of this and related research is to uncover how Human Language is able to construct infinite combinatorial complexity of meaning, in real time. Therefore, while different models of Production will say different things, it is likely that by forcing subjects to generate the forward combinatoric solution for an inflected word, as in this experiment, we will more clearly emphasize the processing necessary to create full sentences on the fly.

However, studying Production in fMRI poses several difficulties. Whereas a behavioral outcome measure from a comprehension or other non-production language experiment would likely be a button-press to signify some choice, discrimination, or judgment, the behavioral outcome measure for production is audible speech. Button-presses are probably the easiest thing to measure in an fMRI setup, aside from the fMRI signal itself, but speech is very difficult. The switching of high-power gradient coils in fMRI makes it so noisy that exposure without ear plugs would quickly cause hearing loss. This is clearly not a favorable environment for recording speech. Noise filtering is rapidly progressing, and magnet-compatible microphones are getting better. However for this experiment no such technology was used. Therefore the first limitation for our Production fMRI experiment was the lack of the preferred behavioral data to analyze along with and correlate with the imaging data. Simple latency to button press was all that was collected, and it is not possible to know with certainty when subjects pressed the button in relation to when they finished the mental utterance, nor how consistent they were (there was a tendency to jump ahead and press the button as soon as the target word appeared, for some subjects some of the time).

The second major difficulty in studying production in fMRI is that speaking causes motion and motion blurs the fMRI image. Therefore it is risky in the first place to have subjects speak out loud. MRI is like a magnetic camera, so in the simplest sense if the subject moves and does so faster than the shutter speed the picture will be blurry. Of course it is more complex than this, and the complexities in this case house the most risk for the final data. Simple head movement – translational shifts of the entire rigid mass in the standard three spatial dimensions – can be largely corrected mathematically if it is not too fast or too drastic. However, speech moves the mouth and tongue, non-rigidly and non-linearly, and these in turn move and vary the air-tissue boundaries within the mouth and throat as well as nasal sinuses. Due to a quirk of quantum physics, the MRI signal in tissue near a boundary with air decays more quickly and less predictably. Unfortunately this is largely the same quirk that is responsible for any *f*MRI signal at all, in that the EPI sequences that pick up the blood oxygenation changes (fMRI's BOLD signal) rely on changes in this particular decay rate (the so-called T2*). In speech, the changes in the air zones means that at some points there will be lasting strong signal in the front of the brain (nearest these zones) and at some points the signal will decay almost immediately. In the best case these fluctuations are orthogonal to the task presentation schedule and in any subtraction they cancel out and basically the extreme frontal regions of the brain are just invisible. In the worst case, the fluctuations interact with the condition schedule (for instance if one type of word systematically requires the throat to open longer or wider), so spurious "activations" occur that have nothing due to brain processing. The brain areas that exhibit the greatest "susceptibility artifact" (spurious signal due to susceptibility to effective magnetic field fluctuations due to air-tissue boundaries) are: the frontal pole, orbitofrontal cortex, temporal pole, and somewhat the ventral temporal surface.

To avoid these problems, the compromise task of "covert production" was employed. Subjects were instructed to do everything they would do to speak the word, except say it out loud. They were asked to almost "hear" the word in their heads as they produced it, silently, and try to clear their minds of other things while they did the task. However, they were not to move their lips or tongue. The subjects just basically *thought* the words, and literally the fMRI was reading their thoughts!

There is precedent for covert production in the language fMRI literature. However, it is obvious that the task is not very natural and it is possible that the subjects can lose attention and become distracted during the experiment more easily if they are not speaking aloud. Erica Palmer

and colleagues did an elegant comparison directly of overt to covert speech in fMRI (Palmer et al., 2001). Special movement-correction sequences were used during scanning, and movement effects reduction mathematics was applied afterward in data processing. Preventative measures included the immobilization of the head with a thermo-plastic mask that was custom-molded for each subject.

Palmer and colleagues report that low-level measures of movement artifact showed a tolerable range for the overt condition, and "regions active during overt task performance were similar to those active during covert task performance, with the addition of several regions commonly associated with motor aspects of speech production."

The take-home message for this research from the Palmer study was two-fold. One message was the *overt* production will be worth trying soon, for future experiments. The second message, more important in this case, is that fMRI activation for covert production is very similar to that for overt production. This means that in the mean time, using covert tasks, we are fortified with an extra measure of credibility in interpreting and generalizing from the present results.

Deanna Barch and colleagues (Barch, Braver, Sabb, & Noll, 2000) performed an fMRI study of overt verb generation. Their methodology included an analysis of the types and degree of head motion. They found that changes of pitch were much more pronounced than yaw or roll, and translation in the z direction was more drastic than x or y. This makes sense as the head coil and pillow usually block fairly strongly head motion from side to side and in rolling motion, but tilting one's head up and down is more free and would account for pitch and z (up-down axis in the scanner frame of reference). This is precisely what the Palmer study sought to eliminate with the thermoplastic masks. The Barch paper focused on the Anterior Cingulate Cortex (ACC) and showed that generating a verb or noun for words with weak or diverse associations (e.g. "ball" versus "bell," because many more words are likely to be associate with ball, whereas bell strongly selects "ring") showed greater ACC activation. They interpreted the role being played as one of inhibiting the larger or stronger set of competing choices in favor of the one ultimately produced; and they interpreted the isolated ACC activity as showing its strong role in the inhibition.

It is important to note that while these conclusions are supported by the paper, a possible confound here applies also to the present work – not just because the Barch work is one of the few overt production imaging studies, but because it shows how technological issues that lead to *null* results can strongly shape cognitive models in this neuroimaging era. Neither of these papers dealt

with the air-tissue fluctuations and resulting susceptibility artifacts from speech, only simple rigid translation of the whole brain mass. The Barch study even showed a large amount of z and pitch motion. Air-tissue fluctuations would cause signal loss in extreme lateral prefrontal areas, frontal pole, and the orbitofrontal cortex. Pitch changes in the head would cause the greatest amount of absolute movement at the most anterior and posterior aspects of the brain, while the more central and medial regions along the axis of movement would move the least. Both of these factors could lead to a reduced fMRI signal in extreme frontal cortical regions relative to the Anterior Cingulate. Therefore even if the two regions saw an equal amount of blood oxygenation change, the confound is that the ACC could be more likely to show activation in an fMRI map. Barch and colleagues take a slightly different view than Thompson-Schill, who would place more of the mental work in such a task on "selection" of the correct response rather than inhibition of the others, and would locate much of this activity in more lateral and anterior LIFC (left inferior frontal cortex). It is therefore possible that fMRI scanner artifact could get in the way of testing the relative contributions of frontolateral areas versus dorsomesial areas like the ACC. Signal dropout due to an interaction between the quantum physics of MRI and motion artifacts could tilt the balance in one study toward only finding ACC activity. Thus quirks of MRI physics can influence the formation of cognitive models, via interpretation of fMRI results.

The conclusion here is that we can for now consider this *covert*-production study likely to be able to see much of the neural processing involved in the task of producing a morphologically appropriate noun or verb. It may be possible that a future *overt*-production study will be able to yield a more accurate picture of production in natural speech, but it is important to remember that technical issues should be firmly grasped when trying to interpret and compare any such data.

5.2.3 LINGUISTIC STIMULI

Target words were English nouns and verbs, both regularly and irregularly inflected. For each category there were 60 words, so the total stimulus list included 240 words. Stimuli were balanced pairwise within each grammatical category (for instance regular noun to irregular noun), and a mix of pairwise and listwise across grammatical categories. Balancing was based on word usage frequency values, syllable number, and orthographic length in all cases. Where there were existing ratings for imageability and familiarity for any of the Irregular words, these were weighted as candidates for the final list and if they made it onto the Irregular list, then Regular pairwise

matches were attempted from those Regulars that also had such ratings. The imageability and familiarity ratings were Paivio norms (Paivio, Yuille, & Madigan, 1968) as contained in the MRC linguistic database (Coltheart, 1981). Frequency matching was done based on Francis & Kučera norms (Francis, 1982) as well as frequency numbers from the AP newswire corpus (Church, 1988). Further ratings were obtained from the CELEX database (Baayen, 1995). A subset of the stimuli were also matched on consonant-vowel structure. Transitivity was not taken into consideration for this study, although in future studies it will be, given the nature of the task with a sentence-final blank. Semantic dimensions aside from the subset of imageability ratings were not considered, for instance semantic category membership (tool, living object, motion-related, etc.).

Matching was done within the context of a relational database, using SQL (structured query language) "query" strings. These queries become like little programs that automatically search and match based on potentially complex and contingent rules about acceptable matches. The author designed, wrote, implemented, and debugged this database to be a conglomeration of 4 major existing corpora and to be searchable by stem or inflected form. The author also wrote all of the SQL queries, which would allow anyone to re-create the final database and to re-create the stimulus match lists. Further description of this database is beyond the scope of this document, and the database is copyrighted to the author.

5.3 Stimulus Presentation for fMRI

5.3.1 Design Type

This study was designed based on a rapid, event-related paradigm (Buckner, 1998). Switching among all task condition types in a continuous run, rather than presenting blocks of a single condition type at a time, affords the *event-related* design the ability to pick out the nature of the brain signal for each type of task and avoids strategy and vigilance shifts within repetitive task blocks. The innovation of *rapid* presentation schedules for event-related designs offers the ability to unravel, or de-convolve, individual signals even when they overlap in time and relies on the near-linear summation of the brain's BOLD response. ((Buckner, 1998), reviewed in (Rosen, Buckner, & Dale, 1998))

In a rapid, event-related design, trials of all types are presented in a mixed run, randomly ordered with respect to each other. The key to unlocking the power of the linear-summation phenomenon is that trials are "jittered" in time with respect to other trials of the same type. This results in some number of examples of pairs of trials separated by each of a range of intervals, with no other trials of that type intervening. With examples of multiple offsets or latencies, it is possible to sample at multiple points and compute what the response curve would roughly look like if the trials were actually separated entirely – by the 24 seconds necessary for the brain blood response to an event to return to baseline. The schematic and power of the rapid, event-related design can be seen in Figure 5, reprinted below from (Buckner, 1998).

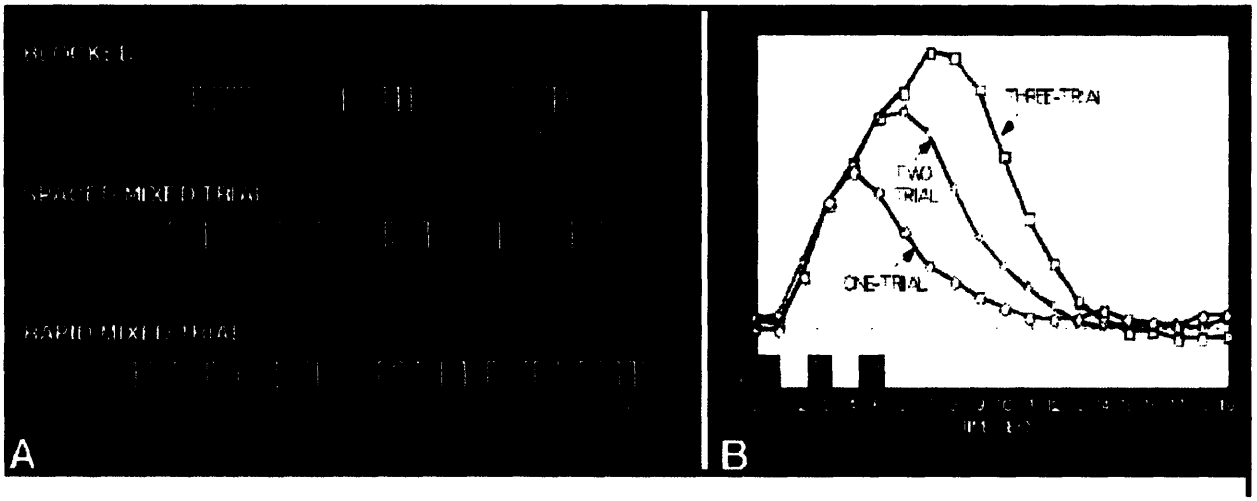


Figure 5: The fundamentals of rapid, event-related design paradigms for fMRI.
This figure reprinted from (Buckner, 1998), p374 (Figure #1 in the paper. Panel C is removed.). Panel A compares the stimulus presentation schedules. In this case there are only 2 condition types, individual trials of each are represented by yellow or red triangles. In the blocked design, blocks are comprised of rapid presentations of only one stimulus type, and the blocks are spaced sufficiently to allow the hemodynamics to return to baseline and for the subject to have a pause and get instructions for the next block. This sequesters trial types from each other so their brain signal is not confused, however there is a major problem of subjects getting tired of a given task or adopting different strategies or attention levels over the block. Also, it is impossible to assess what is often a more natural situation of multiple versions of the task being in context of each other, nor to assess interaction. Finally it is impossible to throw away individual trials on which a subject made an error because the signal is a partial contribution to the steady state signal of much of the block. All these problems are eliminated by going to the spaced, event-related (mixed) design, which allows measurement of the brain hemodynamic signal related to each event or trial (usually averaged over many occurrences of the same type). However, the problem with this design is that the trials must be spaced to allow the hemodynamic response to decay back to baseline – roughly 24 seconds. This makes most cognitive studies practically impossible. The key to getting the best of both worlds is that the hemodynamic responses of temporally overlapping events are essentially additive, as shown in panel B. Using this fact, a randomized schedule with tightly-spaced trials can be given – the "rapid mixed trial" – and the signals can be separated statistically.

5.3.2 DESIGN PARAMETERS

The present study included a large number of condition types (12). Randomization assures that there will be some examples within the presentation sequence where two trials of any given type will be separated by different distances. However, a truly random ordering is not the most efficient for pulling out the most accurate picture of the hemodynamic response function (HRF), because there is no guarantee that all condition types will have the optimal range of offset intervals. With so many condition types it becomes particularly important to have efficient as well as consistent treatments of each, so that between condition differences are not just due to differences in error variance, and because it is less and less likely for the weighted optimal solution to emerge at random.

Efficiency maximization equations have been worked out and parameterized, toward creating the optimum sequence of stimulus presentation (Dale, 1999). This technique attempts to maximize the efficiency for each condition type, and introduces the concept of "NULL" time that is inserted into the sequence both to pad out and space the conditions further and to provide an additional (low) baseline condition for cognitive subtraction analyses. During NULL time the subject performs no task (usually just stares at a fixation point on the stimulus presentation screen), and in practice this just lengthens some of the pauses between task trials – by increments (Temporal Estimate Resolution, or TER) that become the fundamental temporal resolution of the technique.

The optimal amount of NULL time to intersperse throughout the schedule is not known, and is generally set by convention as equivalent to the time needed for one additional condition type (Doug Greve, personal communication). This rule of thumb, however, was derived from studies with fewer condition types than the present. The more conditions, the less NULL time would be recommended by this heuristic, and yet also the more other conditions that need to be optimally separated. This seems unlikely to work outside of the standard 2-4 conditions.

Since the presentation schedule is so important to the entire event-related analysis, and because this study has 12 conditions, the author decided to run a simulation to choose the optimal

amount of NULL time to add to the design. Too little could have the consequence of precluding good estimates of the hemodynamic response for each trial type and raising the noise level in the analysis, and too much would lengthen the total scan time (tiring the subject) or lessen the practical number of trials per condition and thus lower the signal level.

The simulation was run by separately varying two factors: the number of trials per condition, and the total time of all runs (which sets the NULL time as the amount above the time needed to present all stimuli). The parameters were fed into a software module of the MGH FS-FAST suite called "optseq" which computes possible sequences in a brute-force manner and then tests their would-be efficiency based on the equations in (Dale, 1999).

The first part of the simulation sought to examine the gains in efficiency to increased amounts of NULL time randomly interspersed between the trials. First of all the optimal value was not known. Based on recommendations, we should predict that there would not be significant gains after the equivalent amount of time of one additional condition. For our 12-condition study, this would predict (100/13)% time devoted to NULL events, which seems low (7 or 8%). Secondly, the shape of the efficiency function was not known. Would it be linear: continued gains to any increase in NULL time? Would it be geometric? If asymptotic, where would be the asymptote? The simulation was run using a reasonable value for the number of trials per condition (50), and the parameters were fed to *optseq* to general different total percentages of NULL time. The *optseq* was run to produce thousands of simulated stimulus presentation schedules, and test them all for their predicted efficiency as event-related fMRI stimulus presentation schedules. The efficiency measure is a summary of a combination of factors, but basically a description of how well the statistical tests used in the FS-FAST fMRI analysis software could pull apart the average brain response to the various conditions represented here based on these schedule of presentation of each trial. The efficiency of the maximally efficient of all sequences tested is reported in Table 3 below for each NULL percentage.

% NULL	Total TRs	Total time (s)	NULL TRs	Null Time (s)	Max Efficiency
0	400	700.00	0	0.00	**0.0095**
10	445	778.75	45	78.75	**0.1732**
20	500	875.00	100	175.00	**0.2141**
27	550	962.50	150	262.50	**0.2341**

30	570	997.50	170	297.50	**0.2391**
40	667	1167.25	267	467.25	**0.2564**
50	800	1400.00	400	700.00	**0.2683**
60	1000	1750.00	600	1050.00	**0.2772**
70	1333	2332.75	933	1632.75	**0.2840**
80	2000	3500.00	1600	2800.00	**0.2897**
90	4000	7000.00	3600	6300.00	**0.2938**

Table 3: Results of part 1 of simulation to determine parameters for optimum stimulus sequence.
The last column is the maximum efficiency achieved of any sequence tested. The first column in this case shows the manipulated variable – the percentage of the total experiment time that is taken up by NULL (fixation) trials. Since this is a percentage, it is also useful to look at the actual amount of time this implies as devoted to fixation: indicated by the middle columns. The second column is the total number of time units (TR) which in this case are 1.75s each. Most parameters are calculated in units of TR but for transparency the third column is translation of the second, in seconds. The 4th and 5th columns indicate the amount of the total time actually devoted to NULL necessary to yield the percentages in the first column.

The results in Table 3 above show a number of things. First of all, indeed increasing the amount of NULL time always increases sequence efficiency. Also, have no time at all devoted to NULL events gives a drastically lower max efficiency value. Based on these two facts, the recommendation is definitely to have *some* NULL time, and preferably as much as possible. However, the trend in efficiency is not at all linear. In fact, the efficiency returns fall off very quickly after a short while. This is perhaps best seen visually, thus the data were plotted below in Figure 6.

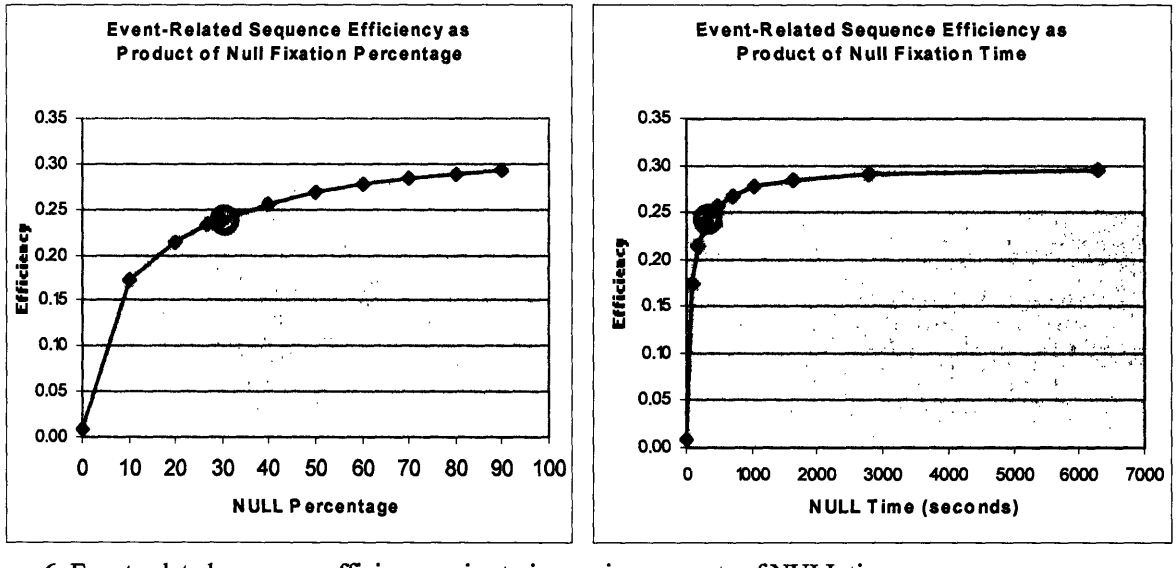


Figure 6: Event-related sequence efficiency gains to increasing amounts of NULL time.
In both plots, the Y axis shows Efficiency, a summary measure of how well the sequence will allow statistically independent event-related analysis of all task conditions. In the first panel, the percentage of the total experimental time that is NULL time or fixation events is plotted. The number of trials per

condition is fixed at 50. It is clear that this is not a linear relationship and that the benefit of increased interspersing of NULL in the sequence drops off quickly and steeply. Since what is plotted in panel A is percentage and since the base amount of live experiment time is fixed, this function does not really show how drastic the drop-off is. The second panel plots actual time, in seconds, that must be added to the base experiment time (700 seconds in this case) to achieve the various percentages. The exponential decay of efficiency gains is even more obvious here. The red circles indicate the NULL amount ultimately chosen.

Based on these results, the author chose to use 27% NULL time. Note that 27% was tested, and not a more 'standardized' number like 25, because it is not the percentage *per se* that is set as a parameter, but rather the number of TRs, and 27% was a middle value that yielded a round value of TRs (550 total), which itself could be decomposed nicely into experimental runs of a reasonable length. Also, a value higher than 27% was not used, even though the efficiency returns were still in the steep part of the function for a little longer, because of course this is not the only factor involved in designing the experiment. Specifically more NULL time means more total time for the experiment and subjects do get tired after a while, and I didn't want to have to drop the number per condition to accommodate.

The next part of the simulation, in fact, was designed specifically for choosing the right N per condition. The number of conditions was set at 12 since that could not change in this study. The 27% value from part 1 was fixed for this part. The simulation was run for candidate designs with 10, 20, 30, 40 50, 60, 70, 80 and 90 trials per condition type. The *optseq* utility was run for each design, and the efficiency results are tabulated below.

n per condition	Maximum Efficiency
10	0.0281
20	0.0803
30	0.1310
40	0.1824
50	0.2336
60	0.2852
70	0.3345
80	0.3866
90	0.4367

Table 4: Results of Part 1 of parametric simulation of sequence optimization efficiency.
The first column shows the number of trials per each of 12 conditions in this design. The second column is the efficiency measurement of the best of all the sequences randomly searched by the program *optseq*. The efficiency measurement units are complex but the reported scalar values can be directly compared to one another.

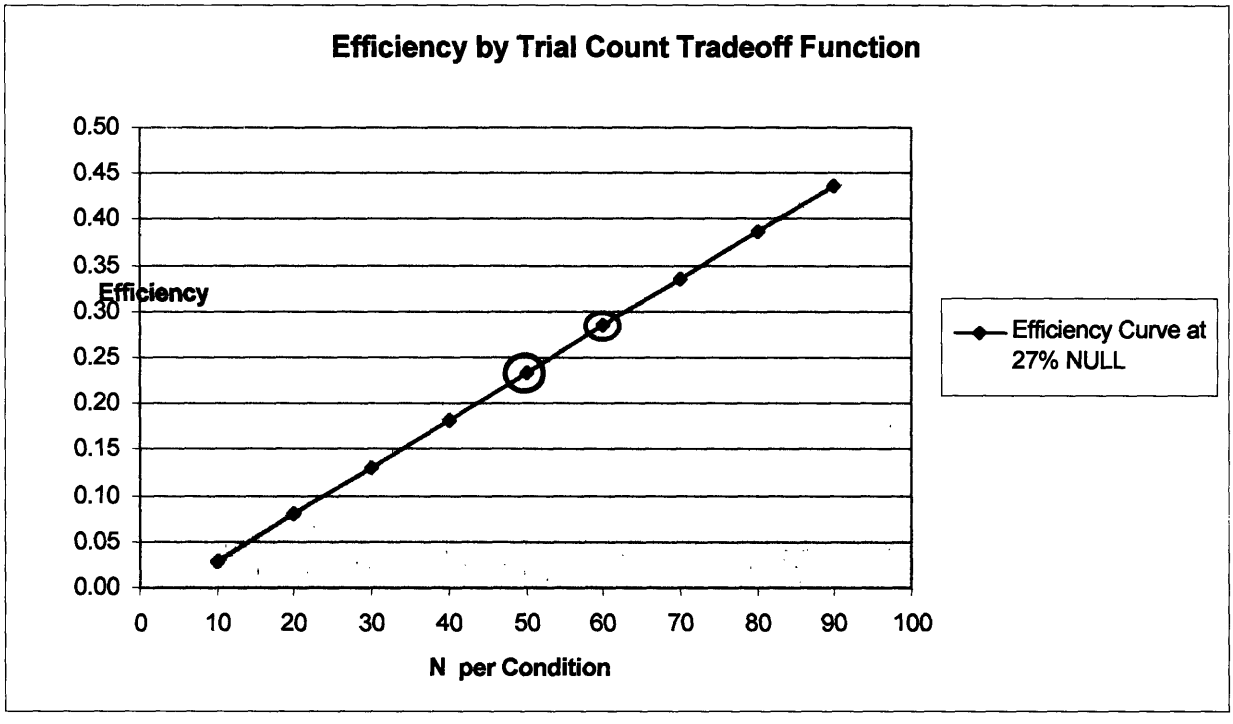


Figure 7: Plot of the data from Table 4

A plot of the efficiency gains as a function of number of trials per condition type. Clearly this is a monotonic linear trend, indicating that the greater the *n* per condition, the better the efficiency. Circled in red is the value (50 per condition) that was used for the first part of the simulation, and thus the equivalent data point to the one circled in each panel of Figure 6. Circled in cyan is the parameter value eventually chosen for the present study. Higher values were precluded by availability of suitable irregular noun stimuli.

Figure 7 shows graphically the tradeoff of efficiency given number of trials per condition. It was indeed expected and hypothesized that increasing the number per condition would have a beneficial effect on efficiency; however it was not obvious to the author that it would be a strictly monotonic linear trend. The alternatives might have been an exponential function showing spectacular gains in efficiency for very high N's, or indeed a function asymptotically reaching a range after which increased numbers negligibly increased efficiency, as in part 1. Upon analysis of this monotonic trend it seems that this may have been obvious by inspection of the equations fundamental to *optseq* but those were not available at the time of this simulation. The take-home message from this part of the simulation was of course to aim to get as many trials per condition as possible. However, the present work was limited by wanting to investigate nouns not just verbs, and to vary the regular-irregular factor throughout. Since there are few irregular nouns, the list of target stimuli and thus the fundamental number per condition was limited. Based on this simulation, part 2, the author chose to use 60 words/trials per condition. The potential efficiency

gains to higher effective N per condition motivated other means of increasing effective *n*, which in this case led to the choice of repeating the entire list.

Once the desired amount of NULL time (27%) and N per condition (60) were determined and the total length was divided into manageable and logical runs (9), the final presentation sequence was computed. The *optseq* utility was run for 54 hours on a dual 1-GHz Pentium III Linux workstation, in which time 695,423 versions of the total sequence were generated and examined. The maximally efficient sequence was used for this study.

Because the design was constrained by the scarce availability of irregular nouns, and especially in light of the computed gains to increased number of trials of each trial type, it was necessary to do something to increase the effective N per condition. Note that since there were three inflectional task conditions (*Overt-Inflect*, *Zero-Inflect*, and *Read*), in a rapid mixed design the word stimuli of any given type (e.g. Regular Verbs, or Irregular Nouns) would have to be apportioned randomly among them. That is to say that our total number of trials per condition for any of the 12 total conditions would be one third of the number of words of each category. Therefore, even though the list of irregularly inflected nouns was pushed to 60, the subject would only see 20 irregular nouns in the *Overt-Inflect* condition, for instance. The chosen way to raise this number was to repeat the entire sequence three times. That is to say, each subject saw any given word on the stimulus list precisely three times. Each repeat through the experiment was analyzed separately and in a pooled analysis – to allow some measure of the repetition priming involved and yet to allow the pooled, increased-power analysis.

5.3.3 PRESENTATION DYNAMICS

All experimental stimuli were presented visually, projected onto a screen mounted on at the rear of the bore of the MRI machine. Subjects saw the screen via a mirror system mounted just above their eyes on the head coil array. When the subjects were aligned on the bed with the sweet spot of the gradient coils and moved into the center of the magnet, they confirmed that they could see the screen through the mirrors.

The LCD projector in the scanner bay was connected via shielded cabling through wave guides in the patch board and around into a relay in the control room. The relay was connected to a desktop computer running the Microsoft Windows 2000 operating system – a shared resource for MGH investigators.

The present experiment was coded using "Presentation" software from Neuro-Behavioral Systems, versions 0.42 to 0.55 (Beta software -- frequently upgraded during the course of this work). The Presentation code was written such that the onset of each trial was triggered by a TTL pulse from the scanner. The TTL pulse was set to issue once every TR during EPI scans, and was sent through a trigger box designed by Robert Savoy at the Roland Institute over the USB bus to the stimulus presentation computer as a keyboard press of the "!" key. Synchronizing the scanner and the stimulus presentation at every trial meant that the two would remain precisely in timing throughout the experiment. Alternative strategies in use at MGH included manually starting the scanner and stimulus presentation computer at the same time, and using a stopwatch to insert a delay between them. In such alternatives, linear drift could occur over the course of the experiment whereby small errors in when the stimuli were actually presented could compound and accumulate. Event-related analysis relies on windowing a continuous set of fMRI data after the fact and assigning various parts to various condition types, purely based on the presentation sequence. Therefore, if even 1 TR's worth of slippage in timing accumulates through the experiment between the scanner computer and the stimulus computer, then the fMRI signal will be attributed to the wrong condition types from then on. This is equivalent to a "frameshift mutation" in DNA. The trial-by-trial synchronization makes it completely impossible for this to occur.

5.4 Subjects

Right-handed volunteers from the MIT and Harvard undergraduate and graduate student bodies gave written consent and participated in this fMRI experiment. All subjects responded yes to questions on a screening form asking if English was their first language and their primary language. In total, 25 subjects were scanned, 13 male and 12 female. The data of 18 of these subjects (mean age 20.56, range 18-25) were fully analyzed and used for all the results presented here: 11 male (mean age 20.09, range 18-23) and 7 female (mean age 21.29, range 19-25).

The data for the other 7 subjects were not used for various reasons: for the first 2 subjects run operator mistakes rendered the data unusable, 1 subject revealed a gross misunderstanding of the task upon post-test debriefing, in 1 case scanner problems necessitated multiple "reboots" of the system which exhausted the allotted scanner time, and in 3 cases technical problems with the head coil array led to inconsistent and unanalyzable data (only later diagnosed as internal fuse failure due to another user's experimental pulse sequences).

Subjects were recruited via an electronic mail list server hosted by MIT's Department of Brain and Cognitive Sciences with announcements describing the experiment, risks, compensation and qualification factors. Subjects were not allowed to participate in this study if they had participated in many (roughly, more than 5) previous fMRI studies, for any lab. This criterion was based on moral views of the author about a culture of experiment participation and risk taking as a source of regular income and about the skewing of scientific results in fields that already accept generalizations from small sample sizes. Aside from the factors relevant to this research (right-handedness, English monolinguality, previous study participation, and scanner-compliant height and weight), subjects were recruited without discrimination as to race, creed, gender, or socioeconomic status. Table 5 below gives a summary of the demographic characteristics of the subjects used for this study.

Subject	Gender	Age at Scan	Weight	Handed	Race (NIH)	Race Specified
NVInfl01_C	M	23	175	R	White	Caucasian
NVInfl01_D	M	19	160	R	Asian	Bengali
NVInfl01_E	M	18	145	R	White	European
NVInfl01_F	M	18	185	R	Asian	Indian
NVInfl01_H	F	21	155	R	White	Caucasian
NVInfl01_I	F	25	124	R	White	Caucasian
NVInfl01_J	M	22	180	R	White	White
NVInfl01_L	M	23	200	R	White	White
NVInfl01_M	M	20	175	R	Hispanic	Black_Hispanic
NVInfl01_Q	F	19	113	R	Asian	Indian
NVInfl01_R	M	19	170	R	White	Caucasian
NVInfl01_S	M	23	170	R	Black	Black
NVInfl01_T	M	18	165	R	White	Caucasian
NVInfl01_U	F	21	135	R	Other	Asian_Caucasian
NVInfl01_V	M	18	179	R	White	White
NVInfl01_W	F	19	124	R	Black	Black

NVInfl01_X	F	21	120	R	Black	Black
NVInfl01_Y	F	23	160	R	White	White

Table 5: Summary of demographics of subjects whose data are reported in this thesis.
The first column contains the subject code. Gender is reported as Male or Female. The age reported is the numerical age of the subject at the time of that subject's scan (scans were spread out over several months). Weight is reported in pounds, according to self-report on a written form. Handedness is also according to self-report. The two columns for race are related to fact that the NIH recognizes a regimented and somewhat non-intuitive standardization of race and ethnicity. The official categories as would be reported to the NIH are in the second to last column, and the values subjects actually entered on the forms are in the second column. In the case of subject M, these values represent a reported race of Black, and reported ethnicity of Hispanic.

Subjects were compensated for their time and travel expenses, regardless of whether their data were eventually used for analysis. Subjects' raw and processed data were at all times kept separate from their personally identifying information, and identified only by codes which were in turn listed only in a special file kept safe and secure.

All subjects were recruited, consented, trained, scanned and de-briefed by the author.

5.5 Subject Consenting and De-Briefing

All subjects gave informed, written consent to participate in this study.

Before arriving at the fMRI scanning facility, subjects had all completed basic pre-screening forms for fMRI or had notified the experimenter they had previously participated without problems in an fMRI experiment. Upon arrival, all subjects gave written, informed consent to participate in the study.

First, they signed a medical device release form for MRI supplied by the Massachusetts General Hospital, covering for instance any medical conditions or surgical implants that might be contraindications. Next they were explained and had the opportunity to read and sign a consent form approved by the Massachusetts Institute of Technology's Committee on the Use of Humans as Experimental Subjects. This form was approved as part of a proposal (COUHES 2898) listing Dr. Steven Pinker as Principal Investigator and the author as the site investigator. Subjects also reviewed and signed a consent form approved by the Massachusetts General Hospital's Institute Review Board (IRB). This form was as part of a proposal with Dr. Eric Halgren (MGH Radiology) as the Principle Investigator and the author as a co-investigator, and was also reviewed by MIT

COUHES. The consent process was carried out in person on site at MGH and subjects had opportunity to ask any questions and were not put under any duress or pressure to consent.

Subjects next filled out a questionnaire covering biographical information as well as lifestyle and physiological factors that might affect the data (for instance, sleeping, drinking and coffee habits and recent amounts).

During the scanning, subjects could signal distress at any time and were aware they could discontinue participation in the study.

After completion of the study, the experimenter walked the subjects through an in-depth debriefing form, writing down the answers. Task completion strategy was assessed, ratings of for instance task difficulty were enumerated, and other subject impressions were recorded.

See **Appendix B** for copies of the subject pre-test questionnaire and post-test debriefing forms.

5.6 Subject Training

Subjects were trained on the task through a combination of explanations and hands-on practice in the presence of the experimenter.

Immediately following the informed consent process, subjects were given a schematic overview of the linguistic task and what they would be expected to do in the way of overt response – when to press the button. Special care was given to a few of the factors of this paradigm that are both important for the correct completion of the task and also different from most studies carried out at MGH.

Many student subjects have participated in other fMRI experiments and such experiments are likely to make a strong impression (they involve travel across town to a hospital, trusting the operator of a potentially deadly medical instrument, and lying in hospital clothing on an elevated bed in a loud high-field magnetic machine in a dark room). It is possible, therefore, that the types of experiments they have participated in would strongly affect their expectations and biases about how to complete this experiment. However, other labs contemporaneously drawing upon the same subject pool mostly required subjects to press the response buttons to signal which of a set of possible responses was the correct one, often required memorization of any list of items shown (or

surprised them with recall tests), and did not explicitly instruct on strategy or mental computation. In contrast this study was purely about the mental computation of the words, the overt button response was mostly to keep them awake and give a very rough reaction time, and we had strong hypotheses about effects of regularity that might be modulated if subjects devoted more or less resources to trying to memorize the items for possible recall tests. Therefore, subjects were told explicitly that the internal silent production of the words was the important part of the task, and the very fact that they would do any button press at all was told only after they demonstrated they understood the linguistic task entirely. They were informed that they would not have to memorize the words, and they were told to press the button as a signal of task completion – after they were done covertly saying the correct word – and that the button press was not what would signal the next trial. Special care was also taken to explain the intended nature of "covert production" – likening the percept to visualization in the "mind's eye" but in this case speaking in the "mind's voice" and noting that the feeling should not be one of just knowing what to say but of actually feeling one is about to say it and can almost hear it.

Subjects were also told not to worry if they did not know the correct form of a word (e.g. the plural of "anastomosis") or if they made a mistake. They were told that since the signal is averaged over all the trials, it was better to get on and do the next one correct and that focusing on a mistake would likely yield a much larger signal and confuse the results. This was important for the task and also served to give subjects a respect for the subtlety of the measurement, hopefully encouraging vigilance.

After the explanation of the task based on standardized examples on paper, the subjects entered the scanner control room, where they had an opportunity to practice the actual task on the stimulus computer. The practice battery was identical in setup to the stimuli to be presented in the scanner, however they were presented 20% more slowly and none of the words on the live stimulus list was used in practice. First, the experimenter demonstrated by speaking out loud the correct word form for the first several trials and making note of when to press the button. Then the experimenter continued by first whispering at a barely audible level and then continuing completely silently. Then the subject took over the console and was instructed to respond out loud to stimuli, and was congratulated for the first few correct answers. The subject was instructed to

continue for roughly 5 minutes of practice, along the way transitioning to silent production. Questions and concerns were solicited and answered.

Subjects entered the scanner to the do the task for fMRI measurement only once the experimenter determined they understood and would perform the task correctly. Understanding was verified upon debriefing examination, and in only one case the subject had obviously been performing the task incorrectly.

5.7 fMRI Data Acquisition

fMRI scanning took place at the Massachusetts General Hospital (MGH), in the research campus in Charlestown, Massachusetts, at the MGH/HMS/MIT Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging. All subjects were scanned on a Siemens Magnetom Trio 3-Tesla whole-body system, using a standard head coil.

High resolution brain structure images were acquired to establish a high-fidelity anatomical substrate for functional data and to allow robust group averaging of data. Two 8-minute MPRAGE structural scans were acquired for each subject, both at the beginning of the scan session for the earlier subjects and for later subjects one at the beginning and one at the end of the session. Separating the structural scans allowed the cognitive task to begin sooner and provided a reference for assessing global subject head motion from the beginning to the end of the scan session. The scans were 3D acquisitions, with single-shot interleaved traversal of K-space, sagittal slice plane, and 1x1x1.33mm voxels. Field of view was 256mm, and 3D shim of the magnetic field was optimized over the volume tightly containing the brain. The shim was propagated through all scans.

Further anatomical scans were taken in many of the subjects but not used for the analyses. These were intended to simplify and assist the process of co-registering the high-resolution anatomical images with the functional volumes. The scans included T1 EPI scans in Anterior/Posterior and Right/Left phase encoding directions, and a T2 high-resolution scan. Ultimately, software tools for co-registration were used to register the 3D anatomical with EPI

functional volumes directly, without the intermediary scans. Also, "Field Maps" scans were acquired that visualized the inhomogeneities of the B0 magnetic field, to allow future correction of the primary scans according to these maps. See **Appendix C** for the details of each sequence.

Functional scans were acquired to show changes in brain blood oxygenation while the subjects performed the cognitive tasks. This blood oxygen-level dependent (BOLD) functional MRI (fMRI) signal was acquired with current parameters in use at MGH, derived from the original invention of fMRI by Ken Kwong, also at MGH (Kwong et al., 1992). Gradient-Echo EPI (echo-planar imaging) sequences were acquired for the functional runs, with near-horizontal slice acquisition plane set according to the Anterior-Commissure / Posterior-Commissure line in one of the mid-sagittal slices of the 3D anatomical images. 25 slices 5mm thick (0.5mm skipped between slices) were acquired with 3.1x3.1mm in-plane resolution each 1.75s second TR (repetition time), to cover the entire cerebral volume. The echo time (TE) was 30ms.

The goal was to have each trial be a single TR or an integer multiple of the TR. This allowed for synchronizing the stimulus presentation to the scanner image acquisition. The trials in this study, however, must be reasonably long so subjects can comfortably process the frame and the target and give the appropriate response in time to move on to the next trial. If the TR were as long as 3.5 or 4 seconds, however, it would be statistically very likely to miss peak signal at any given voxel for any given task. Basically this reduces the number of sampling points on a continuous decay curve. Therefore, the choice was made to make the TR a partial multiple of the trial time and adjust from there. A standard TR is around 2 seconds, and the length of the TR sets the number of slices one can collect (roughly 15 per second of TR on the scanner used for this study). For this reason, and to avoid losing signal due to inadequate time for free induction decay (FID), it was necessary to keep the TR above 1 second. Yet a 2 or 2.5s TR would have meant 4 or 5 second trials which would have necessitated either a very long, tiring experiment or cutting down on numbers of stimuli. The apportioning of the experiment into runs of manageable length was also a factor.

Finally, since our hypotheses covered the entire brain, it was necessary to scan over the entire brain, so number of slices was important. In the end, 1.75s was chosen as a compromise TR,

and this meant at the most 25 or 26 slices. Simulations were run and 25 slices was chosen because the scanner image reconstruction was more stable at 25. To choose slice thickness a male subject with a visibly large head was scanned and used as a reference to determine how thick the 25 slices would have to be to cover the brain. Forsaking the cerebellum, it was possible to cover the brain comfortably if slices were 5mm thick and 0.5mm was skipped between slices. The practice of skipping space between slices is mostly a vestigial protection against "cross-talk" between the nuclei at the border of the slice which was just previously excited by the gradient pulse that selected that slice, and the slice that is currently being excited. With "interleaving" or collecting every other slice then doubling back, this cross-talk is eliminated. However, leaving a skip between slices is still used to extend the reach of an EPI scan slice prescription. This was how some of the scan parameters were decided upon, interactively. Note that of course lowering the TE would also allow more slices, but 30ms is standard at 3T and works well on this scanner. A lower TE could cost dearly in global signal (even though it could actually raise the contrast in extreme frontal and orbital areas), and no manner of interpolation or analysis can bring back the lost signal. It is important to note that most settings for fMRI are free parameters.

Very few factors are dictated by the MRI hardware: mostly the Larmour frequency (RF frequency at which water hydrogen nuclei resonate given the magnetic field), and the speed of switching "gradient coil" magnetic polarity which dictates how many slices can be collected per minute. Also, the scanner will not allow sequences that pump more than a certain amount of RF energy into the subject, for safety reasons. Since most parameters are free, a rigorous assessment of the parameters requires an interactive decision process such as the one carried out for this study.

Scan sessions totaled roughly 1.5 hours (~20 minutes for the structural scans, and ~60 minutes for the 9 runs of the cognitive task during the functional scanning, plus pauses between the runs to interact with subjects). With subject consenting and set-up time, the total time was two hours per subject.

All scanner settings and pulse sequences were chosen by the author, in consultation with a collection of fMRI researchers and physicists, and based on the specific aims of this study.

5.8 Risks

There are no known risks to subjects from participating in well-run neuroimaging experiments. MRI has been used in FDA approved medical devices at hospitals around the world for decades. fMRI and MEG have been used safely at research institutions throughout the world for over a decade. There is a risk, in MRI, if magnetizable items are introduced into the scanner room. This constitutes improper use of the scanner, and could lead to serious injury to the subject. Great care is taken to avoid such situations.

Careful screening for contra-indications to scanning is conducted via written questionnaire, and an oral interview. It is ensured that participants are metal-free prior to their entering the fMRI scan suite. Throughout the duration of the fMRI session, it is ensured that subjects are well and comfortable. Intercom systems allow the experimenter to verbally check in with the subject frequently. The intercom is used also to assure the subject has not fallen asleep during the behavioral (functional) parts of the scans. Data are stored anonymously ensuring confidentiality.

Subjects do not benefit medically from participation in this research. They are furthermore informed that the brain scans taken in this research are not clinical scans and cannot be used to evaluate their health.

5.9 HIPAA Disclaimer

Integrity of practices in this research assured participant privacy, in accordance with HIPAA legislation and sound research protocol. HIPAA, or the Health Insurance Privacy and Accountability Act, is a set of mandates for safe and respectful handling of medical information of all sorts.

Subjects in this study immediately received a code, based only on the project name and the sequential order in which subjects were added to the project. No personally identifying information is embedded into the subject code, and no personally identifying information is ever wedded to any raw collected data. Only the code, such as "NV_Infl_01_W" is in the raw fMRI data headers. Case studies and pilot subjects may have identifiers incorporated into their subject code, but not in a readily apparent way.

The subject code is all that is used to register the subject on the scanner. Subject weight, gender, and year of birth must be used to register an fMRI subject because these are mandated by

the FDA for calculation of deposition of Radio-Frequency energy. Anonymization is assured by universally using January 1st rather than true day of birth.

Further data analysis only depicts the subject code. Therefore, personal information is linked to data only in two places: in the folder containing the consent forms, and in an electronic file linking subject codes to a single identifier such as name. The paper files are kept in the investigator's secure filing cabinet, and the electronic file is kept in a special place on the hard drive of the local Linux workstation with permissions such that only the Investigator or lab members can access it.

5.10 fMRI Data Processing

5.10.1 Overview

Raw fMRI data from individual subjects were pre-processed and post-processed, and individual subject data were averaged to yield results for the group of all 18 subjects included in the final analysis. Raw data consist of 3-dimensional MRI data sets: high-resolution structural images of the brain, and 4-dimensional fMRI data sets: series of images over the course of time showing the changes in brain signal due to dynamics of blood oxygenation. The core of the functional analysis is the parsing of the 4-dimensional data into epochs corresponding to each trial, the averaging of all like-condition epochs, and the statistical comparison of systematic changes between condition types.

Data processing was all carried out using the FS-FAST software stream. FS-FAST stands for **F**reeSurfer-**F**unctional **A**nalysis **St**ream. FreeSurfer is a freely distributed software toolset for creating surface renderings from anatomical MRI images. These surfaces are highly functional mathematical matrices and can be infinitely inflated, rotated, and rendered with functional overlays. The FS-FAST toolset sits on top of FreeSurfer and is for analyzing and displaying function MRI data. FreeSurfer and FS-FAST are developed by the Martinos Center for Biomedical Imaging, in conjunction with CorTechs Labs.

FS-FAST is Linux-based and requires many manual steps that can be quite tedious, especially at the data visualization stage. Furthermore, there is no good way to collate and navigate through large amounts of output maps of brain function that can be derived from FS-FAST. To

address these unmet needs, the author developed a suite of tools that interface with FS-FAST at many stages, in order to automate and standardize the process. Furthermore, at the data visualization and data navigation stage, the author developed a suite of tools for creating and labeling mosaics representing the brain from all views, and for navigating through them in a web-based front-end. These tools increase productivity enormously, shortening data processing time by perhaps a factor of 10, virtually eliminating user intervention, and effectively allowing many more questions to be asked of the data since the incremental cost in time (computer time and Researcher time) is so far reduced. These tools were developed on separate computing resources, outside of core time, and for multiple purposes including but beyond application to research such as the present. The author owns the copyright to this development and is in the process of licensing negotiations with CorTechs Labs.

5.10.2 DATA UNPACKING

Raw data were transported from the scanner in native Siemens DICOM medical image file format. Data were then "unpacked" into formats usable by the FS-FAST. Structural scans were unpacked into "COR" files, and functional scans were unpacked into "bshort" files.

5.10.3 INDIVIDUAL DATA PRE-PROCESSING

5.10.3.1 Motion Correction

Structural and functional scans were processed for motion, and correction algorithms were attempted. The FS-FAST motion correction module borrows the correction algorithms from the AFNI image processing suite (Bob Cox, NIH). Initial acquisitions (volumes) in the 4-dimensional functional timeseries data are used as reference volumes, and each additional volume registered to that volume. This creates stability across time, through rigid transformation of all the data into a single reference frame. This technique is very good at removing linear drift or small random translations, but not gross translations. After the first functional data set for each individual is processed (the first run, of 9 in this case), the algorithm then uses that corrected run as a reference, in order to iterate the motion correction over the rest of the runs. No functional data were rejected or removed from analysis based on computed movement statistics.

5.10.3.2 Spatial Smoothing

Spatial smoothing was carried out on each functional run (EPI volume) for each subject, with a Gaussian full-width half max FWHM of 6mm. The spatial smoothing was a 3-dimensional algorithm, including contribution from any voxel within a 6mm FWHM Gaussian shell around any given voxel in the computation of the activation probability of that voxel. Note that this 3-dimensional or *volumetric* smoothing done at the pre-processing stage is done in contrast to and/or in concert with *surface-based* smoothing done at a much later stage in the analysis. In general, smoothing the data the appropriate amount increases the power of the analysis. The power increase comes from avoiding situations in which true physiological differences in signal ("activation") are spread over multiple voxels in such a way that no one of them (or few of them) reaches statistical significance at the alpha level of the test (which is usually correct in some way for post-hoc analysis or multiple comparisons). As such, the smoothing takes into account the greater protection against Type I errors afforded by *clustering* of activity: weighting towards significance any voxel that also has neighbors that are above or near significance level. Furthermore, the smoothing alleviates problems due to inescapable uncertainties involved in the registration process (marrying the functional to structural volumes). Essentially, blurring the lines between functional voxels can more directly represent the level of error involved in corresponding those voxels to the structural voxels on which they will be overlaid.

Note that this is all in individual subjects. A similar reason for smoothing comes in the fact that eventually individual subjects' data sets are group-averaged so that the power and predictive power of averaging over a sample population can be harnessed. However, corresponding voxels among sets of individual brains results in uncertainty not just related to error in matching these volumes but due to intrinsic variability in the physical brains: different brains look different! Therefore, for all these reasons, it is important to do the appropriate amount of volumetric smoothing of the data, as it is actually more "correct" and not just a technique for getting more powerful activations. However, the big question is "what is the *appropriate* amount of smoothing?"

This is perhaps the single biggest question asked about a given fMRI analysis, and pondered in setting one up for a new study. One reason is the smoothing radius can affect the results so much.

The author completed multiple simulations of full functional analyses with varying smoothing values, precisely to quantify the "correct" smoothing factors. The simulations were complicated by the interactions between the above "volumetric" smoothing, and smoothing of data within the anatomically-relevant confined space of 2-dimensional (or really 2.5 dimensional) cortical surface matrices. In total, over 250 hours of raw processing time were consumed on a Dual 2.8GHz Pentium-4 Multithreading Linux workstation with 2GB RAM and 0.75 TB disk space, and 160GB consumed, in order to run the full random-effects group analysis of all 18 subjects for each of 12 combinations of volumetric and surface smoothing. Results from all the analyses are out of the scope of this document.

However, a few simulations much smaller in magnitude were also run in the earlier stages of this project, one of which is reported below.

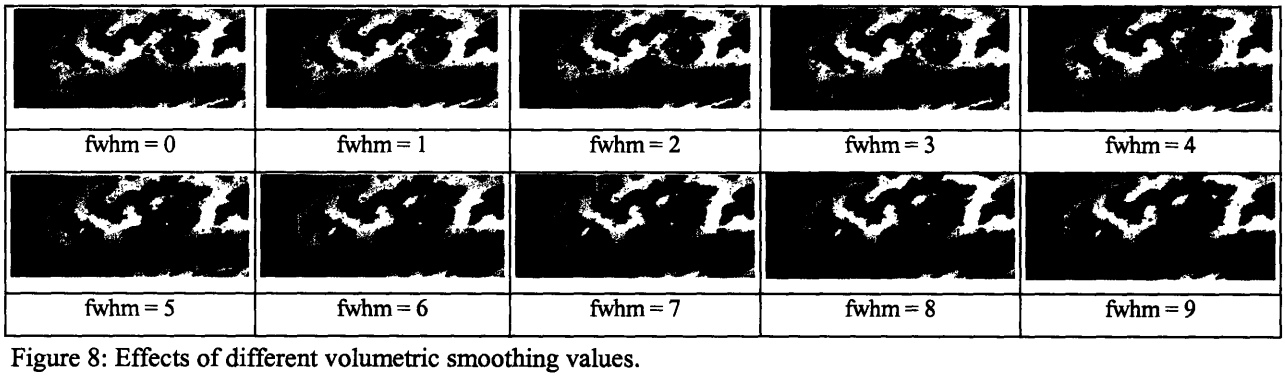


Figure 8: Effects of different volumetric smoothing values.
Images here are excerpts from inflated brain images, including the inferior frontal gyrus of the left hemisphere, and surrounding areas. False-color overlays are the final "activation" maps for a given contrast (All Overt-Inflect V All Read), in an early group average using only 4 subjects and fixed-effects averaging method. Positive differences (Overt-Inflect greater than Read) are in a red to yellow increasing scale of significance level of the t-test, and negative differences (Read activates region more) is on a blue to light blue scale. Each panel shows the results from the same data and same analysis except for one parameter: the full-width half-max (fwhm) of the Gaussian smoothing factor in 3 dimensions around each voxel. An alarming increase in effective activation size is observed for increasing smoothing radii, once the smoothing radius in greater than 1 functional voxel.

We can see from Figure 8 above that the volumetric smoothing factor makes a big difference in the final results from a given data set. The most obvious feature is that increasing volumetric smoothing radii seem to increase the size and significance of the activation clusters

immensely and continuously. Another trend is apparent, namely that there is no difference among resulting activation maps for volumetric smoothing factors of 0,1,2 nor 3mm. The reason is simple and obvious: smoothing concerns biasing a given voxel by all its neighbors within a given radius, so if the radius is less than the fundamental size of the voxel, no neighbors will be considered. Our voxels were 3.1x3.1x5mm so the fact that the effective cutoff for effect was between 3 and 4mm means that the smoothing value is computed from the center of the voxel and is not actually a radius. The most important lessons from this simulation, however, are that 1.) smoothing can increase power a lot and strongly interact with results and interpretation, and 2.) the "correct" smoothing factor depends on the fundamental size of one's voxels.

The second lesson is important in showing that there actually is no correct numerical value for smoothing. In this case we see that at least it interacts with one's voxel size. Therefore at the very least, a recommendation for smoothing should not be a numerical value, but some function of voxel size. Perhaps this would be simply a linear coefficient, or perhaps a more complicated function taking into account extreme non-isotropy possible in some voxel configurations (the present are only mildly anisotropic in being 5mm tall, but 3.1mm in the other two dimensions), physiological constraints due to brain gyral folding frequencies, or other factors.

Unfortunately the complexity does not end there. The extensive simulations alluded to above also revealed the objective truth of another heuristic: that the correct smoothing radius is proportional to the true activation size! As the smoothing factor increased, smaller focal activation clusters actually disappeared while diffuse activation fields became strong pronounced clusters. This would be predicted for complementary reasons to those that led to lack of differences in statistical maps above for smoothing less than a single voxel, yet in reverse. Specifically, when the voxels greater than the true activation cluster size away from a given voxel are included in the calculation of that voxel, the inclusion actually decreases rather than increases the likelihood of reaching significance. This is simply because on average one is including non-activated voxels. Now our smoothing factor recommendation becomes not just a function of voxel size but also the size of activated brain regions one hypothesizes! This is particularly difficult because if the size and nature of the activations can be predicted with a great deal of fidelity then the experiment is likely not worth doing. Moreover, activation sizes vary wildly over the brain, therefore if the smoothing is set to amplify an activation cluster in a large tract of prefrontal cortex, for instance,

this will pretty much rule out ever finding significance in a voxel in the inferior colliculus or amygdala or other region known to have higher spatial frequency of functionally distinct domains.

Taken as a whole, the recommendation for smoothing extent interacts with voxel size, regions of particular interest based on the study hypotheses, literature precedent for activation extent in those regions, and expected effect size for the study. The simulations helped quantify some of these factors, and may prove to be useful to other investigators. For the purpose of the present study, the reported activation maps, unless otherwise noted, will be based on a volumetric smoothing factor of 6mm FWHM, and a surface smoothing factor of 30 steps (covered below).

5.10.3.3 Intensity Normalization

Functional (EPI) data sets often have intrinsic signal inhomogeneities due to head coil artifacts. Essentially, the read-out coil does not receive the RF signal equally from all reaches of the brain so there are brightness differences across the brain images. Accordingly, all runs of all subjects were pre-processed with an Intensity Normalization algorithm. Intensity normalization needs to be done carefully, to equate not just global brightness but also contrast across the image so that 1.) grey matter – white matter boundaries are not harder to distinguish in different parts of the brain, and 2.) the differing grey-white ratio for instance between cortex and *corona radiata* does not confuse the normalization procedure. These considerations were built in to the normalization used here.

5.10.4 INDIVIDUAL DATA POST-PROCESSING

Functional datasets were processed to extract the average signal associated with subject performance of each trial type. The functional (4D) datasets for each run for a given subject were matched up against "paradigm files" that are lists of precisely when each trial was presented and what type of trial (condition) each one was. The paradigm files were created from the *optseq* output and therefore were identical to the stimulus presentation schedule. Since the presentation of stimuli was synchronized to the scanner at each TR, it can be assumed that the presentation, the sequence, and the paradigm file all correspond with a very high fidelity. This, again, was important for assuring the correct assignment of segments of raw fMRI signal to the task conditions being

performed by the subject's brain at that time. The event-related time series data were "epoched," or spliced into trial-related epochs, based on a 24-second time-window beginning 4 seconds before the stimulus presentation and continuing 20 seconds afterward. Then the average brain signal/image for the 60 trials of each condition was computed, and saved as a new brain volume. This virtual 4D volume was basically a picture of 24 seconds of the brain for all the times it was performing a given task condition, and formed the reference against which other virtual condition-brains were compared to generate condition-to-condition "contrasts."

5.10.4.1 Gamma-Fit Analysis

Two fundamental kinds of epoching and therefore analysis were carried out. The first was based on assuming a shape to the response function of blood oxygenation to each spike in neural metabolic activity, the so-called "hemodynamic response function" or HRF. The statistical extraction and averaging of trial-related signal from the continuous functional data, to create the virtual condition brains, was in this case based around a simple gamma function that formed a model of the HRF. The gamma function convolved with the data had a Delta (onset delay) factor of 2.25s and a Tau (dispersion – summary of rise and fall times) factor of 1.25s. This gamma fit algorithm was based on the function: $f(t) = ((t\text{-delta})/tau)^2 * \exp(-(t\text{-delta})/tau)$. In the gamma-fit analyses, a 5^{th}-order polynomial was also fit to pull out drift in the signal.

5.10.4.2 FIR Analysis

The other type of analysis carried out with FS-FAST was a Finite Impulse Response (FIR) analysis. The FIR analysis does not make any assumptions about the shape of the HRF. Basically, the timepoint 0 is taken as an impulse, or sudden stimulus, and the signal at each time point thereafter is treated independently. Therefore, instead of one single number describing the fit of the gamma HRF over all 24 seconds of the time window, the FIR analyses returned values for each time point. These values were not goodness of fit but rather a raw signal magnitude, which could be compared directly in condition-condition contrasts. The FIR analyses were also the ones used for region-of-interest (ROI) analysis later. ROI analysis treats an area of the brain in isolation of the rest of the brain (regaining statistical power by restricting number of tests) and as a single effective voxel.

5.10.4.3 Other Analysis Parameters

In both the FIR and Gamma-fit analyses, temporal whitening was performed to remove the autocorrelation in the signal over time due to the fact that fMRI measurements of the same voxel are not independent but rather are correlated with measurements at previous time points. The maximum time lag for the autocorrelation function was 30 seconds, such that the model would assume zero autocorrelation after that point.

Motion-correction parameters, obtained for each run for each subject based on the motion-correction preprocessing described in section 5.10.3.1, were entered into the model as external regressors. Regardless of the type of model (Gamma-fit or FIR), the motion correction regressors were used to explain away subject-specific variance due to the that subject's motion, and thus increase the SNR.

5.10.5 CORTICAL RECONSTRUCTION

High-resolution structural scans were processed with the FreeSurfer tools to generate cortical surfaces. First, air-tissue contrast thresholds were used to isolate the head. Next, contrast information and the cerebrospinal fluid (CSF) and meningeal border zones were used as landmarks to do a skull-stripping operation. The result was the isolation of the brain image. Further steps in the FreeSurfer stream included the removal of the cerebellum. General "segmentation" was carried out in an automated fashion based on T1 contrast – separating grey matter from white matter. At this stage, the mathematical matrix that represents the brain image is now segregated into grey and white components. Further segregation of these compartments was done in the "parcellation" process – dividing up cortical and subcortical regions into small anatomically-relevant pieces. Finally, this information was used to generate contiguous cortical surfaces fro each brain, and then these surfaces were virtually "inflated." The inflation was done to bring cortical surface area out of the deep invisible reaches of the sulcal folds and onto a visible surface. Deformation was minimized by trying to achieve the minimal changes in distance between sets of vertices, of the 350,000+ triangular tessellations of the surface.

Ultimately, versatile 3D matrices representing the brain structures were created such that they could be infinitely inflated and transformed.

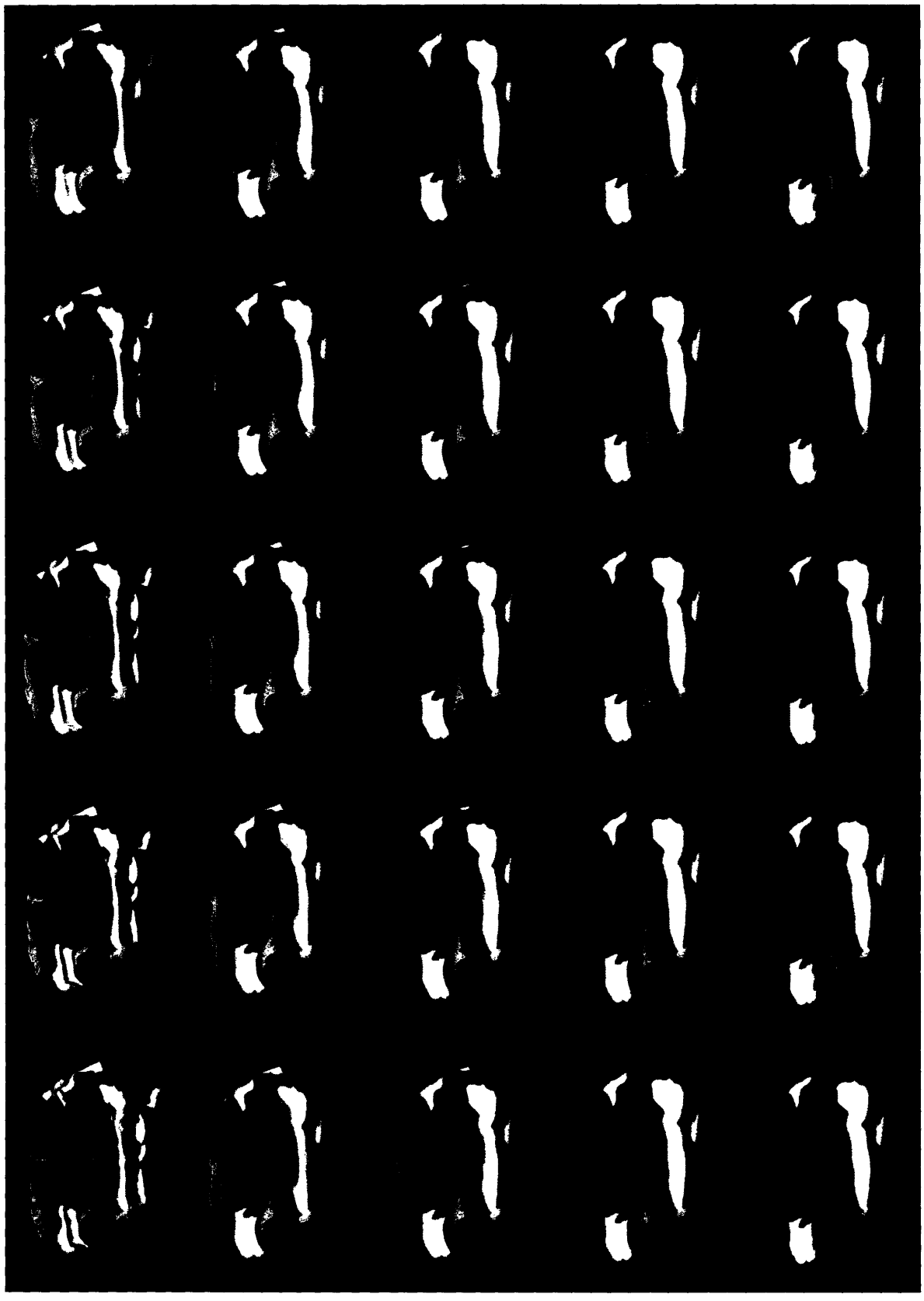


Figure 9: Depiction of brain surface matrix inflation, individual parcellations color-coded

Figure 10: Depiction of brain surface matrix inflation, group average data overlaid.

5.10.6 GROUP AVERAGING

5.10.6.1 Normalization to Common Space

Individual functional volumes were registered to the structural volumes for the same subject. Then the subjects were inflated and normalized to a common space – a spherical coordinate system developed at MGH, as an alternative to the Talairach space. Once all subjects were transformed to a common space, their data could be compared and accumulated in a grand group average.

5.10.6.2 Group-Based Statistical Analysis

Analyses and contrasts very similar to those run for each individual subject were run for the group. Two types of group analyses were carried out: one which treated subjects as a fixed effect in the model, and one which treated subjects as a random effect. Random effects analysis is more strict but more generalizable. Results presented here are all from random-effects analysis.

5.11 fMRI Data Visualization

Cortical surface creation and inflation from the high-resolution anatomical scans was carried out by technicians at the Martinos Center trained to do this specific task. All other data spooling, unpacking, pre-processing, processing, parameter setting, re-analysis, verification and results visualization was carried out by the author.

Software was written for data visualization, errorless recording of parameters on output data visualizations, and navigation and databasing of images with a web-based front-end.

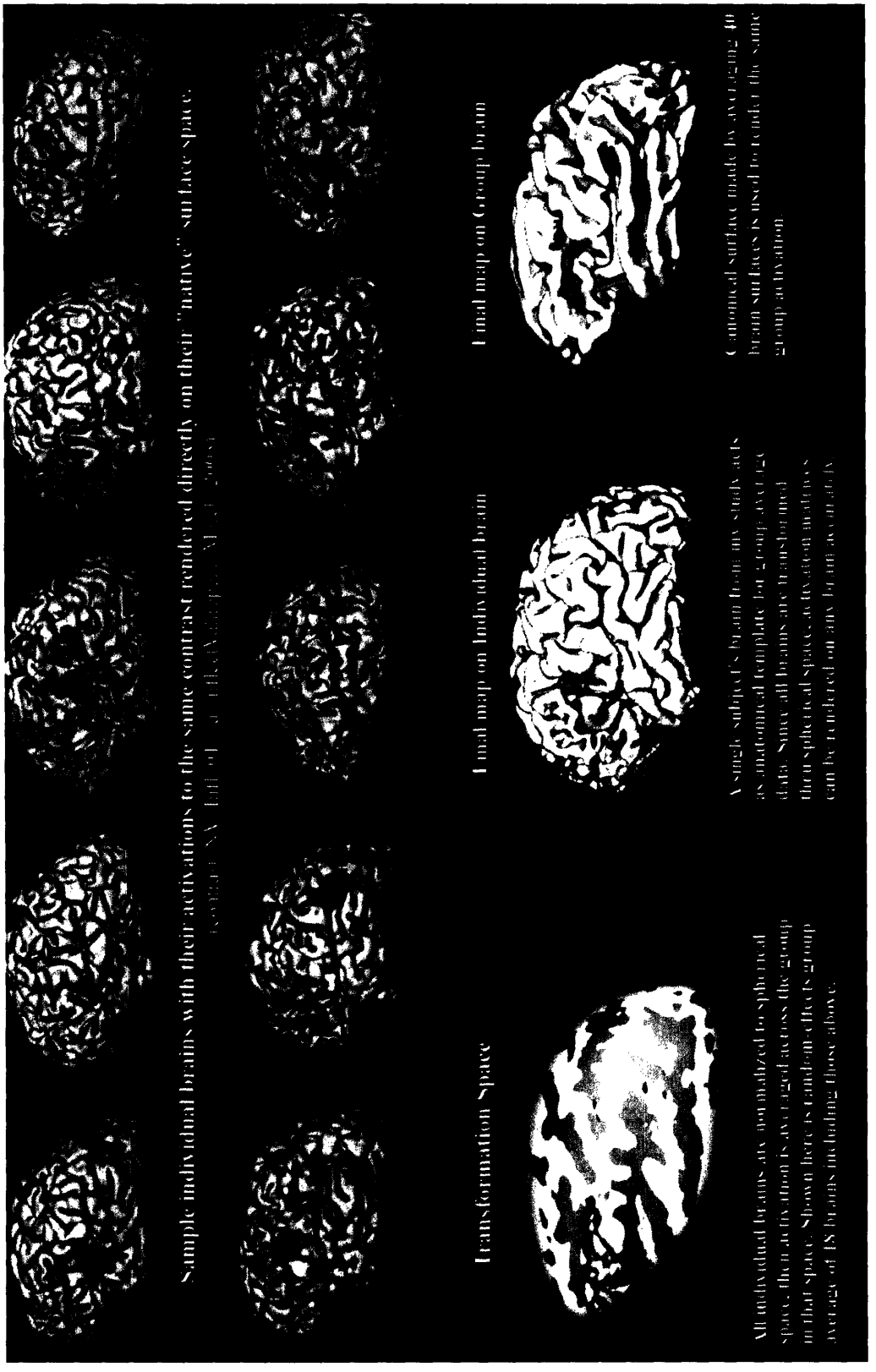


Figure 11: Depiction of group averaging procedure, with data; display on brain matrix of choice.

6 RESULTS: FMRI STATISTICAL MAPS

6.1 Chapter Summary

This chapter presents the main results of the entire study, in one central repository of contrast maps, and provides descriptive and orienting information so they may be interpreted in the context of the discussions that follow or as a stand-alone reference. Maps of "activation" are representations of statistical significance levels of the difference in MR signal between two conditions for each of the voxels in the brain. The matrix of significance levels is depicted as a color map because the eye can pick out many types of relationships from color fields better than tables of numbers. The color map is rendered on a brain-like surface because this is the best way to preserve the complex relationships between each measurement. Any surface that contains all the anatomical units could be used to display the color map, but the brain of an individual has the advantage of being by definition brain-like, and yet does not have "stylized" anatomy of a canonical brain due to averaging across brains of variable anatomy. Accordingly, results are here presented as false-color activation maps on the pial and full-inflated surfaces of the brain of one of the included subjects.

Figure 12: Parcellation Labels

6.2 Chapter Description

The majority of the Results of the fMRI experimentation are represented in this chapter. The use of the terms *results* (not data) and *represented* are deliberate and explained a bit further in prefatory sections below. A statistical map of task-related activity level at each point in the brain, for each *a priori* contrast, is represented on the pial and inflated surfaces of subject NVInfl_01_X as a *representative* brain model.

These maps form a major backbone for all the findings discussed in following chapters. Since they are also to serve as future reference and for further interpretation of the data, they are all placed together in this chapter and referenced, however certain elements are recapitulated in the text of ensuing chapters as findings are discussed.

To aid interpretation of the fMRI Contrast Statistical Maps (CSM's), a section of legends is presented first. Further assistance in digesting and interpreting these high-dimensional plots comes from the fact that they all have a common layout, and all parameters of the underlying analysis are imprinted on the images. Finally, a structure for embedding the CSMs in this document along with descriptions, explanations, and notes aids in perusing them independently of the rest of the document.

Before the CSM legends, there are a few clarifications of terms, toward explaining what these representations are and are not.

6.2.1 WHAT IS AN ACTIVITY MAP?

The underlying raw measurement in these maps is the magnitude of BOLD signal at each TR in a 24-second time window around the trial onset, averaged over all occurrences of that trial type. The results depicted are statistical likelihoods (*t*-test *p*-values) that any differences in these measures between any two conditions are not due to chance. These statistical measures are computed for each of the roughly 30,000 voxels that may be in a total brain volume. The values could be plotted as a bar graph or set in a table, but 30,000 values would not only be uninterpretable but would not encode all the levels of information that come from knowing which of a voxel's neighbor's in 3 dimensions reach what significance level. Furthermore this display would not in itself yield locality in brain space but would have to be translated through some sort of look-up table.

The obvious convenient way to display the statistical measurement, therefore, is on a 3-dimensional rendition of the brain, or a 2-dimension map that has the illusion of three. In fact, since most of our hypotheses deal with relations between known cognitive function areas on the brain surface or cerebral cortex, we can depict the results on the brain surface only and throw away depth dimensions. By displaying the results on a cortical surface instead of some standard graphical coordinate system, we can capitalize on the powerful data-distilling and dimension reduction capabilities of the human visual system, and thus depict/digest extremely high dimensional result matrices. One important trick is exactly how the scalar value depicting significance of between-conditions signal is rendered for each surface voxel. Clearly, a set of numbers superimposed on the representative brain surface would not be of much more use than a data table. They eye is not good at distilling and taking the gist of such information because it is not actually visual information. It would be a visual display, but the information in question would be contained in semantic units only accessible through knowledge of the numerical symbols. On the other hand, *color* information is rapidly processed by the visual system and can be used to recognize complex patterns. Accordingly, the statistics for each fMRI voxel are transformed into hue and saturation values, and it is these that are overlaid on the brain image. This is how false-color fMRI brain maps work, and one main point of discussing this is to note that colorized brain maps are not actual signal intensity maps but rather maps of statistical likelihood of voxelwise activation differences between task conditions.

It is also important to note that FS-FAST basically creates a versatile matrix of these p-values, that can be rendered in many ways. Basically there are two matrices - one that contains the functional results, and one that has visual information for sensible display of the results. As discussed above, it is advantageous to overlay the result matrix on a matrix of brain anatomy. This could be done for any type of matrix that includes all the relevant anatomy in the functional matrix, even if it would result in a completely flat map or one that does not look like a brain. Even in the case of a matrix that is rendered as a brain image, there is choice as to which brain. It is possible to use a canonical brain matrix, and one is included in FS-FAST that was created as a 7th-order icosahedron by averaging 40 healthy adult brains. However, this "brain" has very 'stylized' anatomy - with highly smoothed and simplified gyri and sulci resulting from averaging over brains with anatomical variation. Someone acquainted with gross

neuroanatomy would not recognize standard anatomical landmarks on this brain image, and so rendering our maps on this brain would forfeit this dimension. We can take advantage of the versatility of our results matrix, however. In order to have done any group averaging of functional data, all individual brains in the study had to be transformed and normalized in a common space (in this case, spherical space). This normalization creates a transformation matrix that allows, for instance, activation in one subject's Broca's area to be added to another's Broca's area in the group average and not confused with nearby anatomy, even if the two brains look different. This is obviously necessary for carrying signal forward from individual to group analysis. The trick is that the transformation matrix also works in reverse. At the data visualization stage, the results in the group functional matrix can be back-propagated via the transformation matrix onto any individual brain that was transformed into common spherical space in the first place. This is purely for display. The advantage of a real brain as the map substrate is the anatomy is more recognizable than an averaged brain. Any brain would do. Using the brain of an actual subject in this study is simply a neat touch but is not necessary.

6.3 Clarification of Terms

6.3.1 On the term "Imaging"

fMRI is one of the first techniques that comes to brain scientists' minds when they think of "imaging," however I believe that the term imaging should be much more broadly applied. One reason fMRI is thought of as prototypical brain imaging is that a major and accepted way of representing processed fMRI data is as false-colored *images* of the brain. Or rather, overlays of false color, atop images of the brain. This is of course not why it classifies as an "imaging" technique. What makes it imaging is that through this technique we can measure some sort of signal that can propagate to the sensor from the signal-generating substrate, and is measured along at least 2 dimensions of variation. Such data set can easily be represented as images, and they often involve propagation of electromagnetic radiation of some form (whether it be light or x-rays or radio-frequency waves (RF)), but it is important not to confuse this with what makes them imaging techniques. On this view, certainly fMRI, PET, and CT are imaging techniques, as is near-infrared spectroscopy (NIRS). However, measuring of calcium flux in multiple

synapses in a CA1 cell, for instance, or assaying expression of gene products across time and/or space is also imaging. The signal can be detected remotely, either by a direct coupling of information or radiative energy exchange between the sensor and the intrinsic signal (such as calcium ion flux creating a voltage across two electrodes) or via an intermediary (such as a fluorescent marker coupling with the gene product and being read by light sensors). These techniques "image" relevant change within their systems, just as the RF radiation interacting with magnetically aligned water protons near deoxygenated blood induces a signal that can be read by the head coil elements in an fMRI machine. fMRI is imaging because it allows one to take a 3-dimensional snapshot of blood oxygenation remotely, and in fact a series of snapshots to show change in time.

Importantly it is the process and the type of data collected that make a technique "imaging" in this broad definition. The data form a snapshot of some facet of the system studied, and this dataset can be considered an *image* the way a dataset of reflected electromagnetic radiation in the spectrum we call light forms an *image* of some surface characteristics of an object that would be recognizable in its stead by human visual system. However, these spectral data could be represented with a histogram just as easily as a photograph.

Measuring changes in neuronal firing rate, along some set of relevant dimensions, is also imaging. The dimensions can be spatial (for instance to measure firings of different types of neurons across cortical lamina), and/or temporal (measuring attenuation or habituation, for instance, and/or long-term changes in rates of change of firing), and/or functional (e.g. measuring firing rates in excitatory vs. inhibitory neurons, or those with(out) dopamine receptors of a certain type). These are imaging because they take data from the systems, and these data can form a *representation* of some relevant feature set of the system. They are not the system, but rather represent it; and they do not represent the whole system, but only the features chosen. These are the features chosen to be imaged. Interestingly, one reason to think about measures of neuronal firing is because often the published presentation of such data is halfway to being an "image" in a classical sense, and thus leads nicely to why fMRI data are often represented as pictures.

Measuring neuronal firing by nature leads to high-dimensional data sets. On average, multiple single neurons, or multi-unit activity generators, are recorded multiple times, along

spatial dimensions, under many conditions, from many systems or even animals. Thus a bar graph will not do, when it comes time to communicate data and results. Oftentimes, 2-dimensional so-called *raster plots* are used to display firing patterns over time, as in Panel A of Figure 13 below. Further data dimensions may force the author to resort to a surface representation, as in Panel B.

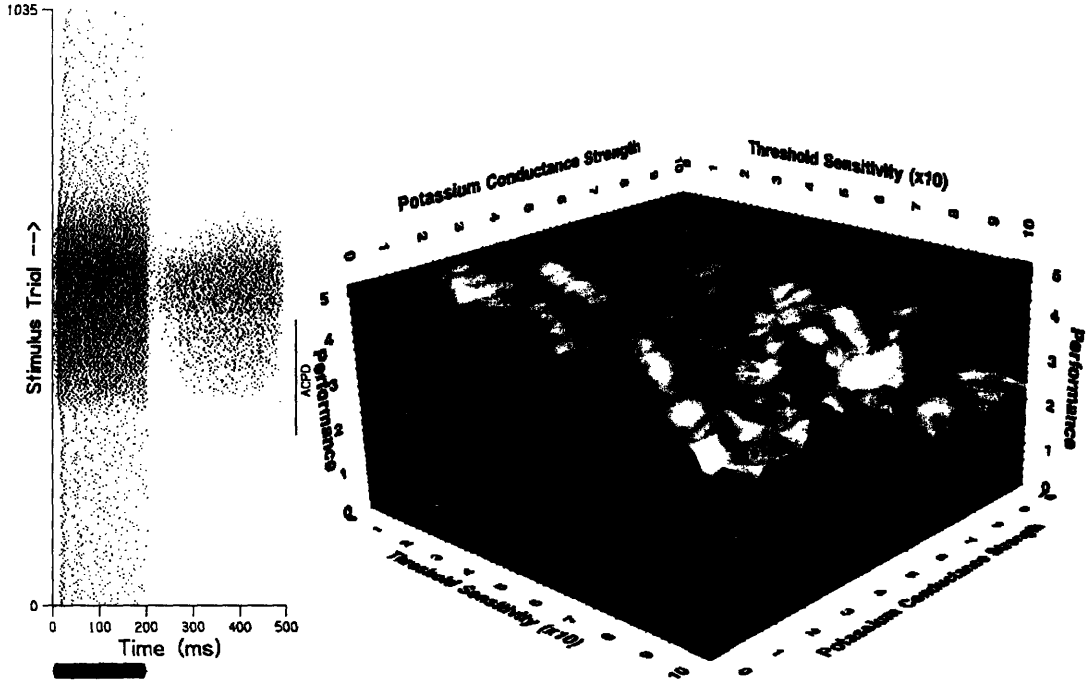


Figure 13: Two and three dimensional representations of neural firing data.
The first panel shows a "raster plot" of neural firing of cat cochlear neuron to sound bursts, before, during and after drug delivery to the neurons (Sanes, *et al.*, 1998). The second panel illustrates representation of neural firing data when even more dimensions must be represented (NR Wilson, et al 2001). In both cases, the techniques themselves are, by the broad definition discussed here, "imaging" techniques. As the data collected get more complex, the representations chosen by authors naturally become themselves more like images – simply because we are good at distilling large amounts of information through our own imaging apparatus – our visual system.

Finally, some techniques yield such high-dimensional data the only option for representation is plots that are fundamentally 3 or 4 dimensional. The reason is simple: "meaning" in these data comes from the intersection of many factors (dimensions) but human readers are not very good at reconstructing complex interactions from text or dozens of related line graphs. However, humans are very skilled at interpretation of complexity in 3 spatial dimensions and time. Therefore, you get 3 or 4 dimensions "for free" in such plots because we have overlearned or even genetically programmed skills for deriving meaning from 3-space. The viewer just needs to map the dimensions (say threshold, K++ conductance, and

performance in example above) onto the plot. Then additional factors beyond 3 or 4 can be represented with less intuitive manipulations such as the orientation and color of the "tensor" representations in this Diffusion-Tensor image of brain connectivity:

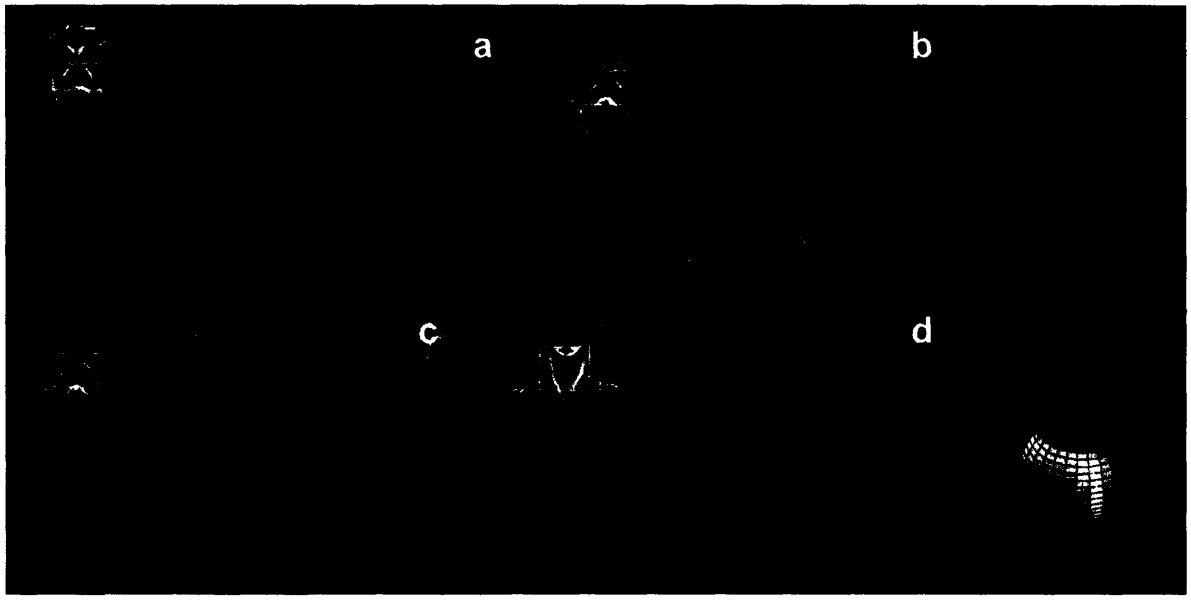


Figure 14: Diffusion Tensor data, reprinted from M.R. Wiegell, *et al*, 2002.

Is the display of results as an image what makes a technique *imaging*? Definitely not. It was imaging to begin with, regardless of the shortcuts used to visually represent the data or results. In fact one good reminder in the opposite direction is that fMRI, this paragon of imaging, is sometimes used most powerfully to compare the global activation intensity for two task conditions in the same region of interest (ROI). For instance, response to angry versus neutral faces may be summed over the entire Amygdala, and reported. This fMRI result can be expressed simply as two scalars, or as a simple bar graph with two bars.

So why are fMRI results often expressed as pictures of brains?

As we see from above, high dimensional data are often represented as 3D objects because then at least 3 of variables in the representation are easily communicated. Another dimension or two may be rendered with color. Note that fMRI results often are not just pictured on abstract surfaces, but brain images themselves are often used. The reason, as discussed above, is that dimensions of information lie in the spatial relationships on the brain surface. For instance an anatomist can look at two place on the cortex and know what white matter tracts connect the region. Brain areas are differentially perfused with blood. Known activation clusters

may be part of measured activity, etc. All of these can be represented with respect to the brain surface. Rendering fMRI activation on a brain or brain-like surface allows viewers to access many untold facets of brain organization. However this further reinforces the fallacy that fMRI is a so-called imaging technique because it results in brain pictures.

The net result of all this is a caution to think of these pictures not as pictures of the brain, but measurements of brain-derived signals conveniently represented on brain surfaces to reduce the number of dimensions required to display the information contained within.

6.3.2 On Data vs Results

Data are the actual primary measurements in any experiment. fRMI activation maps are sometimes labeled data when they clearly are not. The raw data for MRI look like simple waveforms over time in a high-dimensional matrix. These data are averaged, filtered, and processed in as many as a hundred steps, and then analyzed statistically, and represented as a derivative value: the magnitude of the t-test for significant accountability of the variance in the averaged data.

In this context it is incorrect and imprecise to think of these pictures as data, and it is misleading to think of the brain "images" as actual pictures of the brain.

6.4 Reading Contrast Statistical Maps (CSMs)

6.4.1 The Brain Template

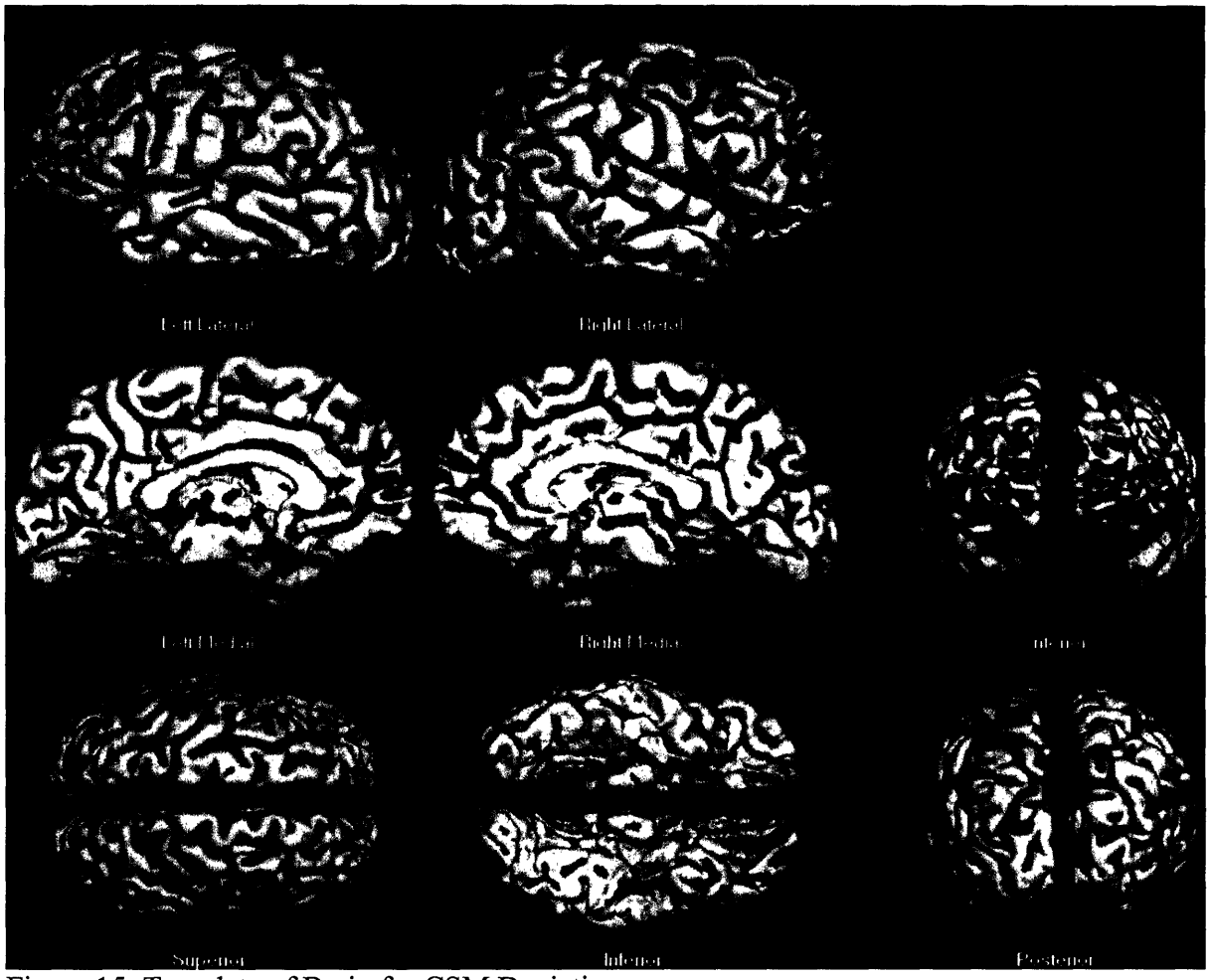


Figure 15: Template of Brain for CSM Depiction

The above template shows all the views of one subject's brain (Subject **`NVInfl_01_X`** in this study). The four large, unpaired views are the lateral and medial surfaces of the left and right hemispheres, as marked. The left, conveniently, is on the left and the right is on the right. Therefore a given hemisphere's medial surface is *below* the lateral surface. The paired surfaces at the bottom show the top and bottom of the brain, with eyes looking to the right in both cases. The paired surfaces on the right show the front and back of the brain. The top one is looking at the reader. Note that the atrophied look of the prefrontal gyral pattern has to do with susceptibility and static magnetic field distortions in the original image acquisition. Remember that the surface here is not a direct image of the brain but a mathematical matrix reconstructed from the high-resolution anatomical MRI image. Given limited integrity of the MR data in the prefrontal region, the system has made its best guess about gyral patterns and in some cases cannot guess what the gyrus should look like. This is not ideal, but it only affects regions

anterior of the Inferior Frontal Gyrus, *pars orbitalis*, so it is not very troublesome here. Also, activations of the corresponding regions would result in color mapping of the degraded gyral convolutions, it would just not be as easily interpretable as in other areas of the brain.

6.4.2 PARCELLATION LABELS AND REGIONS

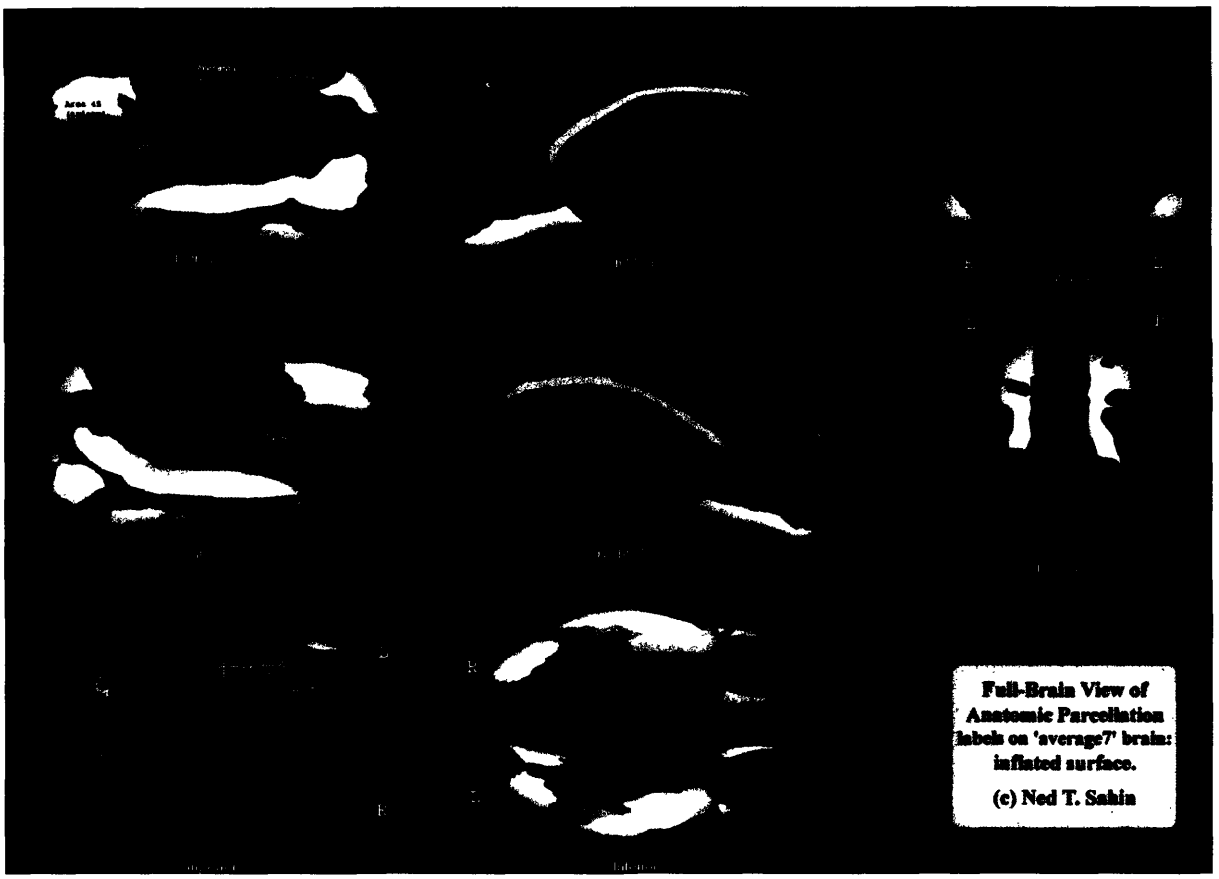


Figure 16: Parcellation map inflated group brain

The mapping in Figure 16 shows the parcellations into which the inflated brain surface is divided.

Figure 17: Parcellations on group brain pial surface

The semi-inflated pial surface map in Figure 17 shows the cortical folding patterns, and the benefit of the previous "inflated" surface mapping for bringing out sulcal activations. The map below demonstrates activations on this surface.

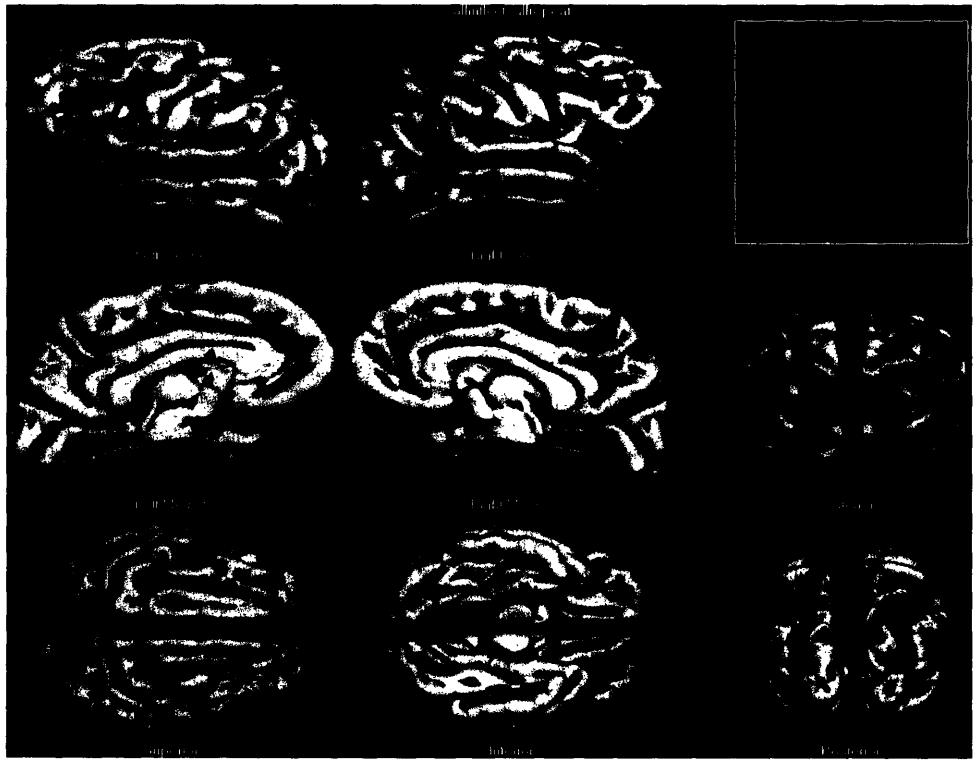


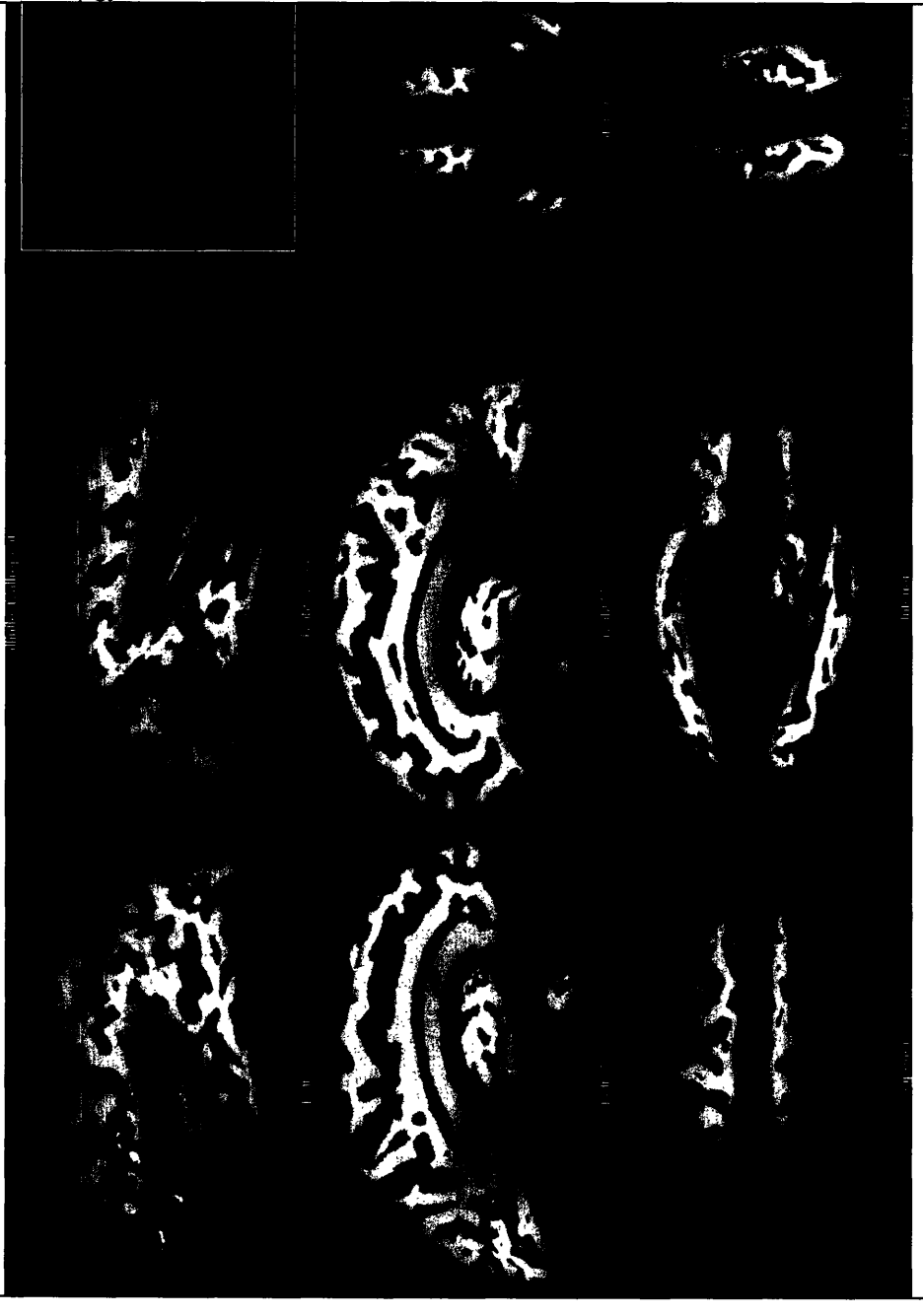
Figure 18: Example activations on group brain pial surface

6.5 List of Contrasts

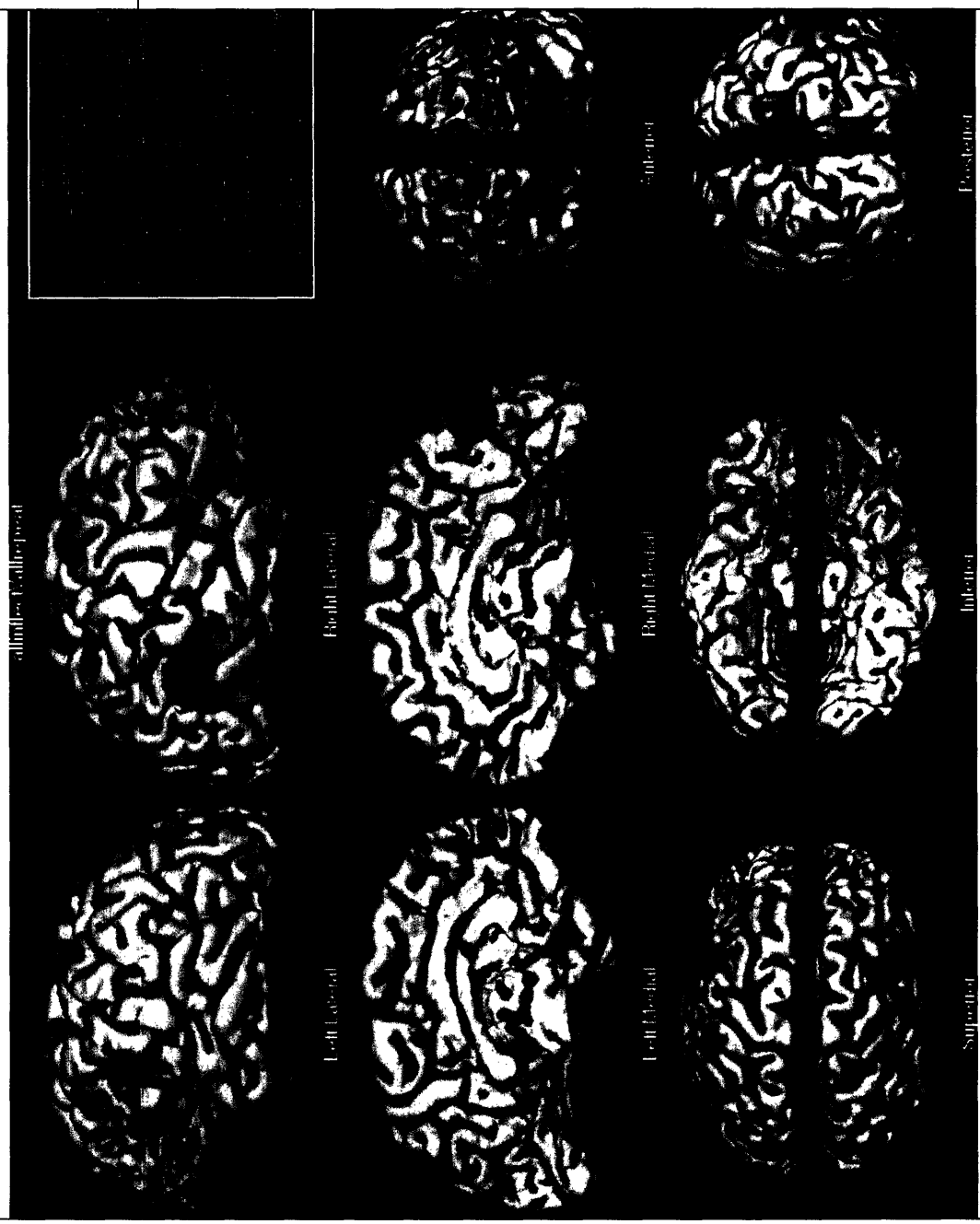
The table of contrasts below indexes the short names of all contrasts, and lists the page on which the Contrast Statistical Map (CSM) can be found.

6.6 Results: All CSMs

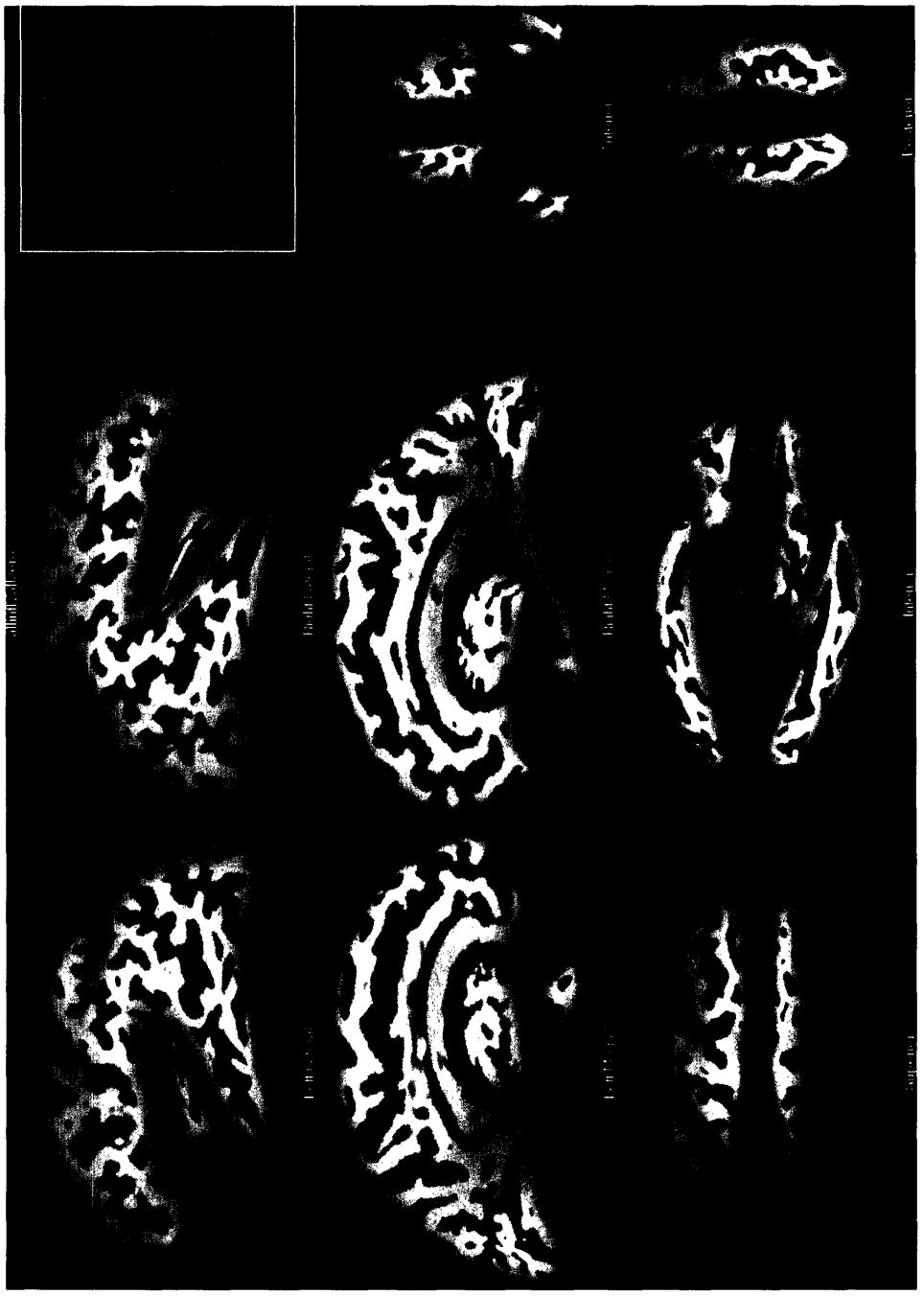
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V All Read	**VRO, VIO, NRO, NIO**	>	**VRR, VIR, NRR, NIR**	24%	>	24%
Hypotheses:	Most gross contrast for inflectional morphology. Should localize activity for inflection, summed across grammatical categories, and independent of regularity.					
Observations:	Strong activation in Broca's area (44). Also, activation in BA47, anterior insula, SMA. "Deactivation" (activation for repeat > inflect) strong in right posterior inferior temporal gyrus, and mild in left extra-striate.					



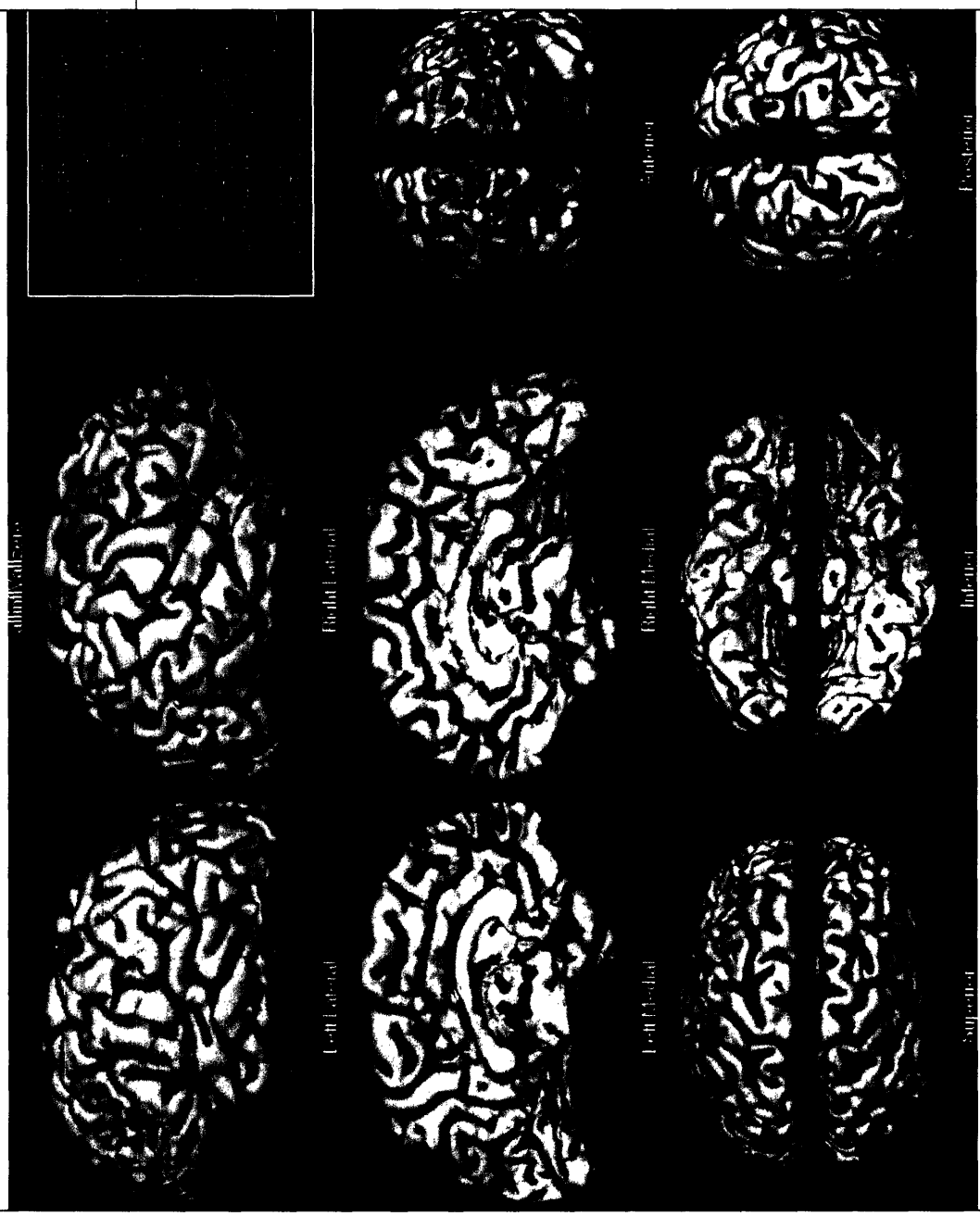
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V All Read	VRO, VIO, NRO, NIO	>	VRR, VIR, NRR, NIR	24%	>	24%
Hypotheses:						
Observations:						



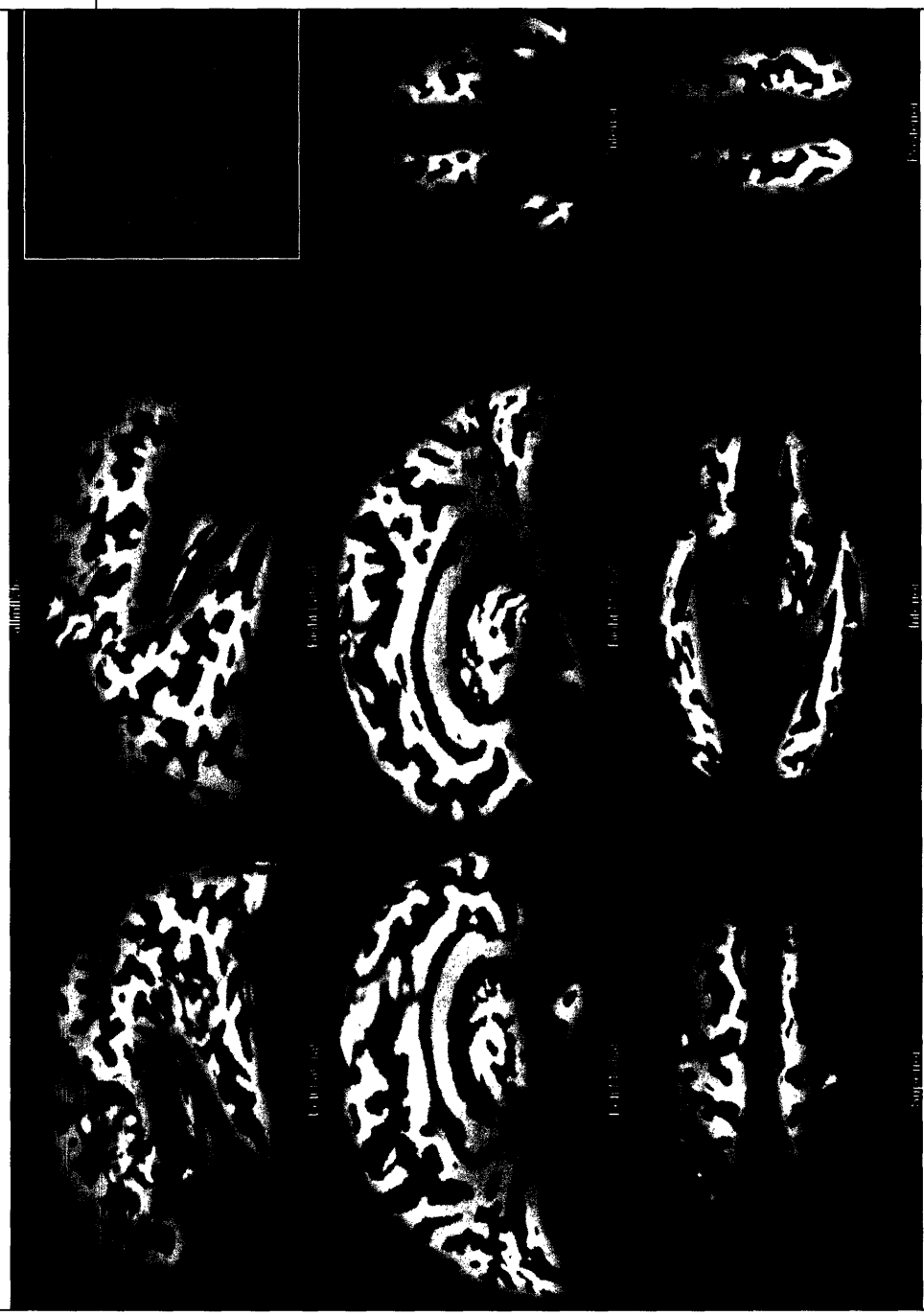
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V All Zero-Inflect	VRO, VIO, NRO, NIO	>	VRZ, VIZ, NRZ, NIZ	24%	>	24%
Hypotheses:						
Observations:						



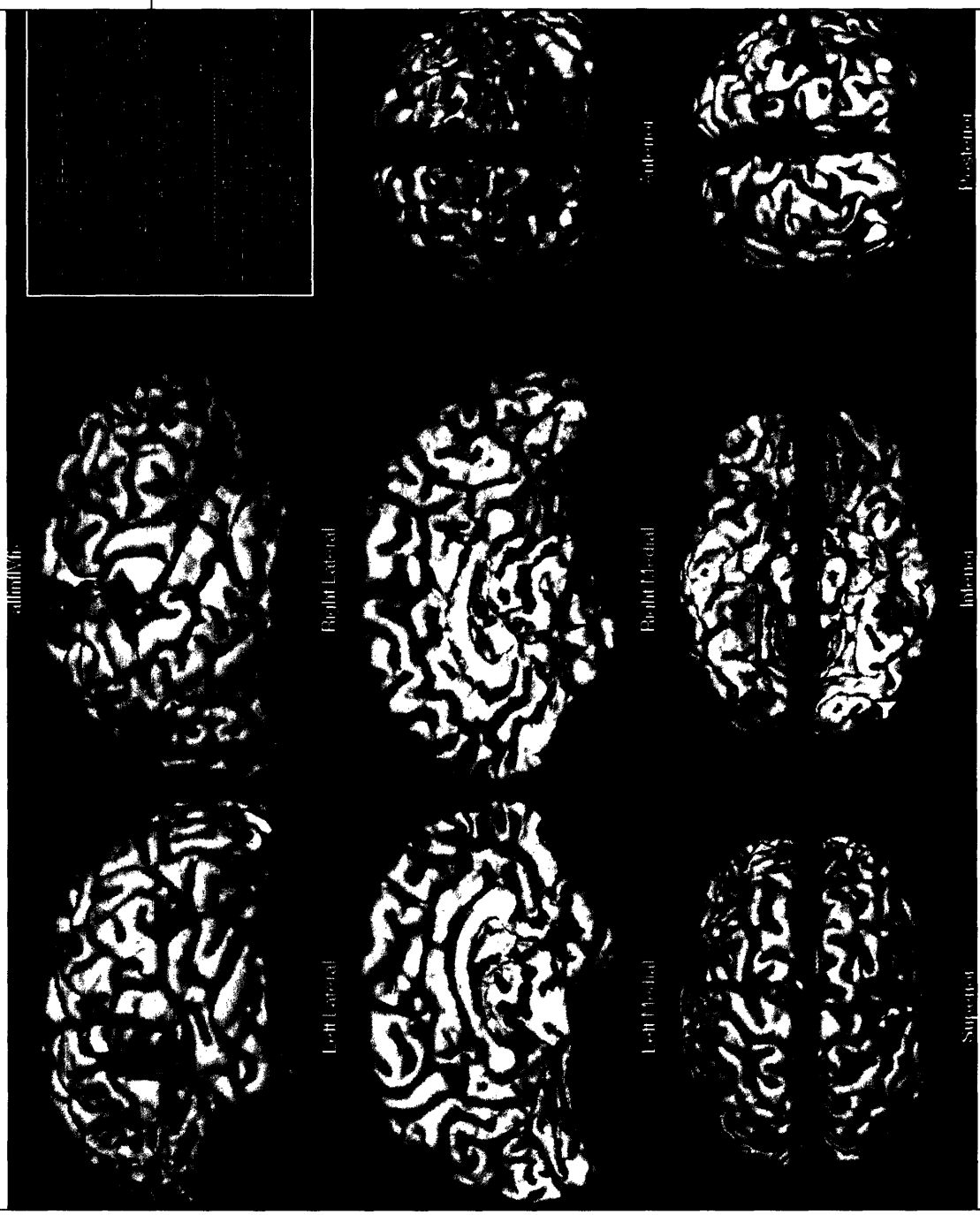
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V All Zero-Inflect	VRO, VIO, NRO, NIO	>	VRZ, VIZ, NRZ, NIZ	24%	>	24%
Hypotheses:						
Observations:						



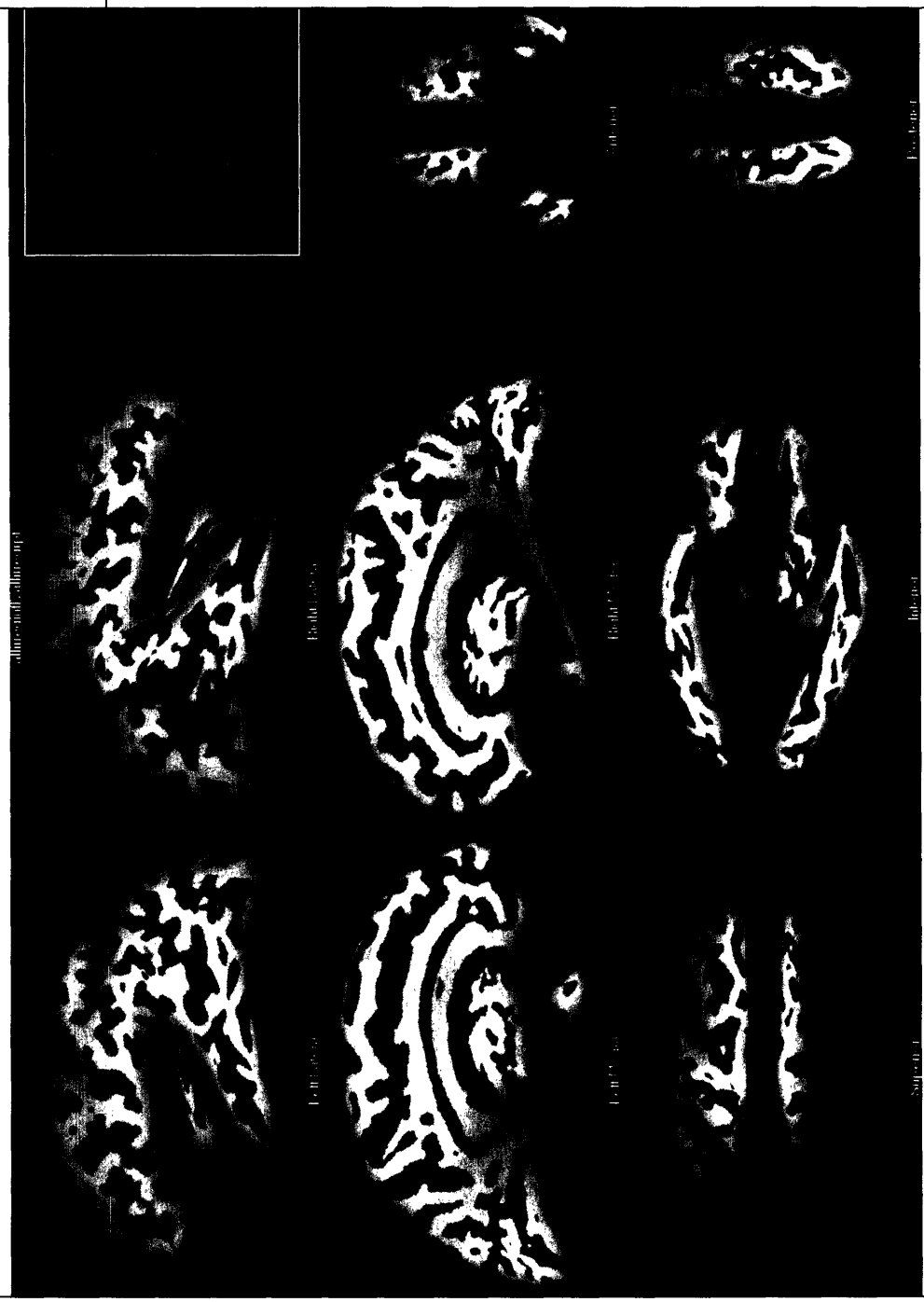
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V Fix	VRO, VIO, NRO, NIO	>	FIX	24%	>	27%
Hypotheses:						
Observations:						



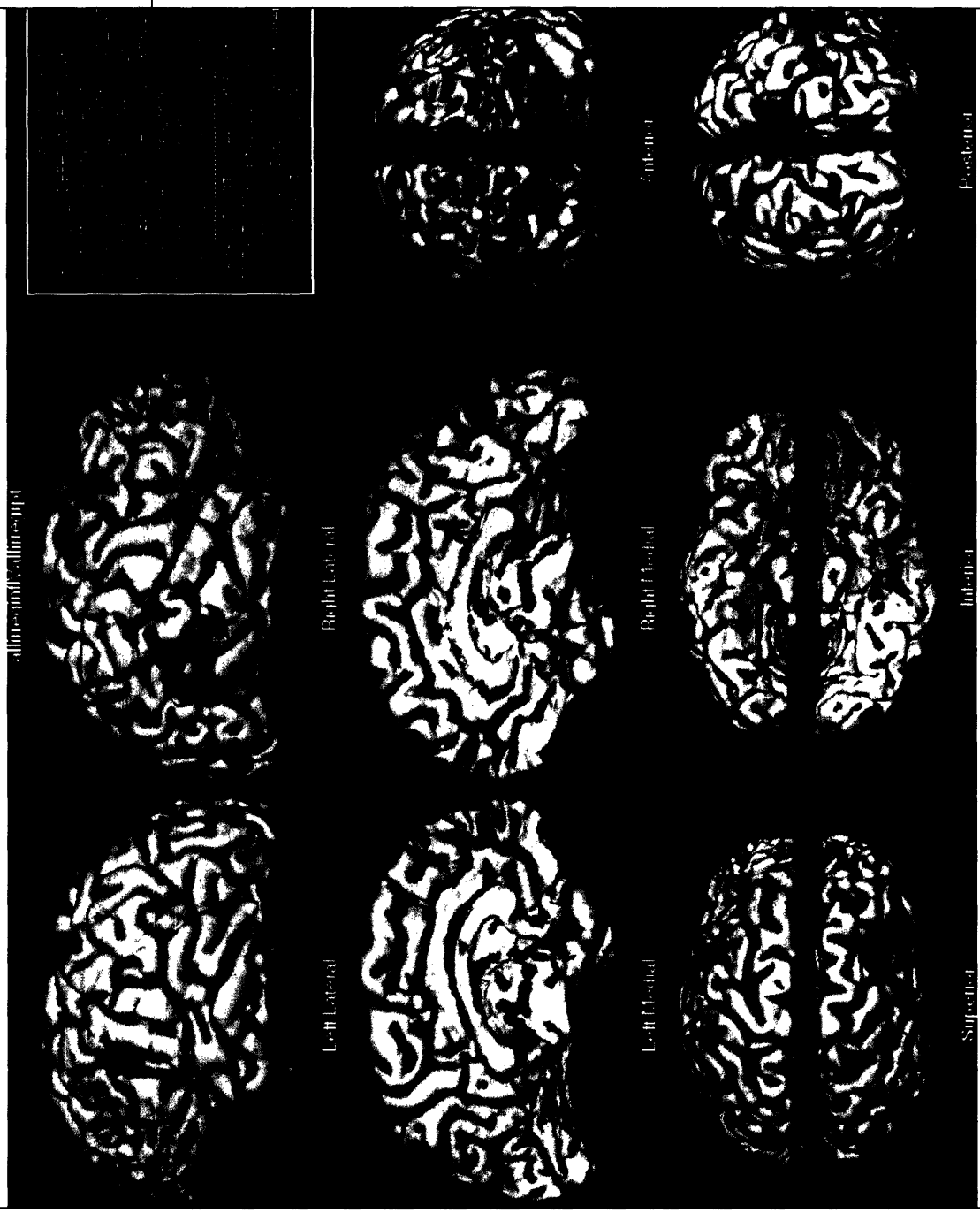
Contrast Name			Conditions Negative	Data Represented		
All Overt-Inflect V Fix	VRO, VIO, NRO, NIO	>	FIX	24%	>	27%
Hypotheses:						
Observations:						



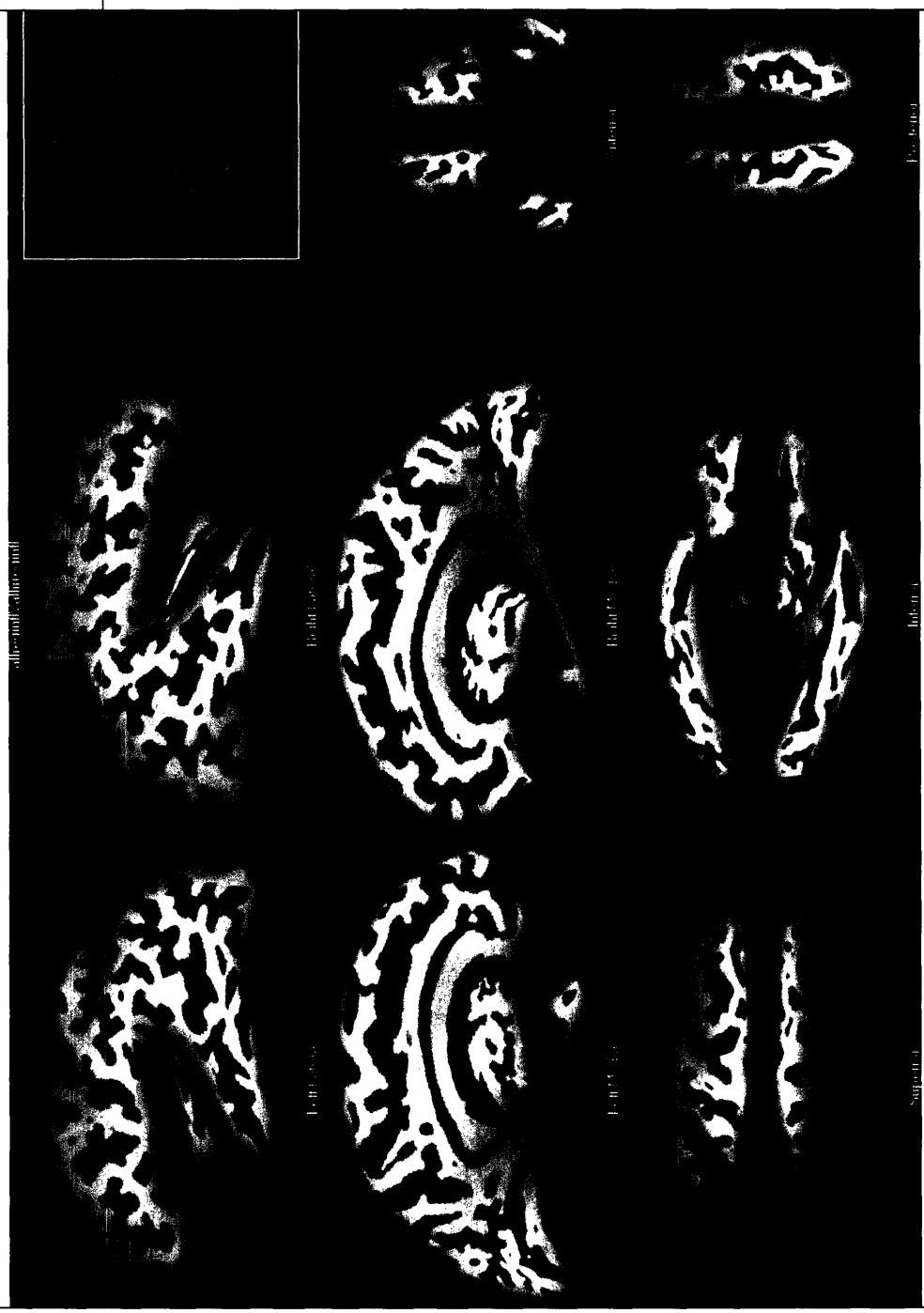
Contrast Name			Conditions Negative	Data Represented		
All Irreg Overt-Inflect V All Irreg Read	**VIO, NIO**	>	**VIR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



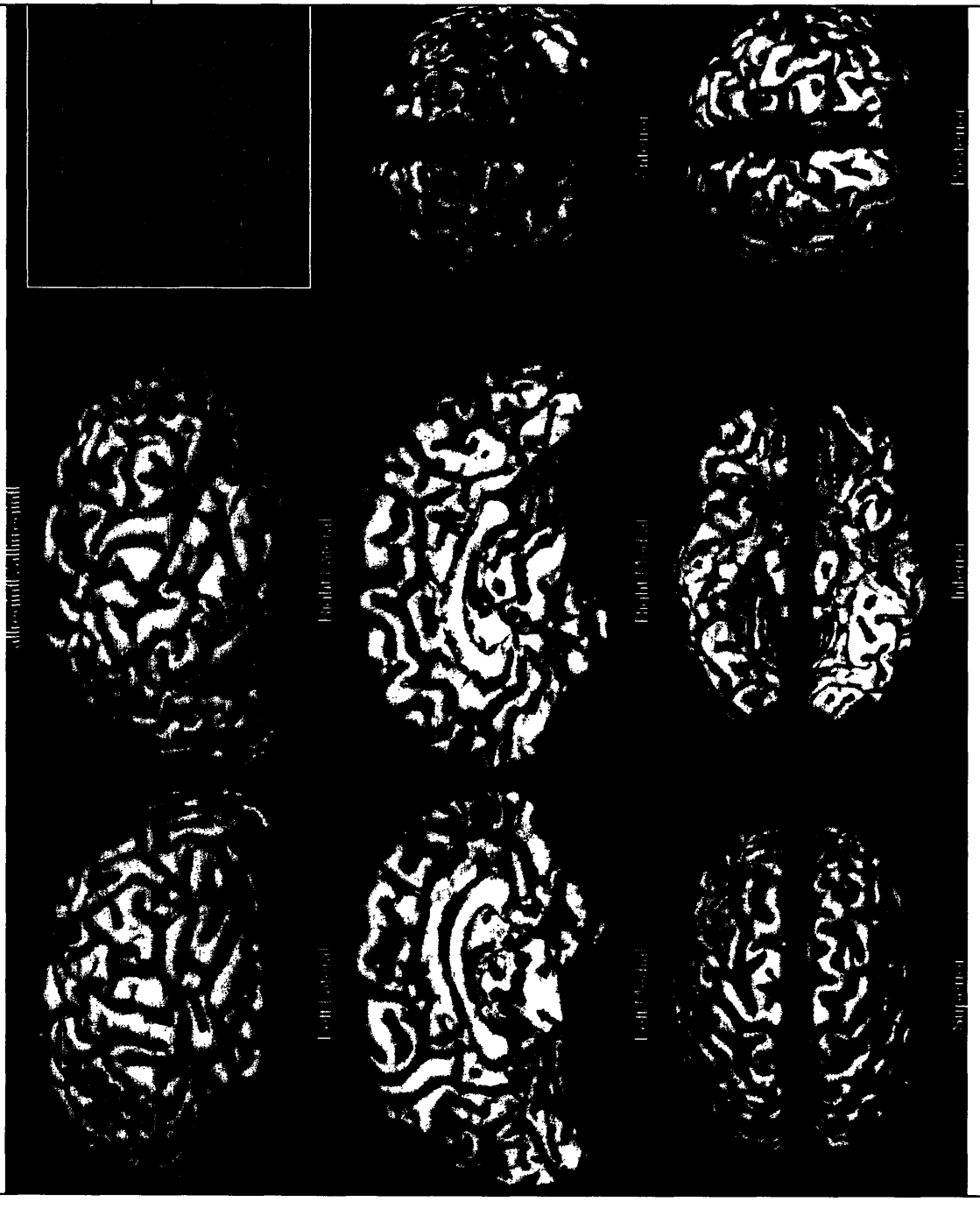
Contrast Name			Conditions Negative	Data Represented		
All Irreg Overt-Inflect V All Irreg Read	VIO, NIO	>	VIR, NIR	12%	>	12%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
All Reg Overt-Inflect V All Irreg Overt-Inflect	**VRO, NRO**	>	**VIO, NIO**	12%	>	12%
Hypotheses:						
Observations:						

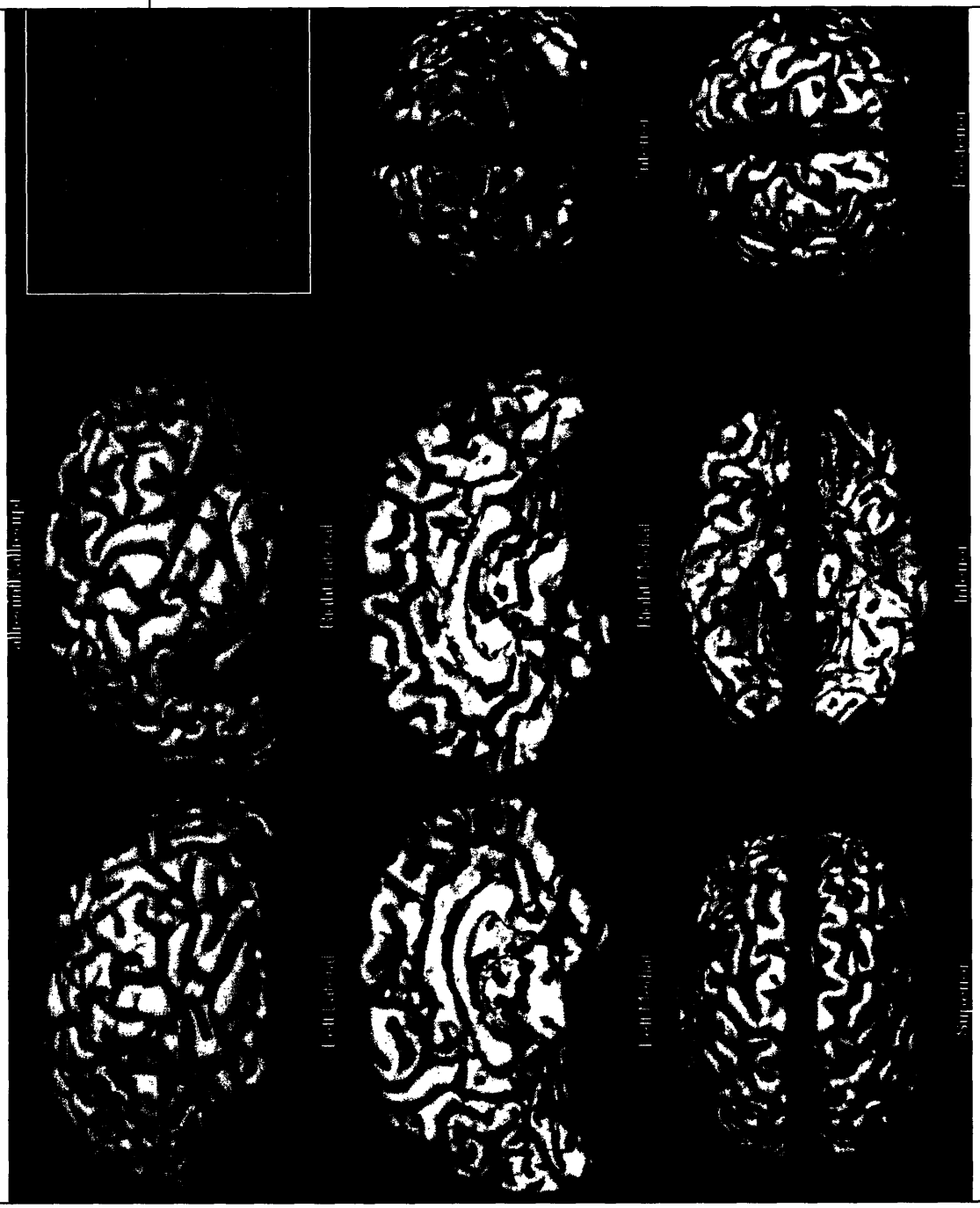


Contrast Name			Conditions Negative	Data Represented		
All Reg Overt-Inflect V All Irreg Overt-Inflect	**VRO, NRO**	>	**VIO, NIO**	12%	>	12%
Hypotheses:						
Observations:						



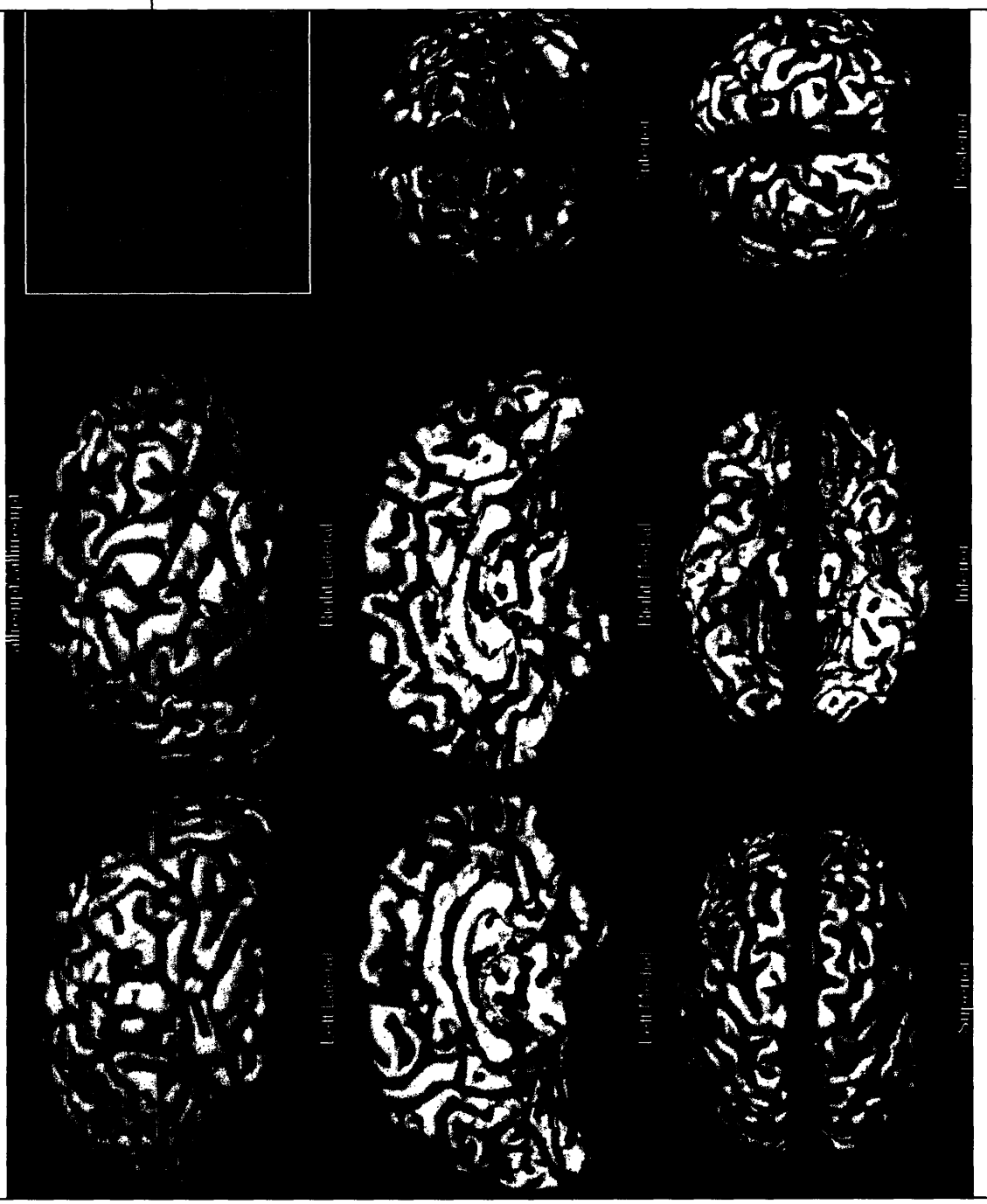
Contrast Name			Conditions Negative	Data Represented		
All Reg Overt-Inflect V All Reg Read	**VRO, NRO**	>	**VRR, NRR**	12%	>	12%
Hypotheses:						
Observations:						

Contrast Name			Conditions Negative	Data Represented		
All Reg Overt-Inflect V All Reg Read	**VRO, NRO**	>	**VRR, NRR**	12%	>	12%
Hypotheses:	Isolates the morphosyntax activation from the reg-irreg effects. "Read" specific signal separated from effects of odd irregulars.					
Observations:						

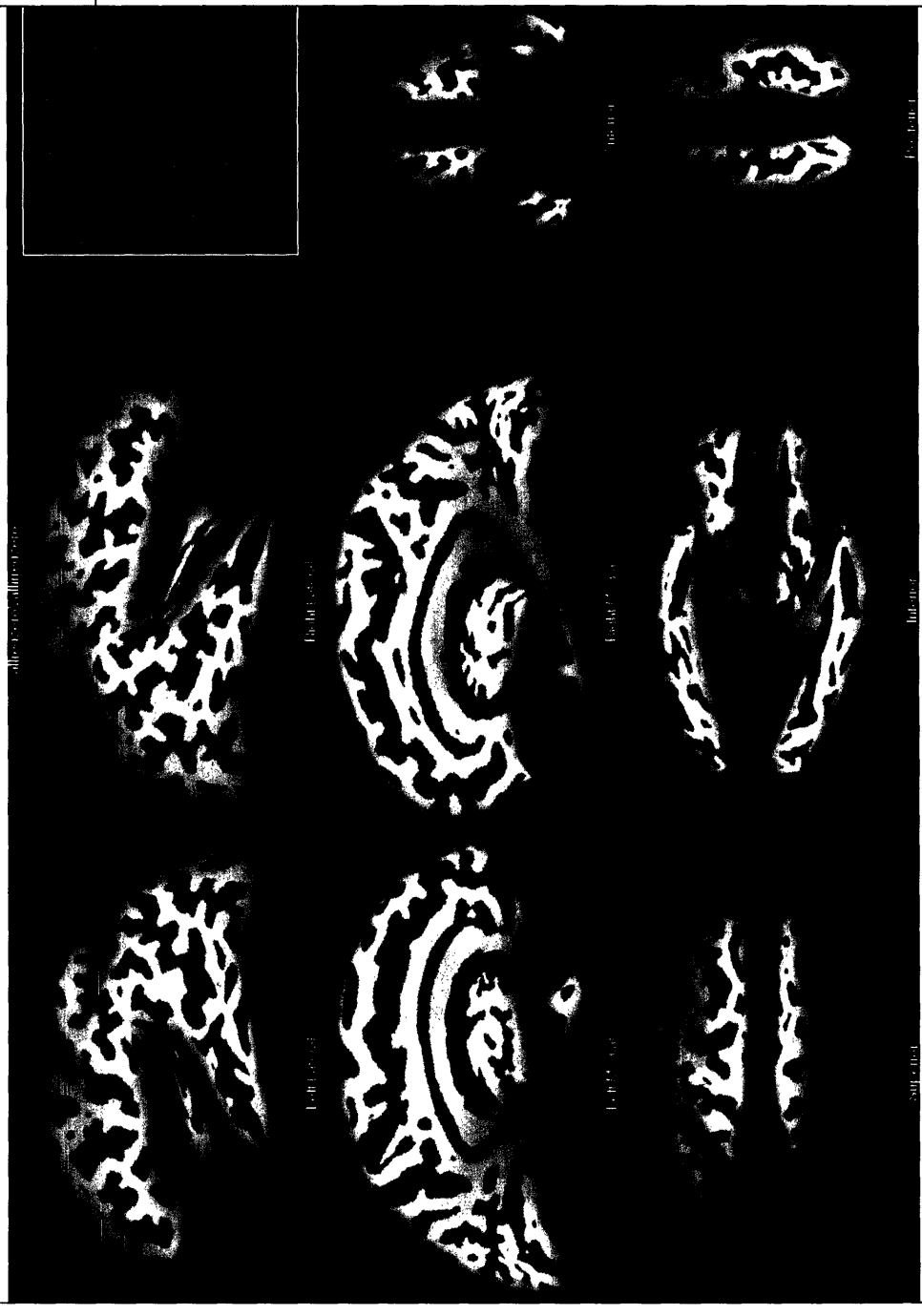


Contrast Name			Conditions Negative	Data Represented		
All Reg Read V All Irreg Read	**VRR, NRR**	>	**VIR, NIR**	12%	>	12%
Hypotheses:						
Observations:						

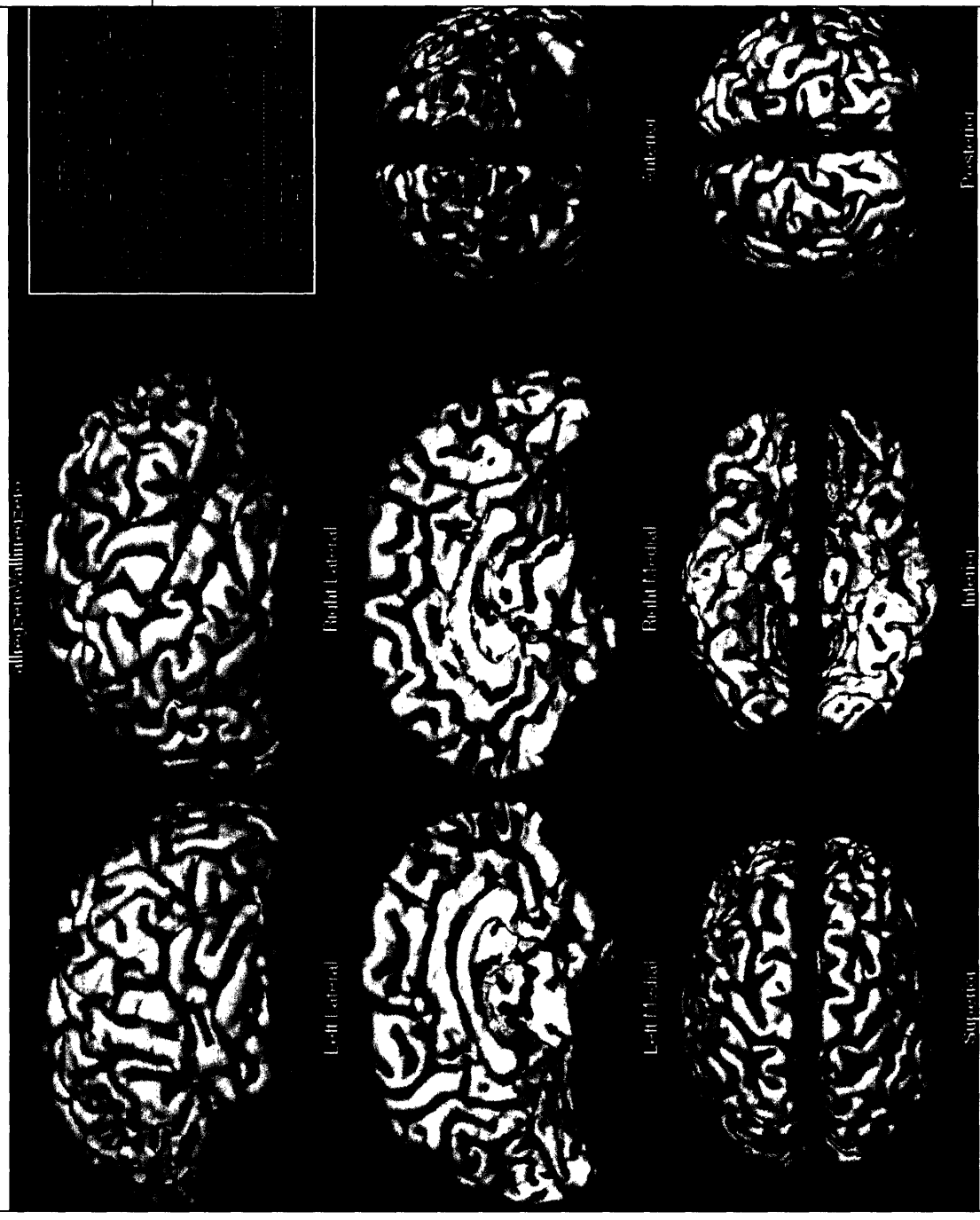
Contrast Name			Conditions Negative	Data Represented		
All Reg Read V All Irreg Read	**VRR, NRR**	>	**VIR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



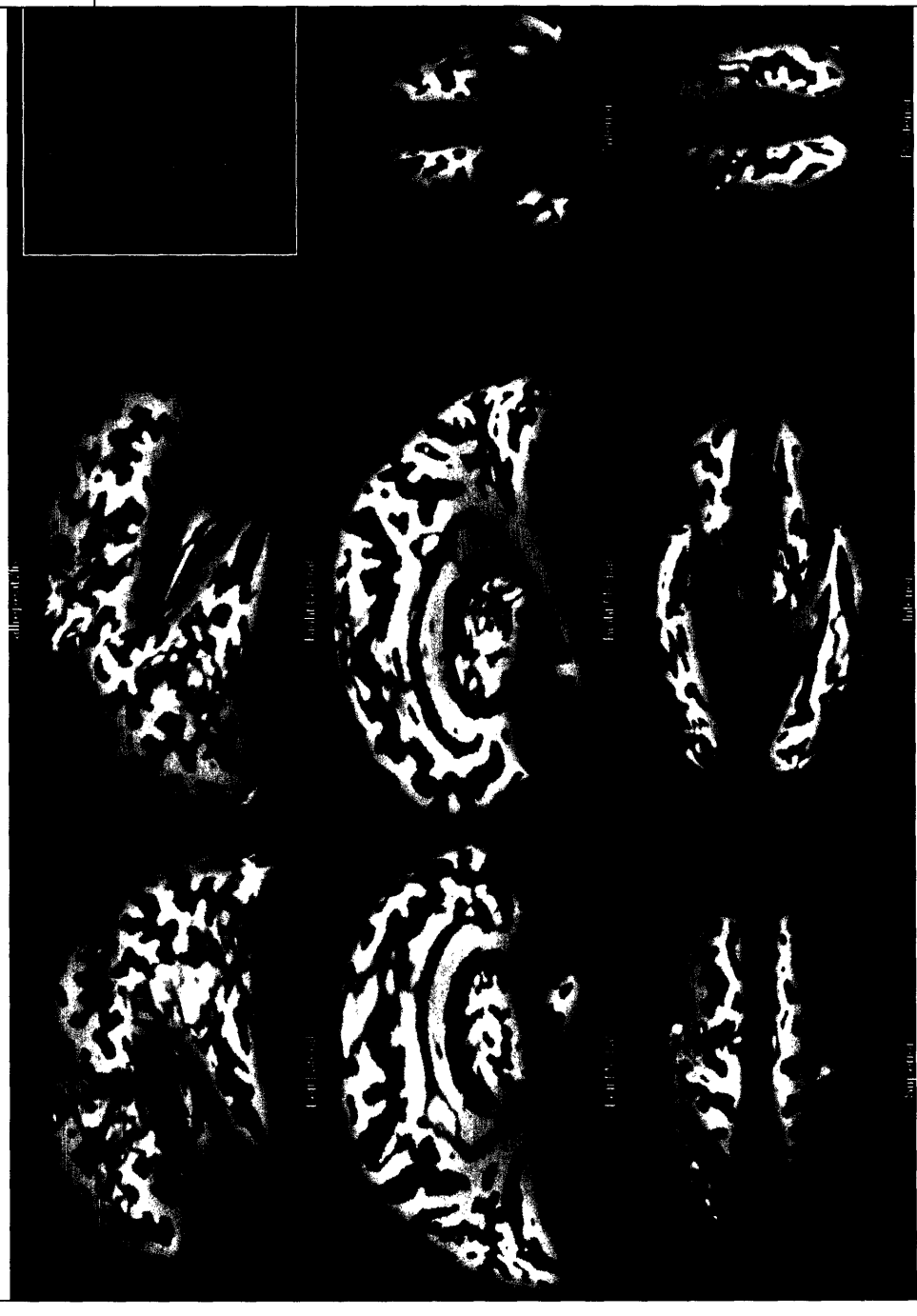
Contrast Name			Conditions Negative	Data Represented		
All Reg Zero-Inflect V All Irreg Zero-Inflect	**VRZ, NRZ**	>	**VIZ, NIZ**	12%	>	12%
Hypotheses:						
Observations:						



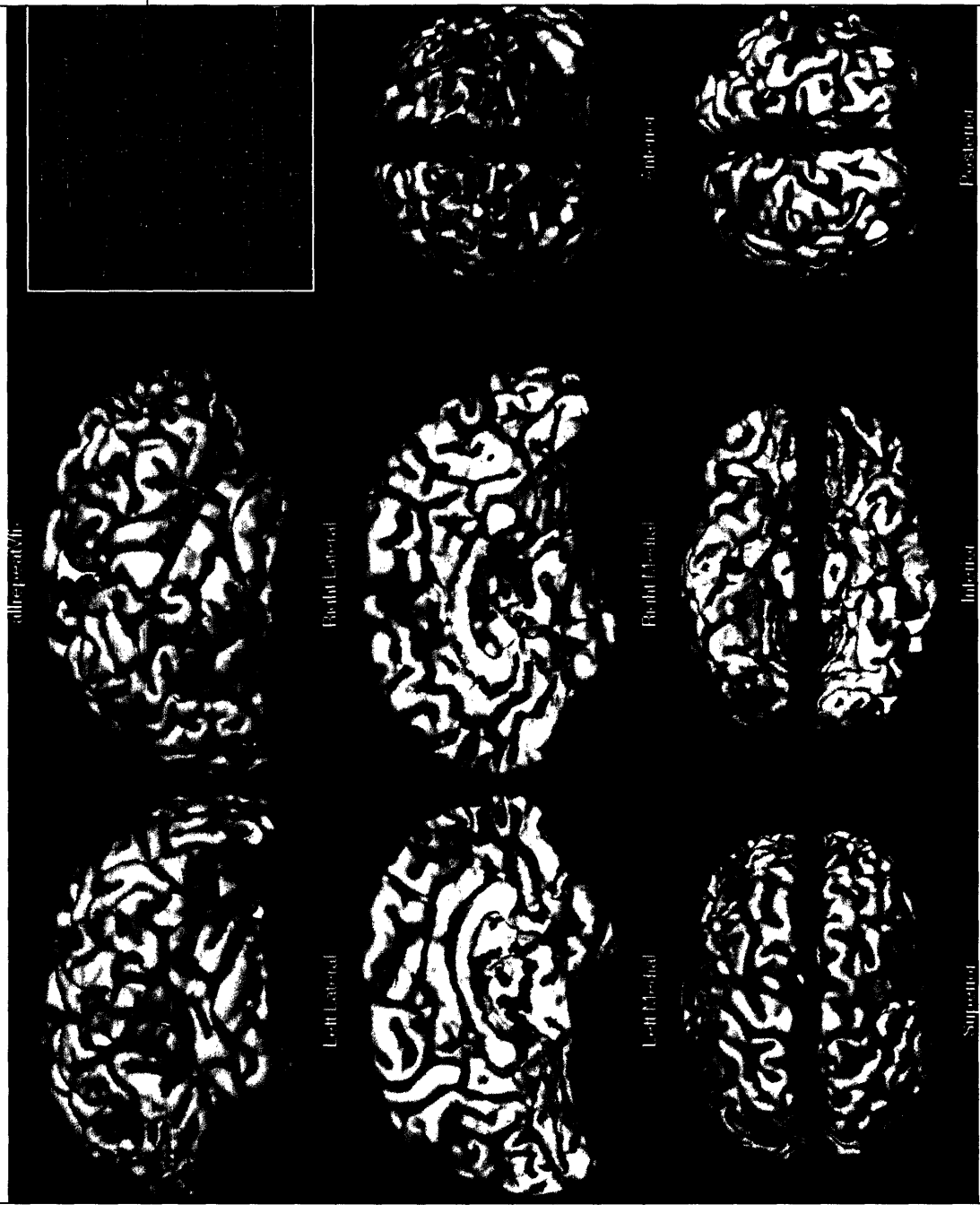
Contrast Name			Conditions Negative	Data Represented		
All Reg Zero-Inflect V All Irreg Zero-Inflect	**VRZ, NRZ**	>	**VIZ, NIZ**	12%	>	12%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
All Read V Fix	**VRR, VIR, NRR, NIR**	>	**FIX**	24%	>	27%
Hypotheses:						
Observations:						

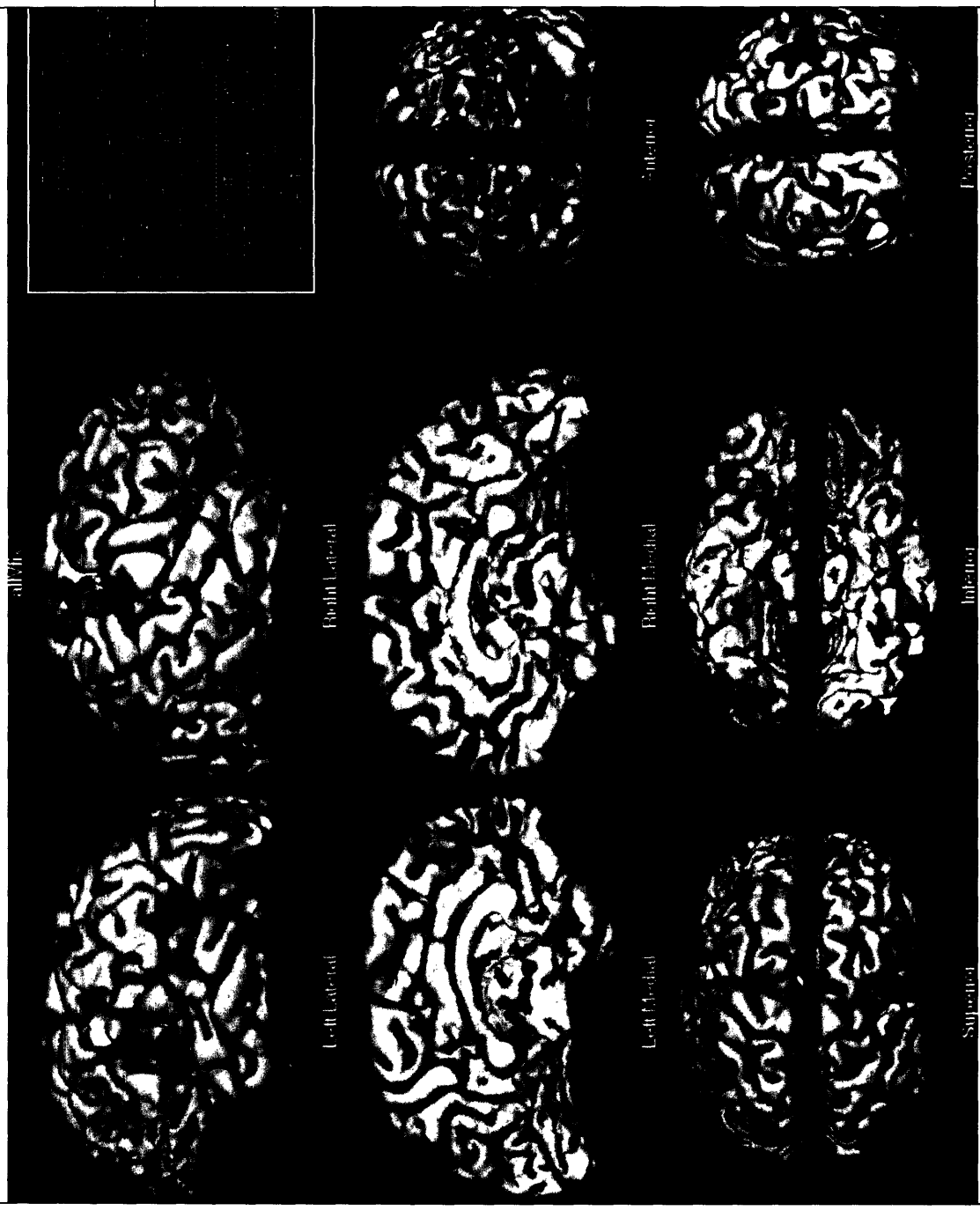


Contrast Name			Conditions Negative	Data Represented		
All Read V Fix	VRR, VIR, NRR, NIR	>	FIX	24%	>	27%
Hypotheses:						
Observations:						

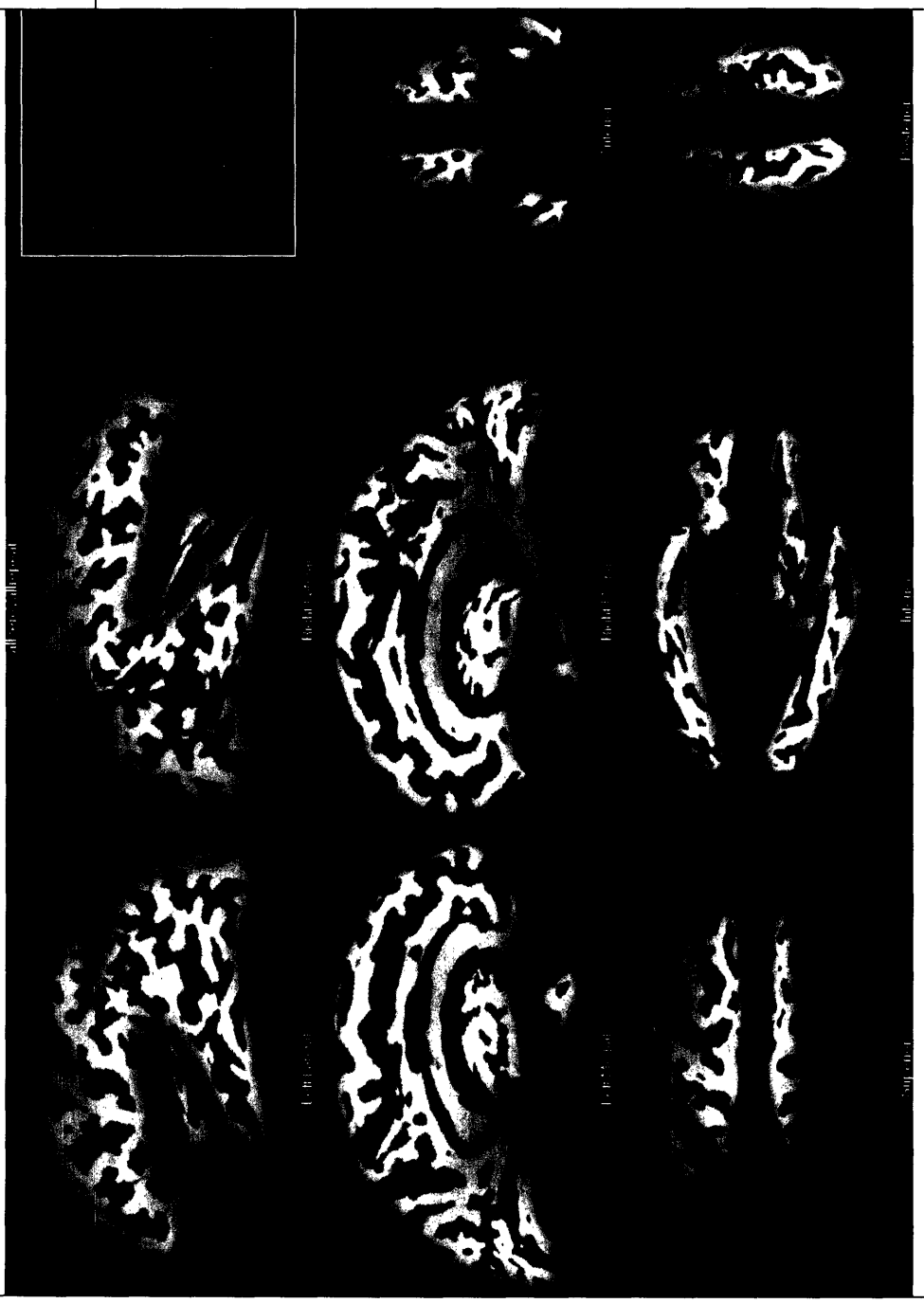


Contrast Name			Conditions Negative	Data Represented		
All V Fixation	VRO, VIO, VRZ, VIZ, VRR, VIR, NRO, NIO, NRZ, NIZ, NRR, NIR	>	FIX	73%	>	27%
Hypotheses:	All brain regions at all involved in doing any part of the task.					
Observations:						

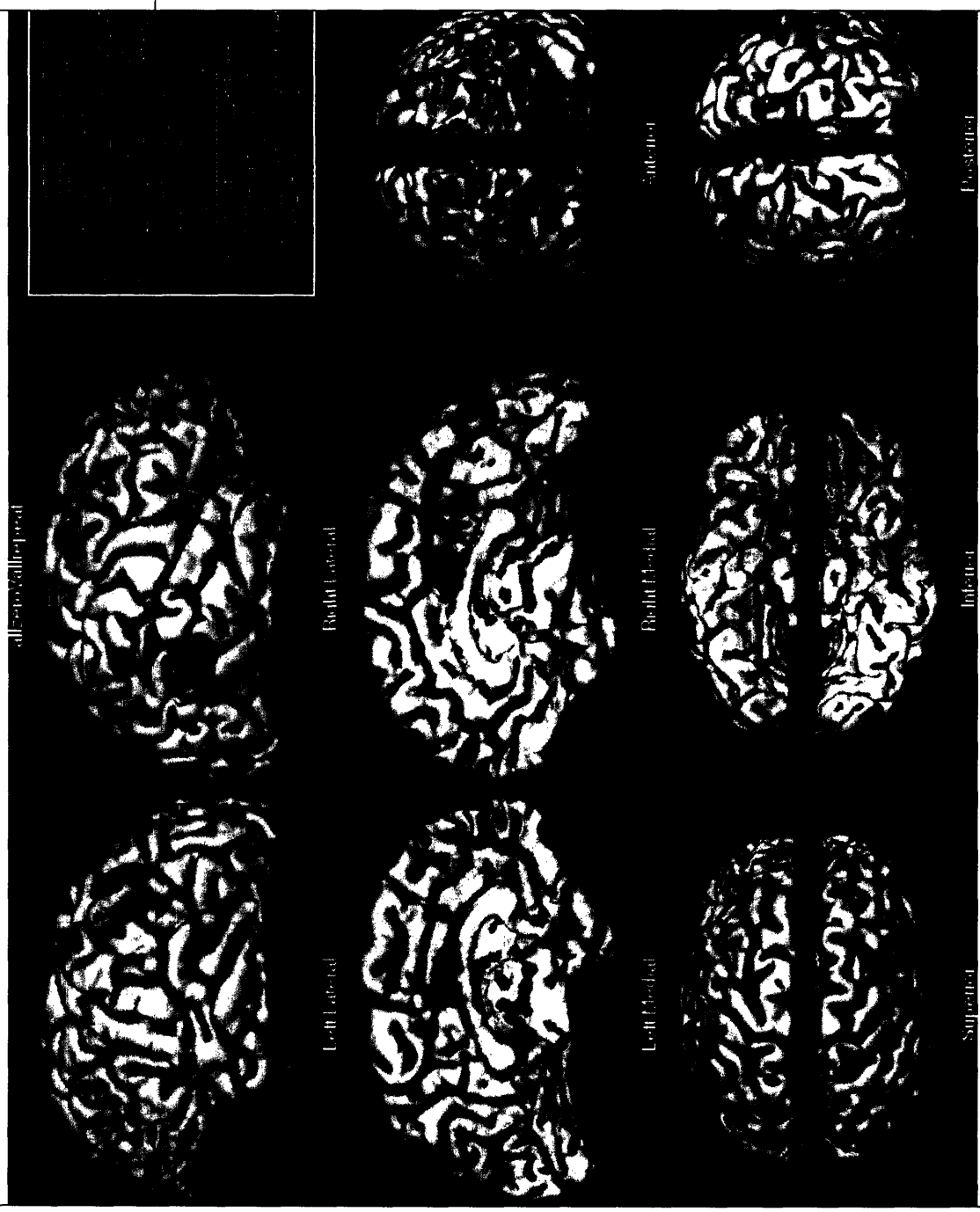
Contrast Name			Conditions Negative	Data Represented		
All V Fixation	VRO, VIO, VRZ, VIZ, VRR, VIR, NRO, NIO, NRZ, NIZ, NRR, NIR	>	FIX	73%	>	27%
Hypotheses:						
Observations:						



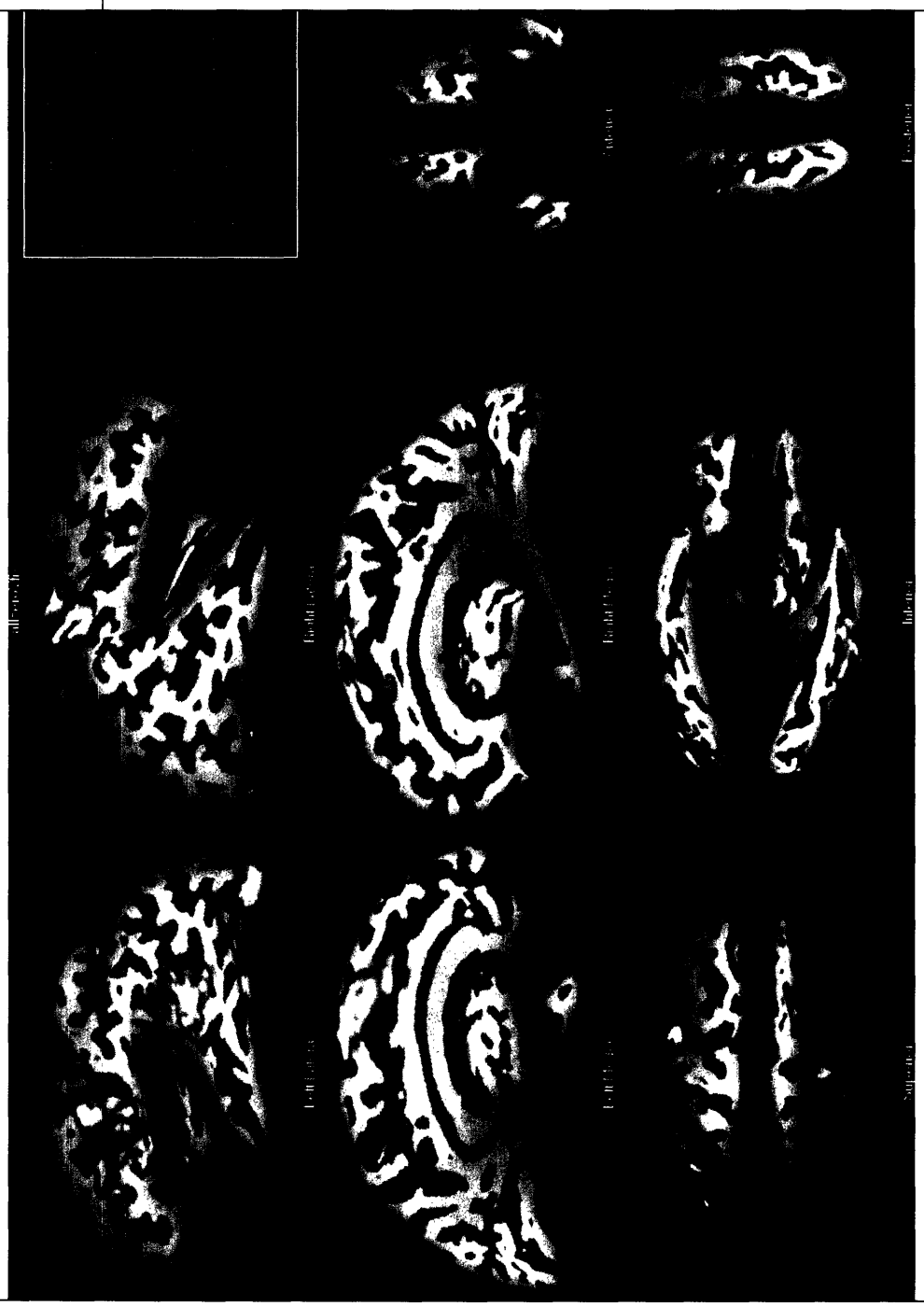
Contrast Name			Conditions Negative	Data Represented		
All Zero-Inflect V All Read	**VRZ, VIZ, NRZ, NIZ**	>	**VRR, VIR, NRR, NIR**	24%	>	24%
Hypotheses:						
Observations:						



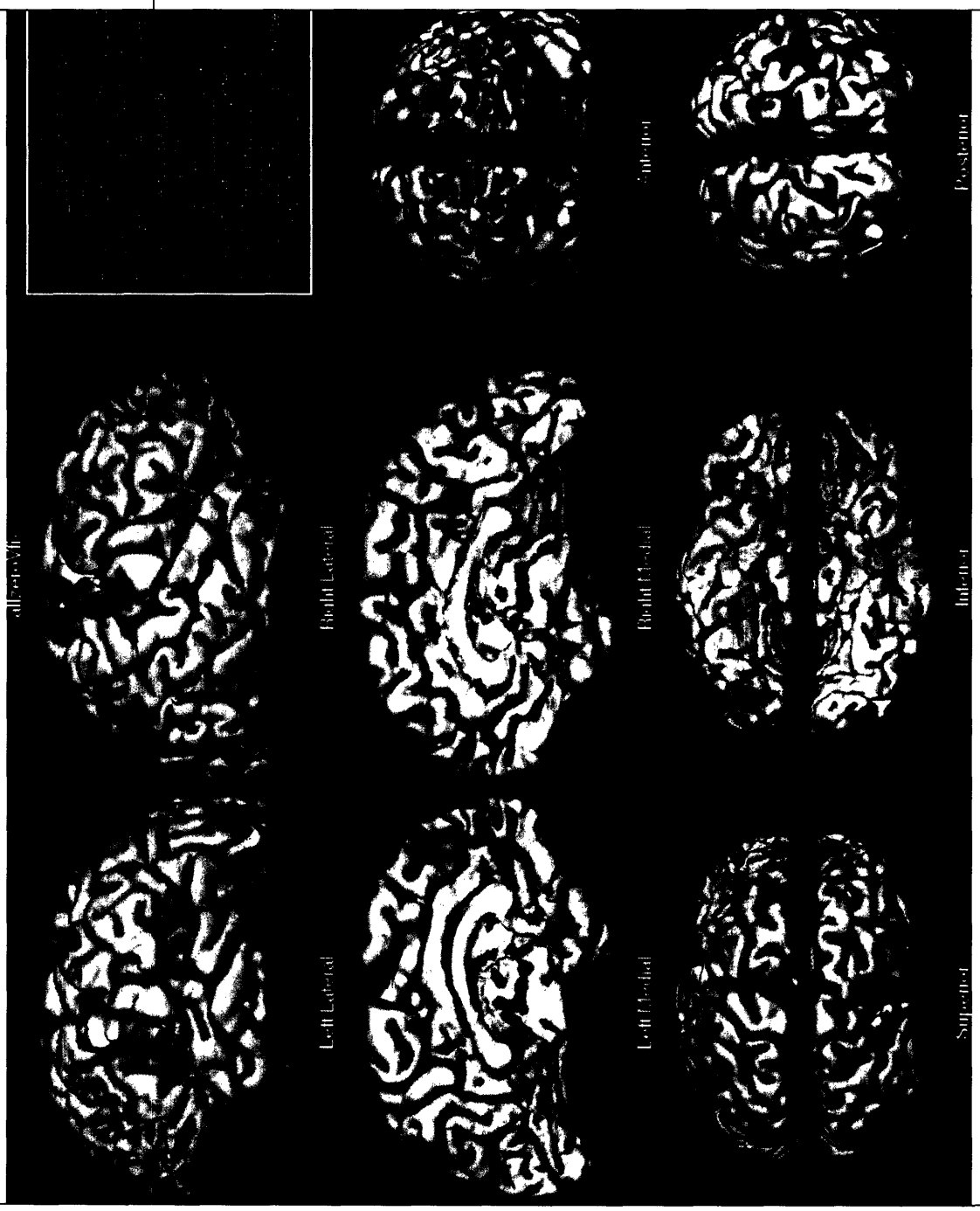
Contrast Name			Conditions Negative	Data Represented		
All Zero-Inflect V All Read	VRZ, VIZ, NRZ, NIZ	>	VRR, VIR, NRR, NIR	24%	>	24%
Hypotheses:						
Observations:						



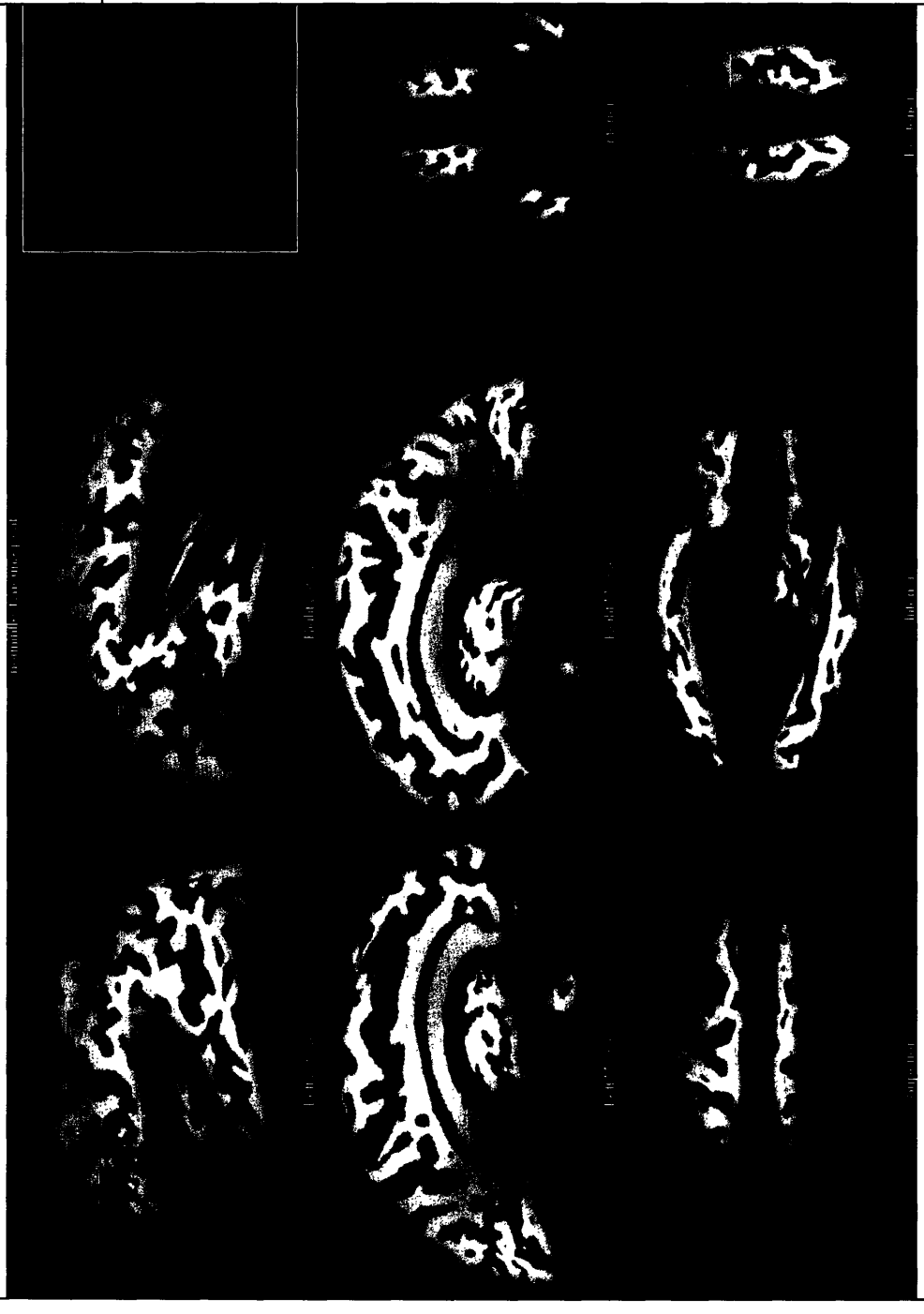
Contrast Name			Conditions Negative	Data Represented		
All Zero-Inflect V Fix	**VRZ, VIZ, NRZ, NIZ**	>	**FIX**	24%	>	27%
Hypotheses:						
Observations:						



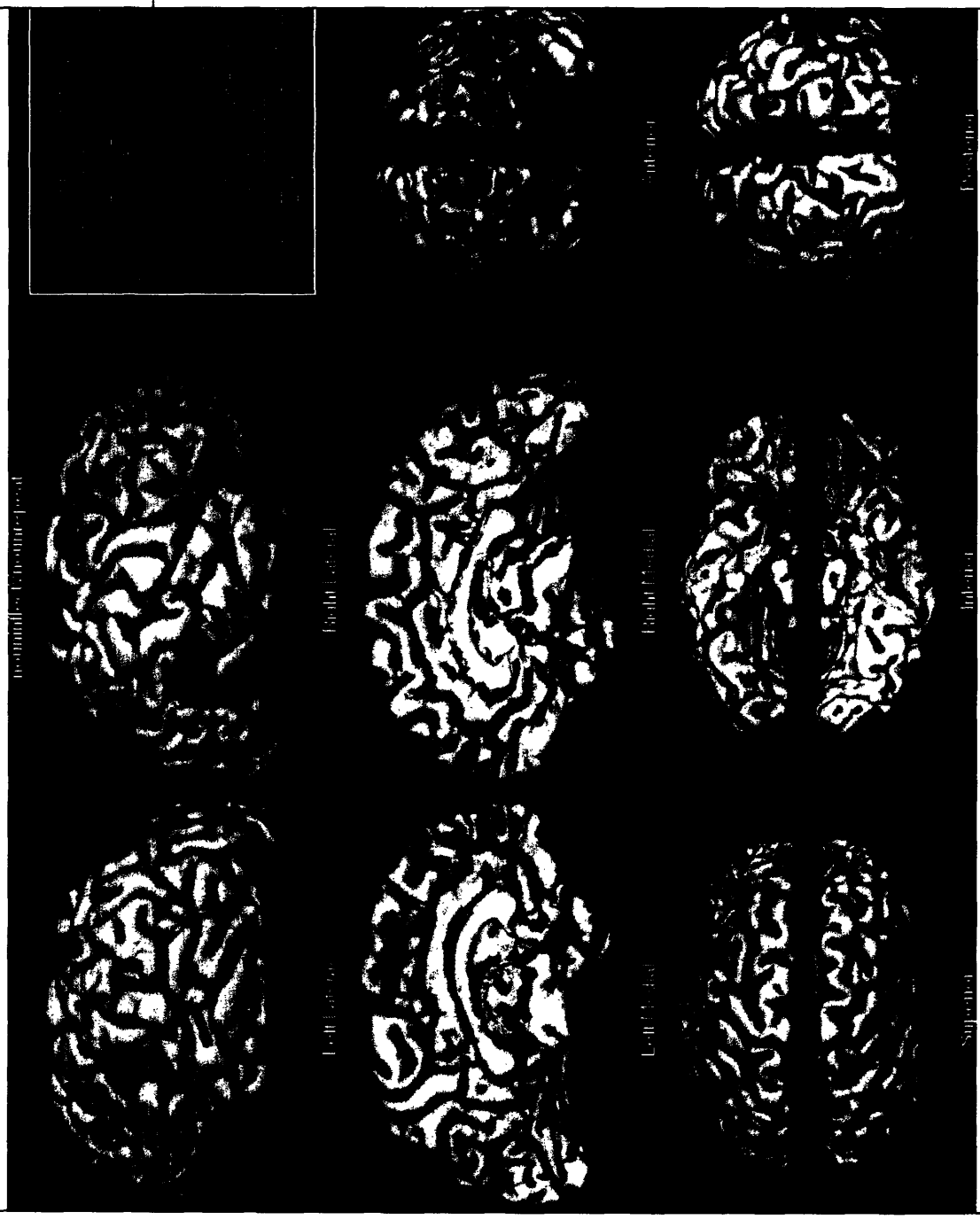
Contrast Name			Conditions Negative	Data Represented		
All Zero-Inflect V Fix	VRZ, VIZ, NRZ, NIZ	>	FIX	24%	>	27%
Hypotheses:						
Observations:						



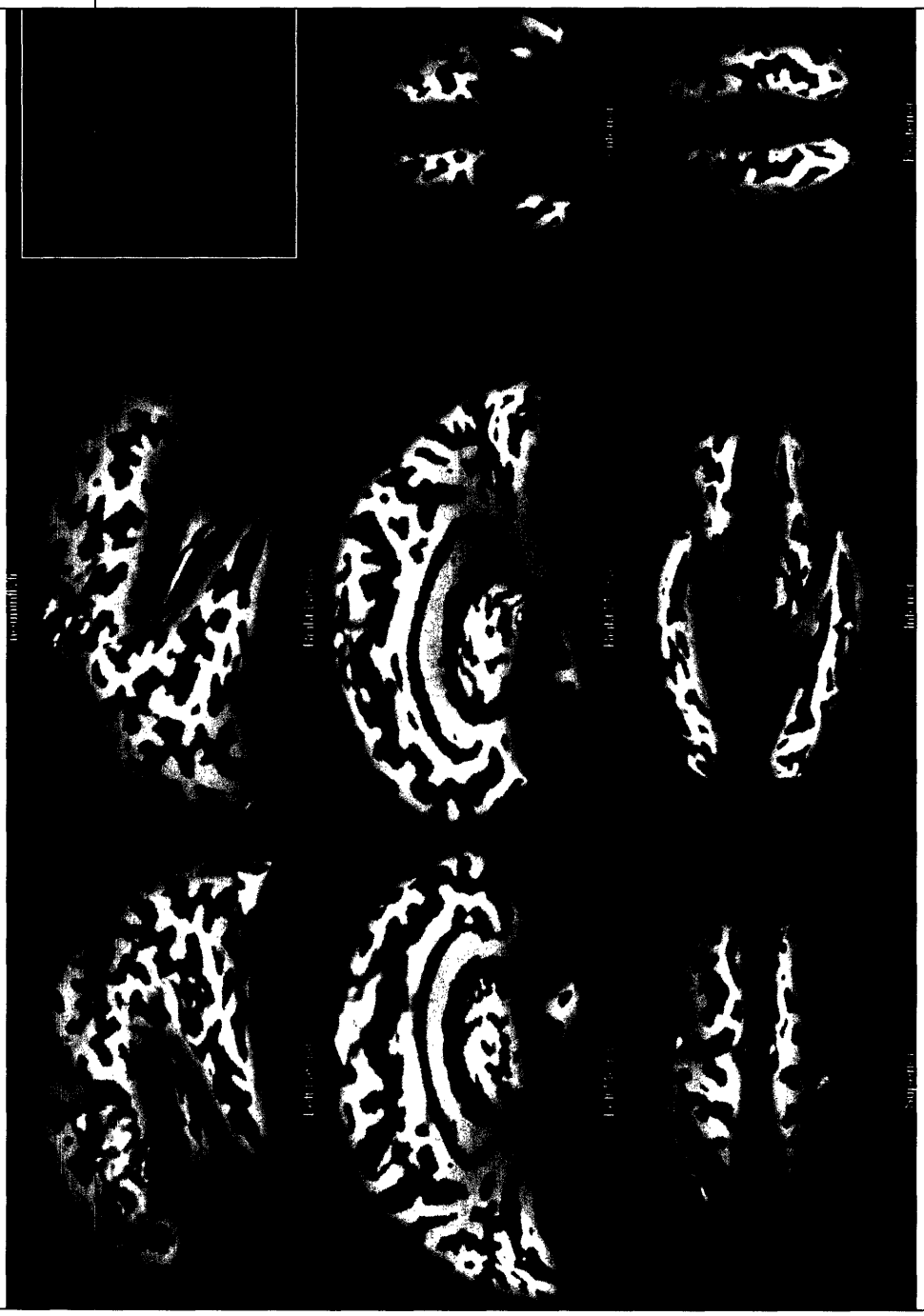
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Noun Read	**NRO, NIO**	>	**NRR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



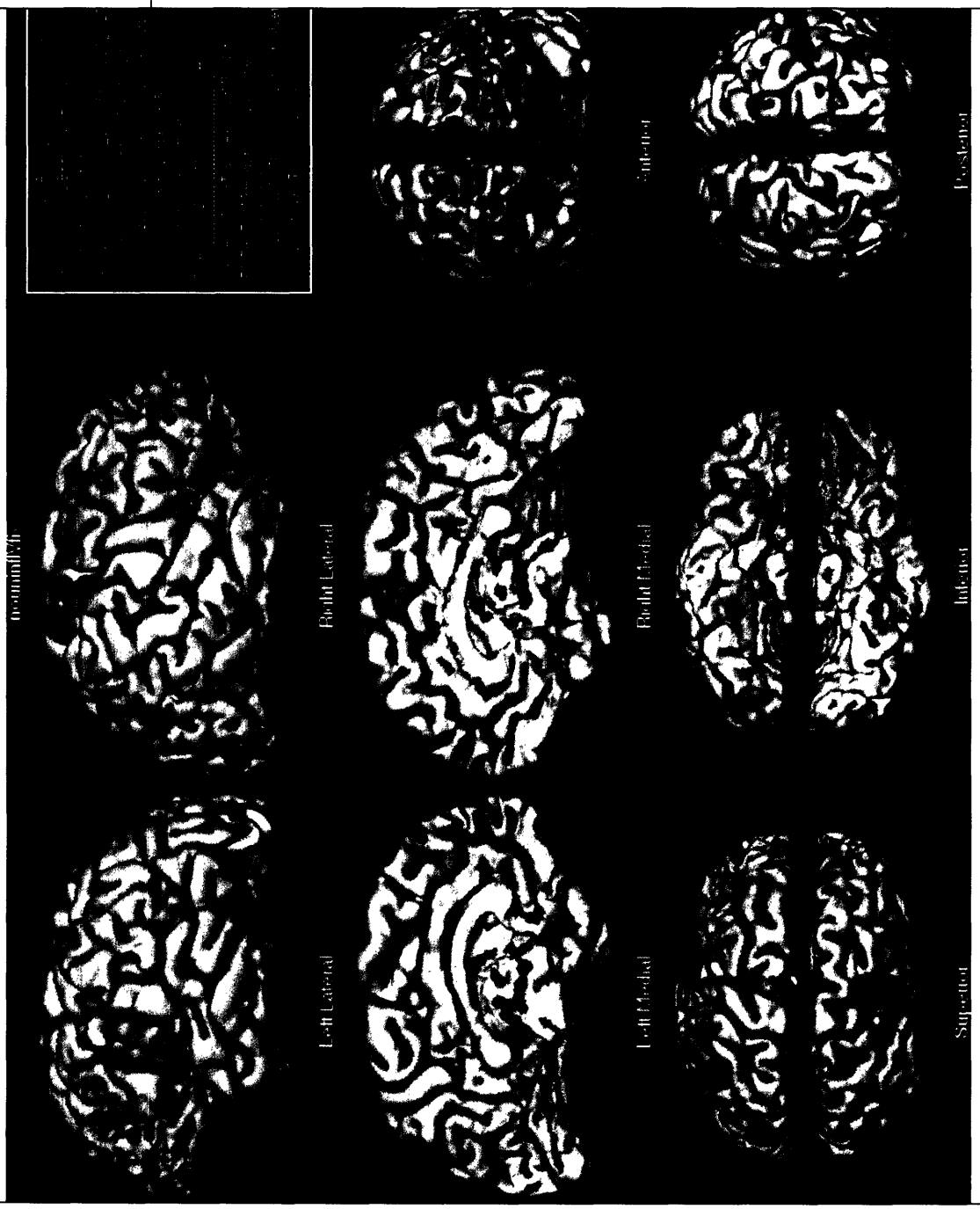
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Noun Read	**NRO, NIO**	>	**NRR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



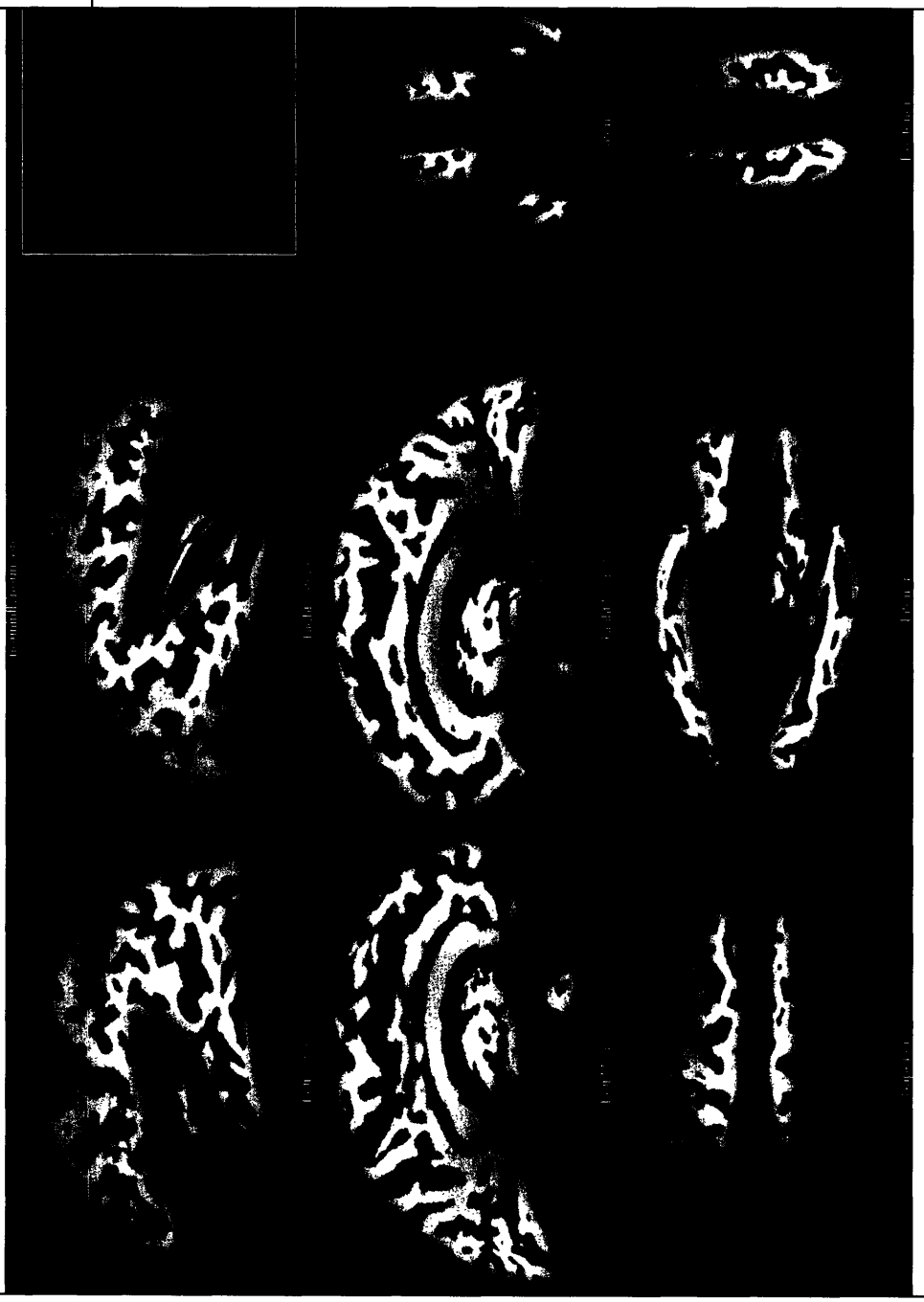
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Fix	**NRO, NIO**	>	**FIX**	24%	>	27%
Hypotheses:						
Observations:						



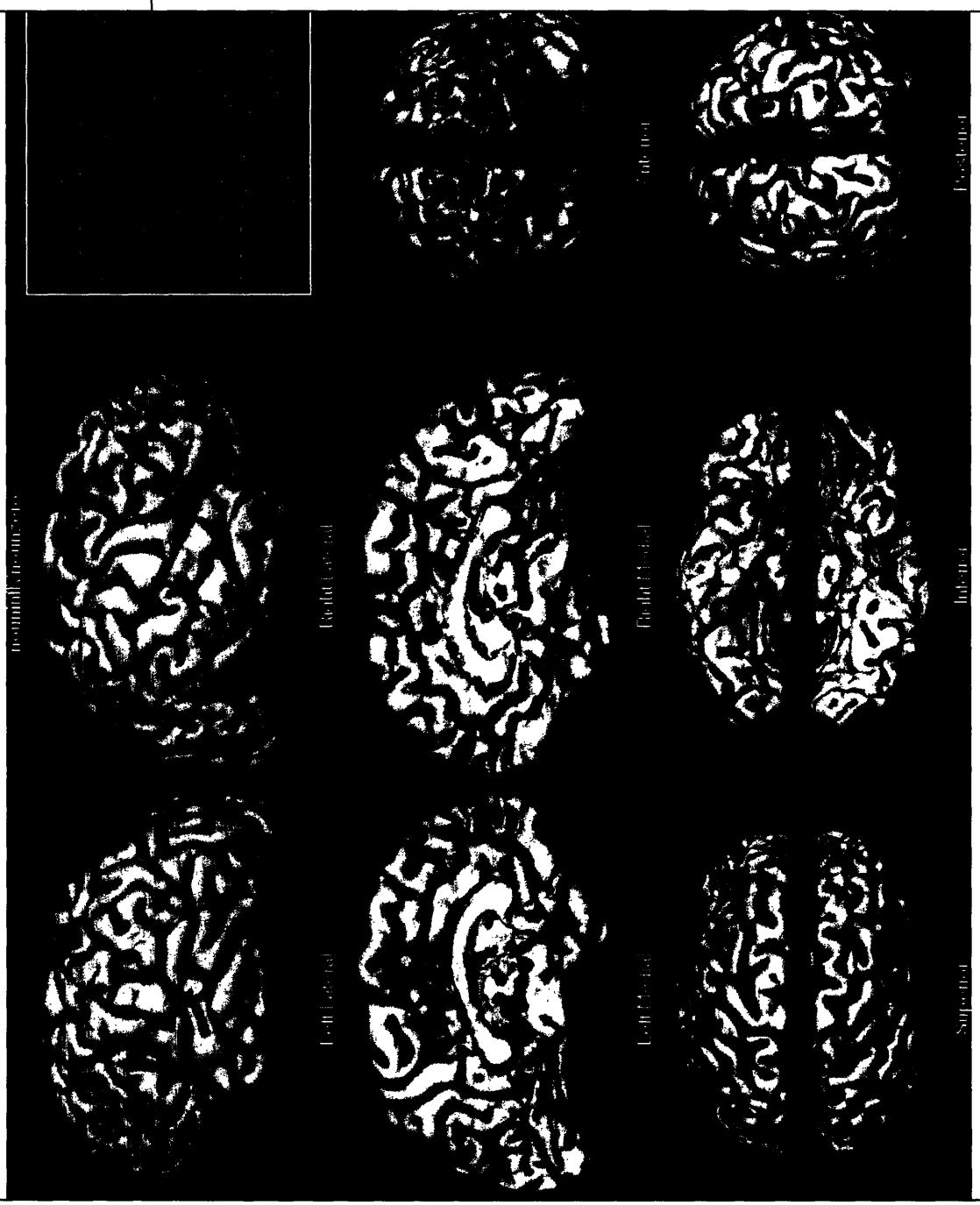
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Fix	**NRO, NIO**	>	**FIX**	24%	>	27%
Hypotheses:						
Observations:						



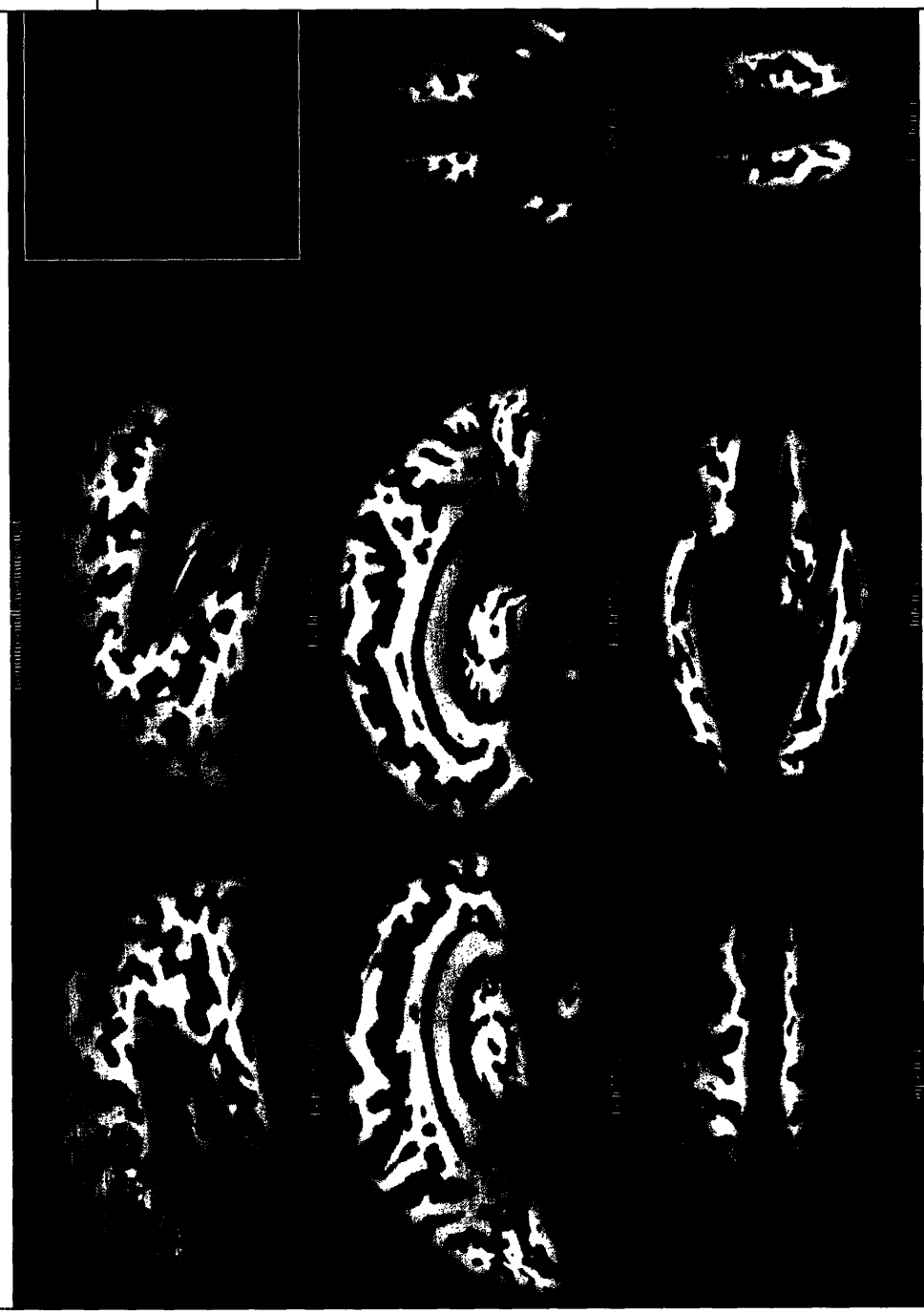
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Noun Zero-Inflect	**NRO, NIO**	>	**NRZ, NIZ**	12%	>	12%
Hypotheses:						
Observations:						



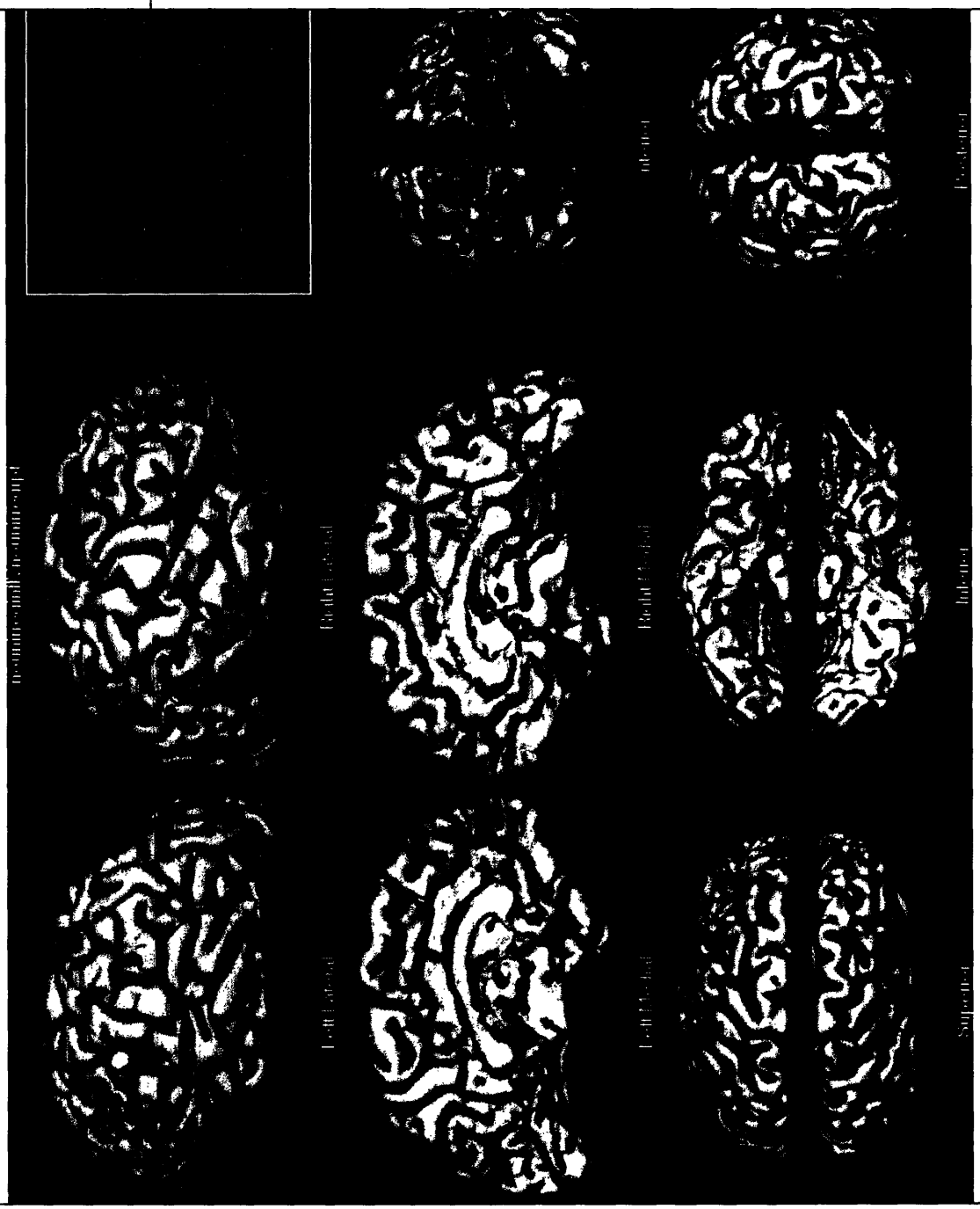
Contrast Name			Conditions Negative	Data Represented		
Noun Overt-Inflect V Noun Zero-Inflect	**NRO, NIO**	>	**NRZ, NIZ**	12%	>	12%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
Noun Irreg Overt-Inflect V Noun Irreg Read	**NIO**	>	**NIR**	6%	>	6%
Hypotheses:						
Observations:						

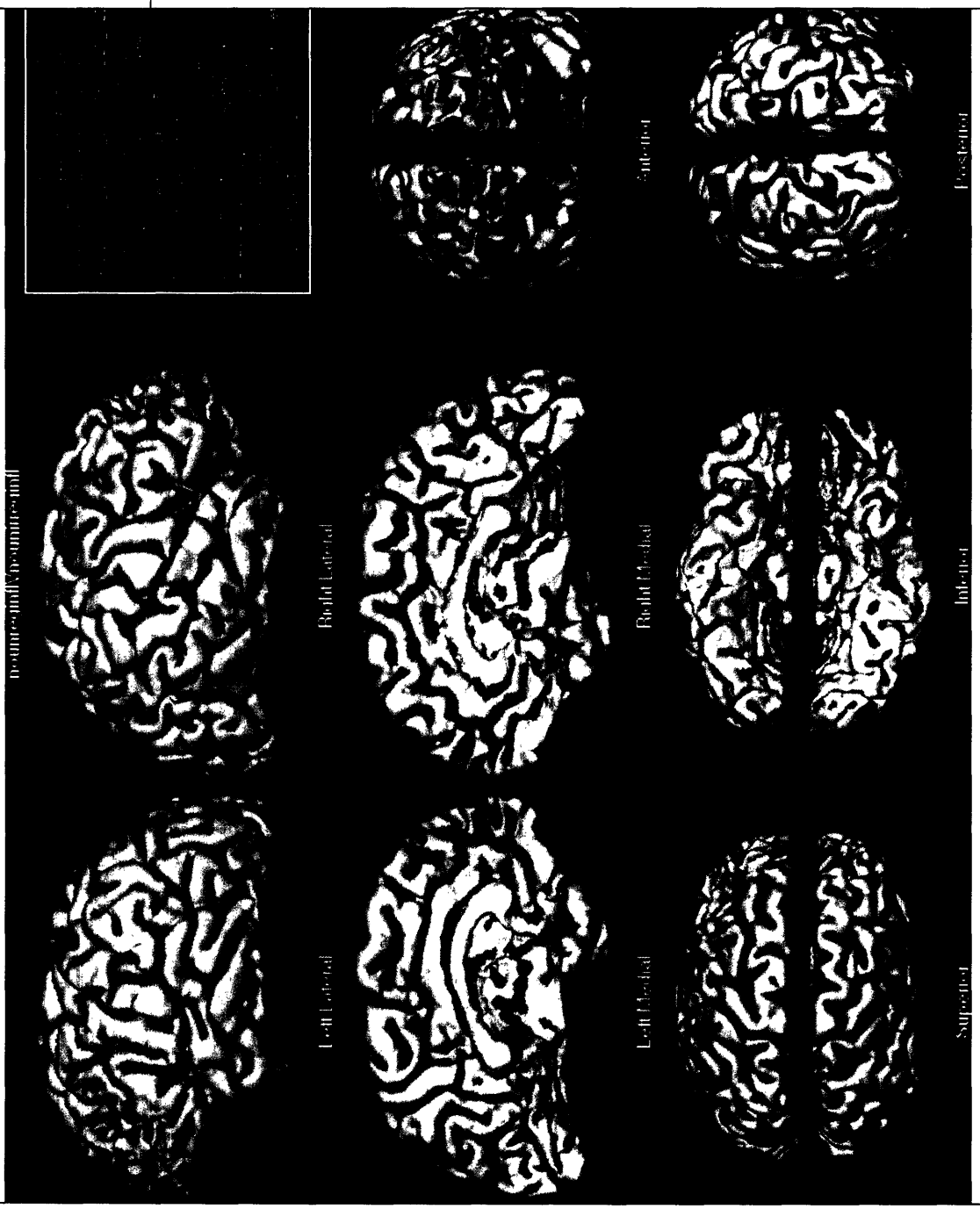


Contrast Name			Conditions Negative	Data Represented		
Noun Irreg Overt-Inflect V Noun Irreg Read	**NIO**	>	**NIR**	6%	>	6%
Hypotheses:						
Observations:						

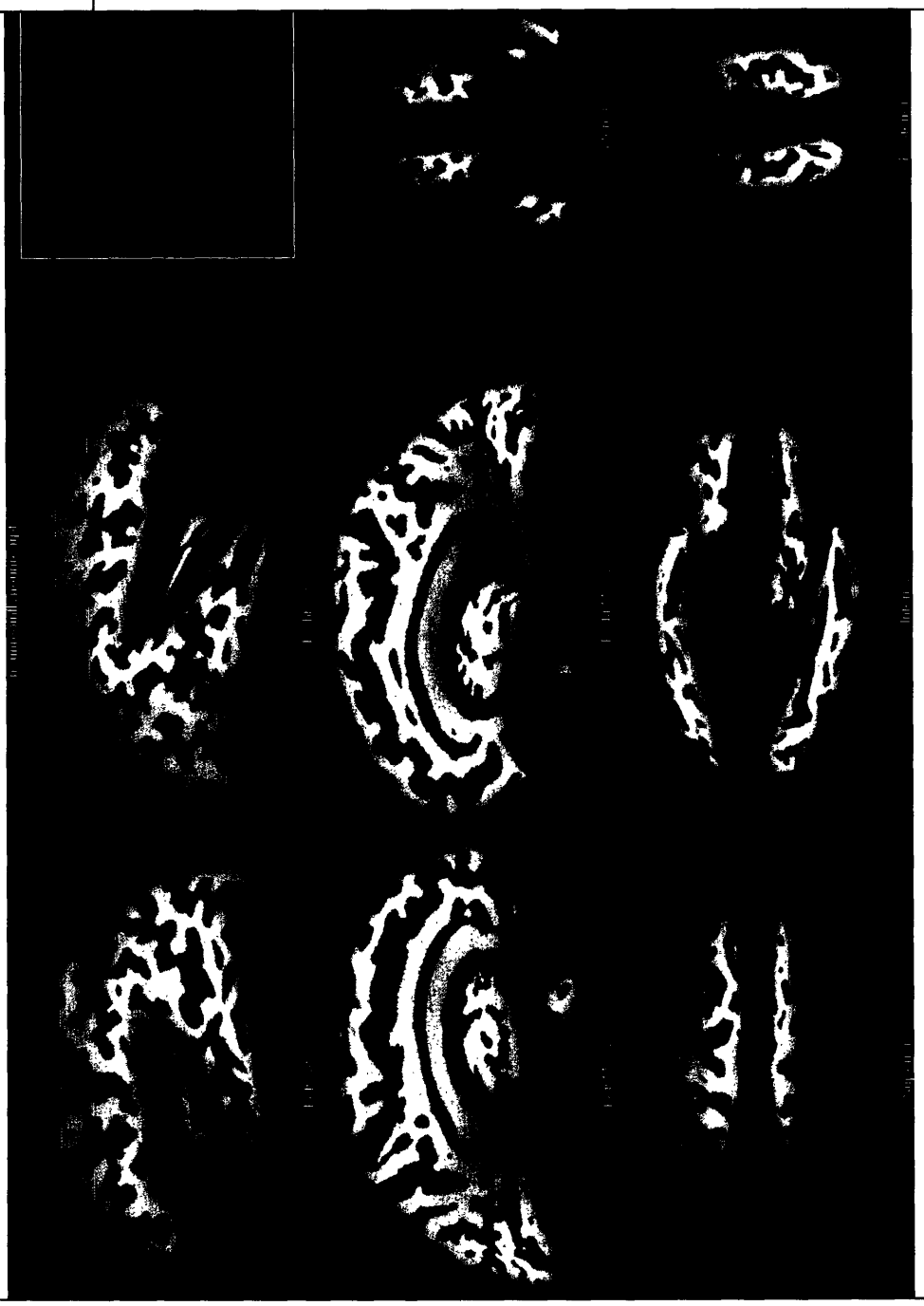


Contrast Name			Conditions Negative	Data Represented		
Noun Reg Overt-Inflect V Noun Irreg Overt-Inflect	**NRO**	>	**NIO**	6%	>	6%
Hypotheses:						
Observations:						

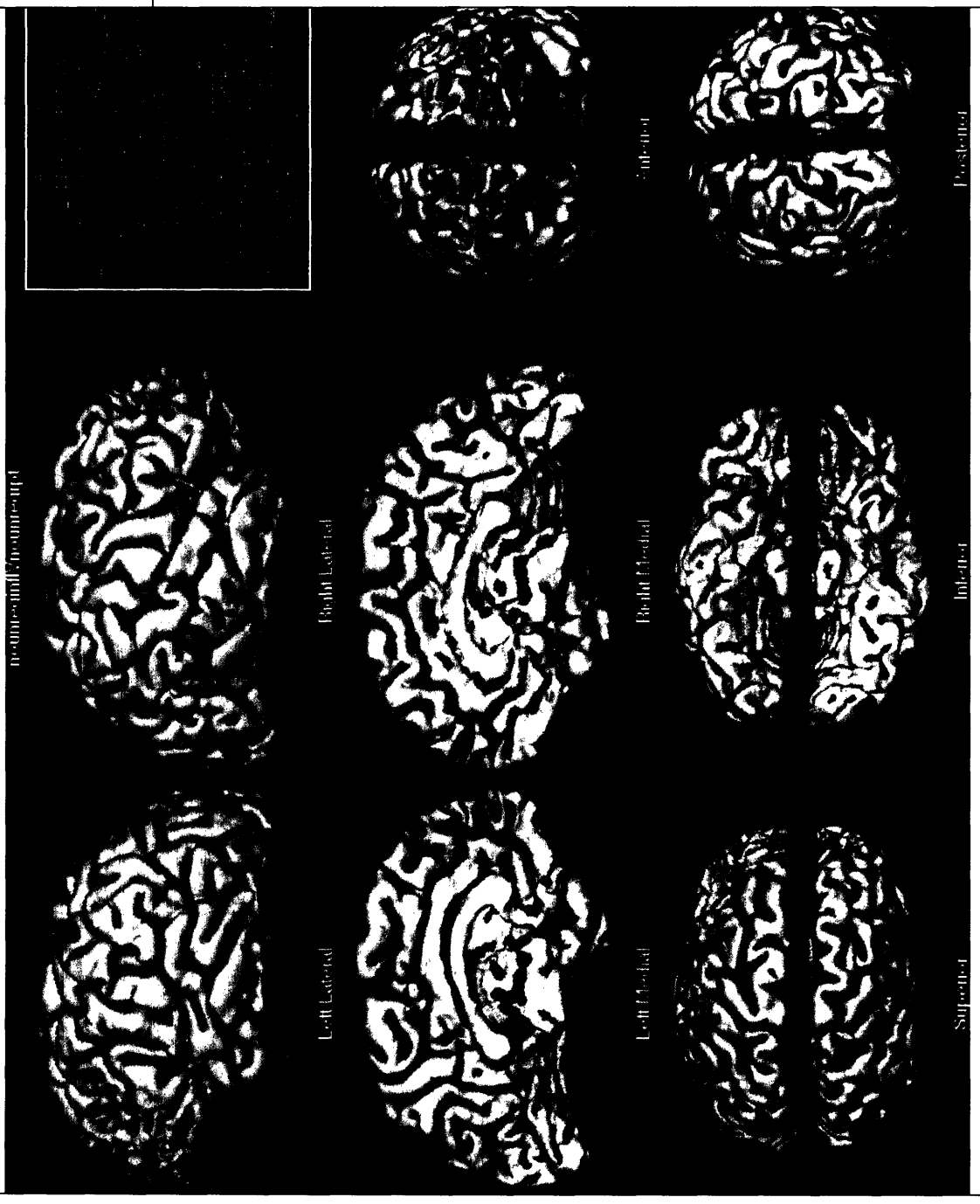
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Overt-Inflect V Noun Irreg Overt-Inflect	**NRO**	>	**NIO**	6%	>	6%
Hypotheses:						
Observations:						



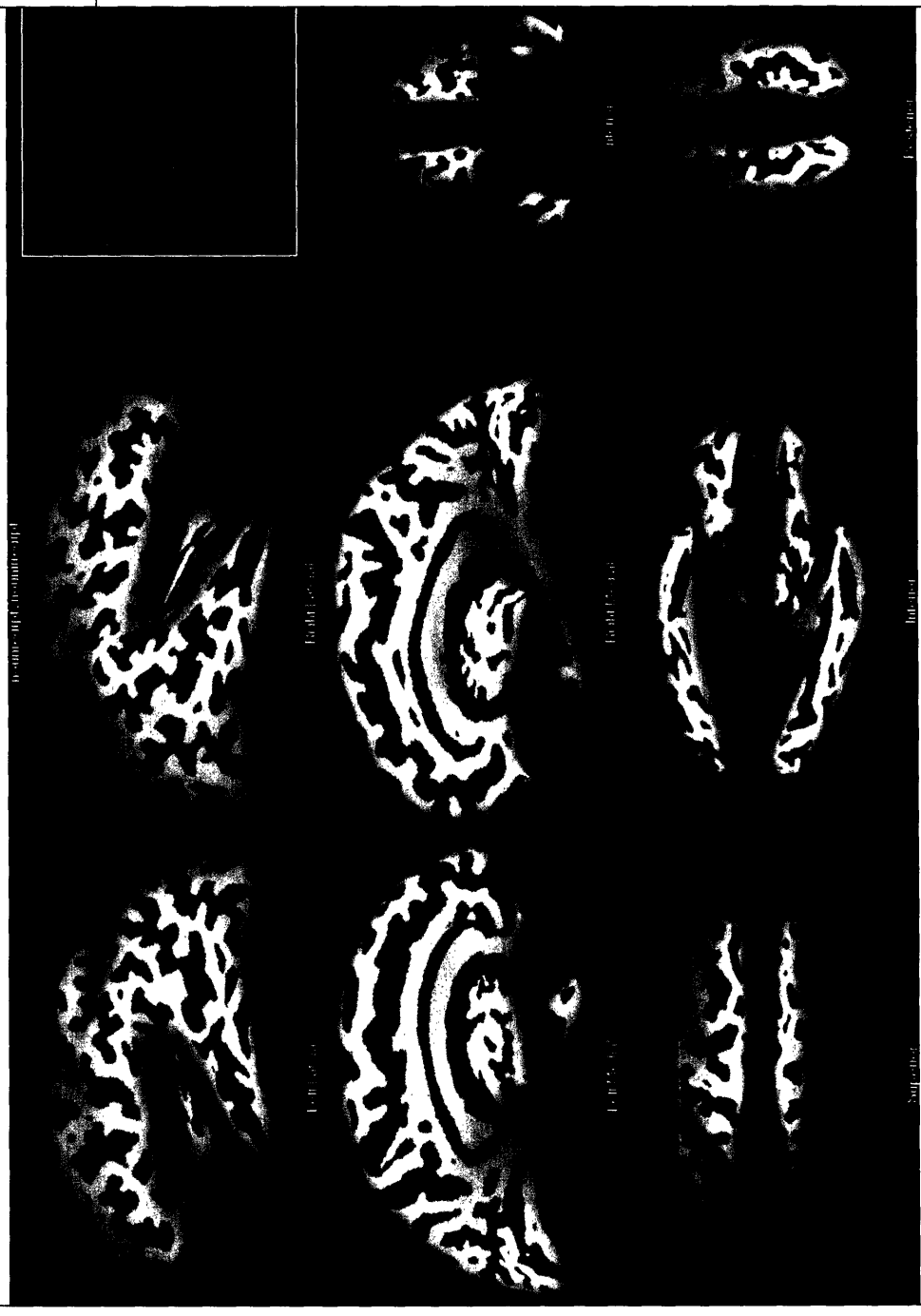
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Overt-Inflect V Noun Reg Read	**NRO**	>	**NRR**	6%	>	6%
Hypotheses:						
Observations:						



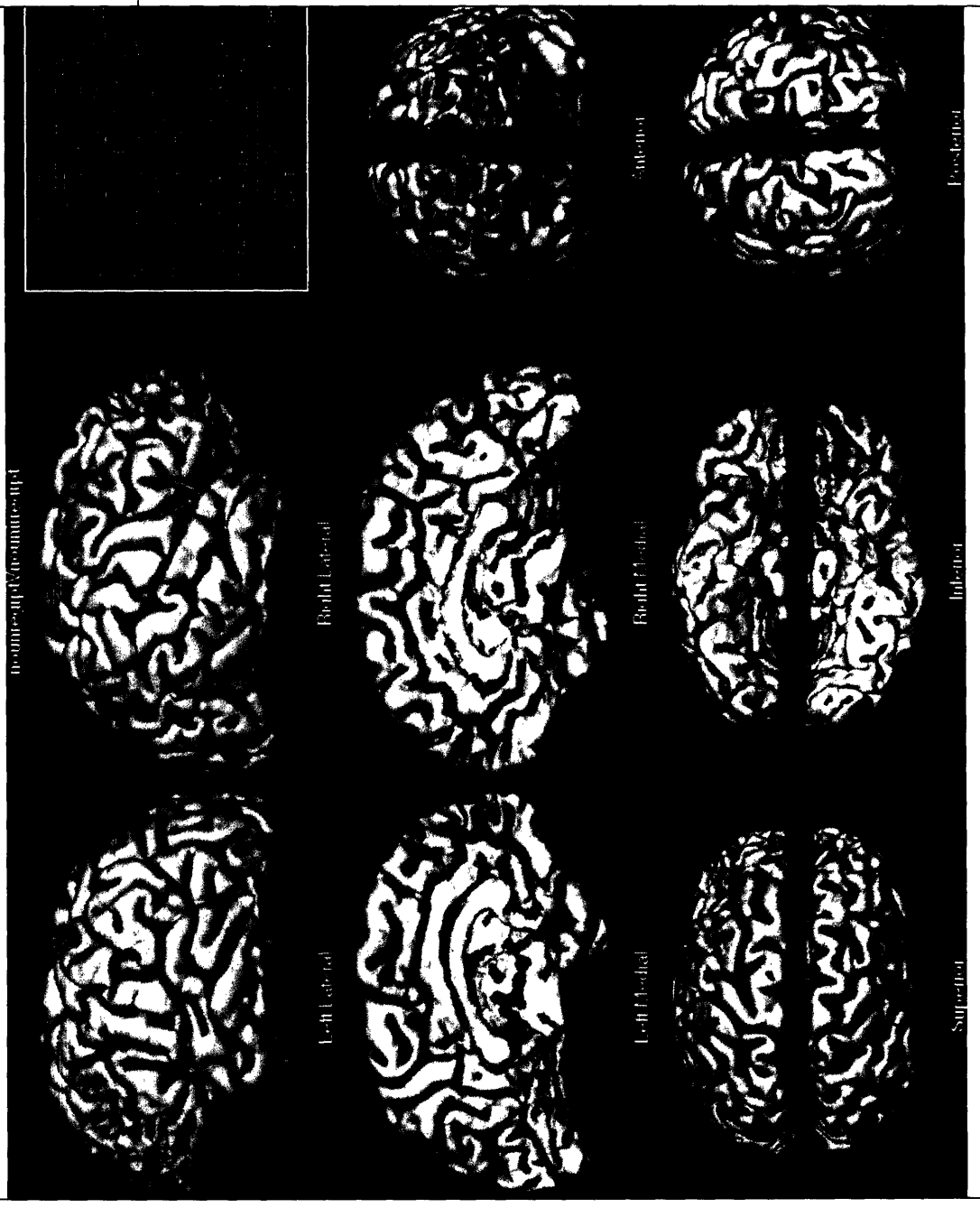
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Overt-Inflect V Noun Reg Read	**NRO**	>	**NRR**	6%	>	6%
Hypotheses:						
Observations:						



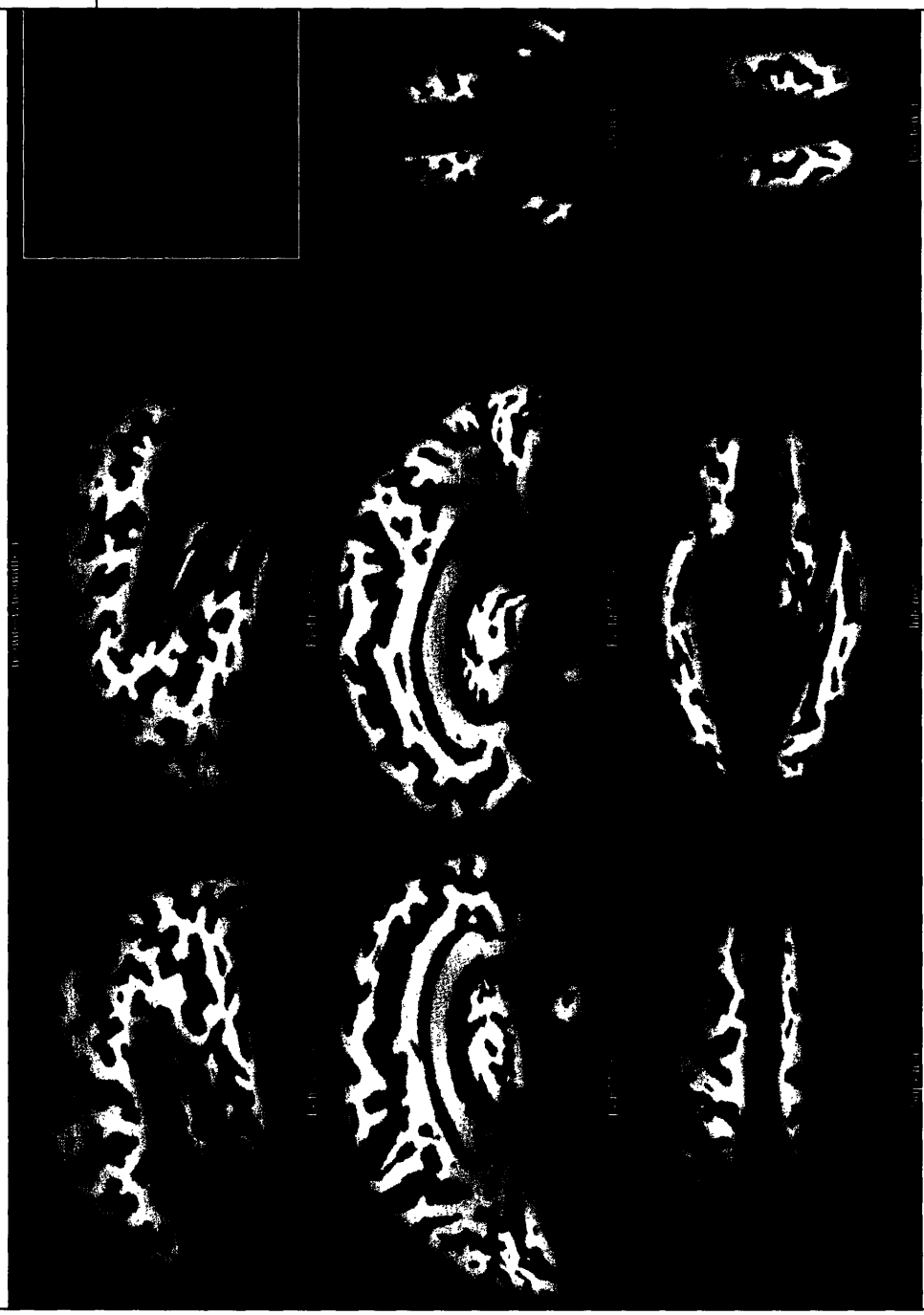
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Read V Noun Irreg Read	**NRR**	>	**NIR**	6%	>	6%
Hypotheses:						
Observations:						



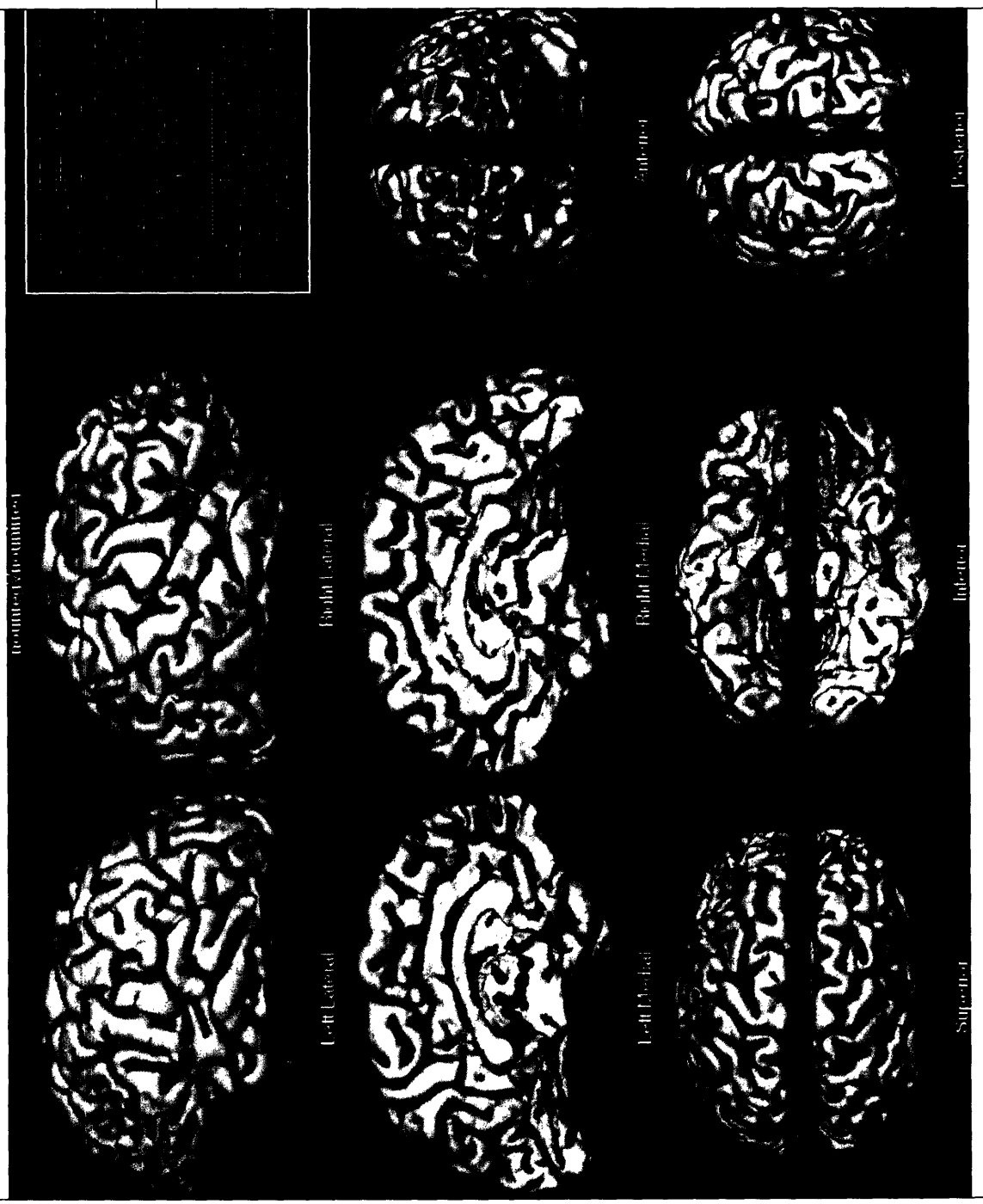
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Read V Noun Irreg Read	**NRR**	>	**NIR**	6%	>	6%
Hypotheses:						
Observations:						



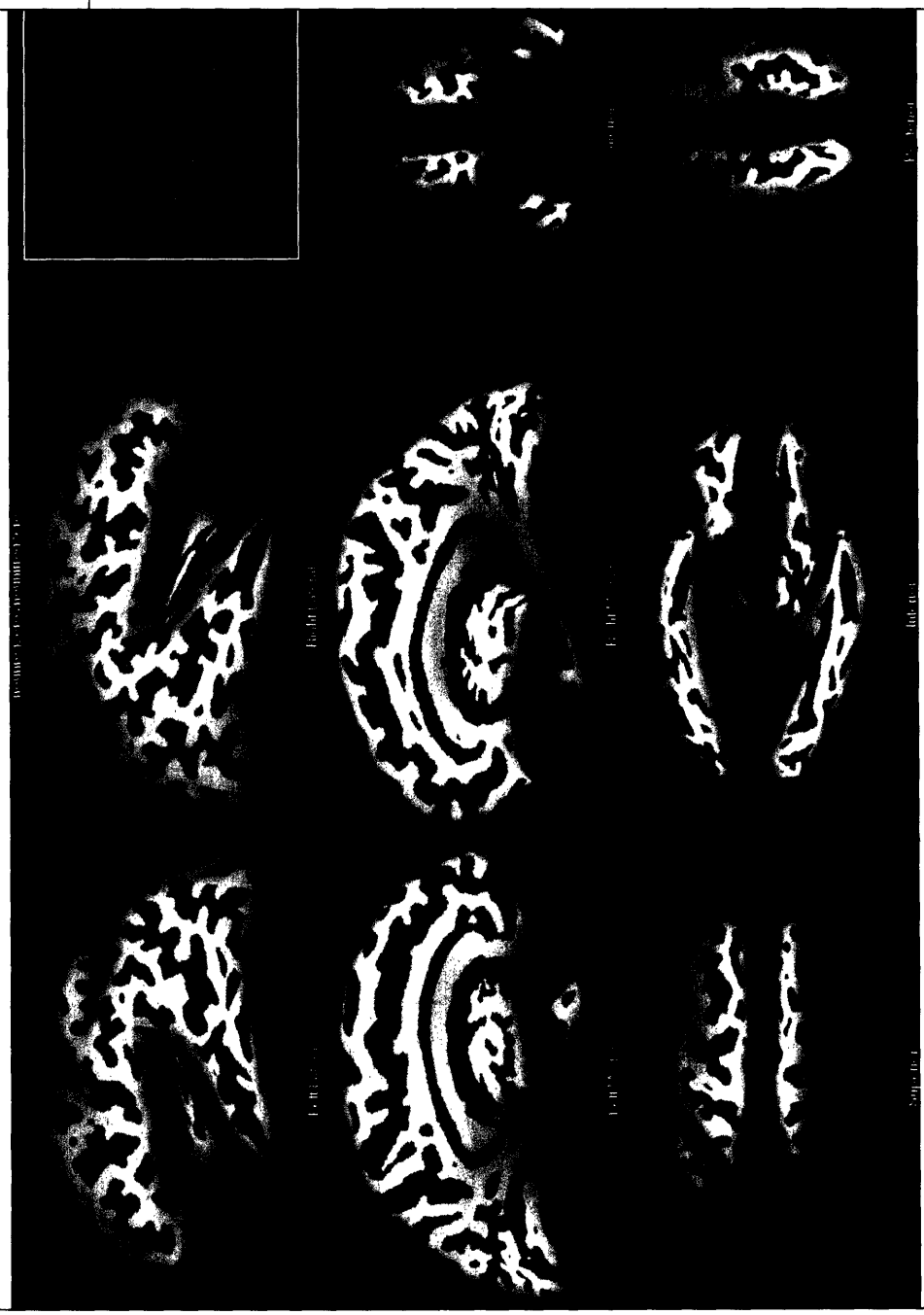
Contrast Name			Conditions Negative	Data Represented		
Noun Reg All V Noun Irreg All	**NRO, NRZ, NRR**	>	**NIO, NIZ, NIR**	18%	>	18%
Hypotheses:						
Observations:						



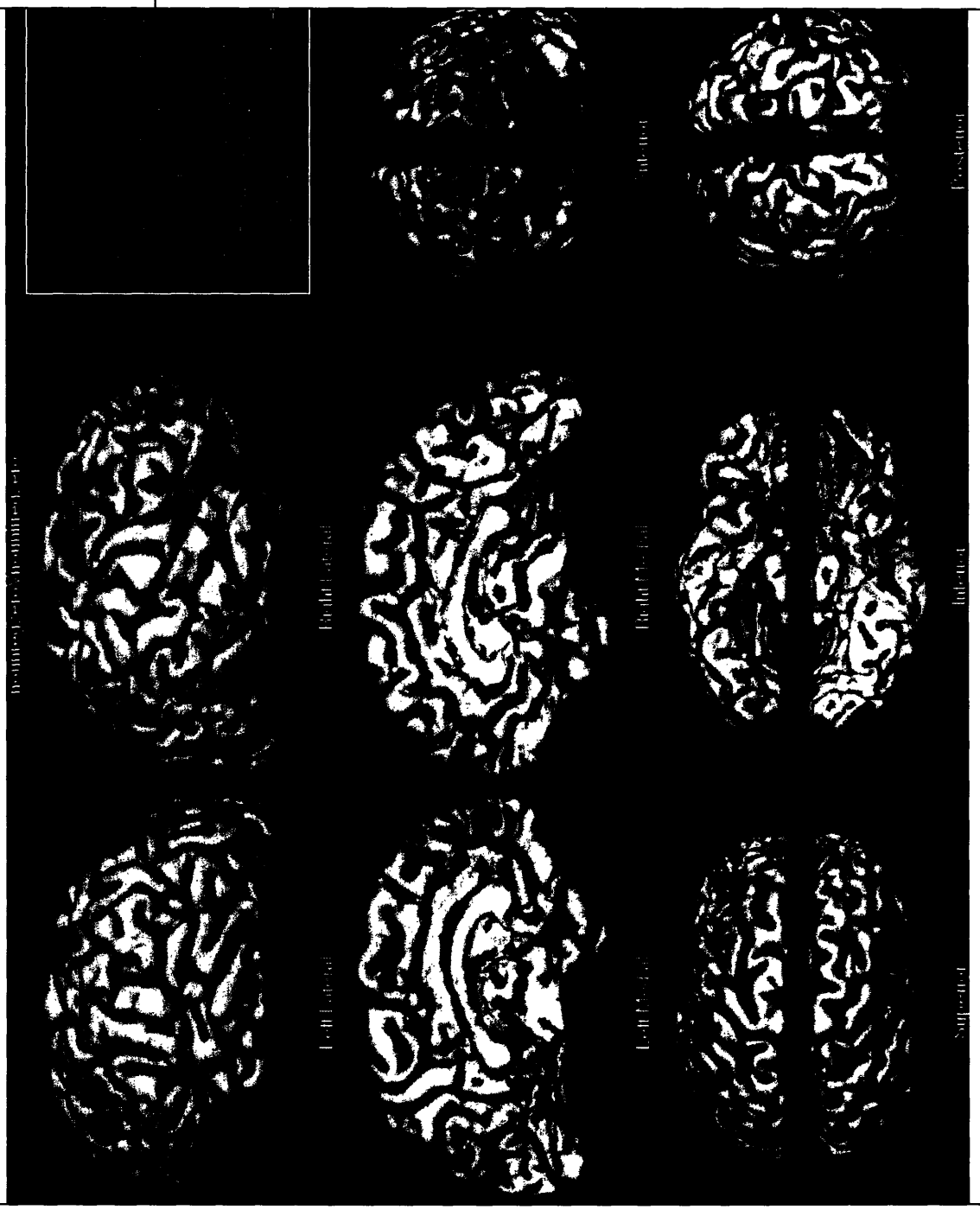
Contrast Name			Conditions Negative	Data Represented		
Noun Reg All V Noun Irreg All	NRO, NRZ, NRR	>	NIO, NIZ, NIR	18%	>	18%
Hypotheses:						
Observations:						



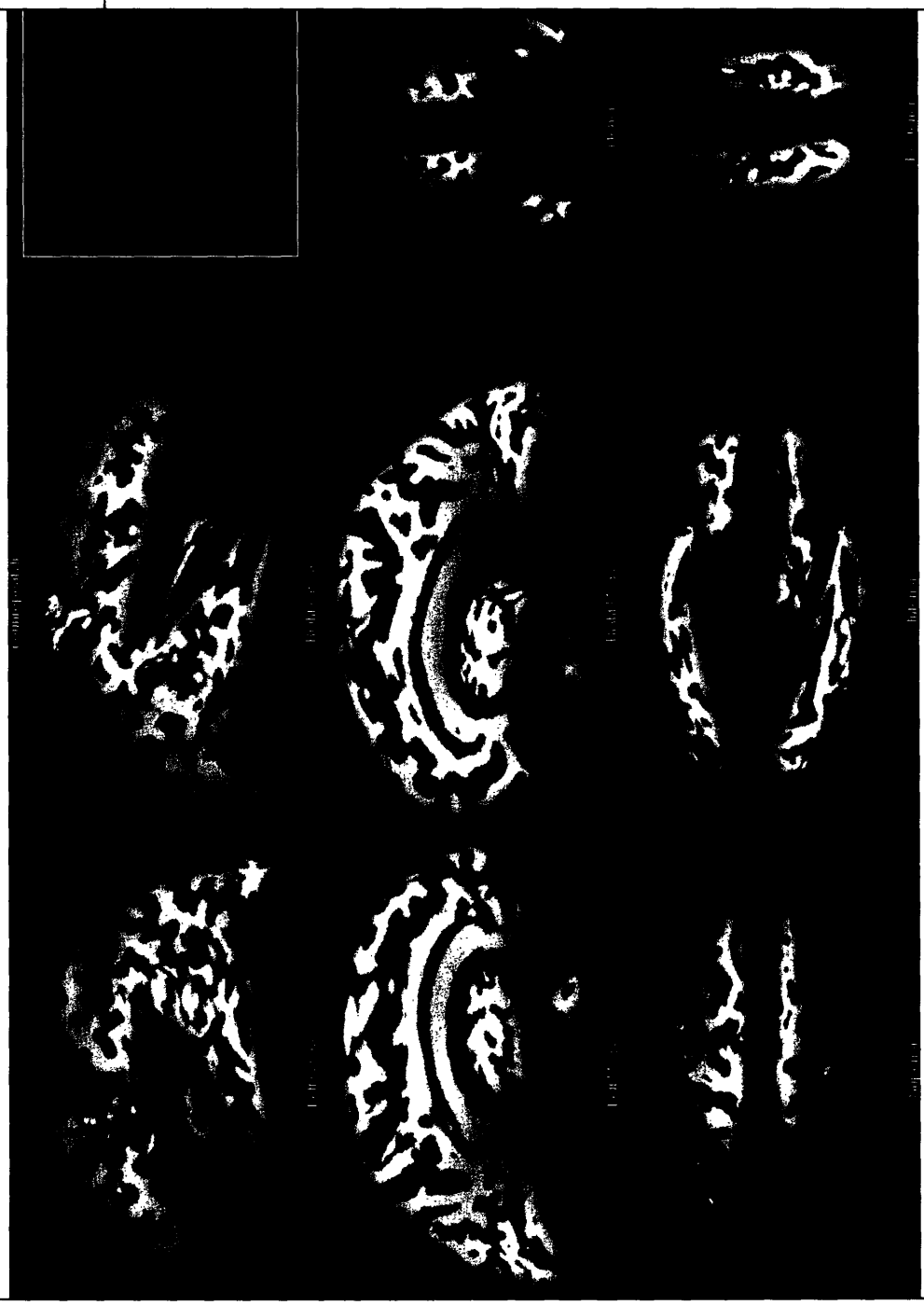
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Zero-Inflect V Noun Irreg Zero-Inflect	NRZ	>	NIZ	6%	>	6%
Hypotheses:						
Observations:						



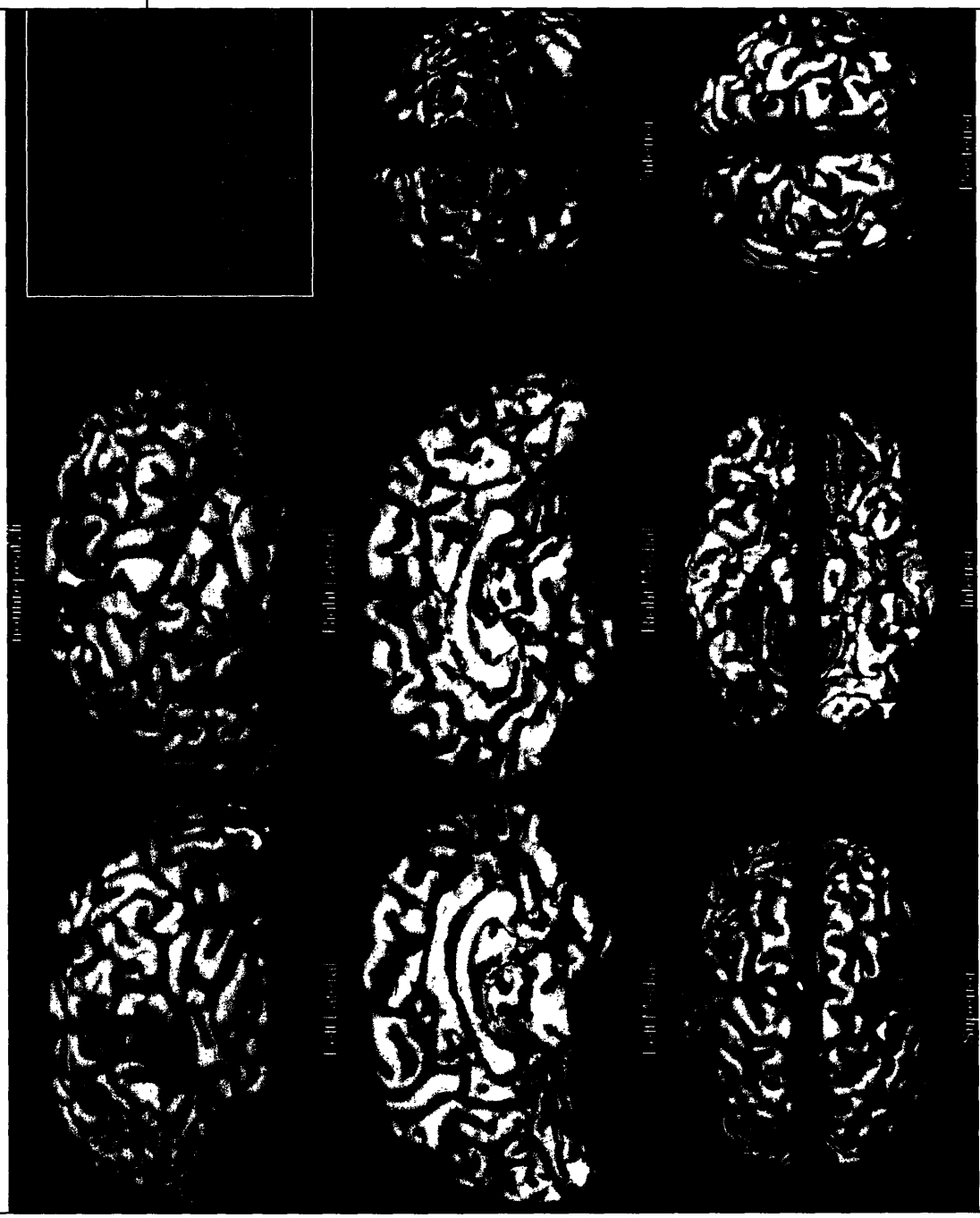
Contrast Name			Conditions Negative	Data Represented		
Noun Reg Zero-Inflect V Noun Irreg Zero-Inflect	**NRZ**	>	**NIZ**	6%	>	6%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
Noun Read V Fix	**NRR, NIR**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						

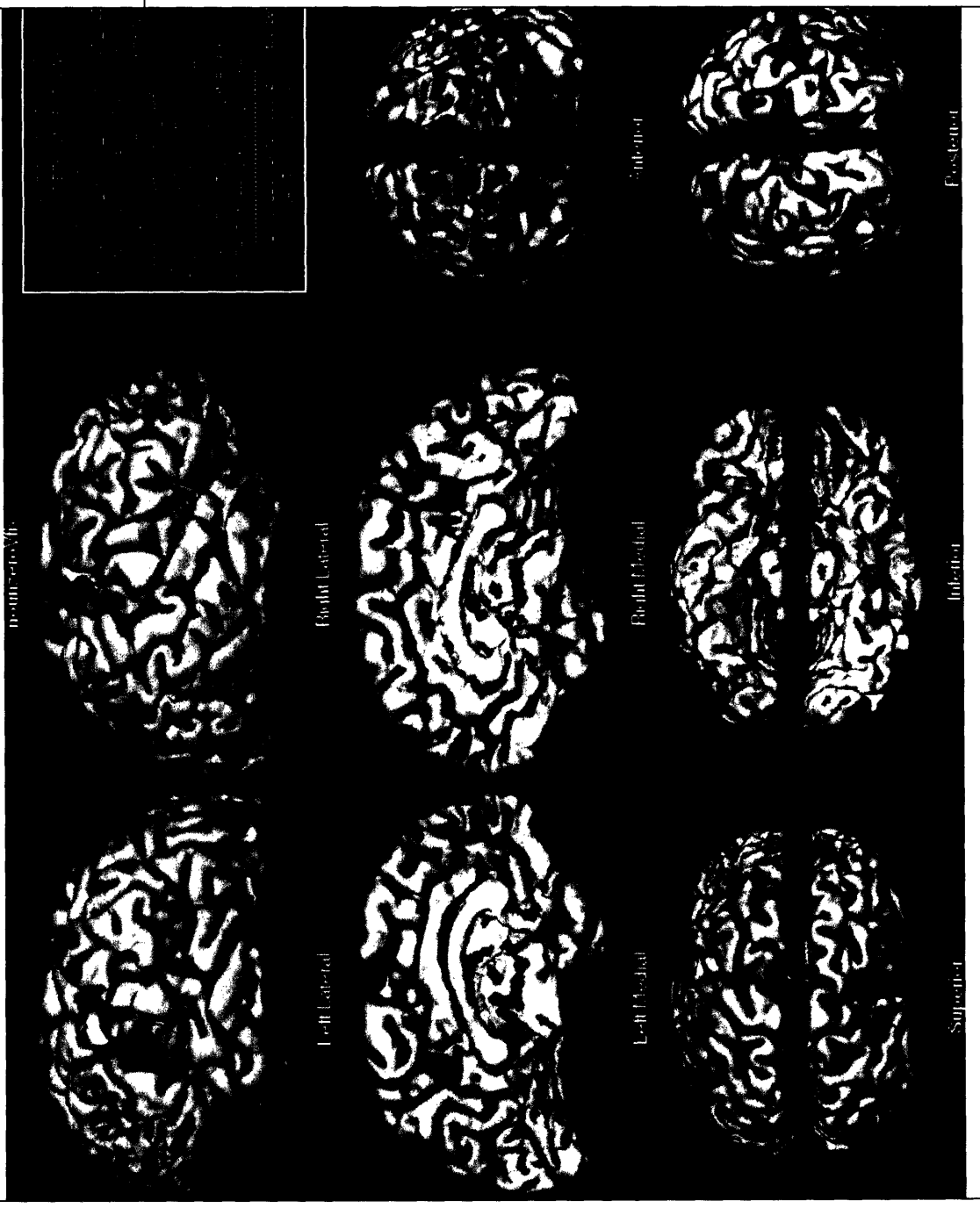


Contrast Name			Conditions Negative	Data Represented		
Noun Read V Fix	**NRR, NIR**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



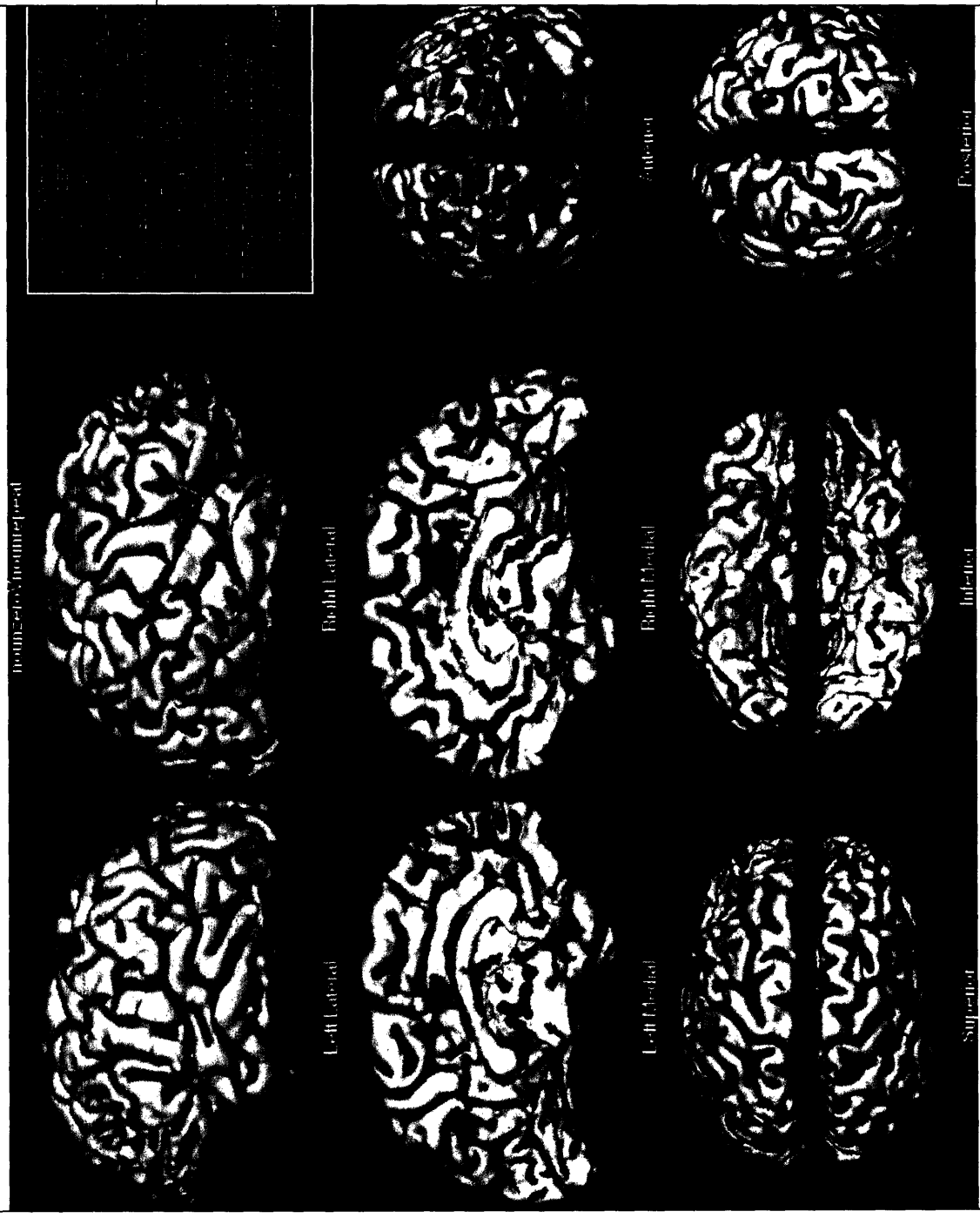
Contrast Name			Conditions Negative	Data Represented		
Noun Zero-Inflect V Fix	**NRZ, NIZ**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						

Contrast Name			Conditions Negative	Data Represented		
Noun Zero-Inflect V Fix	**NRZ, NIZ**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						

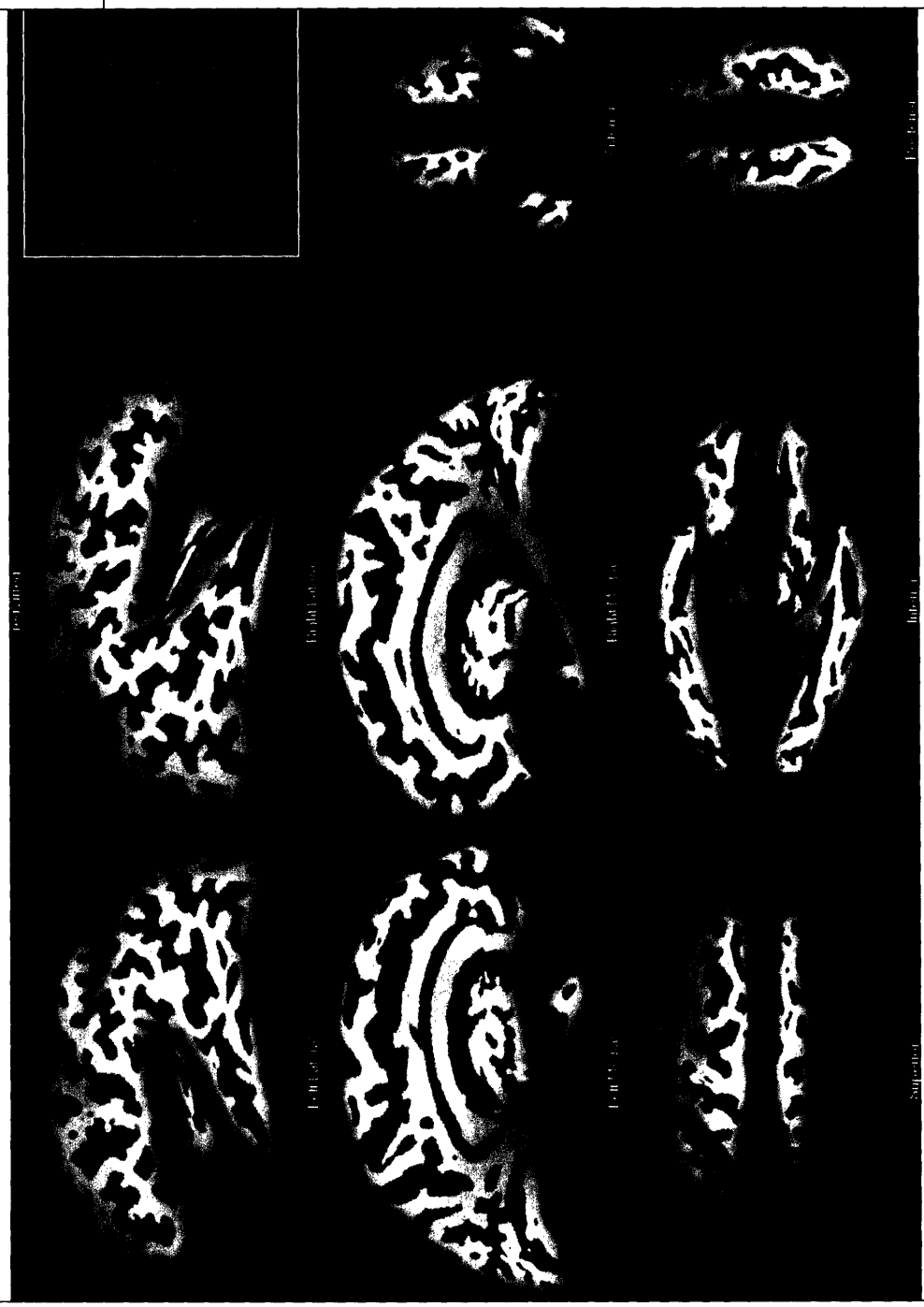


Contrast Name			Conditions Negative	Data Represented		
Noun Zero-Inflect V Noun Read	**NRZ, NIZ**	>	**NRR, NIR**	12%	>	12%
Hypotheses:						
Observations:						

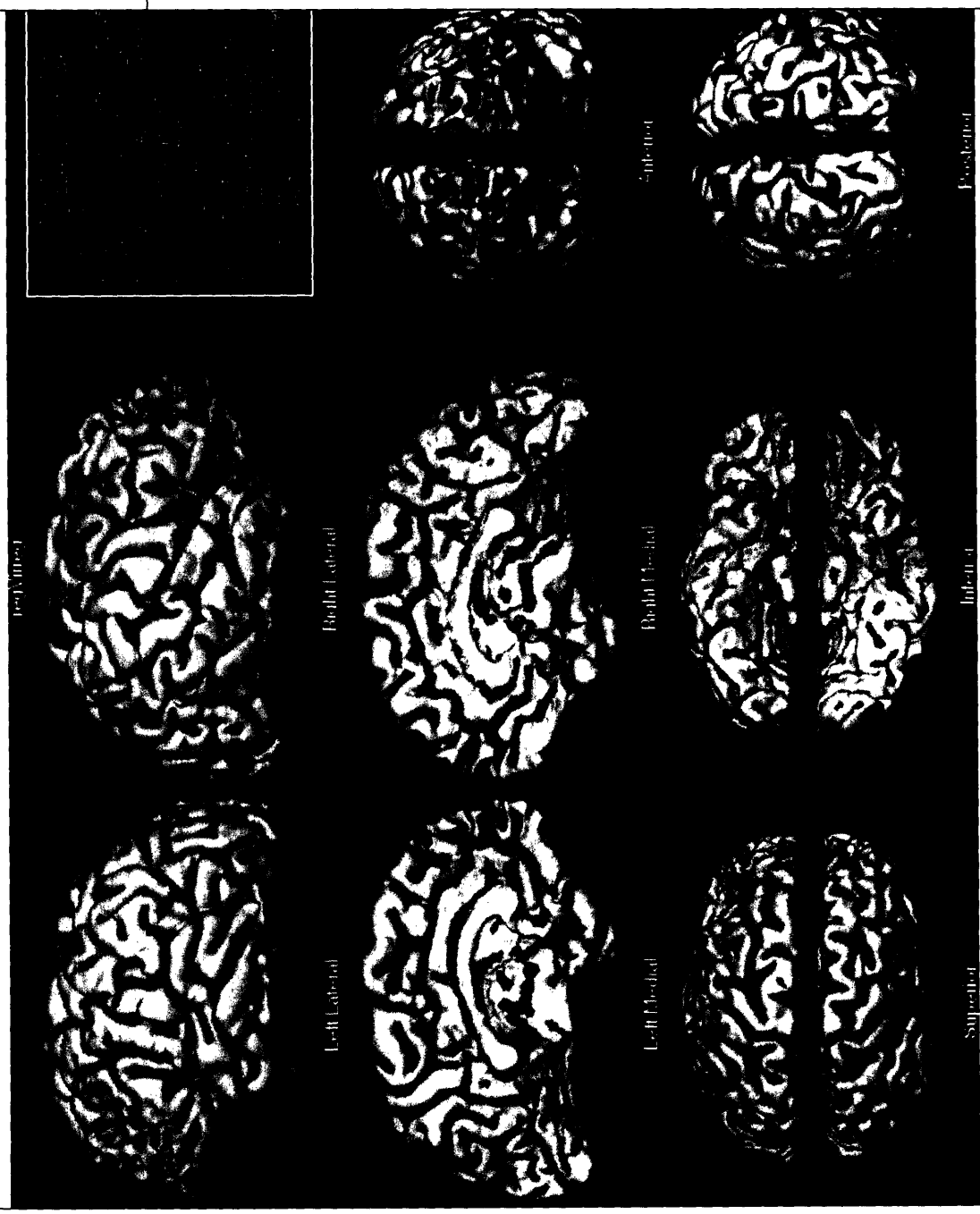
Contrast Name			Conditions Negative	Data Represented		
Noun Zero-Inflect V Noun Read	NRZ, NIZ	>	NRR, NIR	12%	>	12%
Hypotheses:						
Observations:						



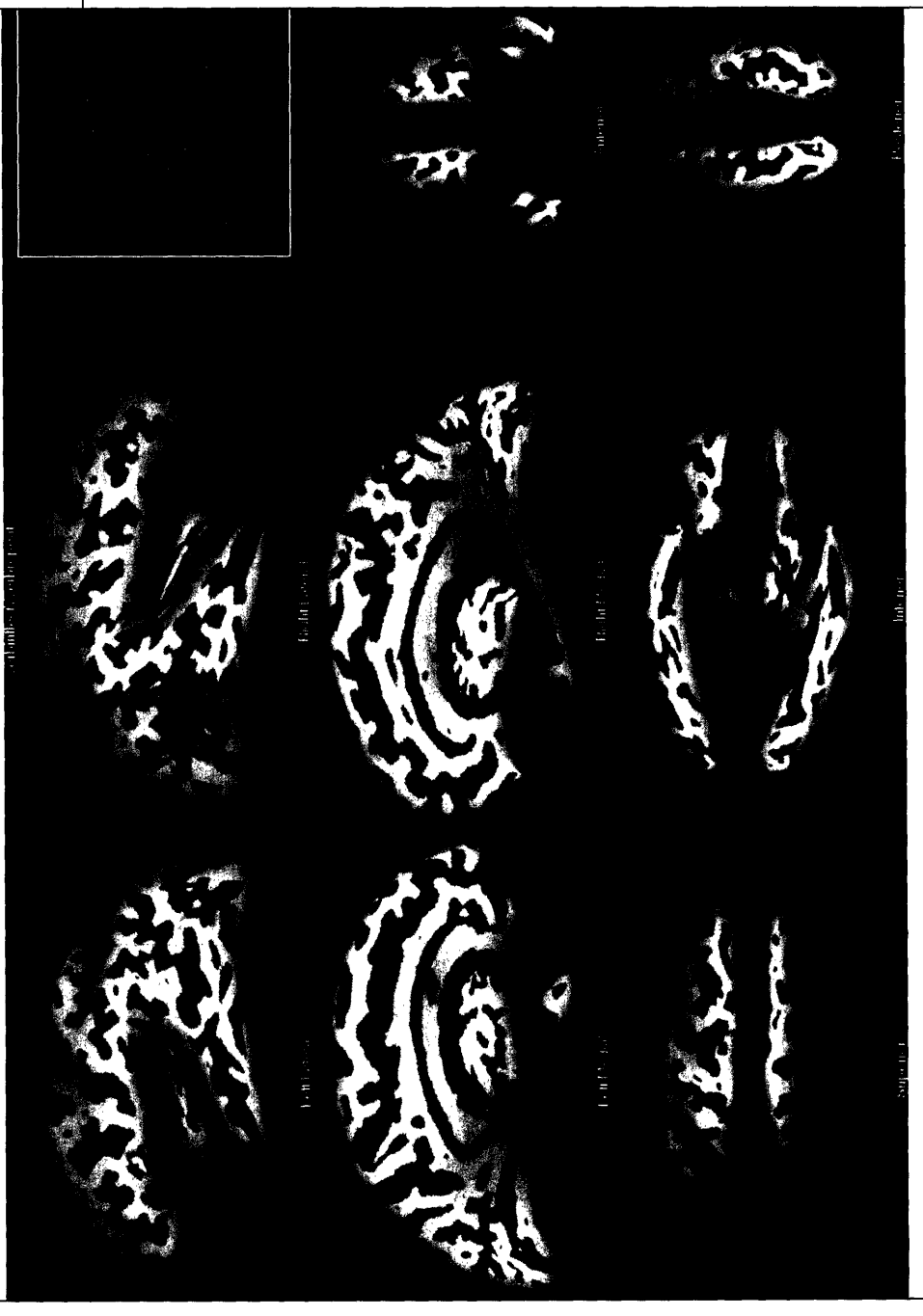
Contrast Name			Conditions Negative	Data Represented		
Reg V Irreg	VRO, VRZ, VRR, NRO, NRZ, NRR	>	VIO, VIZ, VIR, NIO, NIO, NIR	36%	>	36%
Hypotheses:						
Observations:						



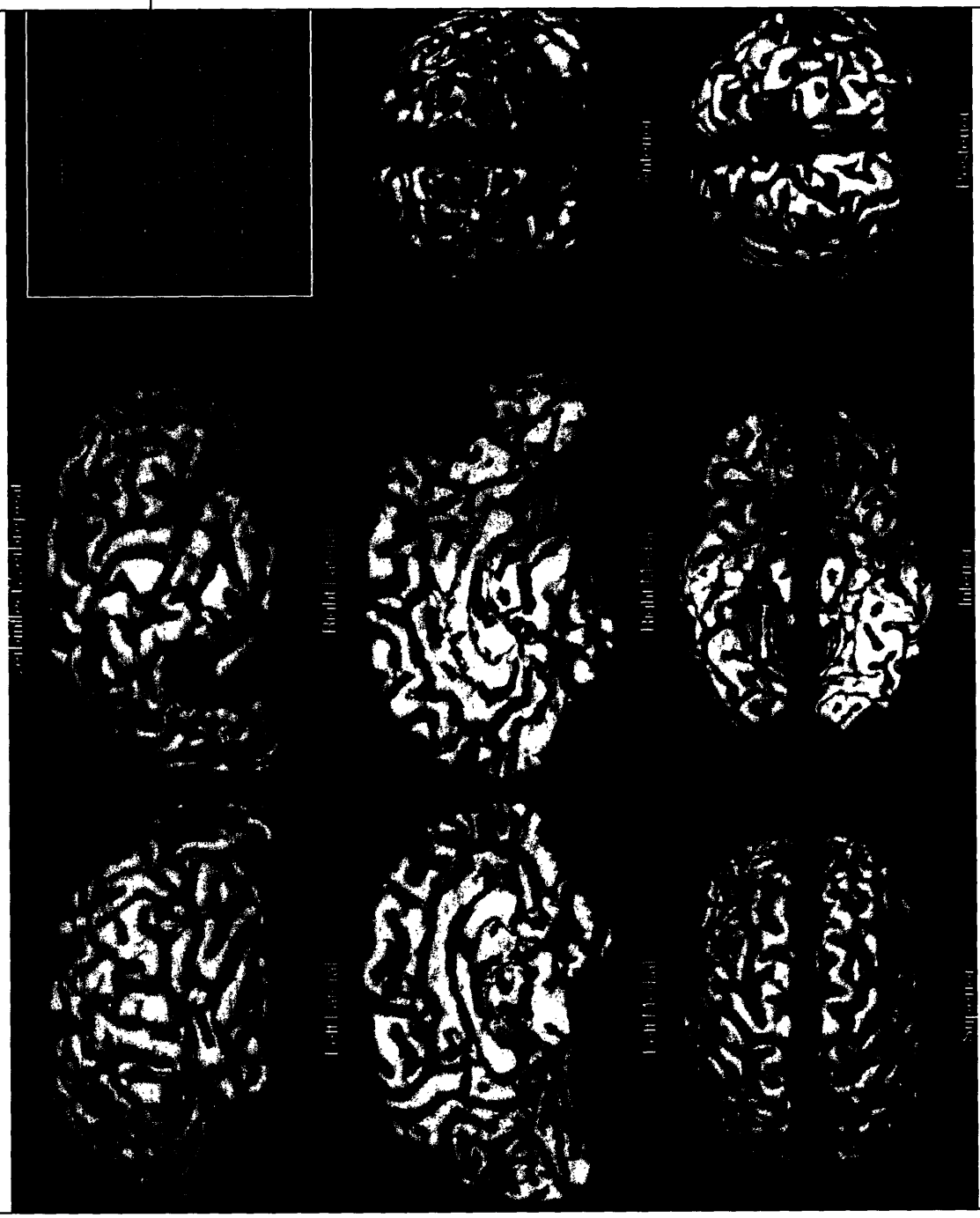
Contrast Name			Conditions Negative	Data Represented		
Reg V Irreg	VRO, VRZ, VRR, NRO, NRZ, NRR	>	VIO, VIZ, VIR, NIO, NIO, NIR	36%	>	36%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Verb Read	**VRO, VIO**	>	**VRR, VIR**	12%	>	12%
Hypotheses:						
Observations:						

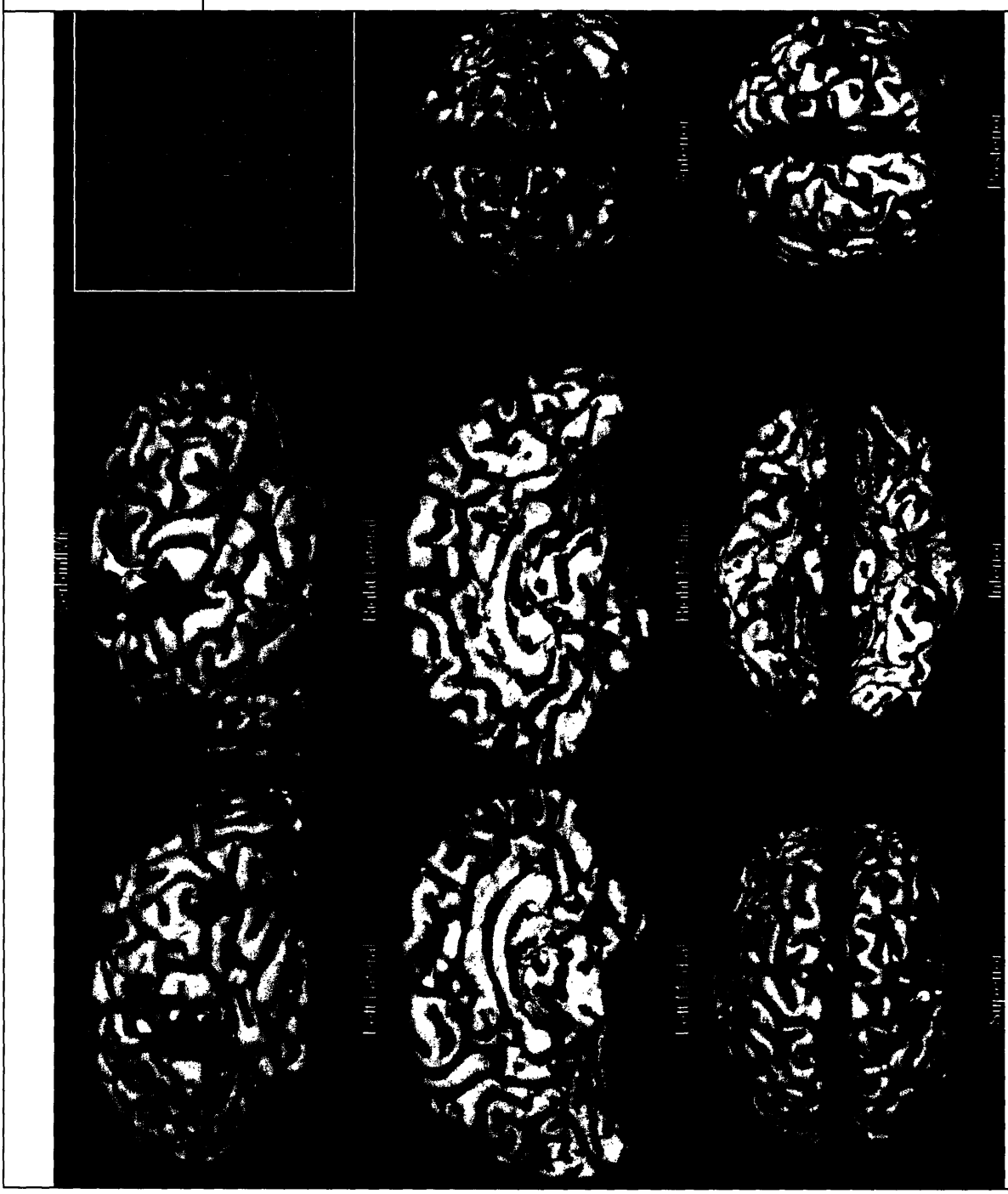


Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Verb Read	**VRO, VIO**	>	**VRR, VIR**	12%	>	12%
Hypotheses:						
Observations:						

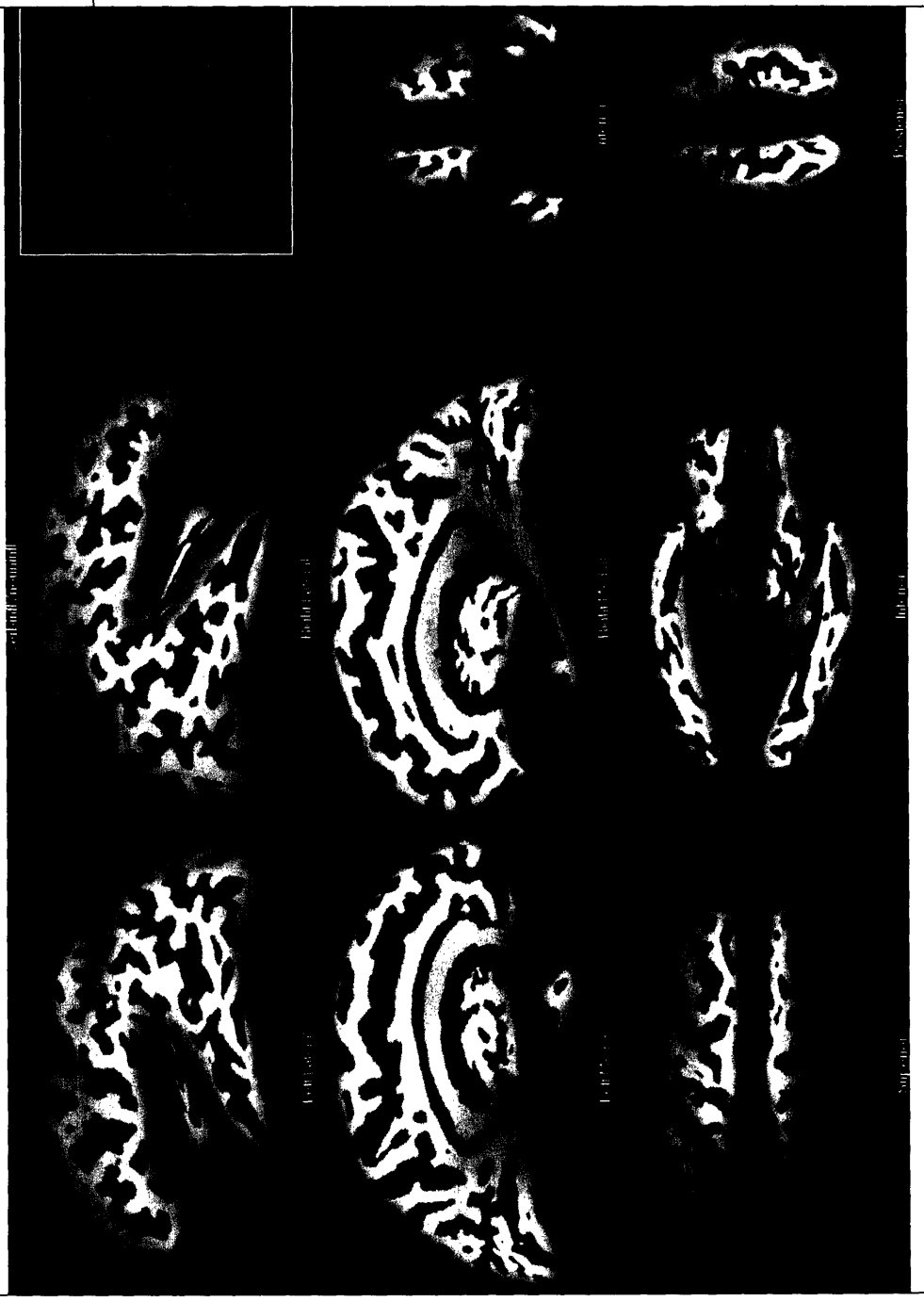


Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Fix	**VRO, VIO**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						

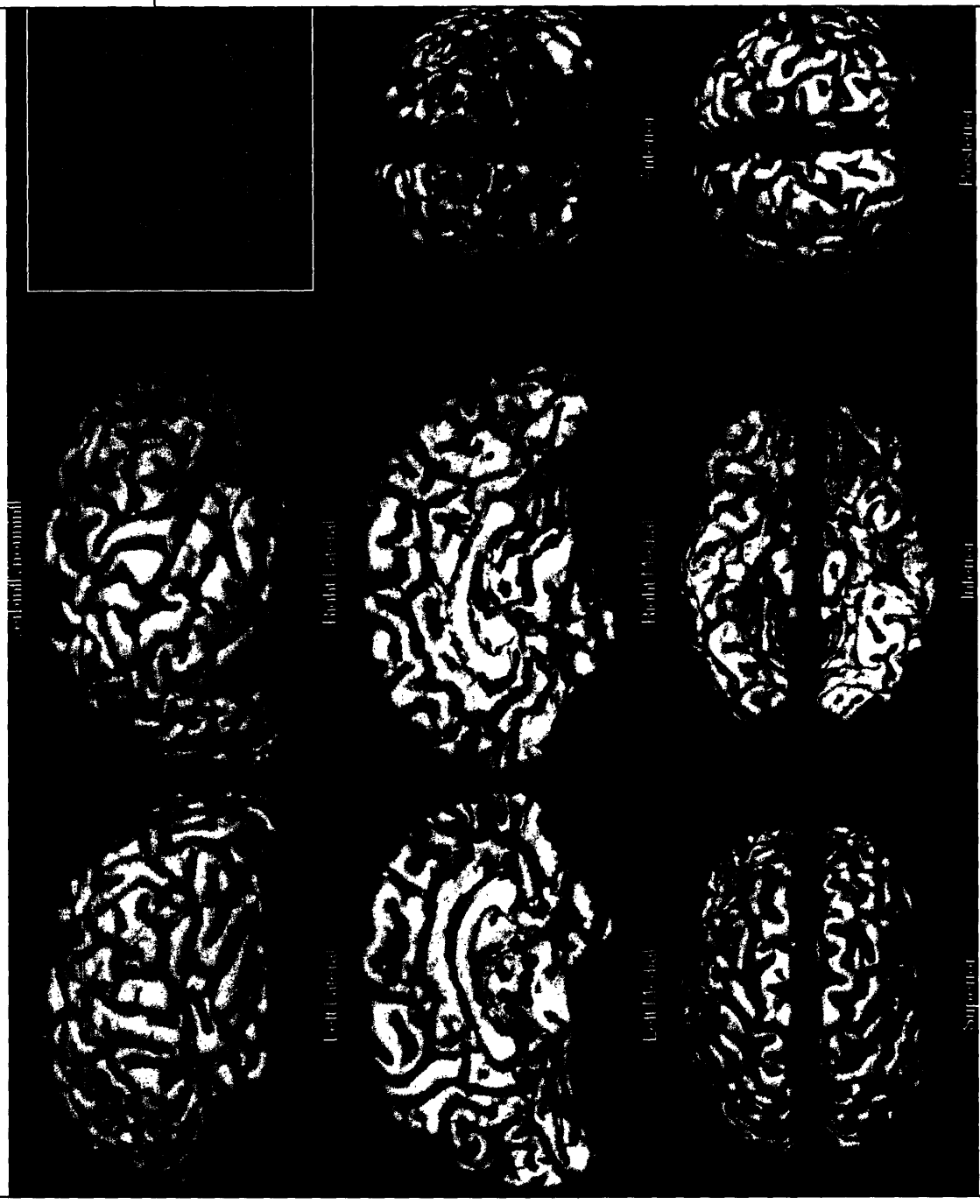
Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Fix	**VRO, VIO**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



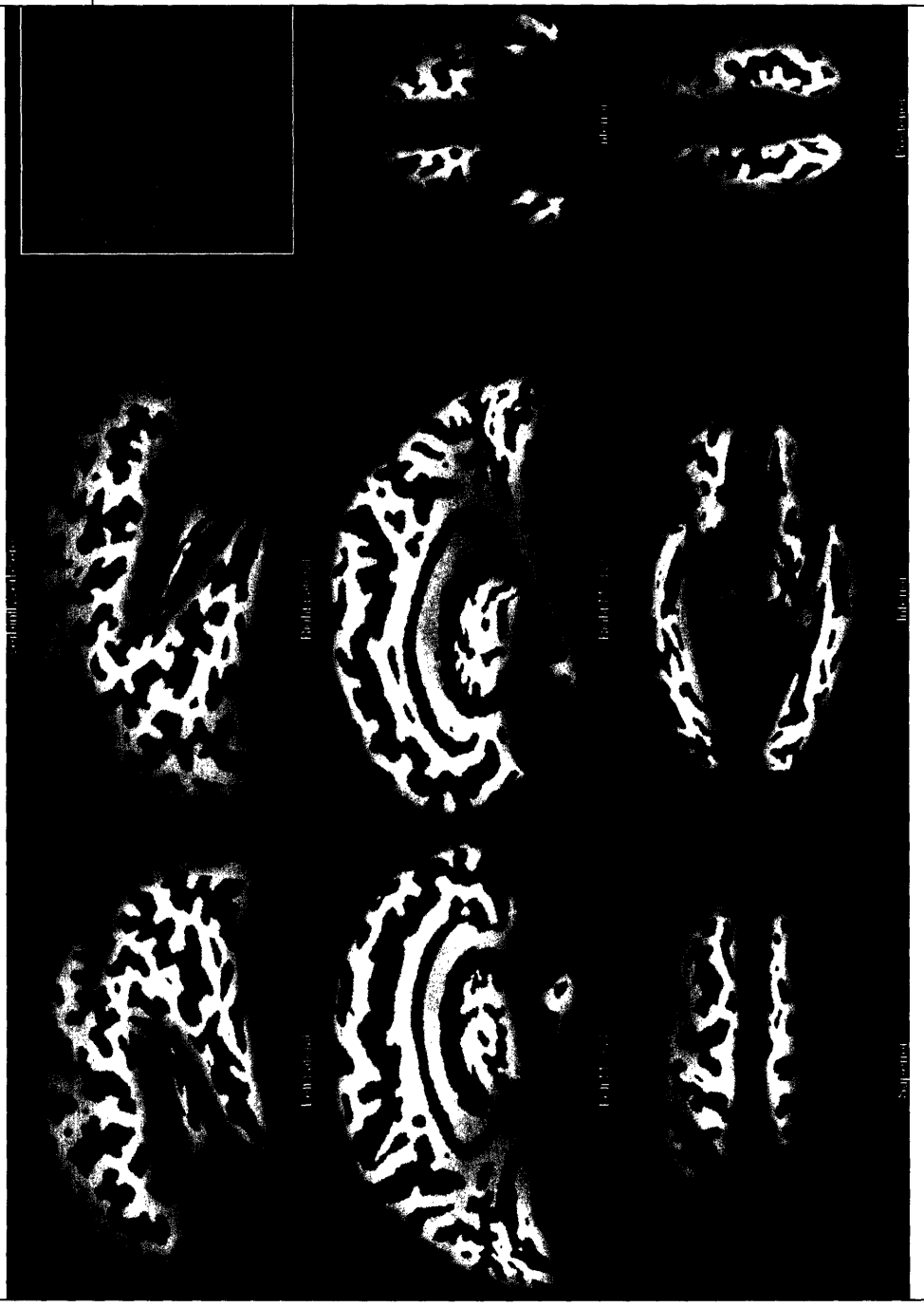
Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Noun Overt-Inflect	**VRO, VIO**	>	**NRO, NIO**	12%	>	12%
Hypotheses:						
Observations:						



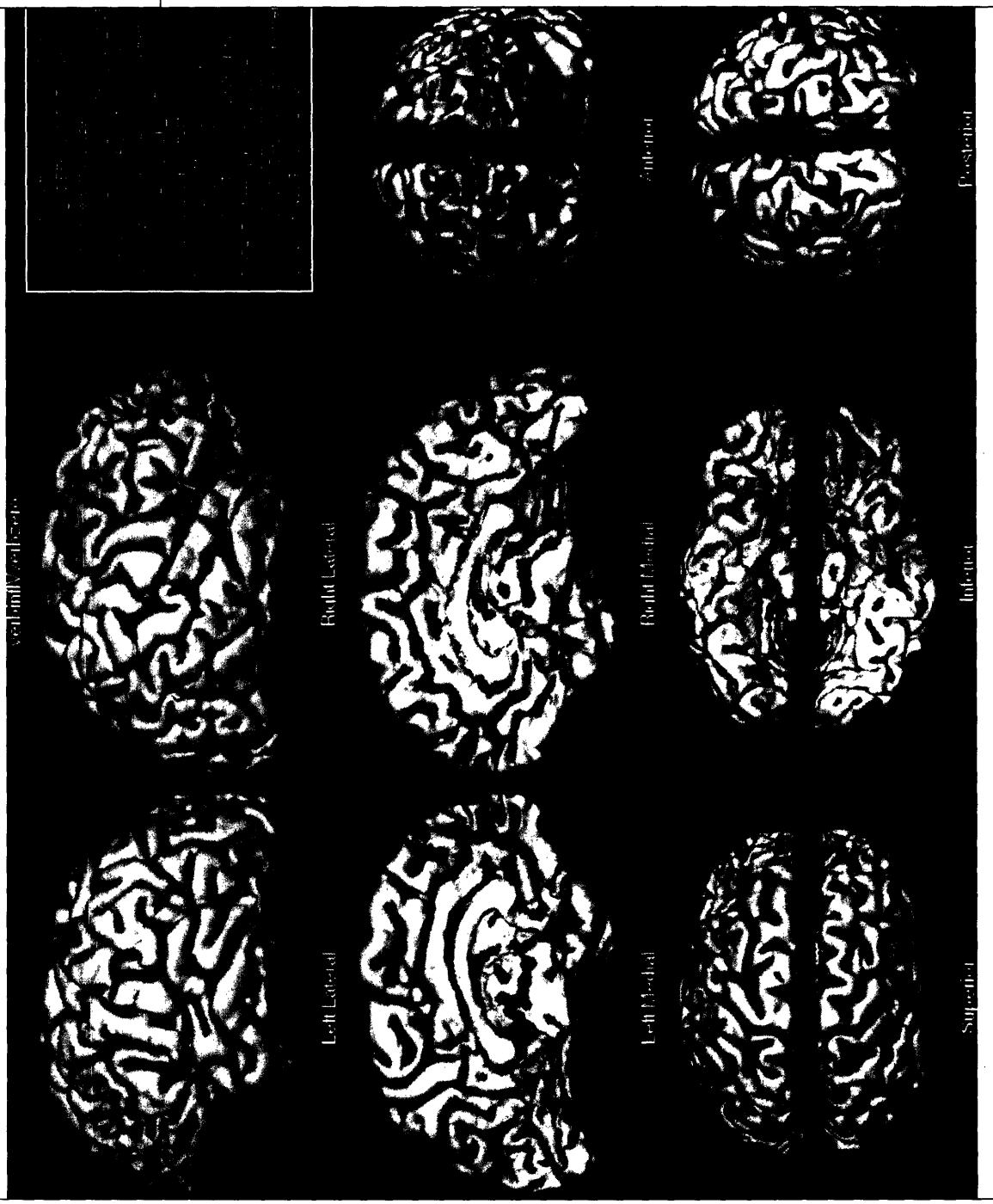
Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Noun Overt-Inflect	**VRO, VIO**	>	**NRO, NIO**	12%	>	12%
Hypotheses:						
Observations:						



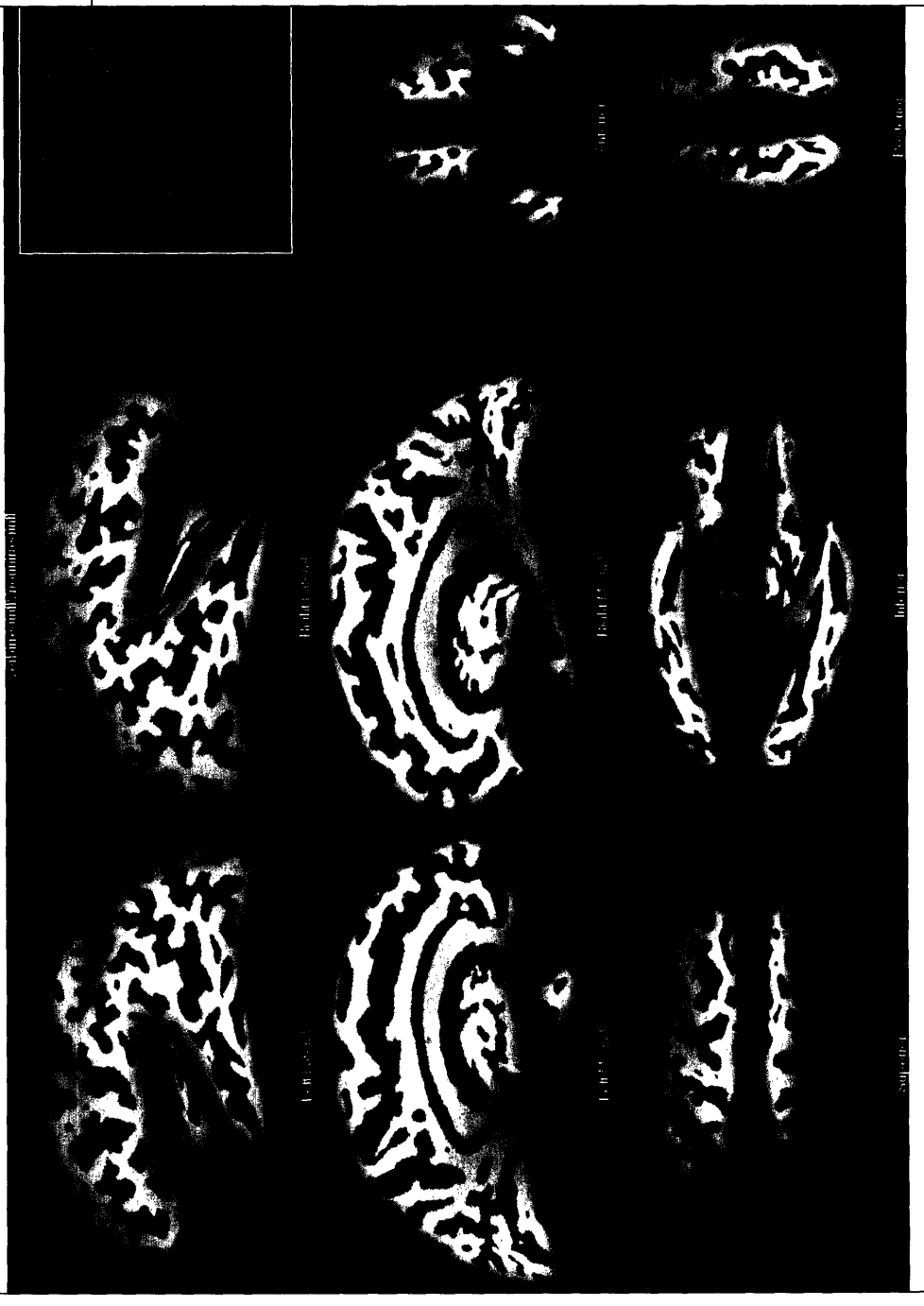
Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Verb Zero-Inflect	VRO, VIO	>	VRZ, VIZ	12%	>	12%
Hypotheses:						
Observations:						



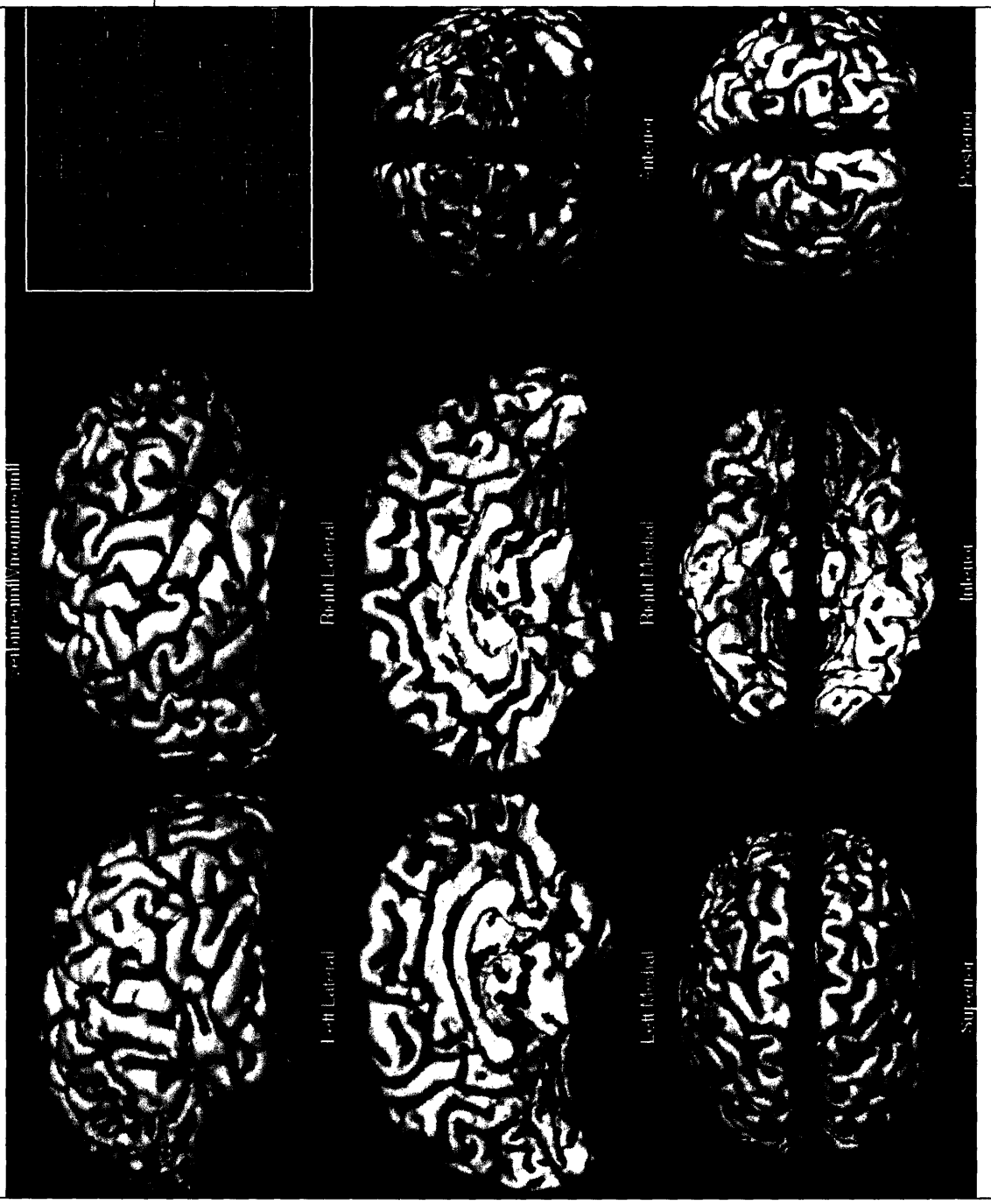
Contrast Name			Conditions Negative	Data Represented		
Verb Overt-Inflect V Verb Zero-Inflect	**VRO, VIO**	>	**VRZ, VIZ**	12%	>	12%
Hypotheses:						
Observations:						



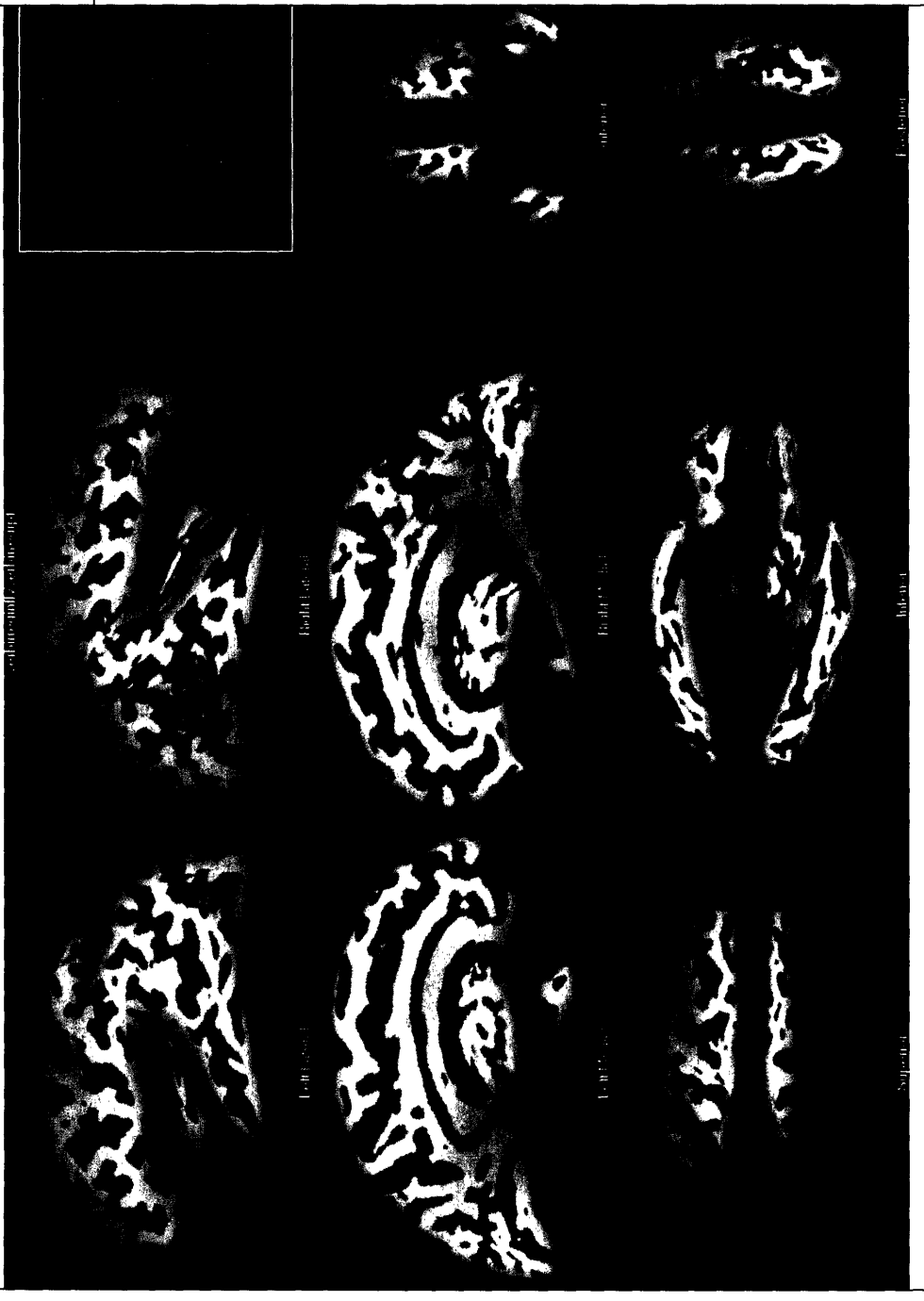
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Overt-Inflect V Noun Irreg Overt-Inflect	**VIO**	>	**NIO**	6%	>	6%
Hypotheses:						
Observations:						



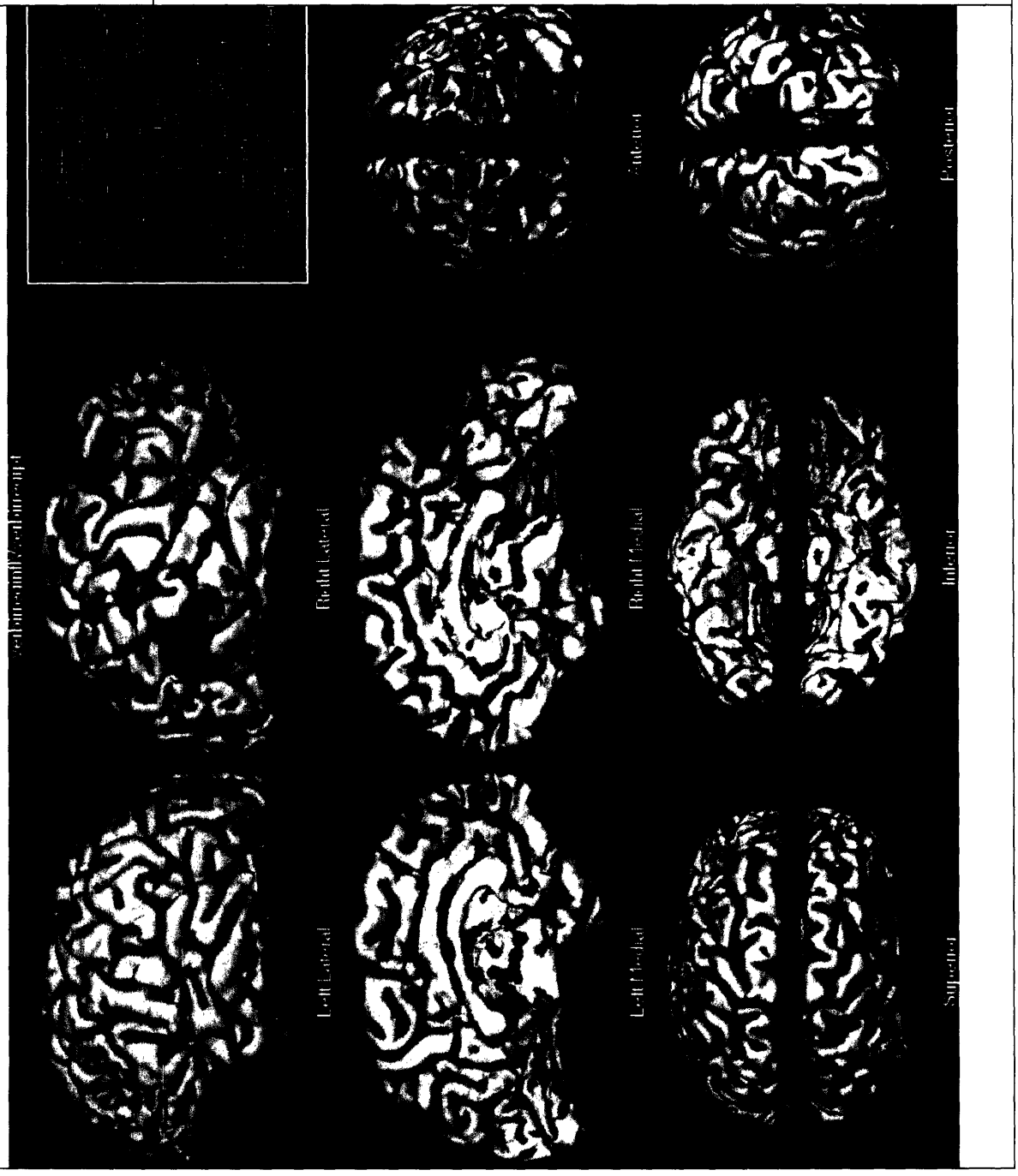
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Overt-Inflect V Noun Irreg Overt-Inflect	**VIO**	>	**NIO**	6%	>	6%
Hypotheses:						
Observations:						



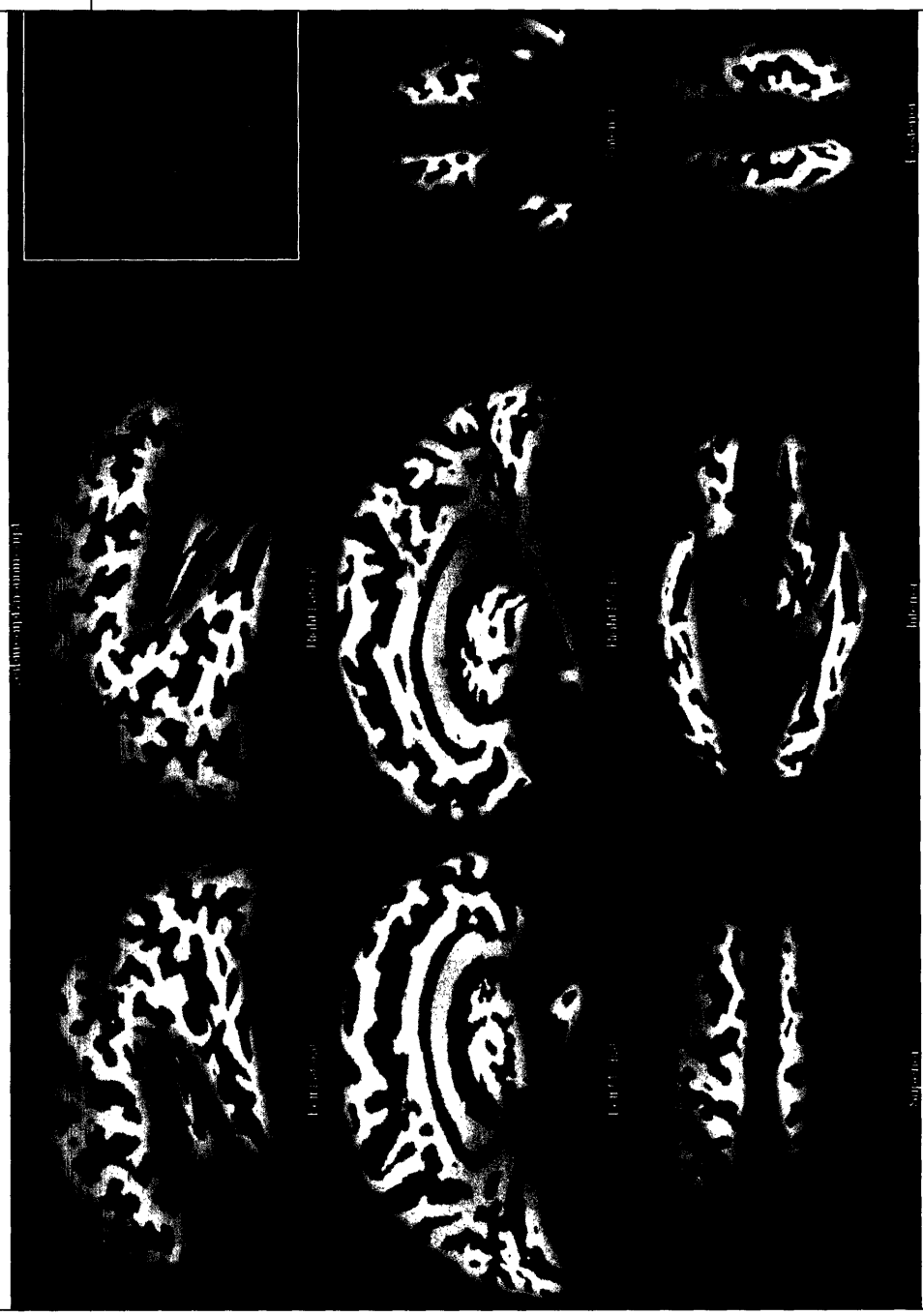
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Overt-Inflect V Verb Irreg Read	**VIO**	>	**VIR**	6%	>	6%
Hypotheses:						
Observations:						



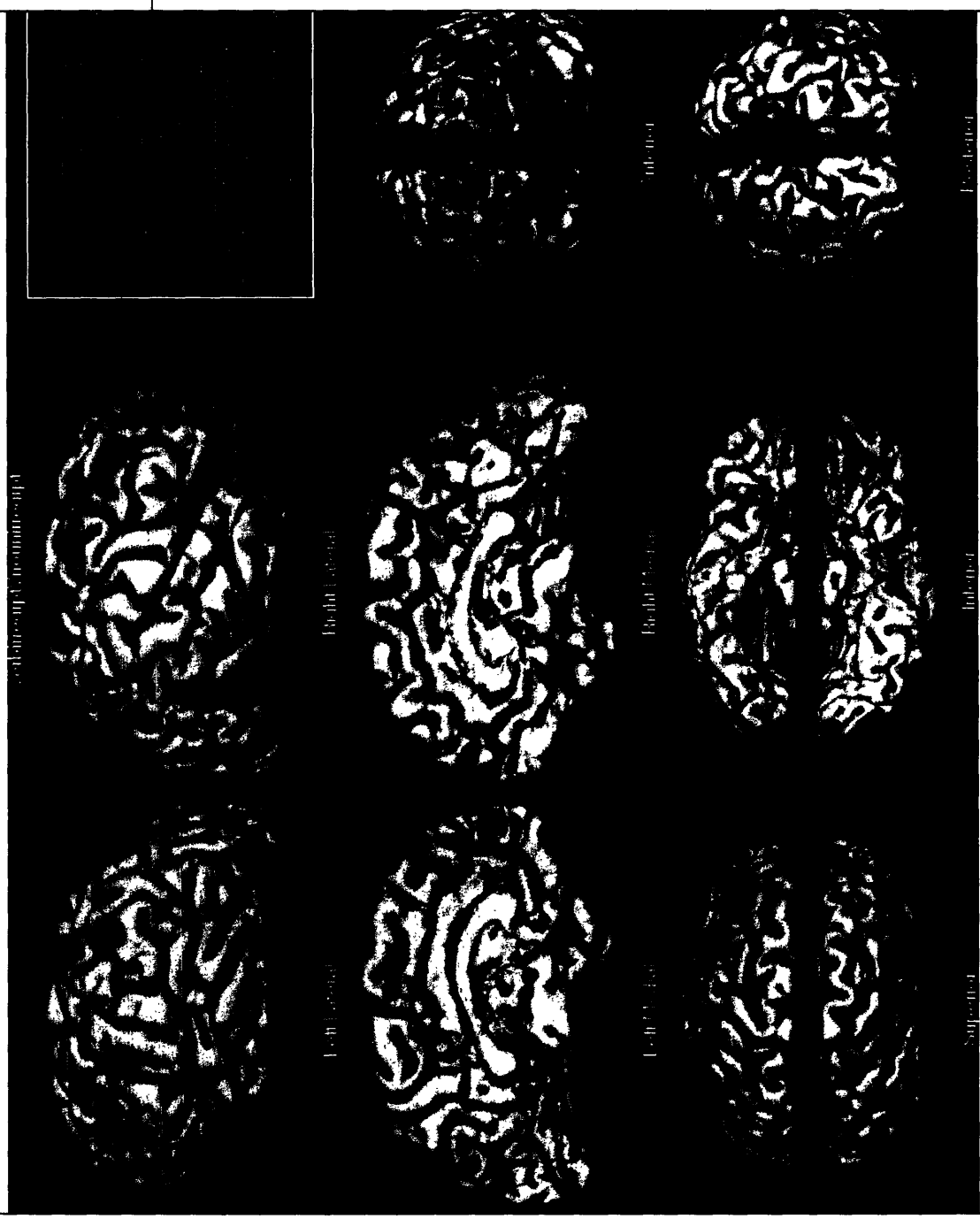
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Overt-Inflect V Verb Irreg Read	VIO	>	VIR	6%	>	6%
Hypotheses:						
Observations:						



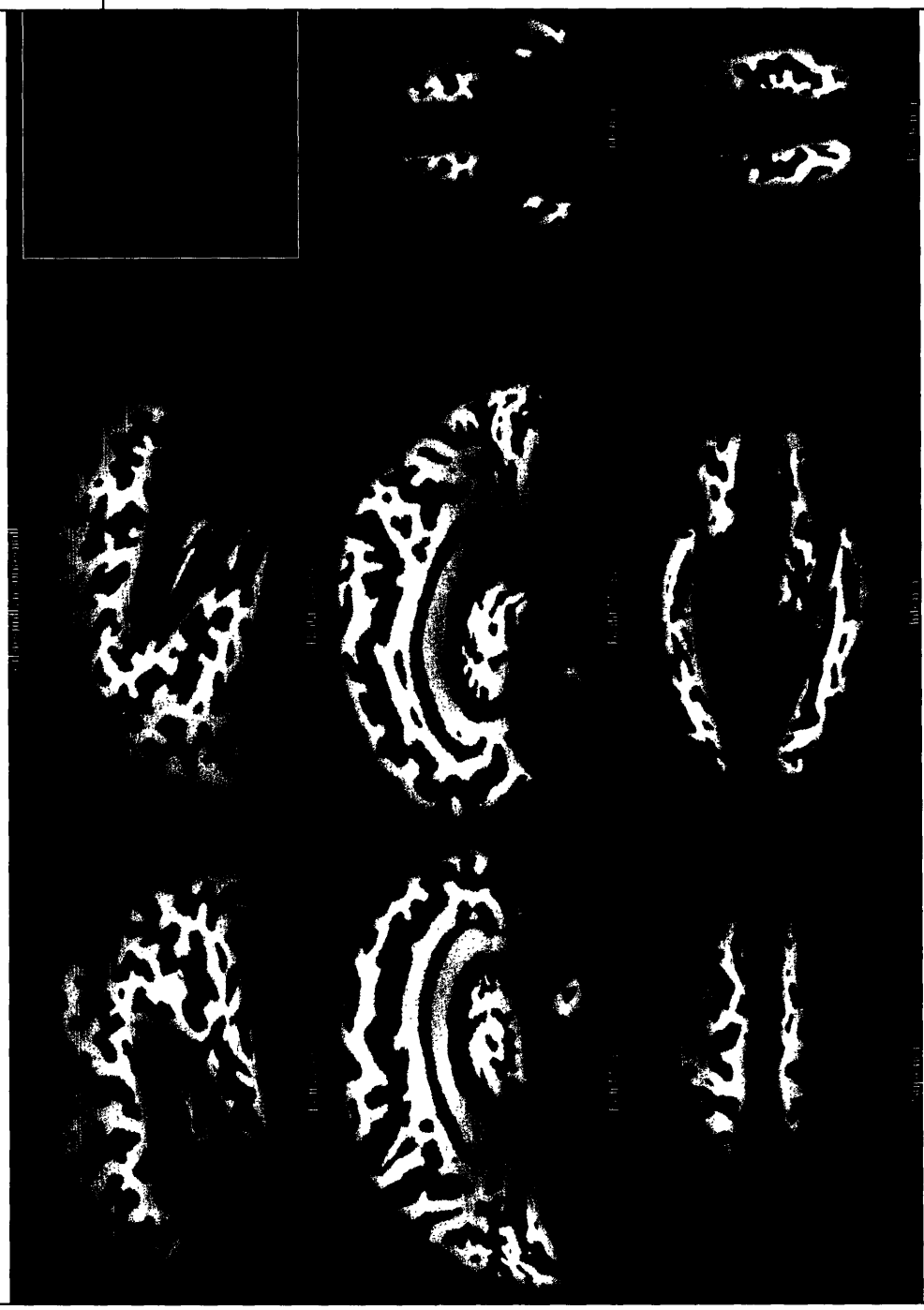
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Read V Noun Irreg Read	VIR	>	NIR	6%	>	6%
Hypotheses:						
Observations:						



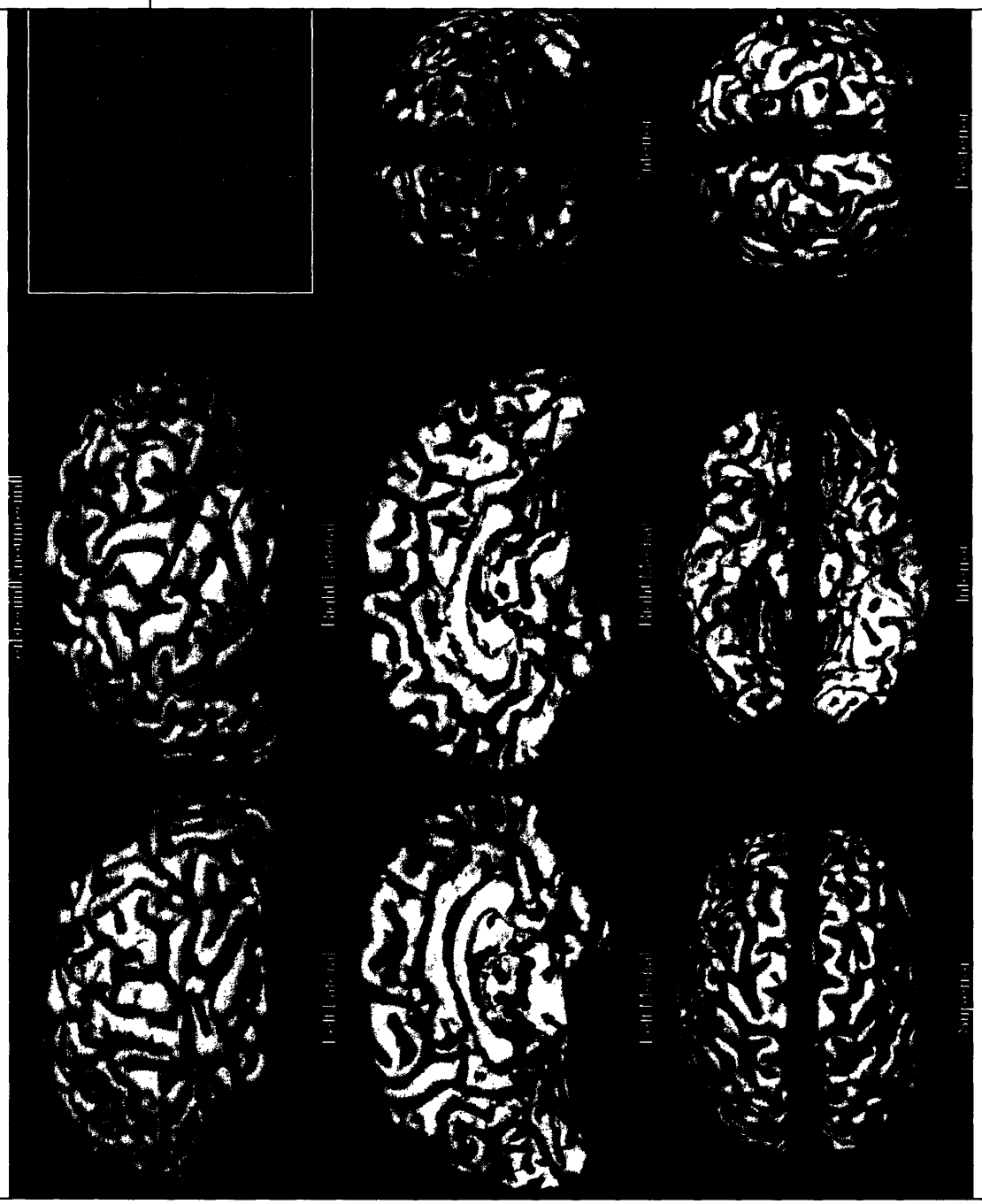
Contrast Name			Conditions Negative	Data Represented		
Verb Irreg Read V Noun Irreg Read	**VIR**	>	**NIR**	6%	>	6%
Hypotheses:						
Observations:						



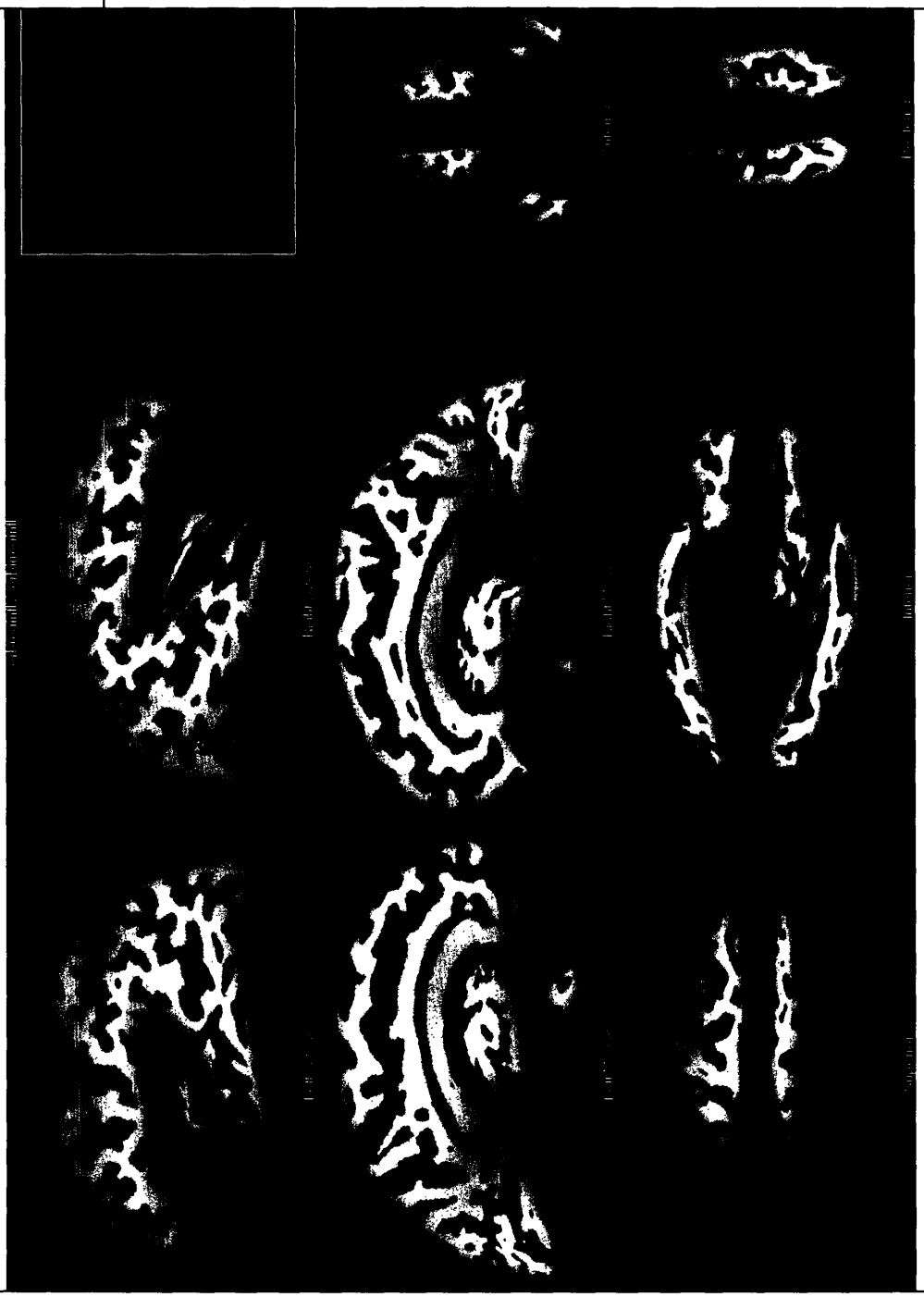
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Noun Reg Overt-Inflect	**VRO**	>	**NRO**	6%	>	6%
Hypotheses:						
Observations:						



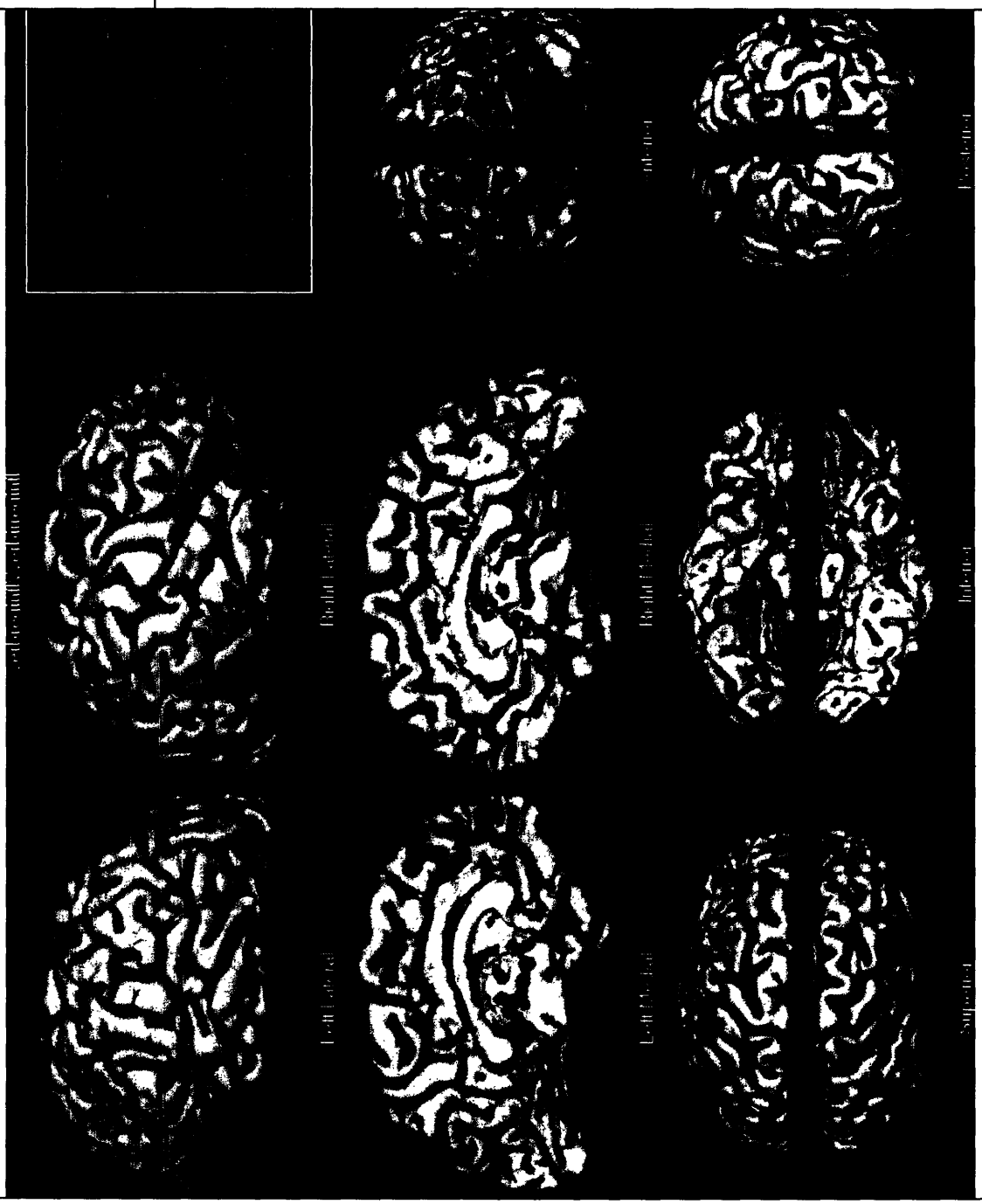
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Noun Reg Overt-Inflect	**VRO**	>	**NRO**	6%	>	6%
Hypotheses:						
Observations:						



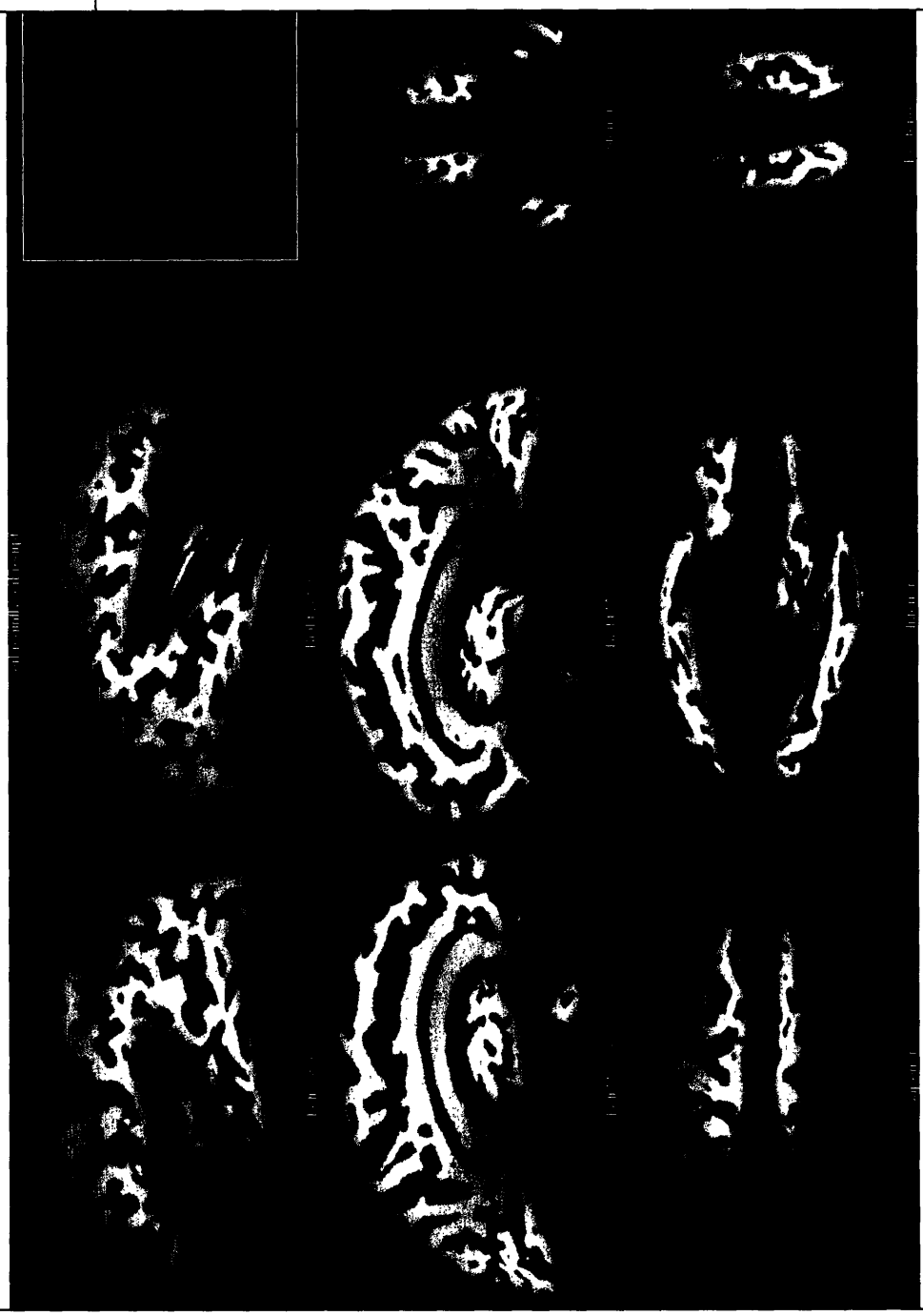
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Verb Irreg Overt-Inflect	**VRO**	>	**VIO**	6%	>	6%
Hypotheses:						
Observations:						



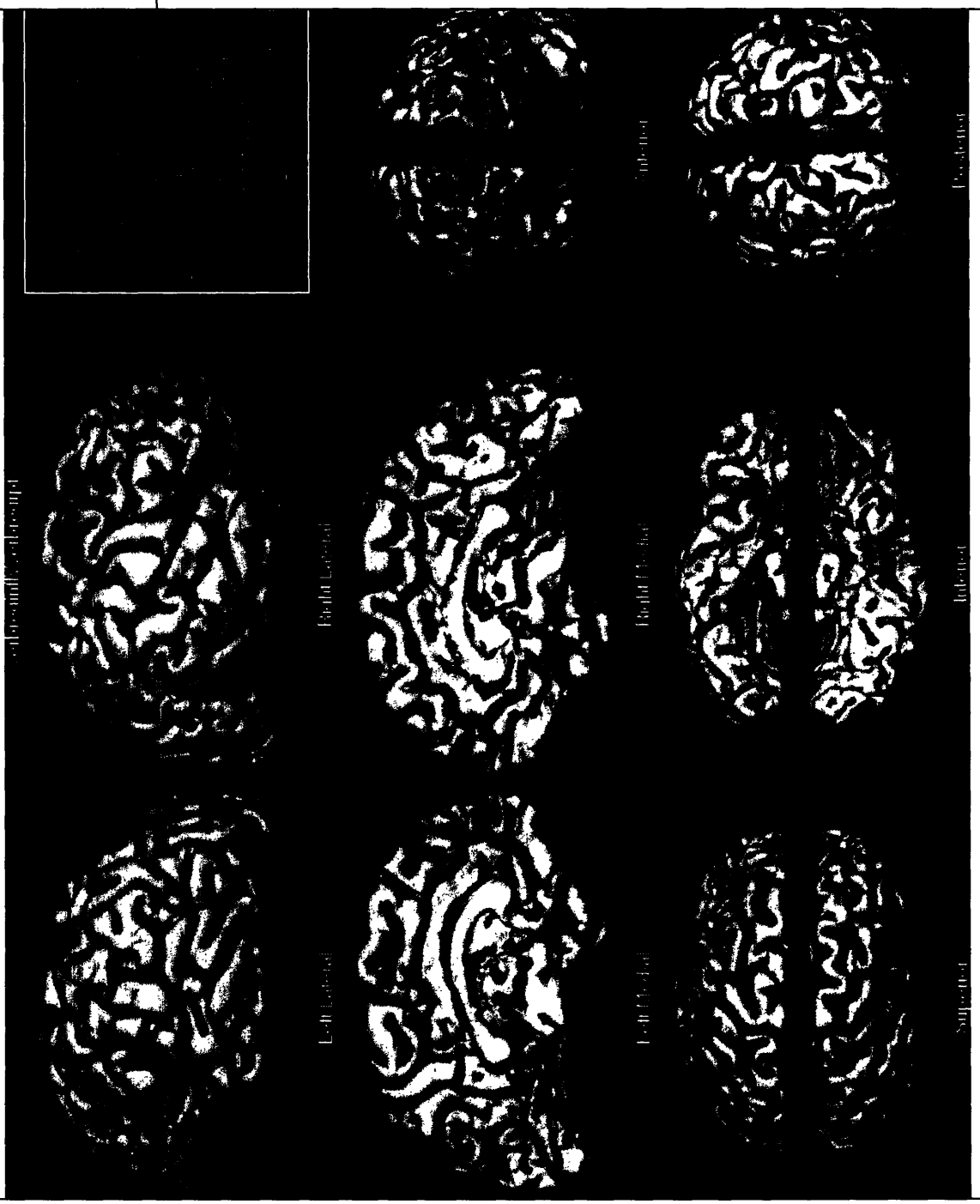
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Verb Irreg Overt-Inflect	VRO	>	VIO	6%	>	6%
Hypotheses:						
Observations:						



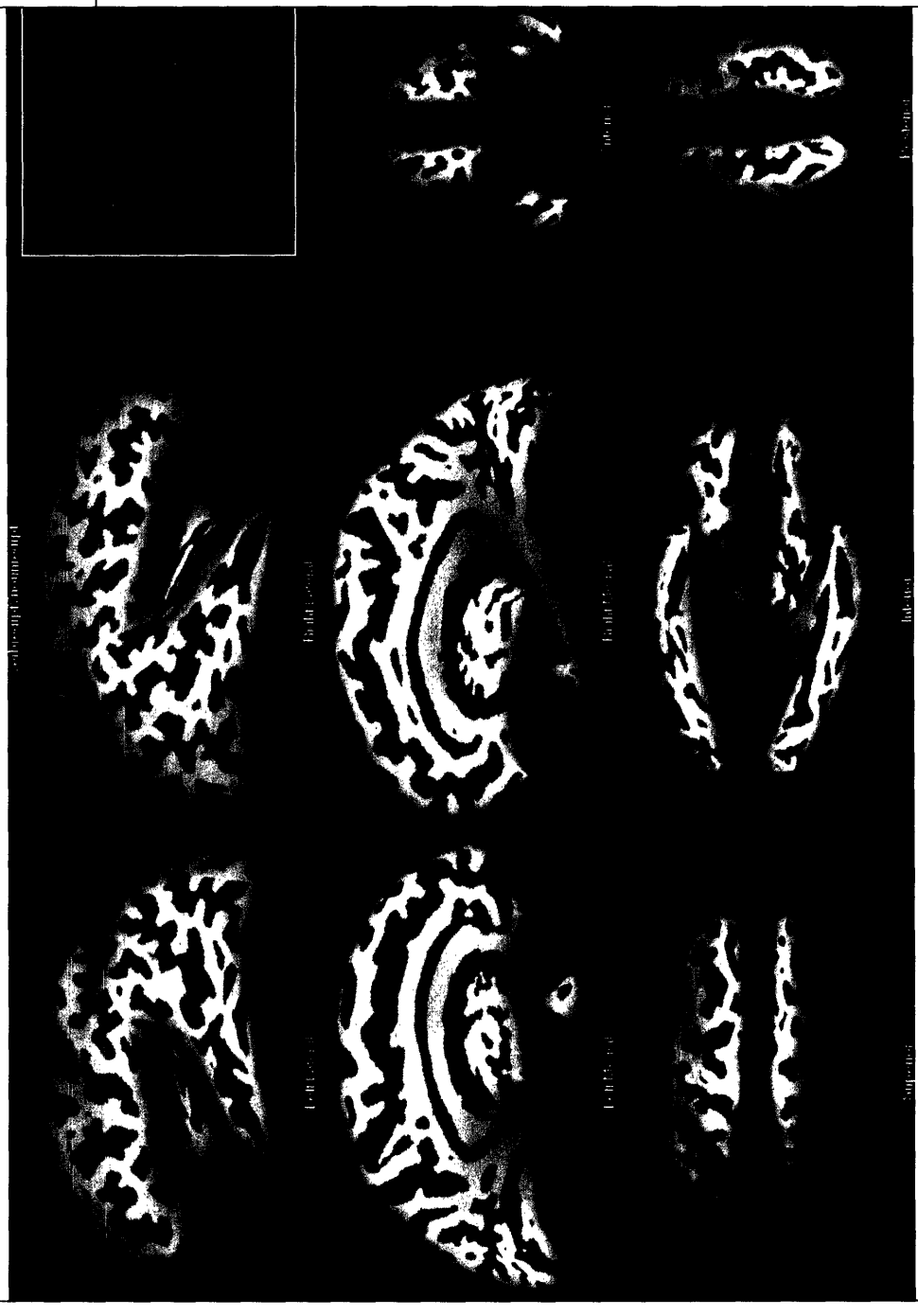
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Verb Reg Read	**VRO**	>	**VRR**	6%	>	6%
Hypotheses:						
Observations:						



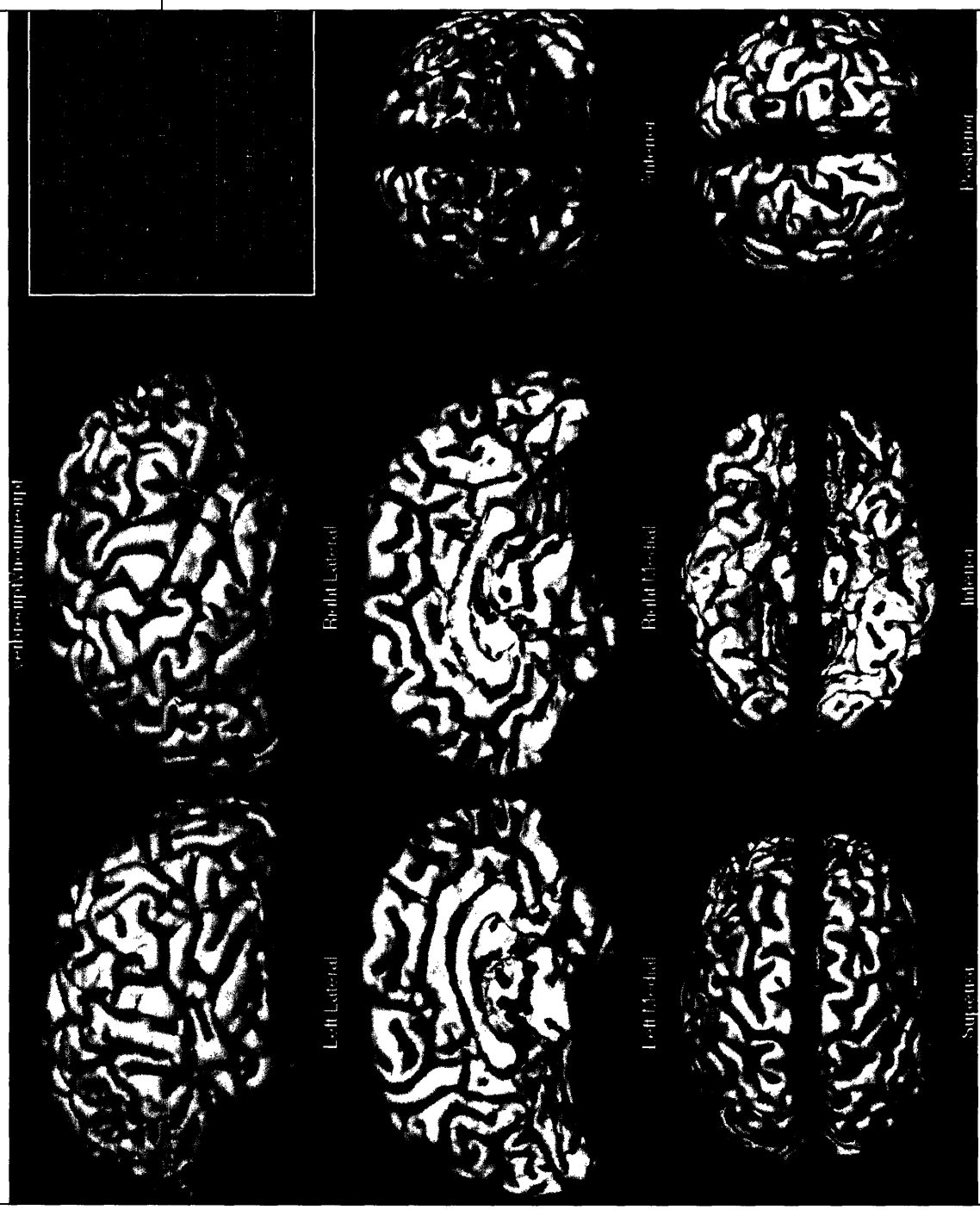
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Overt-Inflect V Verb Reg Read	**VRO**	>	**VRR**	6%	>	6%
Hypotheses:						
Observations:						



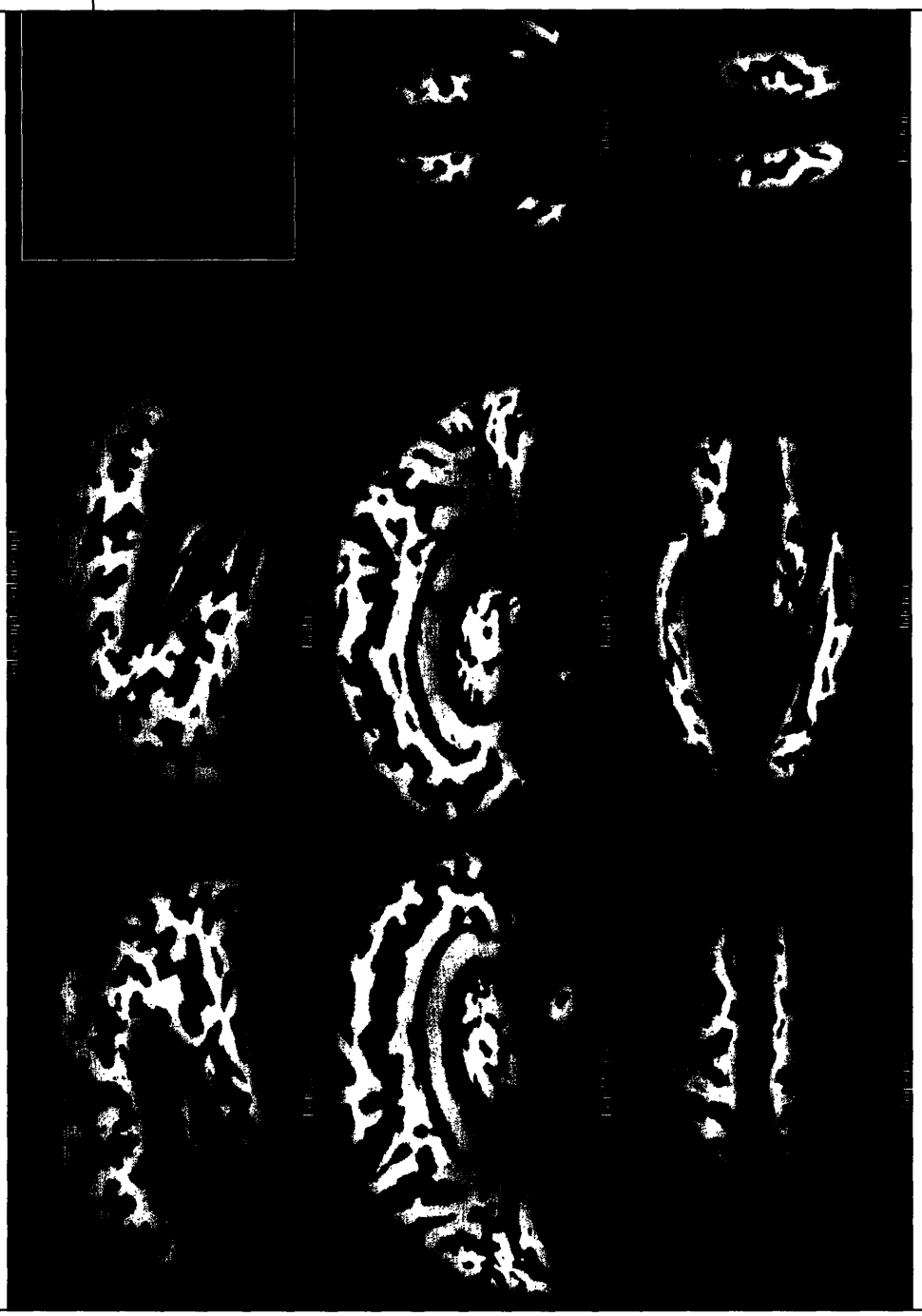
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Read V Noun Reg Read	VRR	>	NRR	6%	>	6%
Hypotheses:						
Observations:						



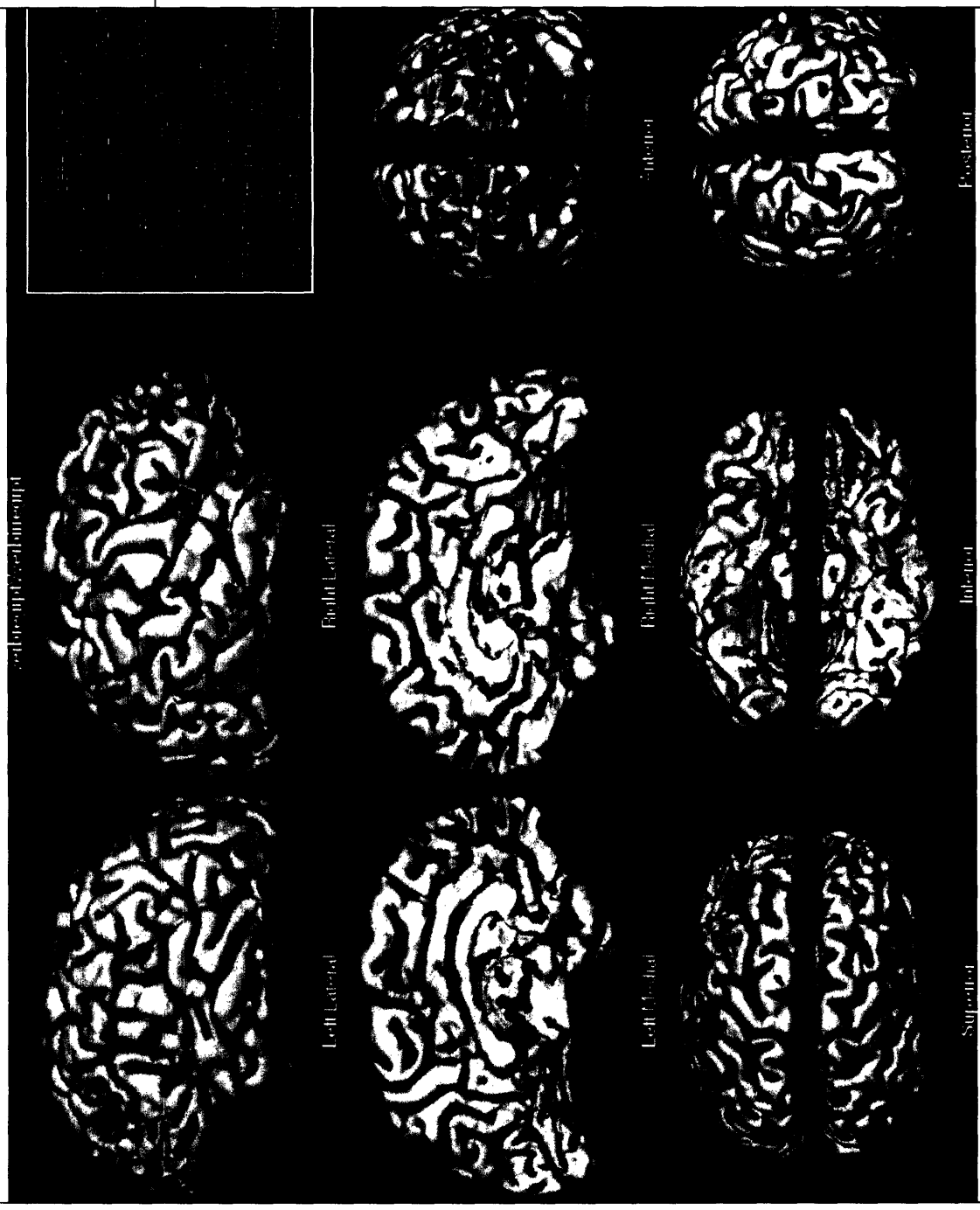
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Read V Noun Reg Read	**VRR**	>	**NRR**	6%	>	6%
Hypotheses:						
Observations:						



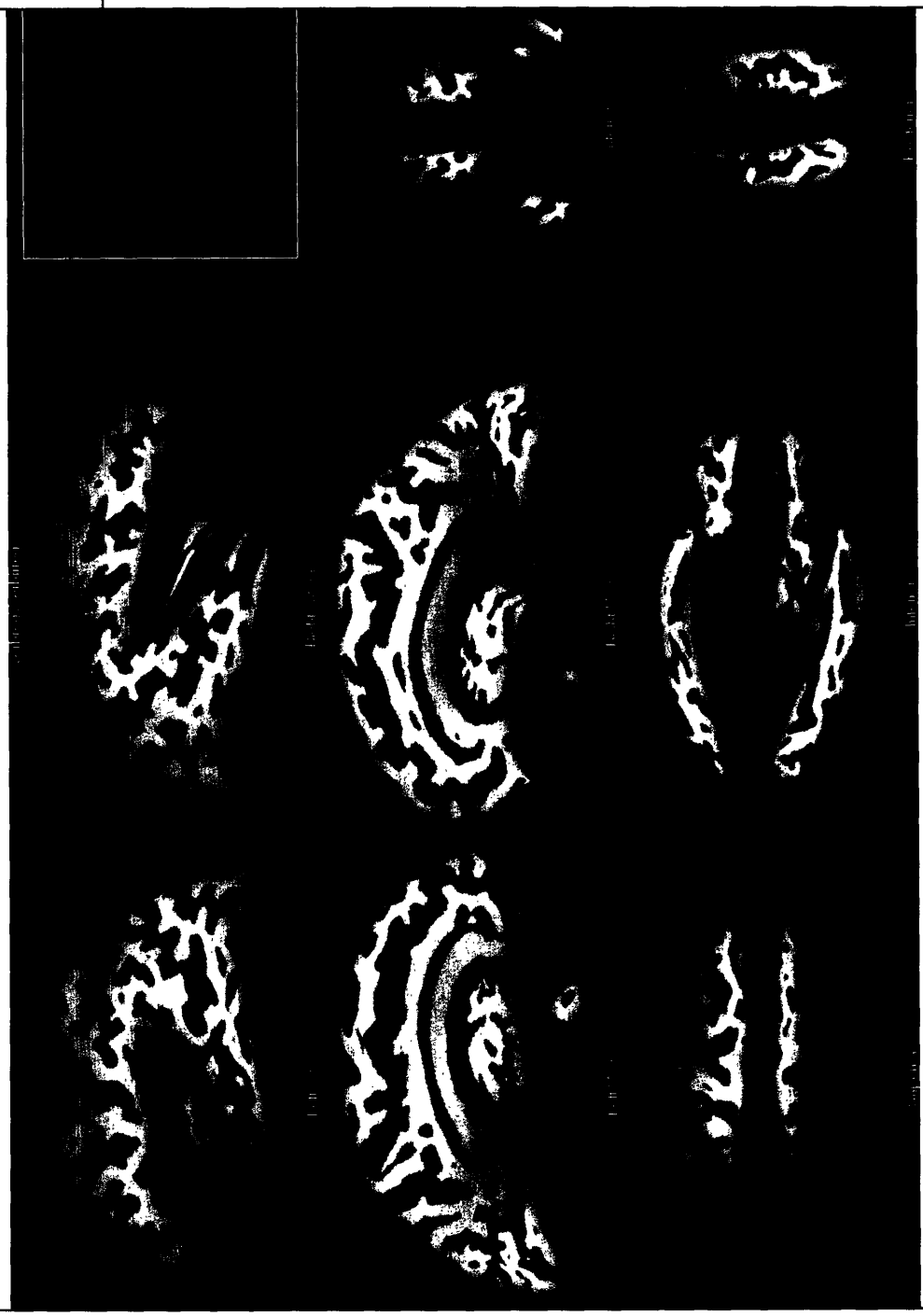
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Read V Verb Irreg Read	**VRR**	>	**VIR**	6%	>	6%
Hypotheses:						
Observations:						



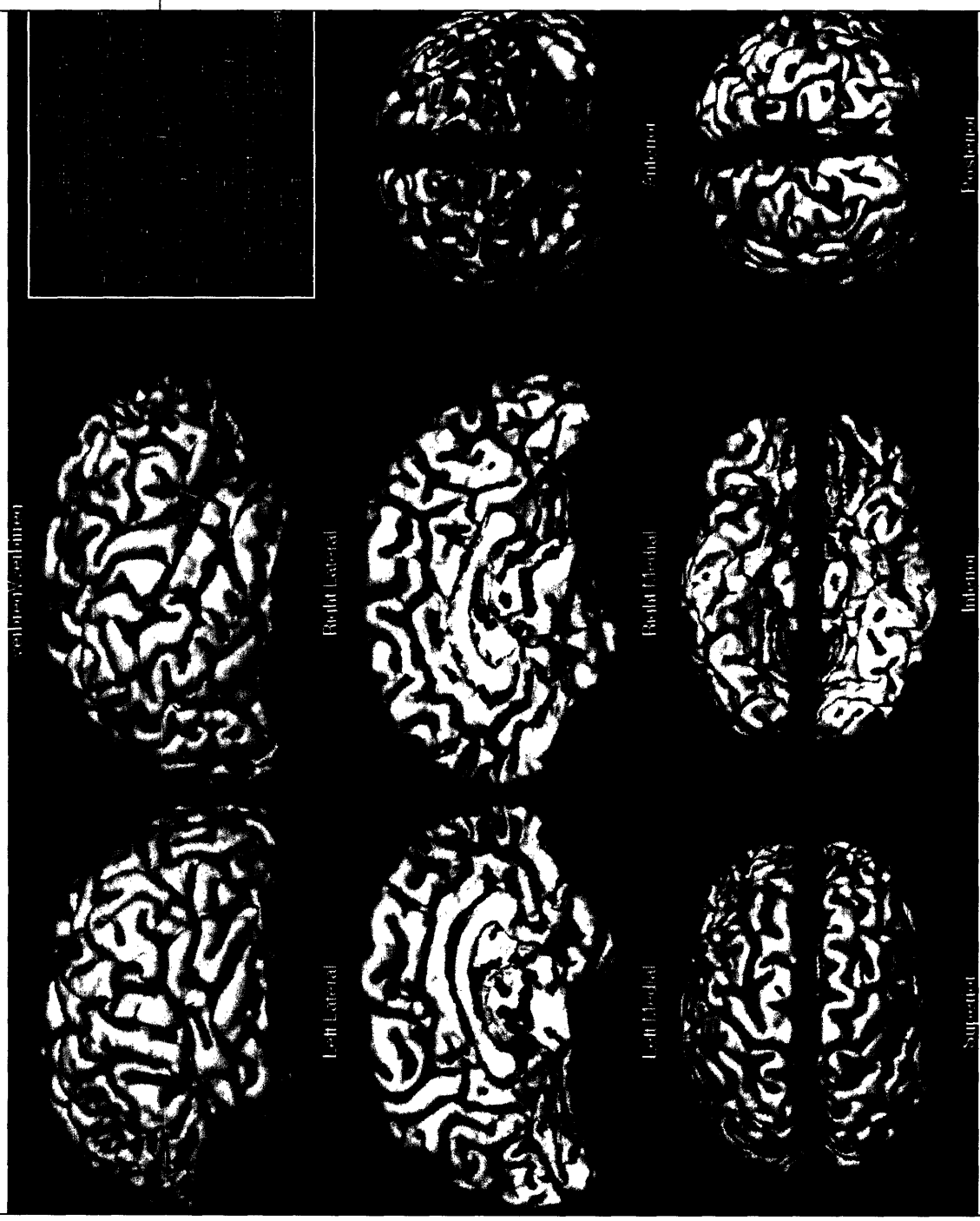
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Read V Verb Irreg Read	**VRR**	>	**VIR**	6%	>	6%
Hypotheses:						
Observations:						



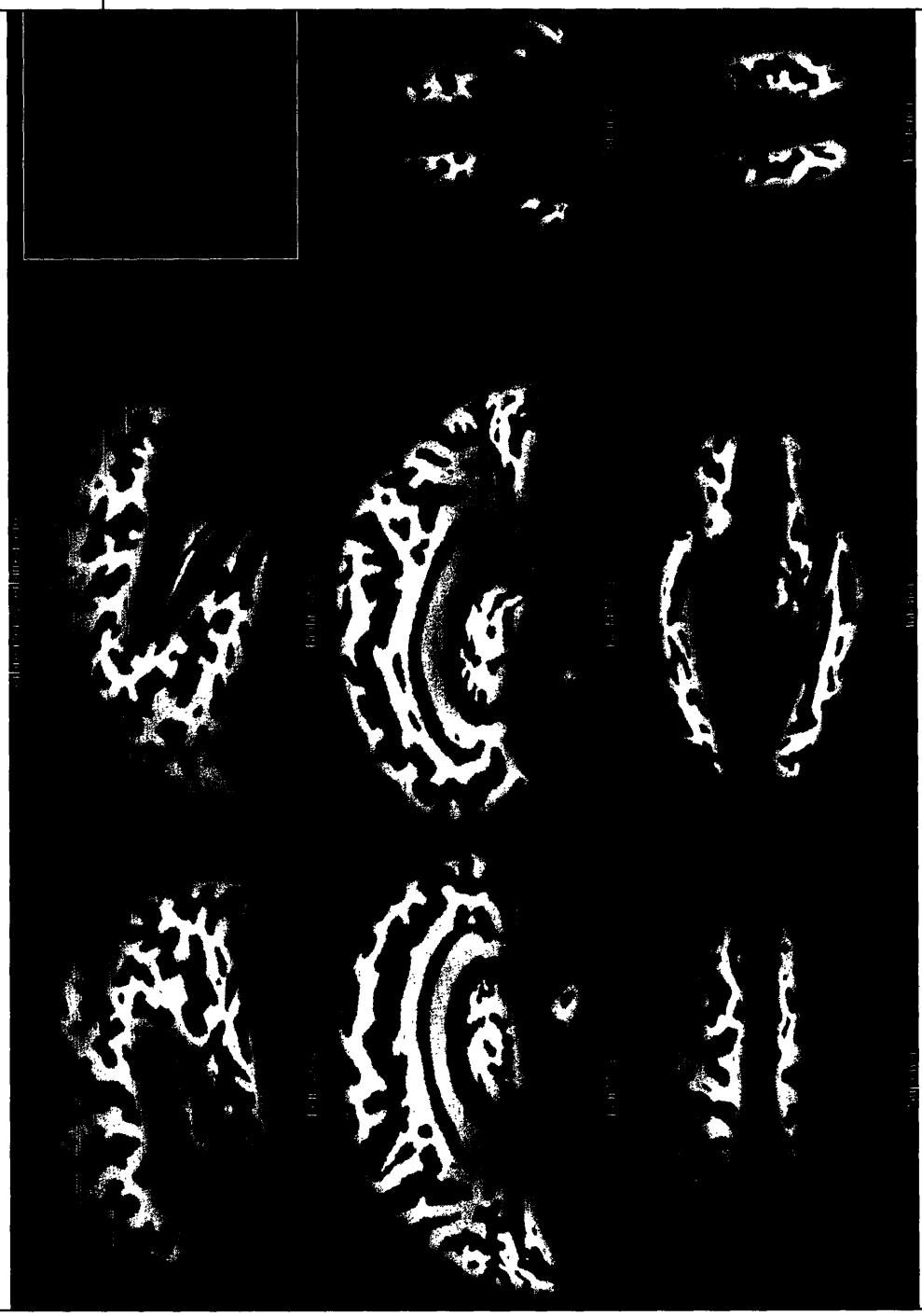
Contrast Name			Conditions Negative	Data Represented		
Verb Reg V Verb Irreg	**VRO, VRZ, VRR**	>	**VIO, VIZ, VIR**	18%	>	18%
Hypotheses:						
Observations:						



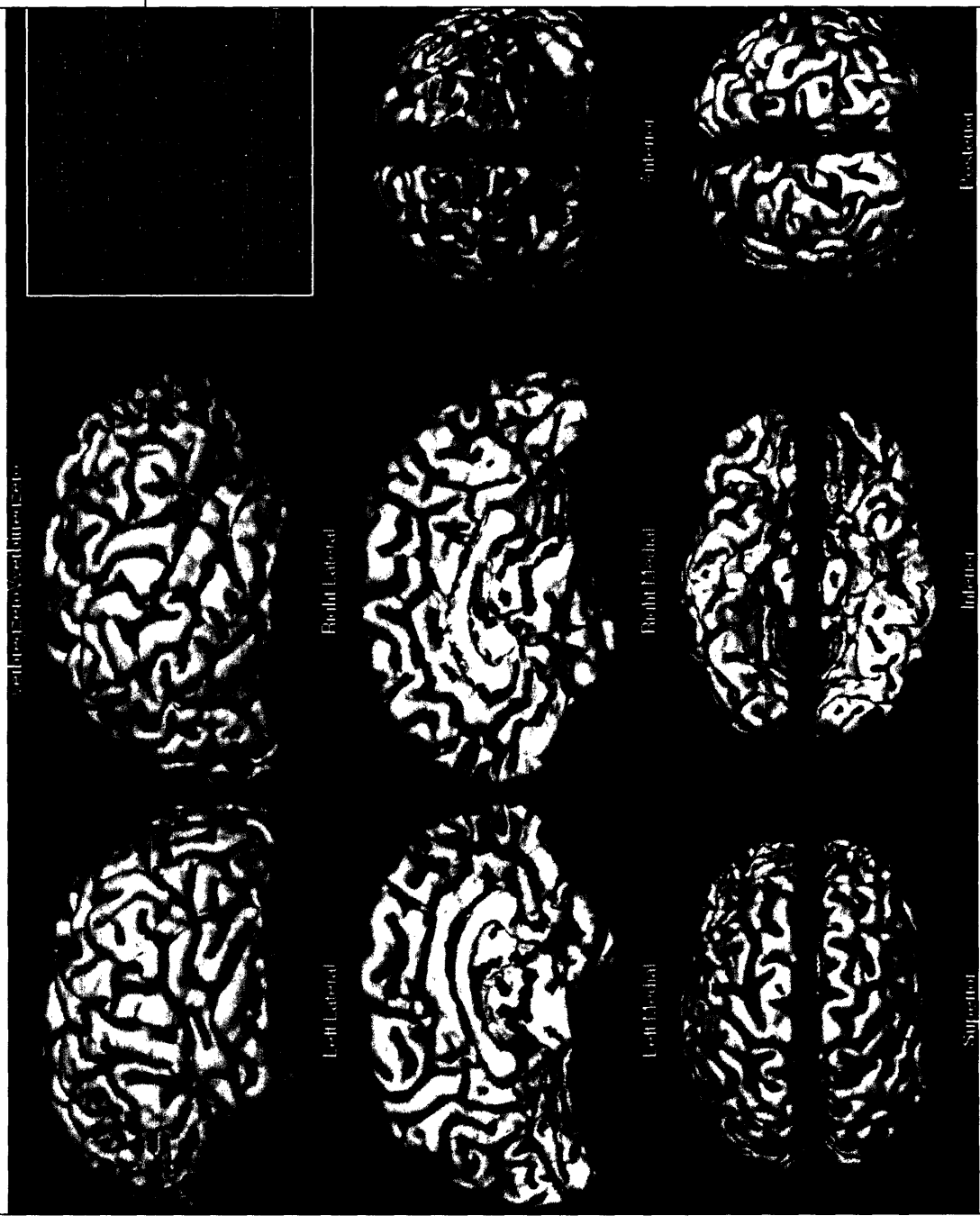
Contrast Name			Conditions Negative	Data Represented		
Verb Reg V Verb Irreg	**VRO, VRZ, VRR**	>	**VIO, VIZ, VIR**	18%	>	18%
Hypotheses:						
Observations:						



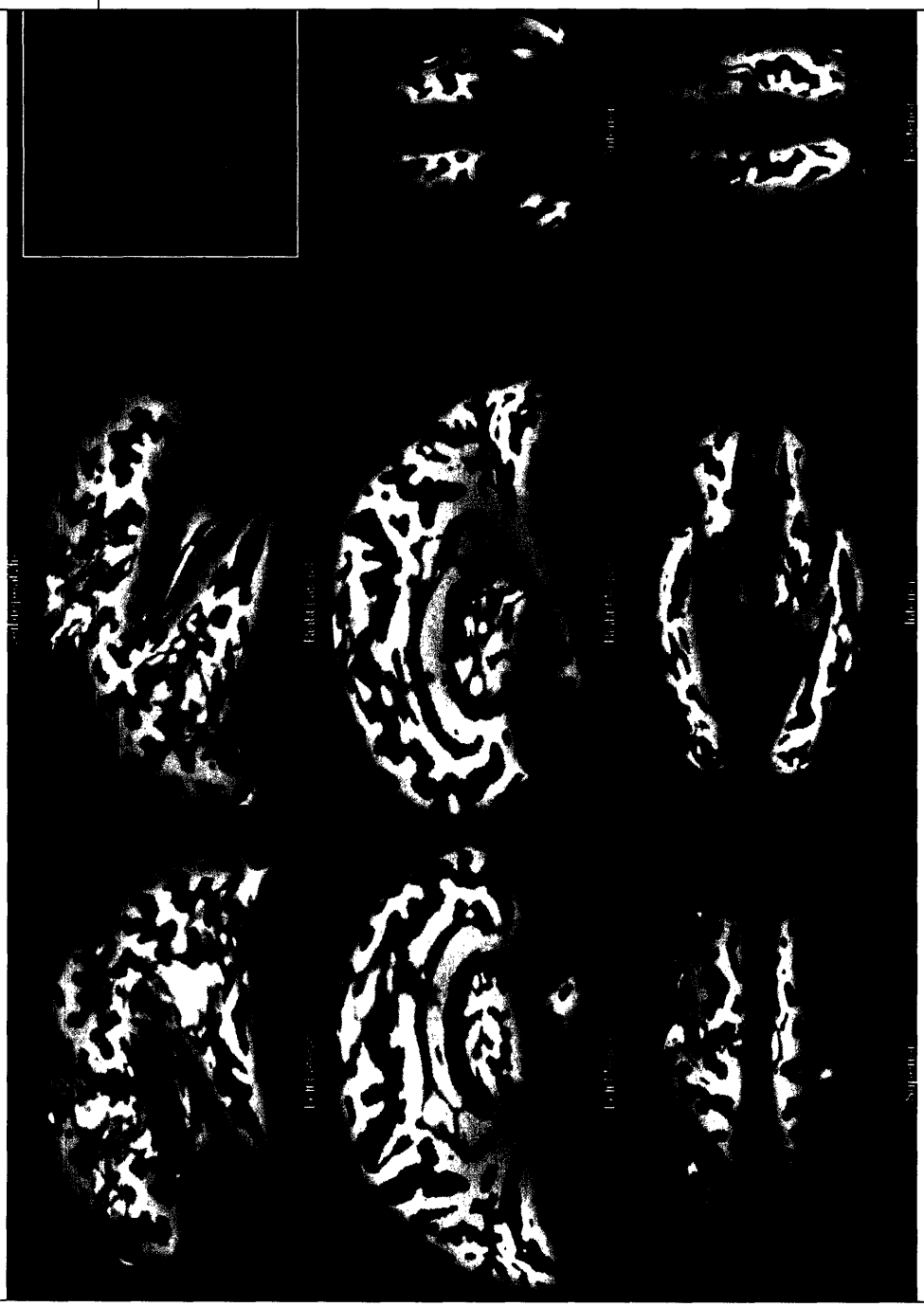
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Zero-Inflect V Verb Irreg Zero-Inflect	**VRZ**	>	**VIZ**	6%	>	6%
Hypotheses:						
Observations:						



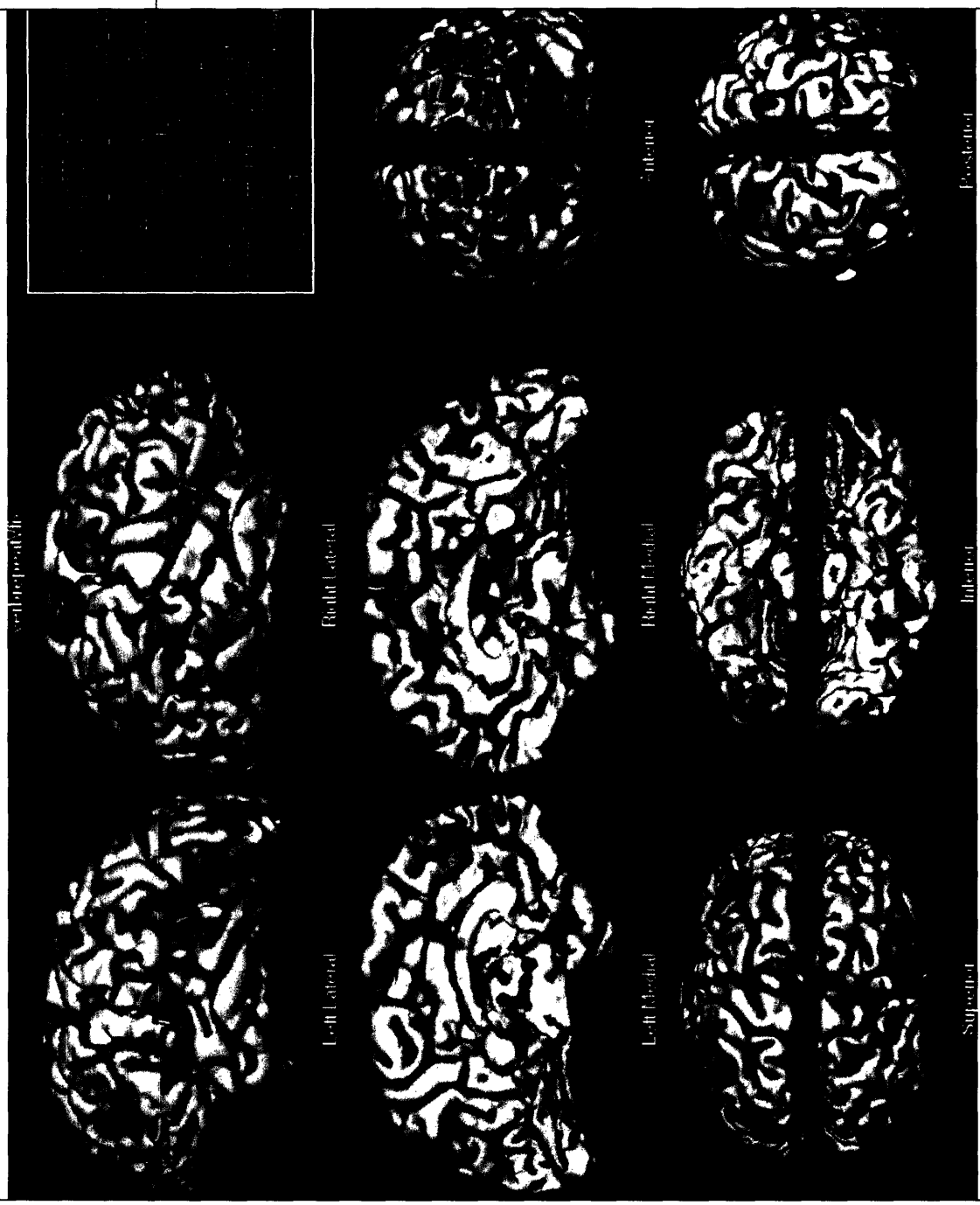
Contrast Name			Conditions Negative	Data Represented		
Verb Reg Zero-Inflect V Verb Irreg Zero-Inflect	**VRZ**	>	**VIZ**	6%	>	6%
Hypotheses:						
Observations:						



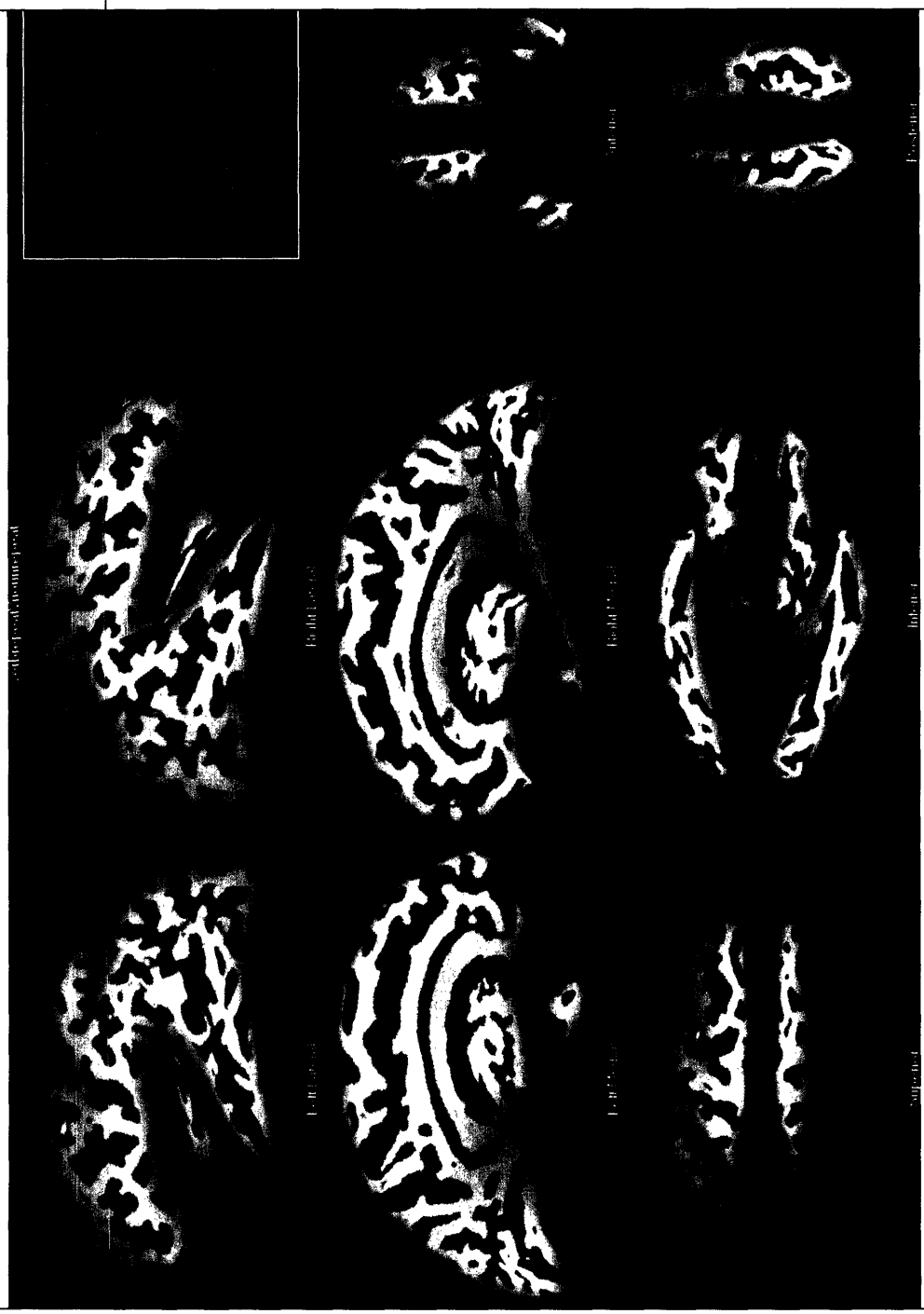
Contrast Name			Conditions Negative	Data Represented		
Verb Read V Fix	**VRR, VIR**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



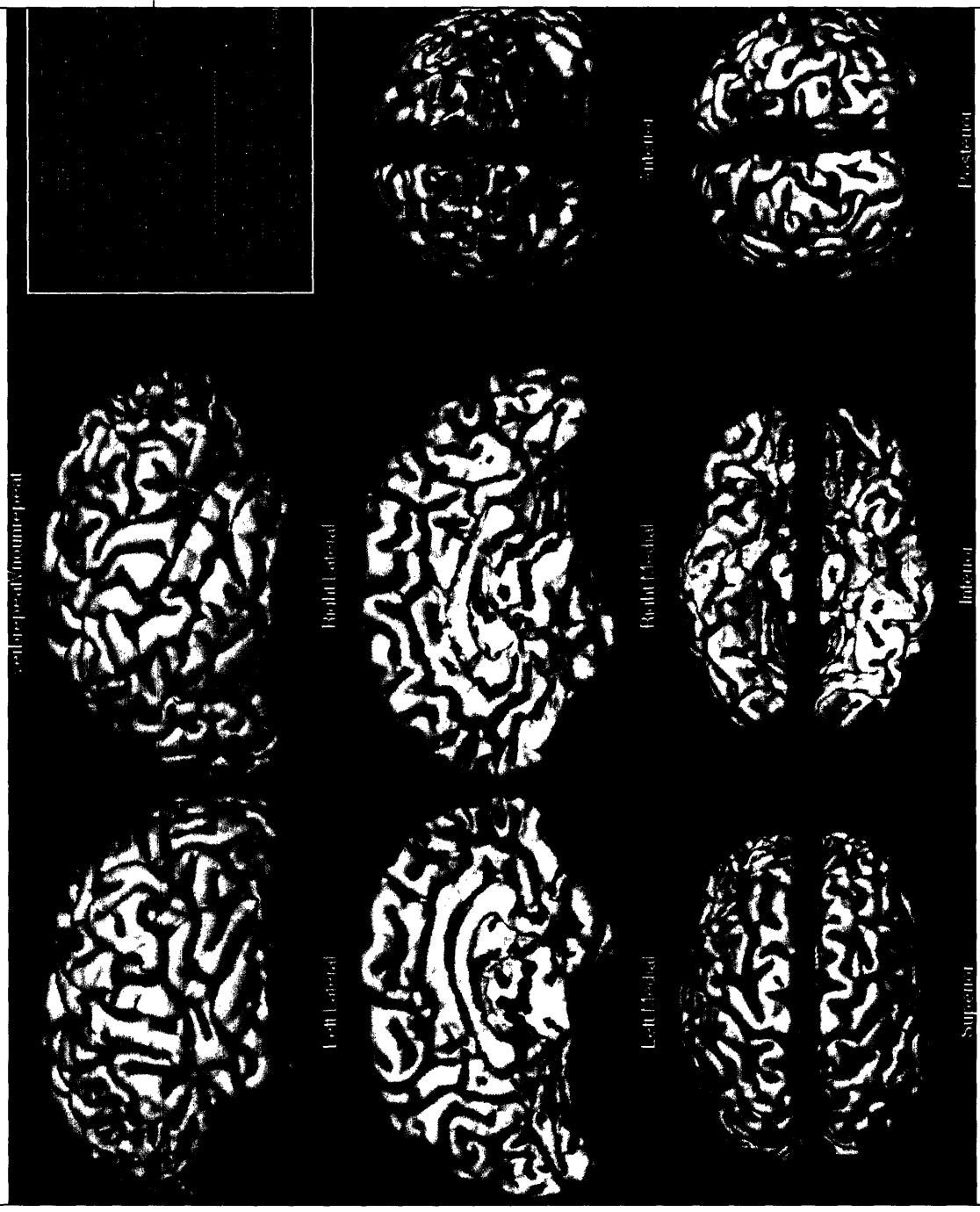
Contrast Name			Conditions Negative	Data Represented		
Verb Read V Fix	**VRR, VIR**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



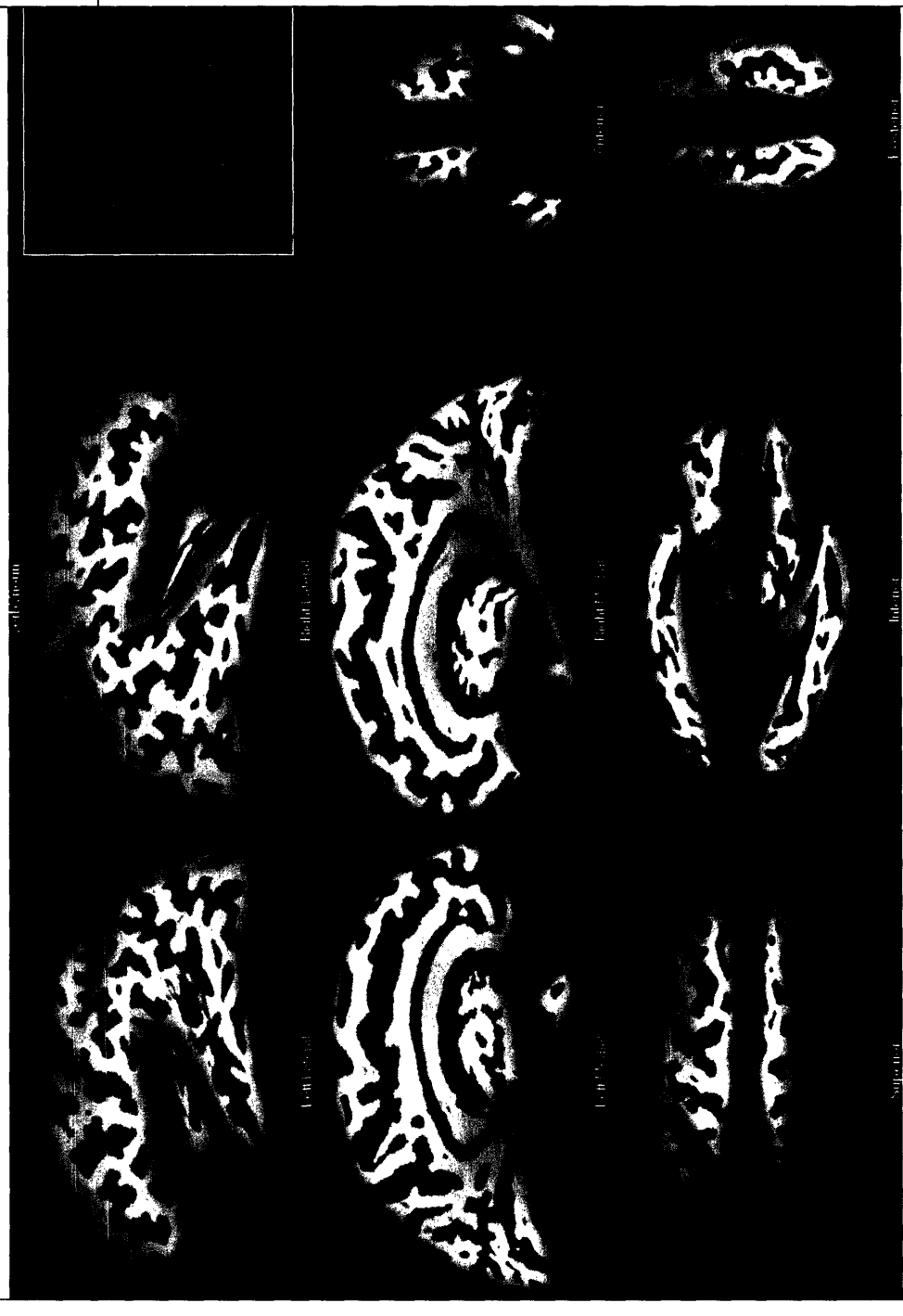
Contrast Name			Conditions Negative	Data Represented		
Verb Read V Noun Read	**VRR, VIR**	>	**NRR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



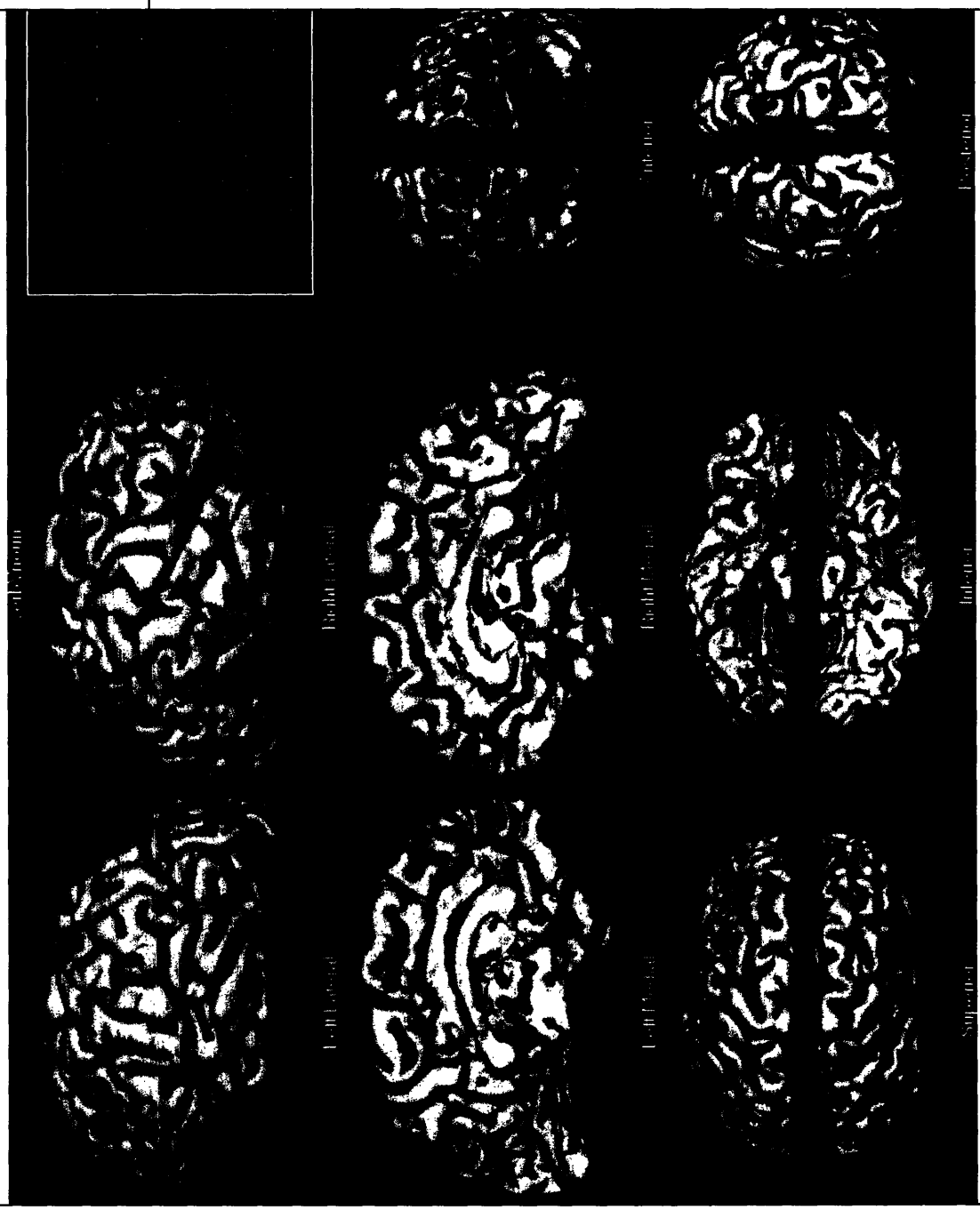
Contrast Name			Conditions Negative	Data Represented		
Verb Read V Noun Read	**VRR, VIR**	>	**NRR, NIR**	12%	>	12%
Hypotheses:						
Observations:						



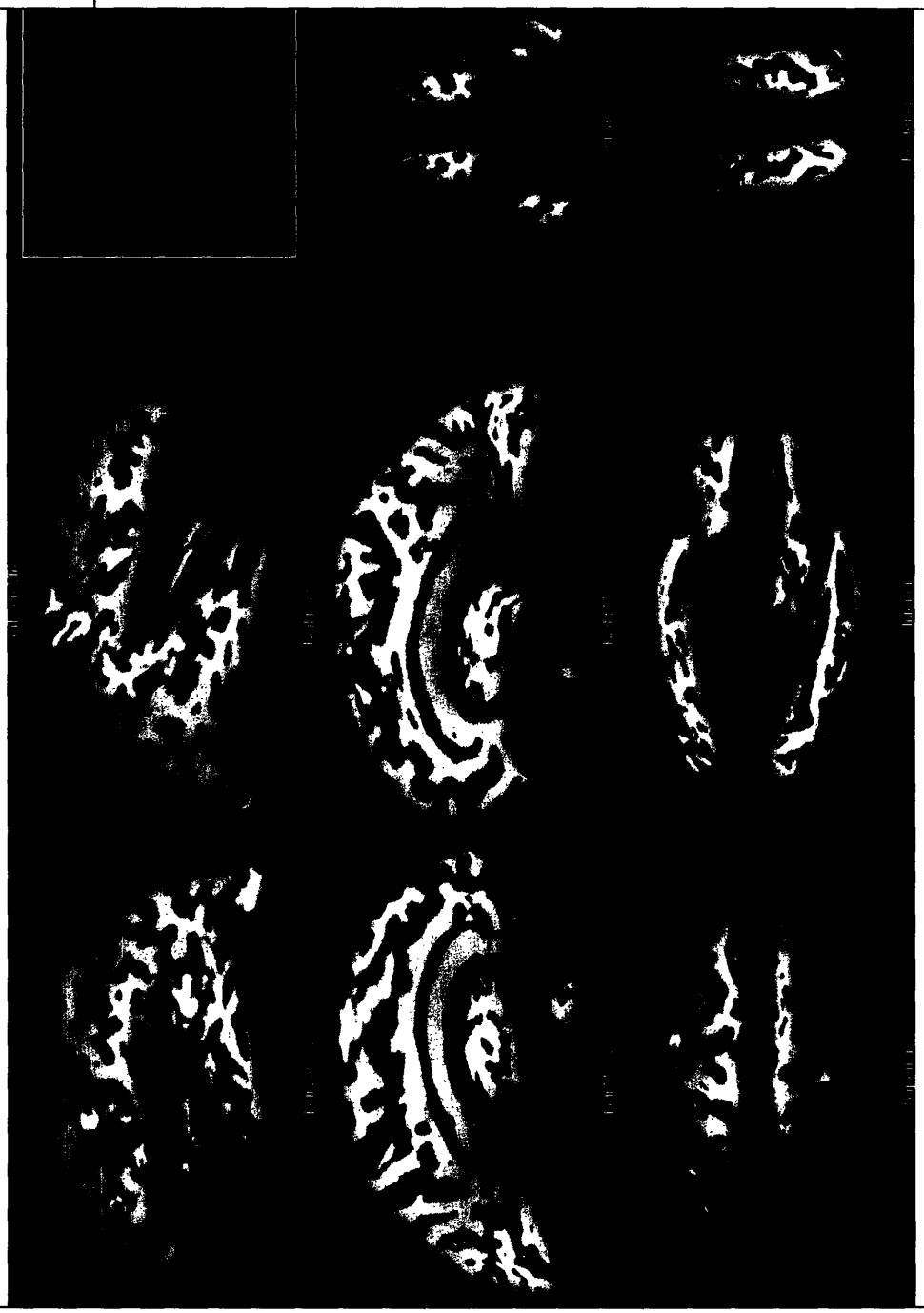
Contrast Name			Conditions Negative	Data Represented		
Verb V Noun	VRO, VIO, VRZ, VIZ, VRR, VIR	>	NRO, NIO, NRZ, NIZ, NRR, NIR	36%	>	36%
Hypotheses:						
Observations:						



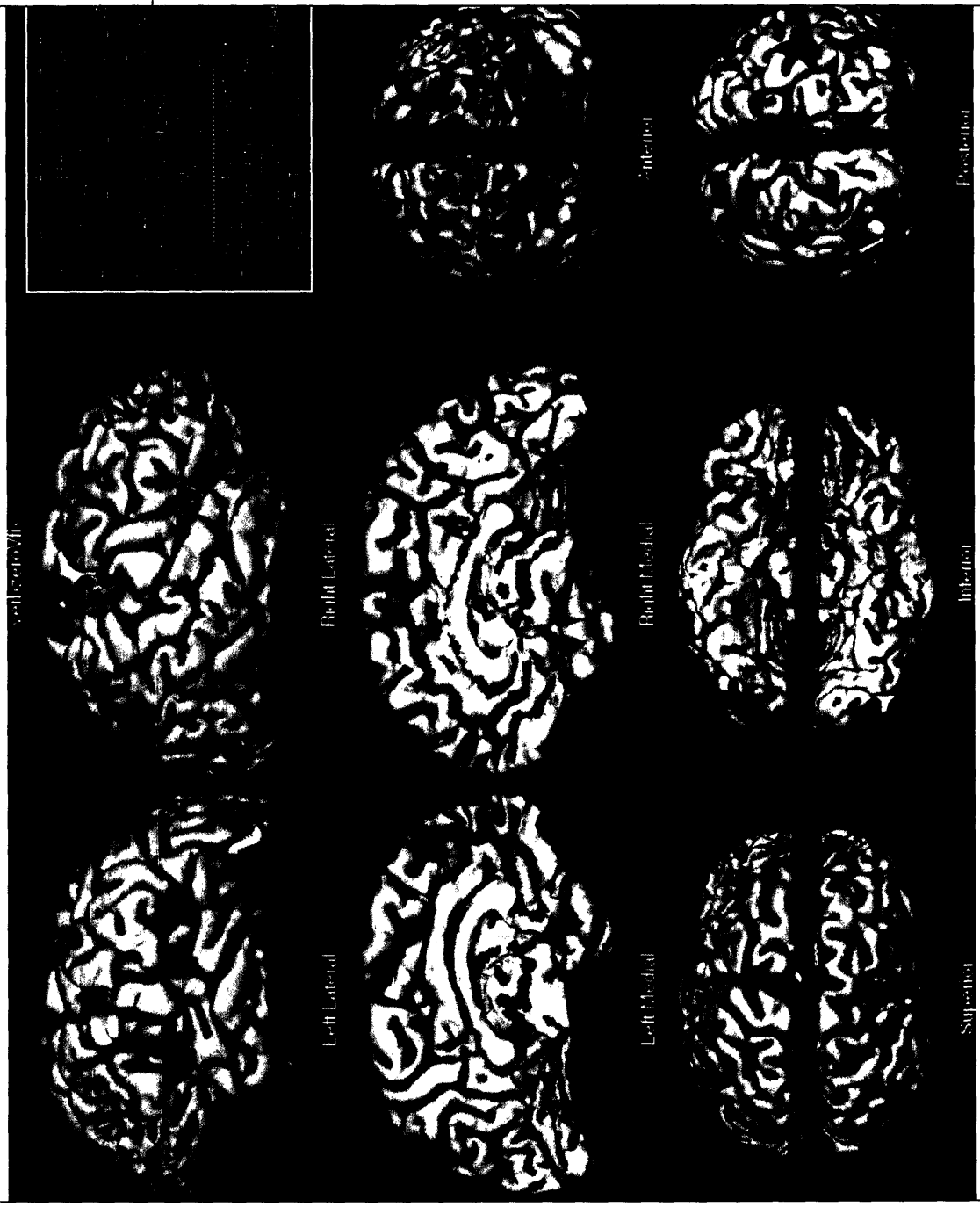
Contrast Name			Conditions Negative	Data Represented		
Verb V Noun	VRO, VIO, VRZ, VIZ, VRR, VIR	>	NRO, NIO, NRZ, NIZ, NRR, NIR	36%	>	36%
Hypotheses:						
Observations:						



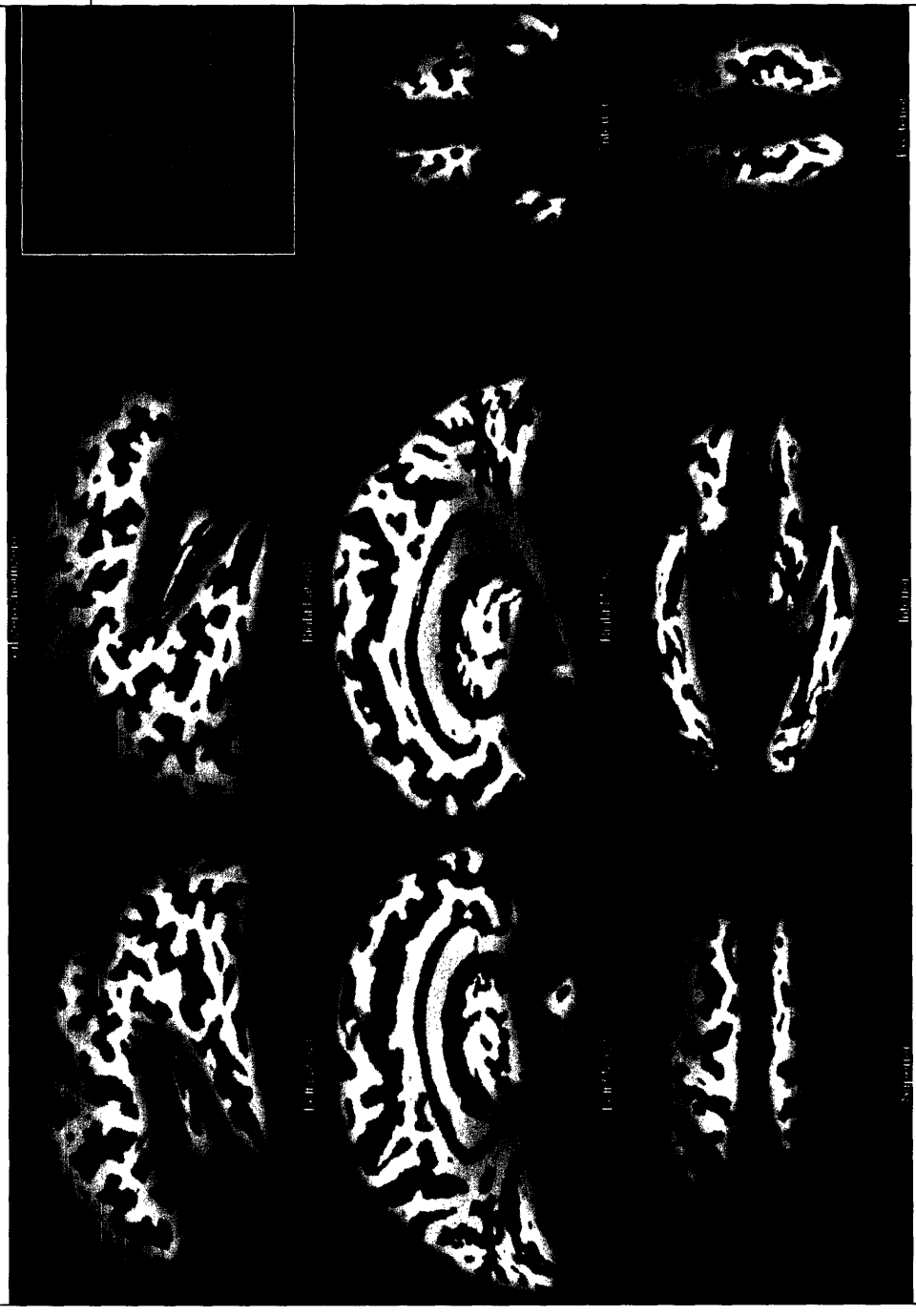
Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Fix	**VRZ, VIZ**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



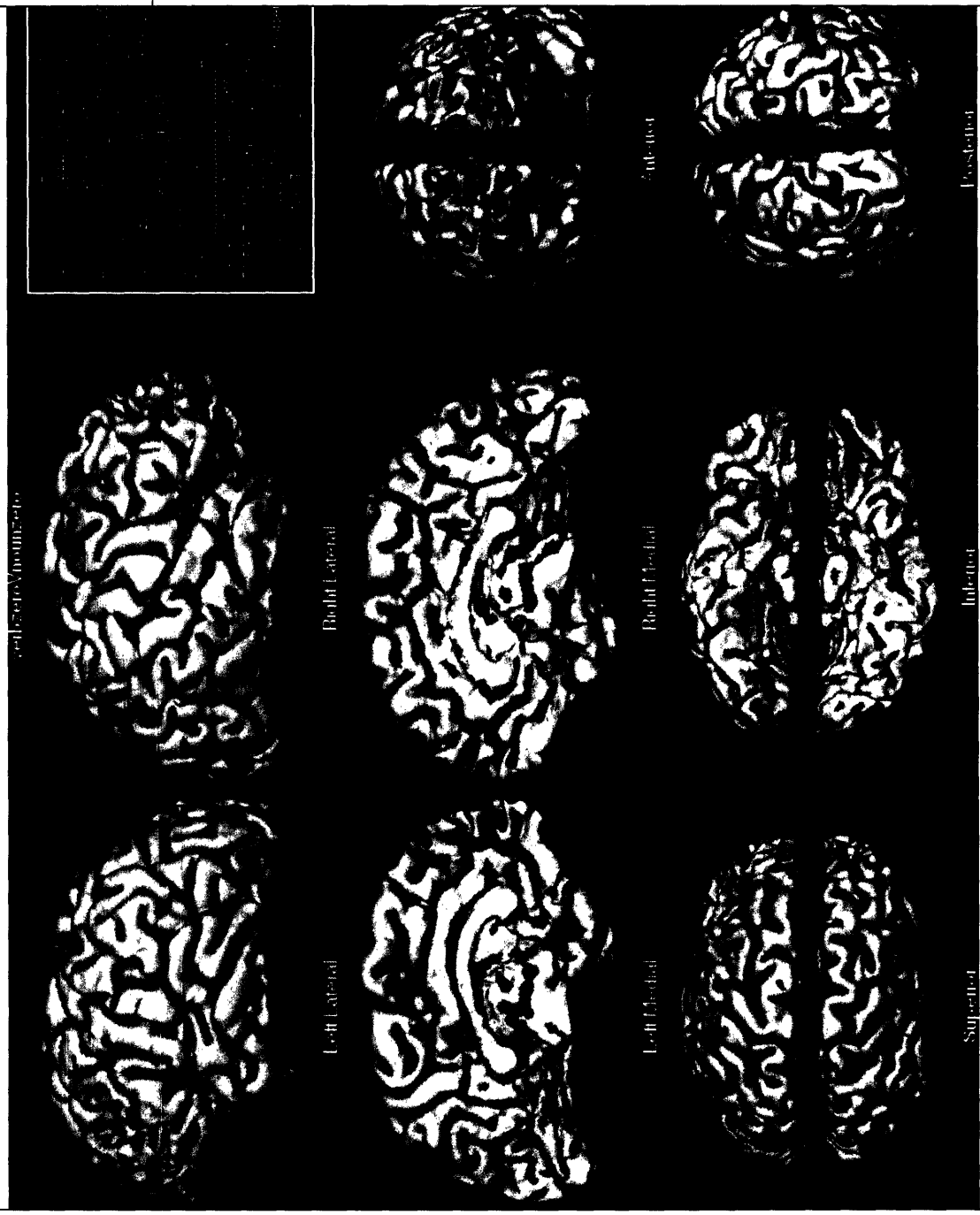
Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Fix	**VRZ, VIZ**	>	**FIX**	12%	>	27%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Noun Zero	**VRZ, VIZ**	>	**NRZ, NIZ**	12%	>	12%
Hypotheses:						
Observations:						

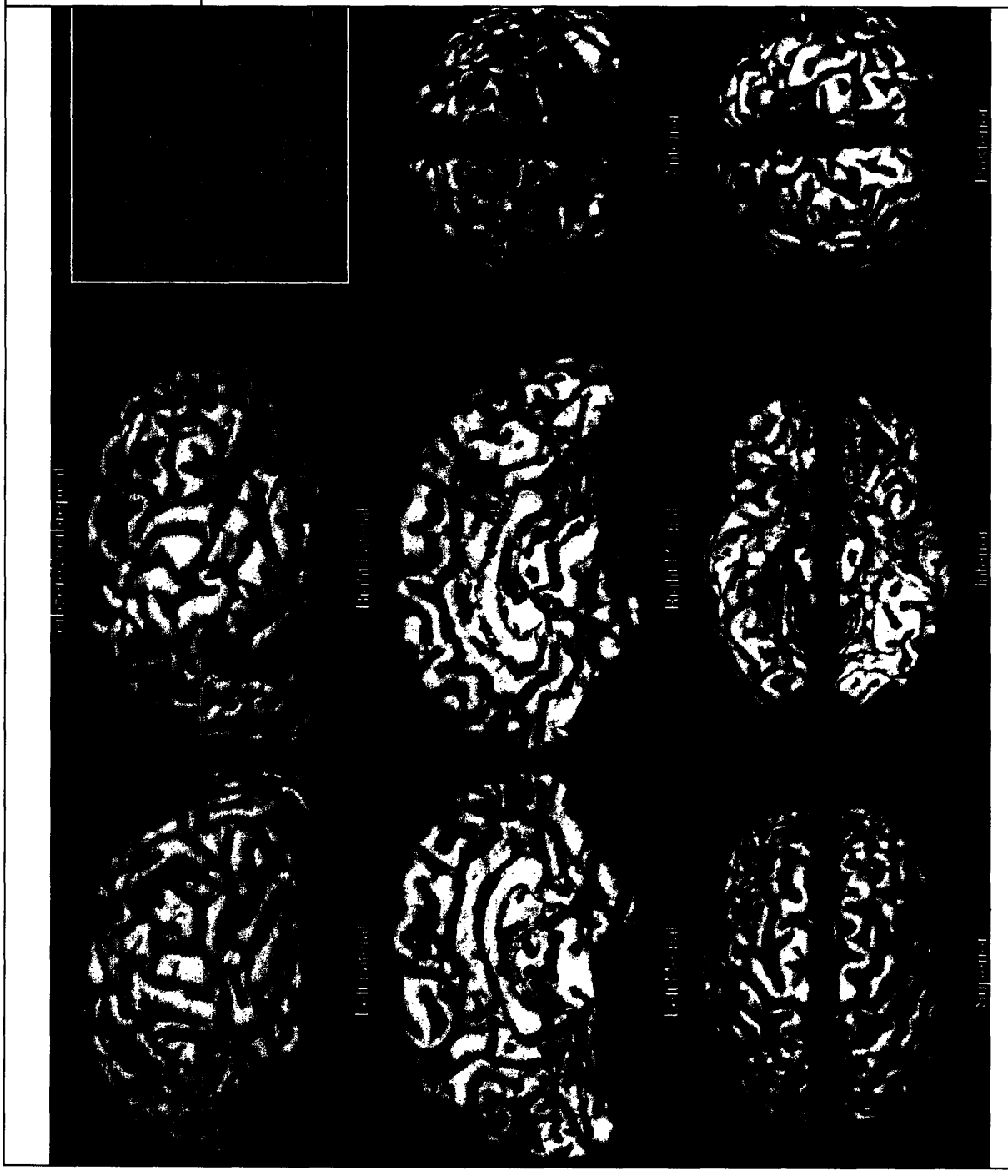


Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Noun Zero	VRZ, VIZ	>	NRZ, NIZ	12%	>	12%
Hypotheses:						
Observations:						



Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Verb Read	**VRZ, VIZ**	>	**VRR, VIR**	12%	>	12%
Hypotheses:						
Observations:						

Contrast Name			Conditions Negative	Data Represented		
Verb Zero-Inflect V Verb Read	**VRZ, VIZ**	>	**VRR, VIR**	12%	>	12%
Hypotheses:						
Observations:						



7 DEPTH ELECTROPHYSIOLOGY METHODS

7.1 Chapter Summary

Methodology is presented for obtaining intra-cranial *in-vivo* electrophysiological recordings from human patients. This is a case of close collaboration with clinicians, to harvest a type of precious data already being collected for clinical purposes. Namely, epilepsy patients who are in the hospital for surgery, have electrodes implanted to localize the part of the brain causing the Epilepsy. This recording may last a week or two, before the second part of the surgery: removing the offending brain region. During this time, if the patient gives consent, it is possible to get copies of the clinical recordings, for the time during which the patient is doing cognitive tasks. The same types of tasks used for fMRI can be administered on a computer screen in the patient's hospital room. The computer presentation of the stimuli and recording of the subject's responses is also coupled with precise electronic marker-pulses or triggers that are fused directly into the stream of data being recorded from the implanted electrodes. Later, the brain electrical response to each trial (or average of trial type) can be reconstructed from these data.

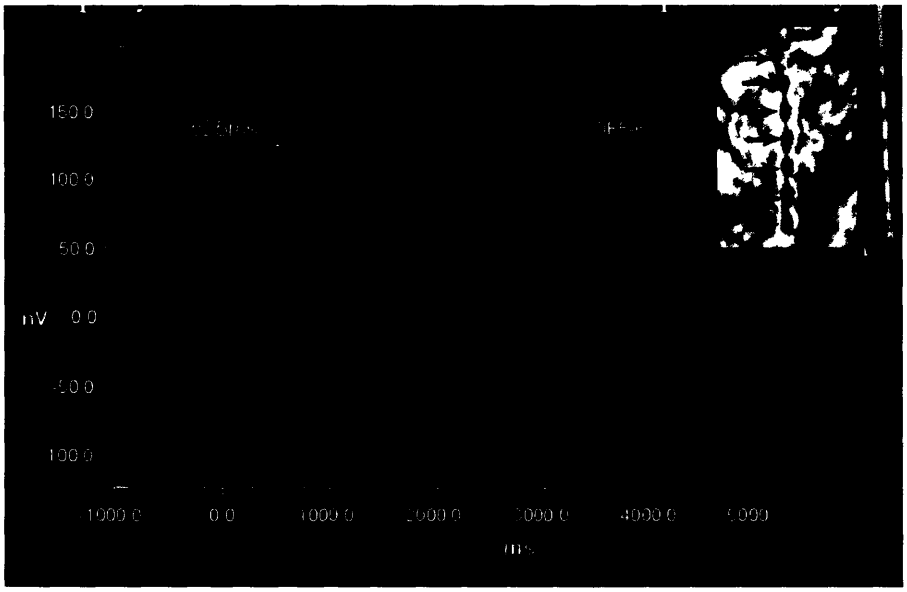


Figure 19: Example of electrophysiological data that can be recovered from this methodology.

7.2 Some Limitations of fMRI

fMRI has opened the door to an enormous amount of scientific questions, and here I use it to address some subtleties of language processing, yet interpretation is often tenuous because of indirect nature of the measure. fMRI measures changes in magnetic signal, resulting from changes in blood oxygenation, linked to changes in blood flow, linked in an unknown way to bulk changes in metabolism, putatively linked to very recent changes in electrical activity in sets of hundreds of millions of neurons (perhaps spikes, perhaps EPSPs, or both), which by nature have an unknown relationship to the cognitive tasks performed! Furthermore, the fMRI response has a time lag of 6-24 seconds. Therefore, I like to say that fMRI measures "The Ghost of Brain Blood Past."

However, fMRI and other non-invasive imaging techniques will clearly be the way of the future, for cognitive mapping of the human brain. Invasive techniques such as depth electrophysiology will have limited use, exactly because of their invasive nature. However, the benefit of intra-cranial work is that it provides direct recording of neural, electrical events. This is, historically anyway, the gold standard of transient behavior-related neural activity. Therefore, the acquisition of Depth electrophysiological data from the same brain on the same tasks, as an fMRI experiment, allows calibration and validation of the fMRI results. This means that the implications of data such as those I collected extend beyond just a more unambiguous localization and electrical signature (including timecourse info) of neural response to my task, and include general validation toward future high-credibility use of fMRI-only approaches.

7.3 Case Summary

Two chronic Epilepsy patients, undergoing seizure focus localization, were clinically implanted with depth macroelectrodes and research-specific laminar microelectrodes, and in one case a grid of sub-dural surface electrodes. The patients (BI-11, and BI-12) consented to research recording of their brain signals, and performed the identical cognitive task as designed for the accompanying fMRI experiment. Patient BI-11 also participated in the fMRI experiment, with the fMRI recording occurring 1 day before implantation of the electrodes. The electrophysiological recordings in this patient were taken 10 days after her implantation.

7.4 Data Acquisition

Data from only the macroelectrodes are analyzed and presented here. Primary raw data are voltage deflections from baseline at each of 64 channels. Each channel is a difference in voltage between two physical contacts on an electrode. The macro-electrodes have 8 contacts, so the 8 channels for each electrode represent the differences between successive pairings, numbering from the deepest contact first, with the 8^{th} channel in each case being the difference between the first and last physical contact. The baseline voltage is derived from the epoch before the event of interest. Therefore, the time before each stimulus presentation is taken as the baseline against which the response to that stimulus is measured.

7.5 Data Analysis

The analysis process involves averaging, much like the event-related fMRI analysis procedure. The trigger codes sent by the stimulus presentation program indelibly embed markings (square-wave deflections of the voltage signal in one of the special channels reserved for such markers) that can be used as a code to determine what trial type occurred precisely when. This code, continuously embedded as the voltage recording marches through time, is similar to code schemes imprinted on sides of movie film, used for editing or to reconstruct timing and sound. Using the code, the analysis program selects all the time snippets corresponding to each event/trial type. In this case, each of our 12 task conditions would be considered separately.

Next, the signal across all instances of the given trial type is averaged together into one average wave form for that trial type. During this process, the baseline calculation is used, in order to make sure that each instance of a trial type is entered into the average on "equal footing" (basically slow-wave trends are removed by normalizing based on the baseline). This means that the "epoch" has to be chosen at this stage – the amount of time before and after the stimulus onset (defined as time 0) that is to be considered. Epoching and averaging can take a fairly long time.

Averaged condition waveforms were compared in some cases for a single condition, across electrode channels. This gave localization and time course information for the neural

processing involved in that task condition. This is somewhat analogous to fMRI global mapping of a condition against a baseline (fixation) condition, but with some elements of repeated ROI analyses.

Another type of comparison used was to look at individual channels and compare two or more task conditions. The information one can obtain from this type of analysis is the differential types and magnitudes of processing (in that location) across task conditions. This is most analogous to subtraction-based fMRI mapping.

There are many other ways to analyze these data, but these are the two reported here.

All processing was carried out using NeuroScan software (© CompuMedics Neuroscan, El Paso, TX and Victoria, Australia) on Windows XP workstations equipped with the NeuroScan hardware license dongle (licensed to Eric Halgren).

7.6 Epilepsy Surgery

Please refer to **Figure 20** below, a schematic process flow of the type of epilepsy surgery involved here, for the following comments on the 5 stages depicted. Before getting to Stage 1, the patient obviously has been long diagnosed with Epilepsy, and the Epilepsy is deemed disruptive enough to the patients life to warrant surgery. The patient is almost always on anti-epileptic drug (AED) treatment, and usually responds with variable success.

Stage 1, according to this schematic, involves all the pre-operative workup and mapping procedures. Usually scalp-mount EEG electrodes are used to listed to the epileptiform discharges that underlie the patient's seizures. Based on the preliminary mapping, surgeons have some idea whether the patient is at all a good candidate for surgery (e.g. the seizure seem to be coming all from the same place and that area is operable) and also a vague idea of the seizure focus localization.

Stage 2 involves actually opening the skull. Based on the information from **Stage 1**, the surgeons decide where precisely to implant electrodes, and what kinds of electrodes to implant. They map this out all beforehand, and then open the skull in the appropriate place accordingly.

Stage 3 involves implanting the actual electrodes. Pictured in the schematic are what are meant to represent depth macroelectrodes, with their wire leads dangling.

The pictures in the middle represent 3 major types of electrodes. First is the macroelectrode. What is seen here, to scale according to the standard pencil top, is the end of a macroelectrode of the type used in these surgeries. The silver bands around the end of the shaft are the electrode contacts – the arrows point to the contacts. The stalk itself is a semi-rigid plastic tube – it is actually hollow. The wires for each contact are embedded in the thin plastic walls of the shaft. The other end of the shaft, which sticks out of the head, has read-out contacts that are eventually hooked up to the recording computer. **Figure 22** below shows the full length of such an electrode, and **Figure 21** gives a closer view of the tip. This type of electrode is used to record evoked potentials from neurons in the local environs of each contact, as the electrode penetrates, for instance, from the inferior frontal gyrus right through to the hippocampus or anterior cingulated. The gold tip of the electrode has a small hole in it.

Through this hole can be inserted the next type of electrode: the microelectrode. This type of electrode is also called a laminar electrode, because it allows ultra fine scale recordings and thus separate recordings from the cellular lamina of the cortex. This electrode has 24 contacts, spaced only 200 microns apart. The assembly, of the micro within macro electrode, may be inserted so that the laminar recordings come directly from the lamina in one part of the hippocampus, for instance.

The third type of electrode, is the grid of surface (sub-dural) electrodes. These are inserted against the brain (pial) surface, and record EEG signals. These recordings will bear the most resemblance to scalp-mounted EEG/ERP recordings, but of course since the signal is not smeared by the skull and the pools of blood in the venous sinuses beneath it, the signal is more much clearly localized.

Stage 4 of the diagram in **Figure 20** depicts the closing of the skull, with the electrodes implanted and wires protruding, and the connecting of those wires to a patchboard. From the patch, the signals are sent through a series of pre-amplifiers and amplifiers and to the recording computer(s). There is some variability in the position along the chain of each of those devices but the net effect is that the patient's electrical signals are recorded while the patient remains awake, relatively comfortable, and free to sit up in the hospital bed and participate in experimentation. As the diagram also indicates, the clinical recordings may take as long as 2 weeks. During this time, the patient is weaned off the AED's, and seizures return slowly. The clinicians use the information captured by each seizure to determine unambiguously the focus.

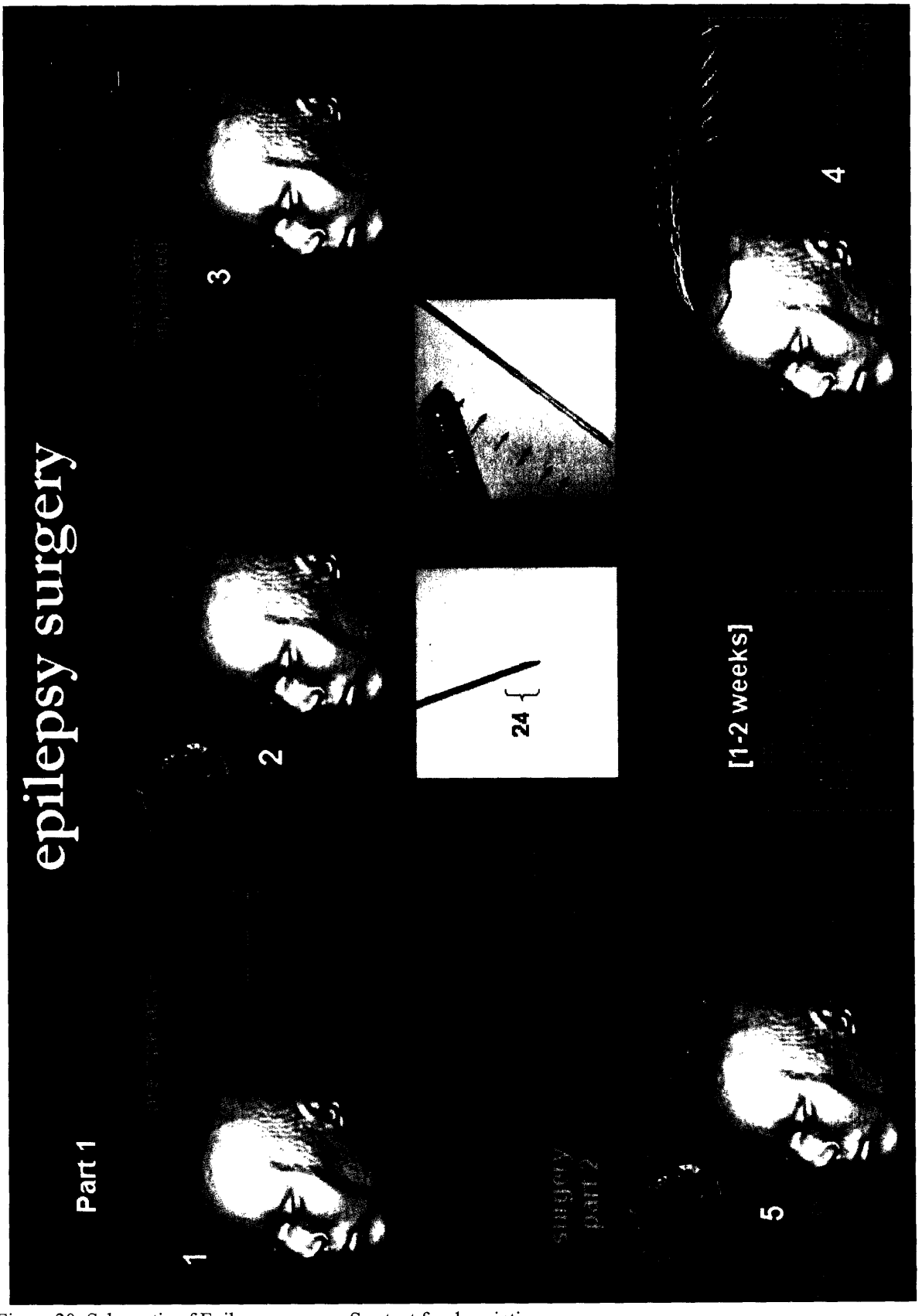


Figure 20: Schematic of Epilepsy surgery. See text for description.

Stage 5 is the actual surgery, where the brain tissue that is causing the seizures is removed. Actually, because of the way the brain deals with physical insult (i.e. not very well!), no brain tissue is actually cut and removed in a traditional sense. A vacuum-based tool is used to suck away and ablate the tissue, leaving something like scar but at least not bleeding, which would kill more tissue. Hopefully, the procedure works, and the patient now has no or very few seizures. Patients who have had seizures since childhood, and thus have not been able to maintain any serious job, can return to their lives and build a career again, without the nagging worry that they will end up picking themselves up off the floor a few times a day, unaware (directly) of how they got there! While it is a brutal sort of surgery, the effects can be really life-changing.

Of course, the clinical aspect is not what I intersect with. Officially, I am just concerned with getting good, clean data.

There are two points in this process where I can get data. Between **Stage 1** and **Stage 2**, before the patient goes in for the implantation surgery, the patient can participate in my fMRI studies. Then between **Stage 4** and **Stage 5**, during the clinical electrophysiological recordings, the patient can participate in my study while I capture the recordings.

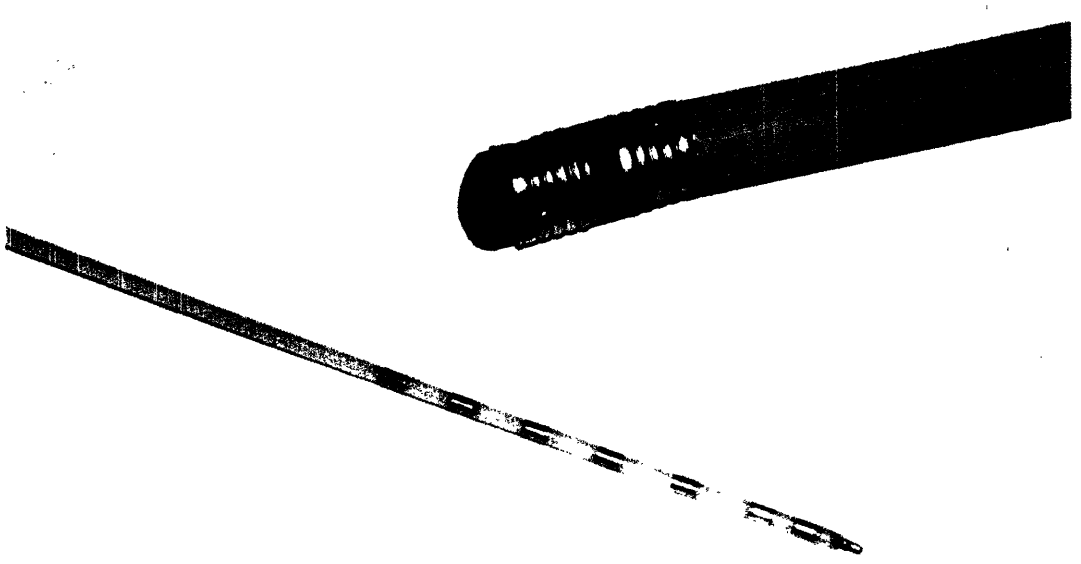


Figure 21: Contacts at tip of depth macroelectrode.
The shaft of the electrode is a hollow, semi-rigid plastic tube.

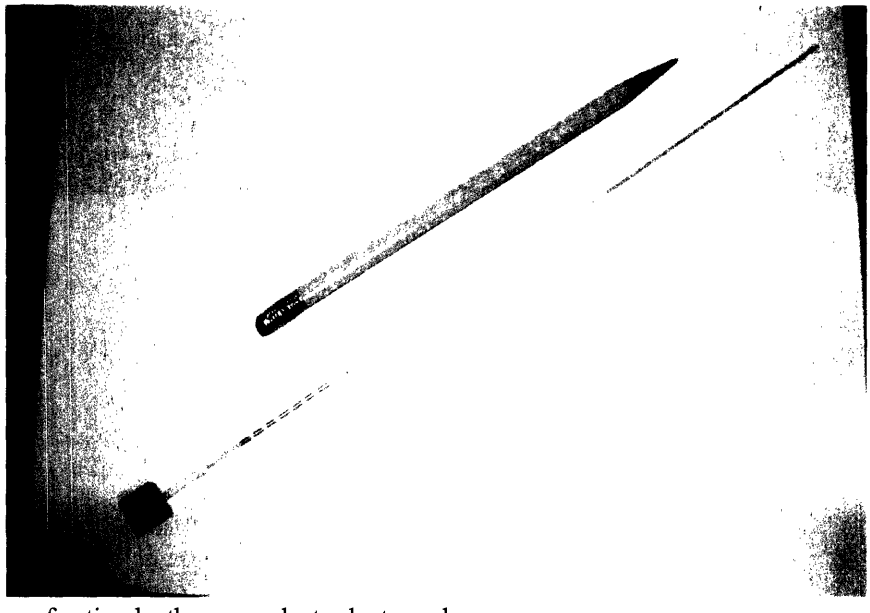


Figure 22: Picture of entire depth macro-electrode, to scale.
The brain-penetrating contacts at the tip are wired internally through the hollow plastic shaft to the contacts at the proximal end.

7.7 Data Management

Because this part of my research is highly collaborative, it has been important to enact a procedure for procurement, management, and storage of the data. This will not be detailed here, but a few of the steps involved will be mentioned. The clinical (macroelectrode) data, otherwise known as telemetry data because they are remotely recorded from the patient, are spooled onto a clinical computer. The high-bandwidth laminar data are recorded directly into research computers owned by Halgren lab and stationed at each hospital with which we collaborate. Both sets of data are eventually released by the hospital clinical EEG group. The time periods of the days of data that correspond to my tasks need to be extracted. Meanwhile, data regarding the patient's performance of the task are recorded on my laptop. These data need to be pooled and cross-referenced. Clinical MRI scans need to be release and reconstituted by me. My own MRI and fMRI data need to be processed and co-registered. The clinical mapping of electrode placement plannings and actual implementations need to be used to decode the channel numbers and corresponding locations on the electrophysiological data. The all the electrophysiological data analysis and visualization must be done. Many studies are done on each patient, and these should be compared. The many more steps add complexity to keeping track of the data.

8 INTRACRANIAL ELECTROPHYSIOLOGY: RESULTS AND CASE DETAILS

8.1 Images from Surgery

Images were obtained from the surgery of patient BI-11. They are reproduced here, to illustrate the stages of the process, as schematically overviewed in **Figure 20**.

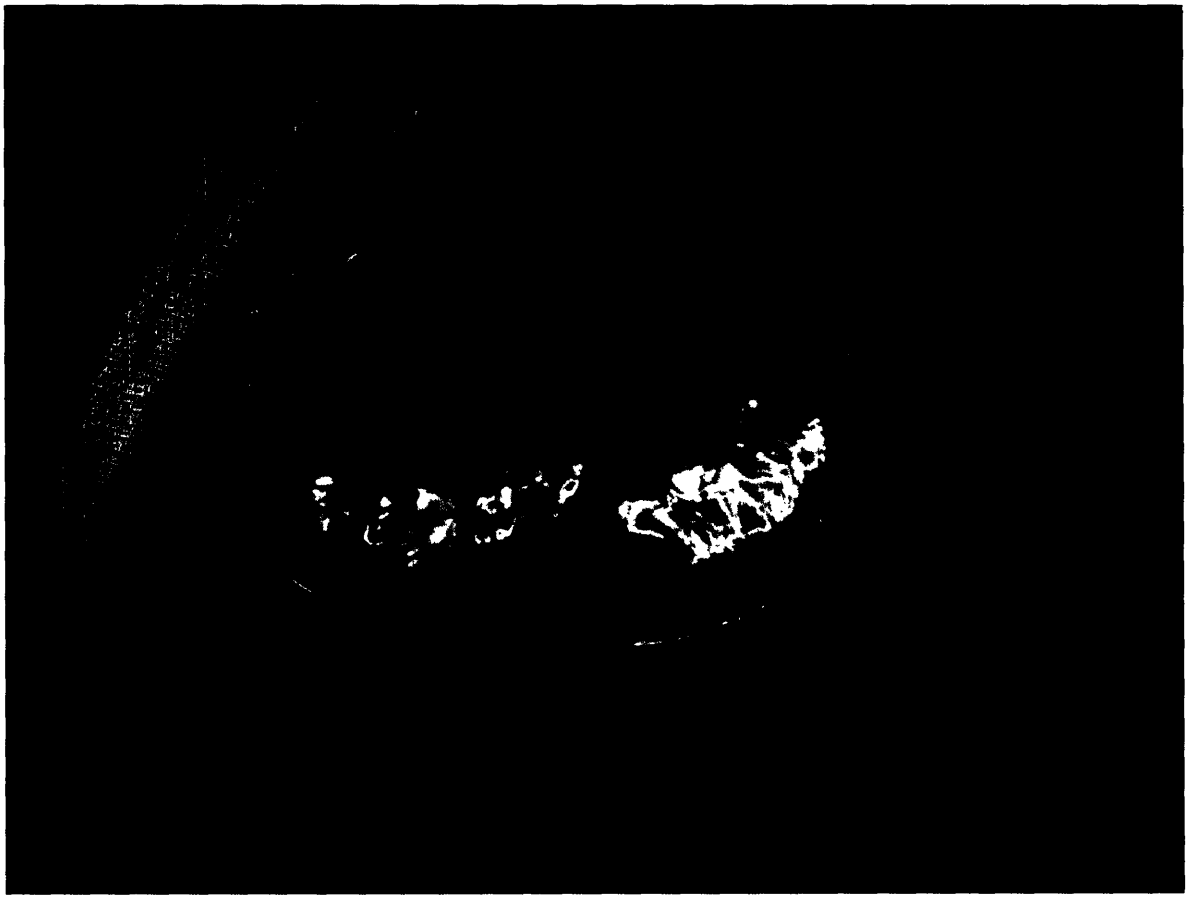


Figure 23: Surgery - Image 2: Clear subdural view of left perisylvian cortex.

Above one can see the left perisylvian cortex of patient BI-11 – the Language areas as rarely seen! Observe the *dura mater* pulled up, in the upper right of the photograph. The patient's face, though obscured by bandages, is to the left looking along the plane of the page. You are looking through removed skull.

The next image is from roughly the same vantage, but includes more of the prepped skull, which allows the viewer to put the brain and incision location into perspective. The branching pattern of the middle cerebral artery is visible beneath the pia. Both of these images are from what is shown as **Stage 2** in **Figure 20.**

Figure 24: Brain surgery: opening of skull in perisylvian area

The brain is now ready for the implantation of the various types of electrodes. The next images show the implantation process. In Figure 25 below, can be seen the grid of surface electrodes. 64 channels (8*8 grid) sense EEG with complete temporal precision and with the ability to localize signals unambiguously at the resolution of the grid or better.

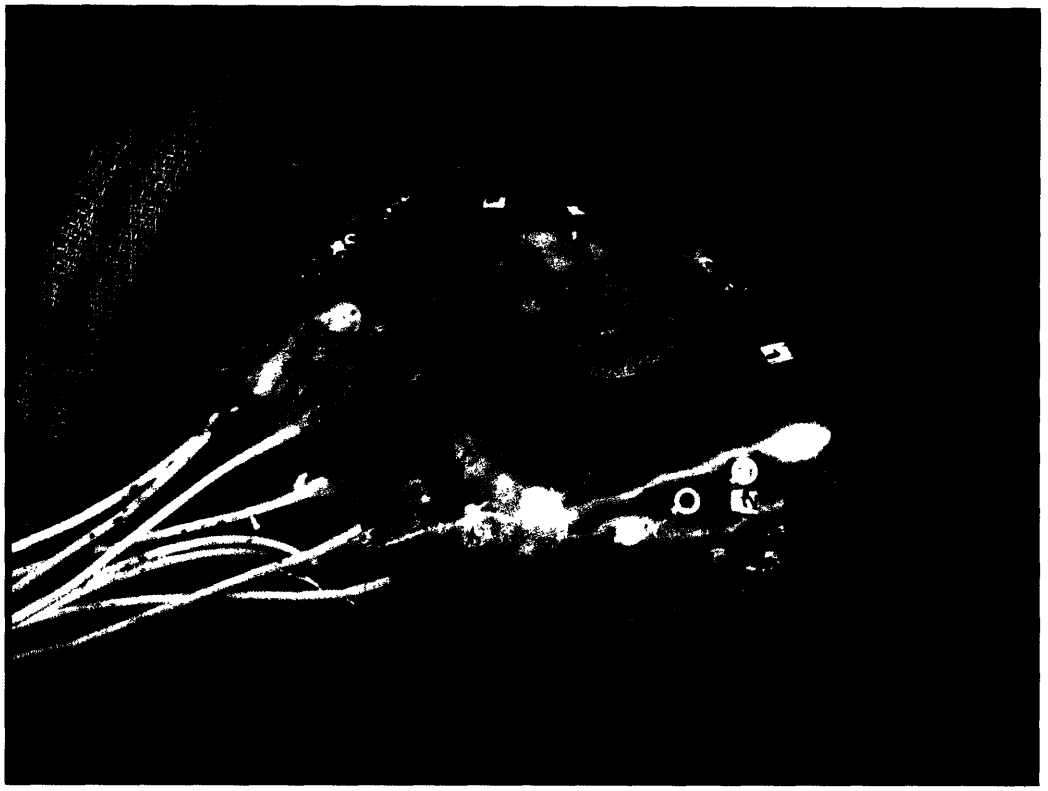


Figure 25: Surgery - Image 3: Grid of cortical surface electrodes implanted subdurally.

Figure 26: Surgery - Image 4: Introduction of the Depth electrodes.

The wires extend to interface boxes and multiplexers, so the signals can be read out by hospital clinical telemetry systems. The wires will be passed through an incision in the skin, so that the extracted bone can be replaced and the hole sutured up for the duration of the implantation period. In the final image from this surgery, in Figure 26 above, some new things are visible. First of all the *dura mater* flap is plain visible in the upper right. Secondly, the electrode leads from the grid have been tunneled through the skin. The most important element, though, is the appearance of 4 new wires. These are the leads for depth Macroelectrodes which penetrate through the tissue of the brain. They have 8 contacts spaced over roughly 3.5 cm, and all eight wires are embedded in the walls of the visible white wires, which are hollow.

Through the hollow wires (terminating in a small aperture at the tip) are threaded the Laminar electrodes. The ones used here have 24 contacts, spaced 150 micrometers apart. These ones terminate in the hippocampus, amygdala, orbitofrontal cortex, and the anterior cingulate cortex. These electrodes allow very high-bandwidth multichannel recording from the various cortical laminations in the targeted region.

The goal of the implantation is to be recording while the patient comes off anti-seizure medication. When the patient has seizures, electrical signals recorded from the electrodes will help the neurosurgeon (and clinical EEG team) to localize the focus of the epileptiform seizure activity. Once enough seizures have taken place (can be many days) in order to localize the focus well enough, the final stages of the surgery can begin.

If the seizure focus is operable, the neurosurgeons then ressect the relevant part of cortex and/or subcortical regions. Very often the hippocampus on one side of the brain must be removed, along with the temporal pole. This is general information and in no way reflects any medical information about the current patient. All attempts have been made to guard any personally identifying information about this patient. Any resemblance of any sort to any person is both unlikely and purely coincidental!

8.2 Electrode Placements

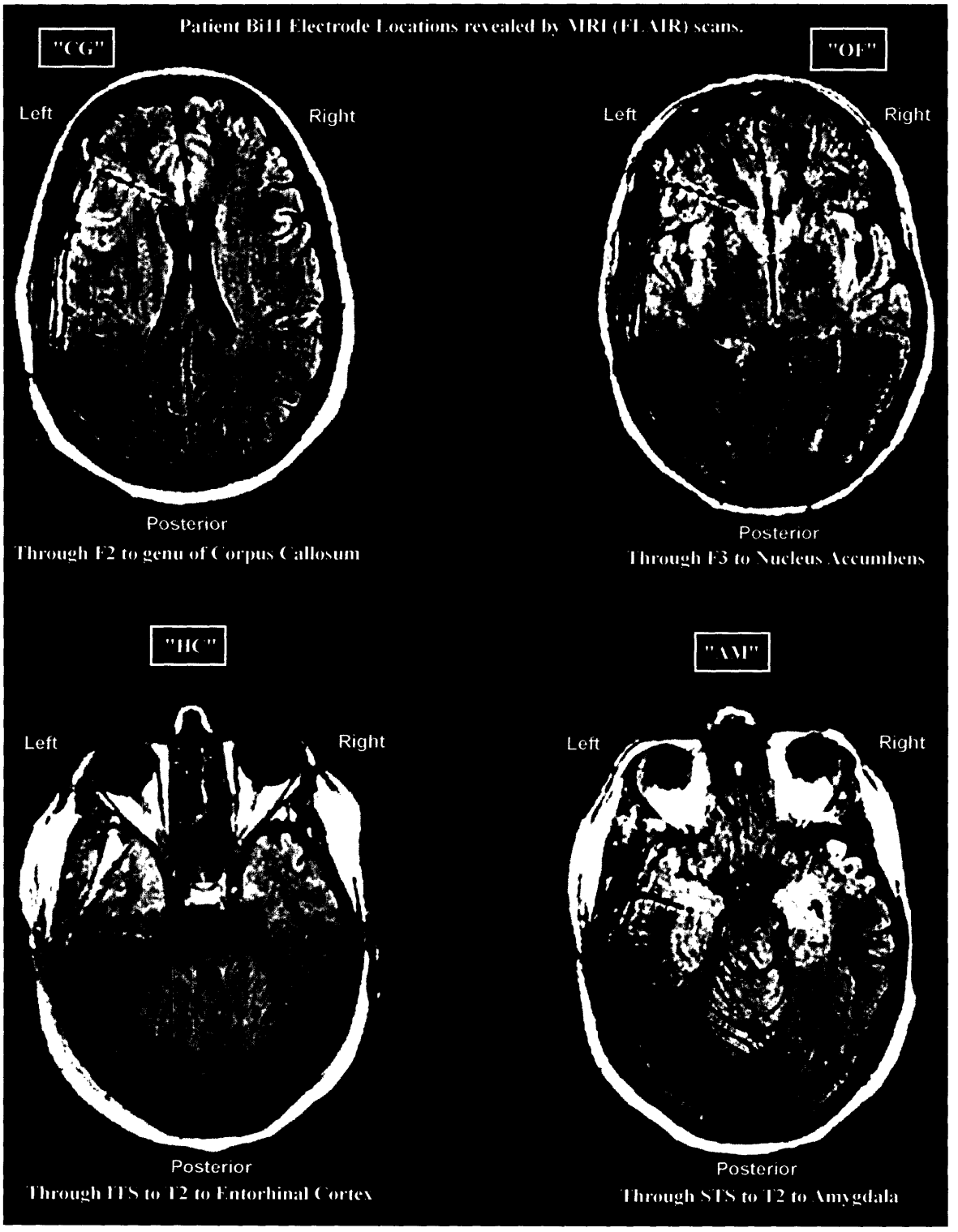


Figure 27: Trajectories of macroelectrodes visualized in clinical MRI scans of patient BI-11.

Figure 27 shows patient BI-11's clinical MRI scans, with the trajectories of the macroelectrodes. These scans were taken after the surgery depicted above. Miraculously the MR field does not interact deleteriously with the metallic electrodes to cause tissue damage. Obviously there are susceptibility interactions, however: the very dark blobs along the trajectory of each electrode are much bigger than the width of the electrodes. They look big because these are not pictures of the electrodes, but rather they are images of the magnetic susceptibility interaction between the local magnetic field inhomogeneities created by eddy currents induced in the metal contacts and water-proton resonance signal from surrounding tissue. This harkens back to the discussion of what exactly this technique *images* – sometimes just the ghost of what is there. In any case, such MR maps are invaluable in reconstructing the precise anatomical location of electrode contacts, to correlate functional MRI and depth electrophysiological data.

8.3 fMRI Results – Patient BI-11

A full set of fMRI contrast maps were made for this patient's data: a full set of CSMs just as in the middle of this thesis for the 18-subject group data.

Below is a single representative CSM, the most global contrast: All vs Fixation. This contrast should reveal all the brain regions that are involved in any way in the task. First all, the speckled nature of the activation must be explained: I used much smaller voxels in this acquisition so the fundamental unit of an activation cluster is smaller. Then I did not spatially smooth the data very much in the preprocessing steps, so contributions of voxels are not patially distributed to neighboring voxels. Also, this map is at a low threshold. Thus the final rendering shows speckles of activation, and they are distributed over a large percentage of the cortical ribbon. Nonetheless one can also quickly see patterns emerge that closely resemble the group data. First of all the supplementary motor area and cingulate show bright activations. This is very much in line with group data. However on this patient, the activation is much more bilateral than the group., and this trend extends to other activation clusters. Extrastriate and especially Inferior Temporal activation, presumably related to visual word form processing seems to be bilateral, and even M1/S1 activations for the button press are not fully right-lateralized as they should be. This may be related to the subject crossing her hands over each other and stabilizing the button box with her right hand, as she was observed to do, however it is more likely a result of less-lateralized organization of her language functions.

The most drastic difference in lateralization is of course the entire perisylvian activation cluster set. It appears from the map above that this patient's language is not left-lateralized. This is confirmed by looking at a slice-by-slice maps of her fMRI activations. This does not, however, preclude us from getting very useful data from this patient.

First of all, one major goal of this combined approach has nothing to do with the lateralization or indeed localization of cognitive function. The goal is to correlate, within the same subject, fMRI BOLD activation clusters with direct measurement of neural electrical activity. This can be done so long as the patient is likely to activate the same regions both during the fMRI run of the task and during the depth recording sessions. These fMRI activations fall within very much hypothesized regions, just bilaterally, and furthermore if the fundamental neural substrate of a task would be expected to shift drastically on the second versus first exposure to the task, even a highly over-learned language task, then our whole endeavor would be quite decidedly doomed.

Another utility of these data, aside from co-registering the two major techniques employed, is extracting time course information for the task-related activations. Furthermore, I was able to settle a problem that had long been bothering me: that I could not separate the BOLD contribution of the frame from the target epochs of the trials. These are inseparable with fMRI because they are always exactly 1 TR apart, and the BOLD signal would smear across the time interval. With depth electrophysiology, I was able to show that the contribution to at least one task-related channel of the target epoch was much greater than that of the frame epoch, even though the frame could be considered more salient in most low-level and even high-level ways. By comparing the Depth response averaged over frames to targets, I showed a higher amplitude in the same peak components in the time following the targets.

In these cases, the unambiguous time and localization information of electrophysiological recordings added meaningful information to the fMRI results.

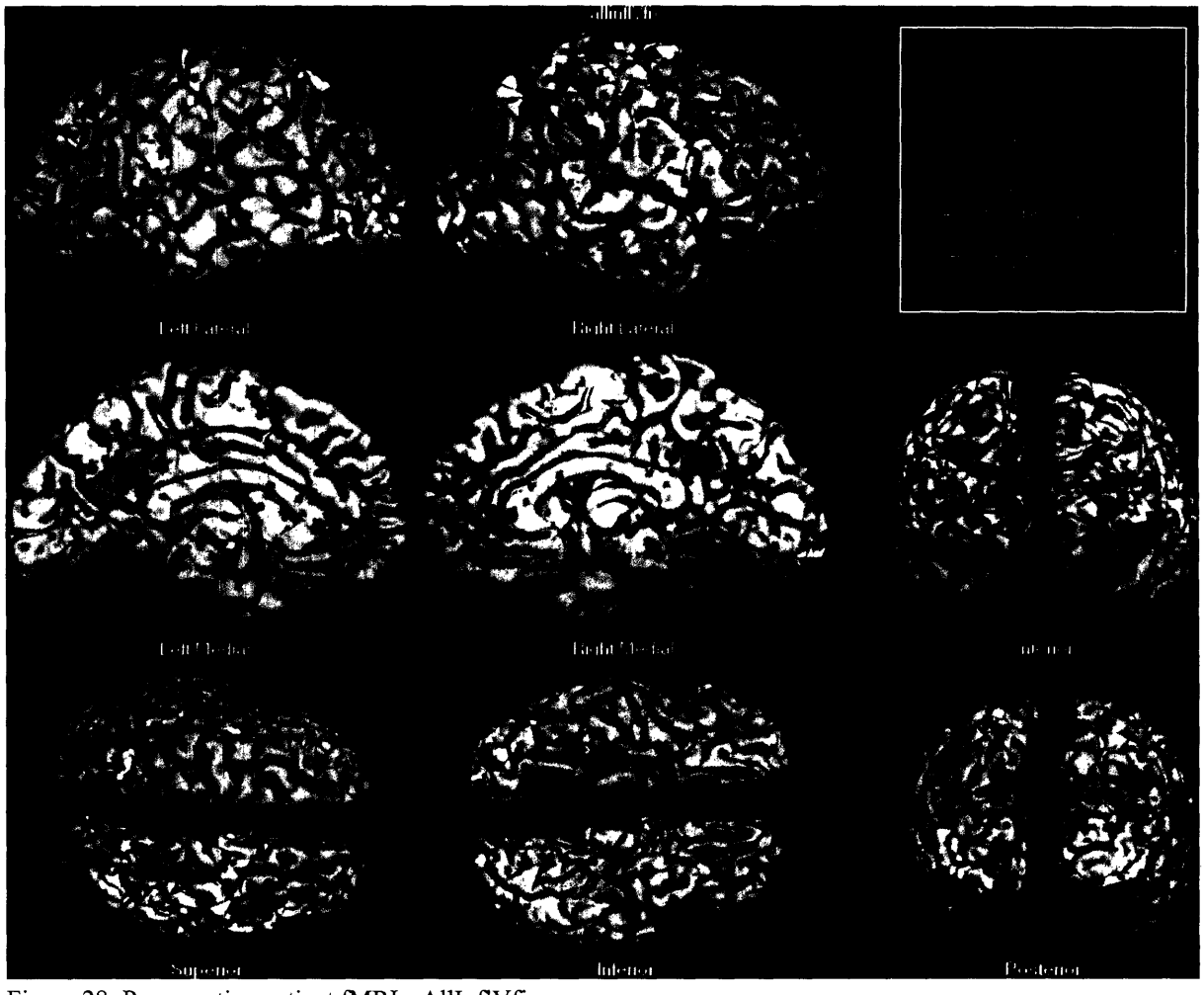


Figure 28: Preoperative patient fMRI - AllInflVfix

8.4 Electrophysiological Results – Patient BI-12

Patient BI-12 participated only in the intracranial recording session, not the fMRI. Patient BI-12 was extremely co-operative and very bright, performing the task very well and with the accuracy and speed within an order of magnitude of a motivated MIT undergrad.

Intracranial data for BI-12 were analyzed in the second manner described above: namely in terms of contrasts of pairs of conditions, for each electrode channel. A few of the cardinal contrasts of use to the analyses presented here, are depicted below. Note that each column of channels is scaled separately, and the scale is indicated on the bottom-most channel.

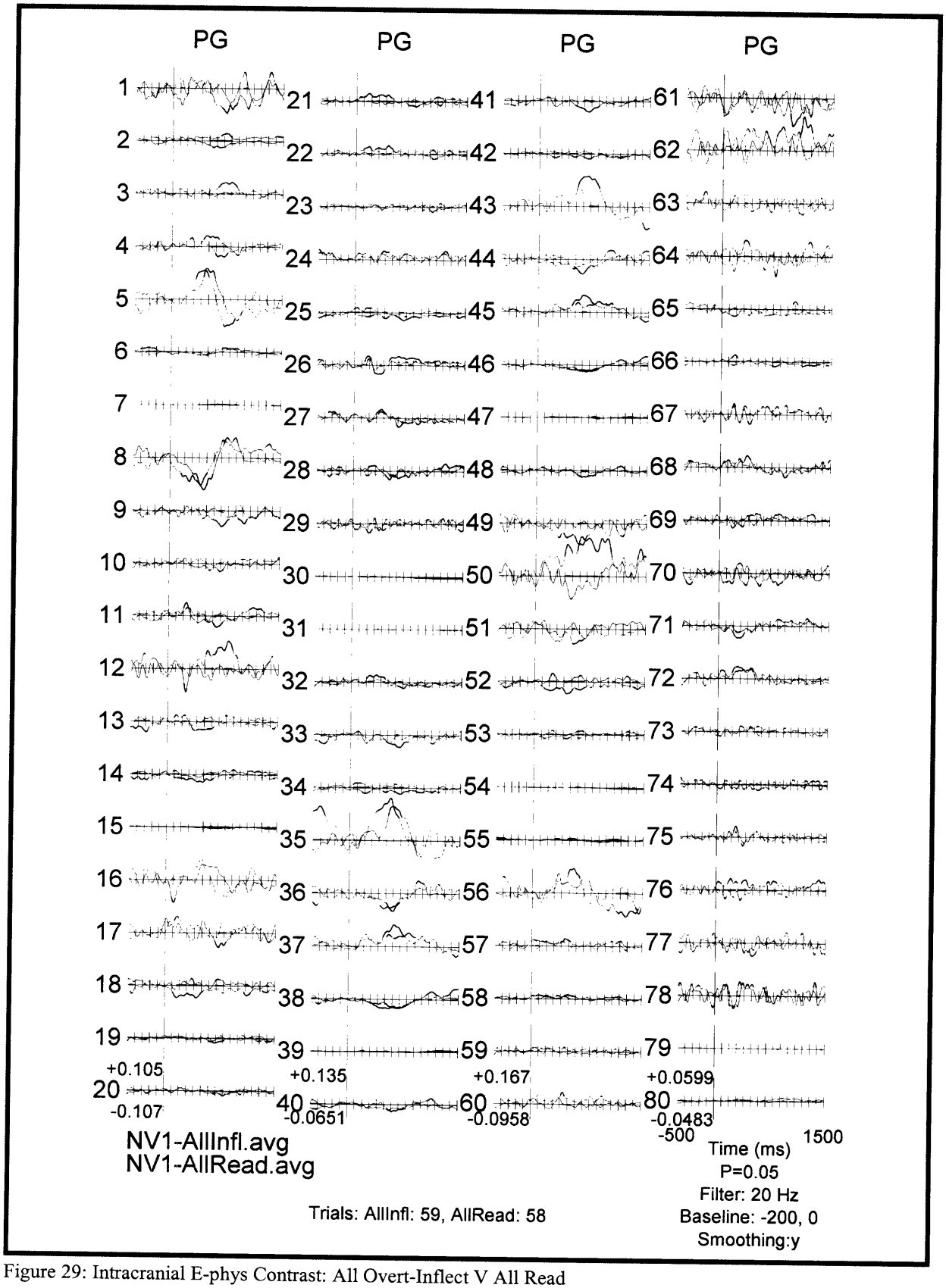


Figure 29: Intracranial E-phys Contrast: All Overt-Inflect V All Read

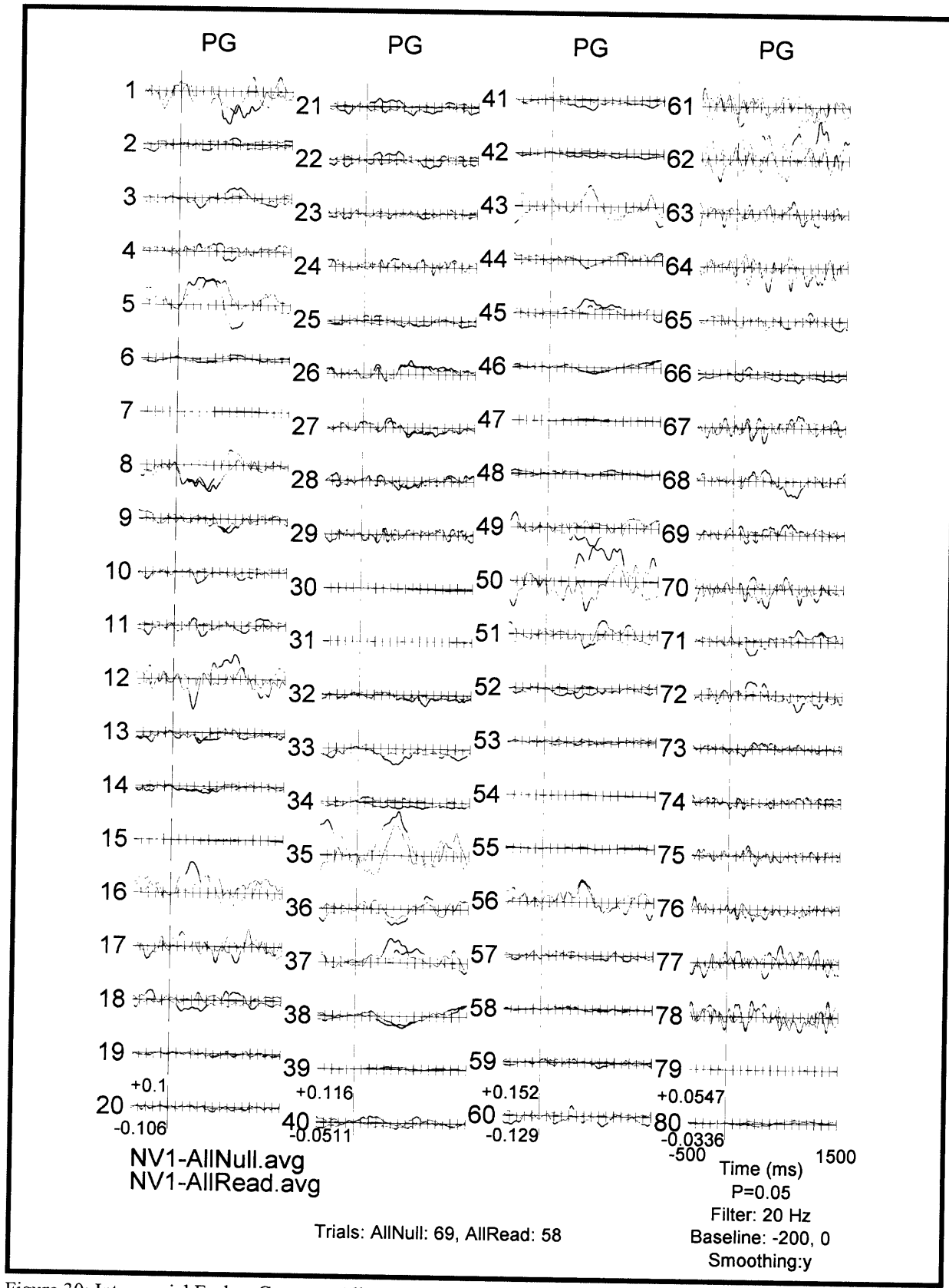


Figure 30: Intracranial E-phys Contrast: All Zero-Inflect V All Read

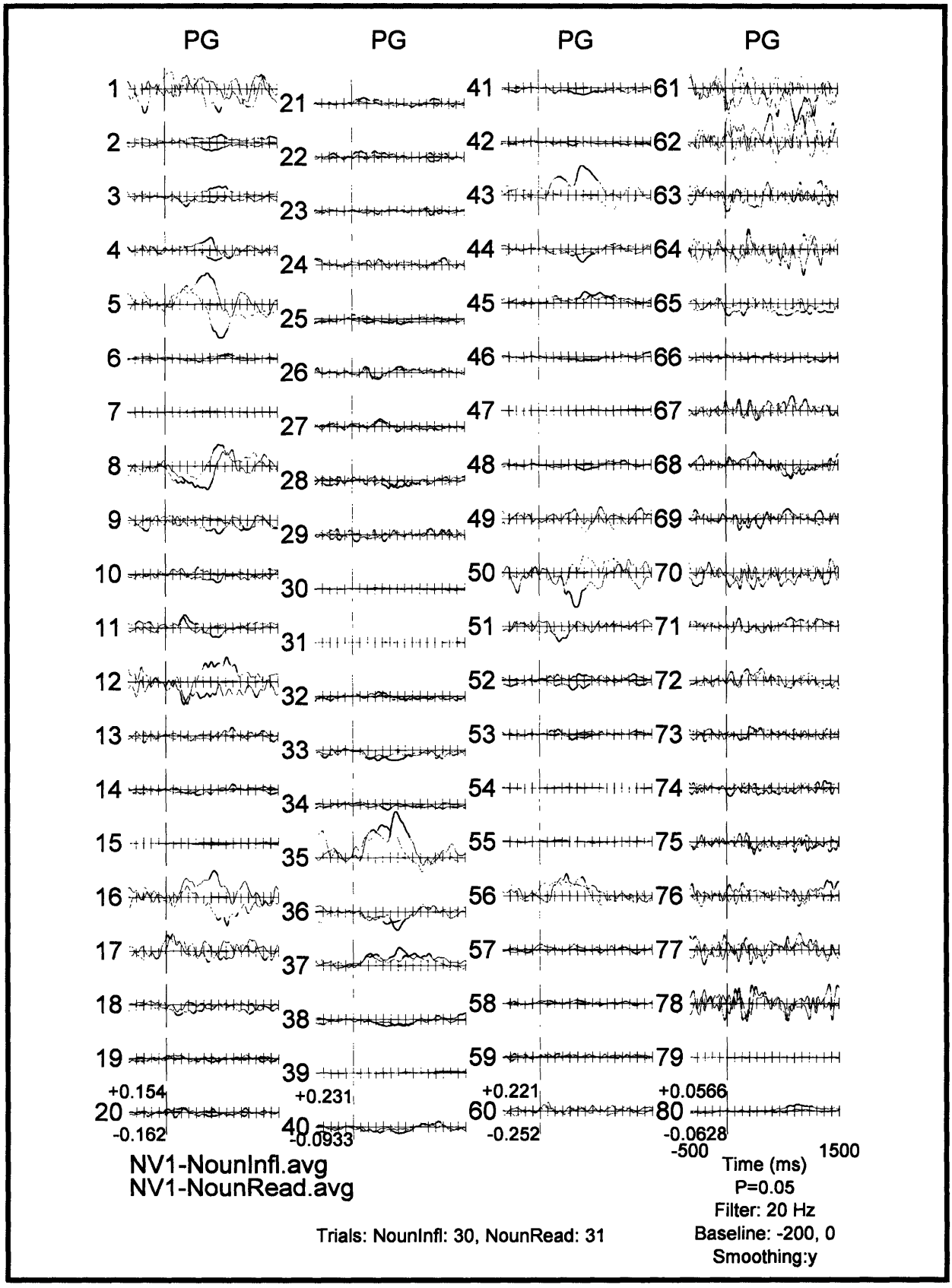


Figure 31: Intracranial E-phys Contrast: Noun Overt-Inflect V Noun Read

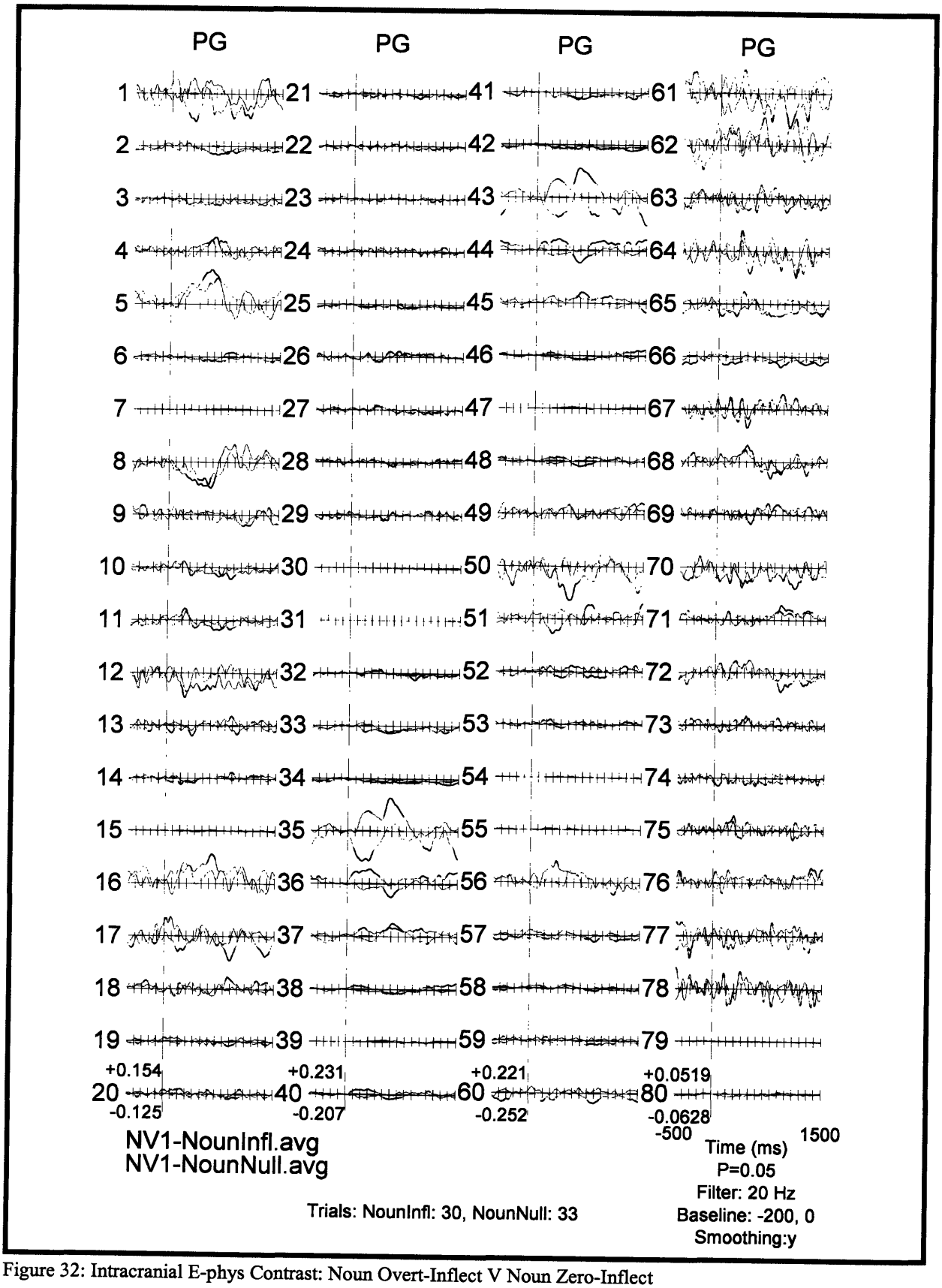


Figure 32: Intracranial E-phys Contrast: Noun Overt-Inflect V Noun Zero-Inflect

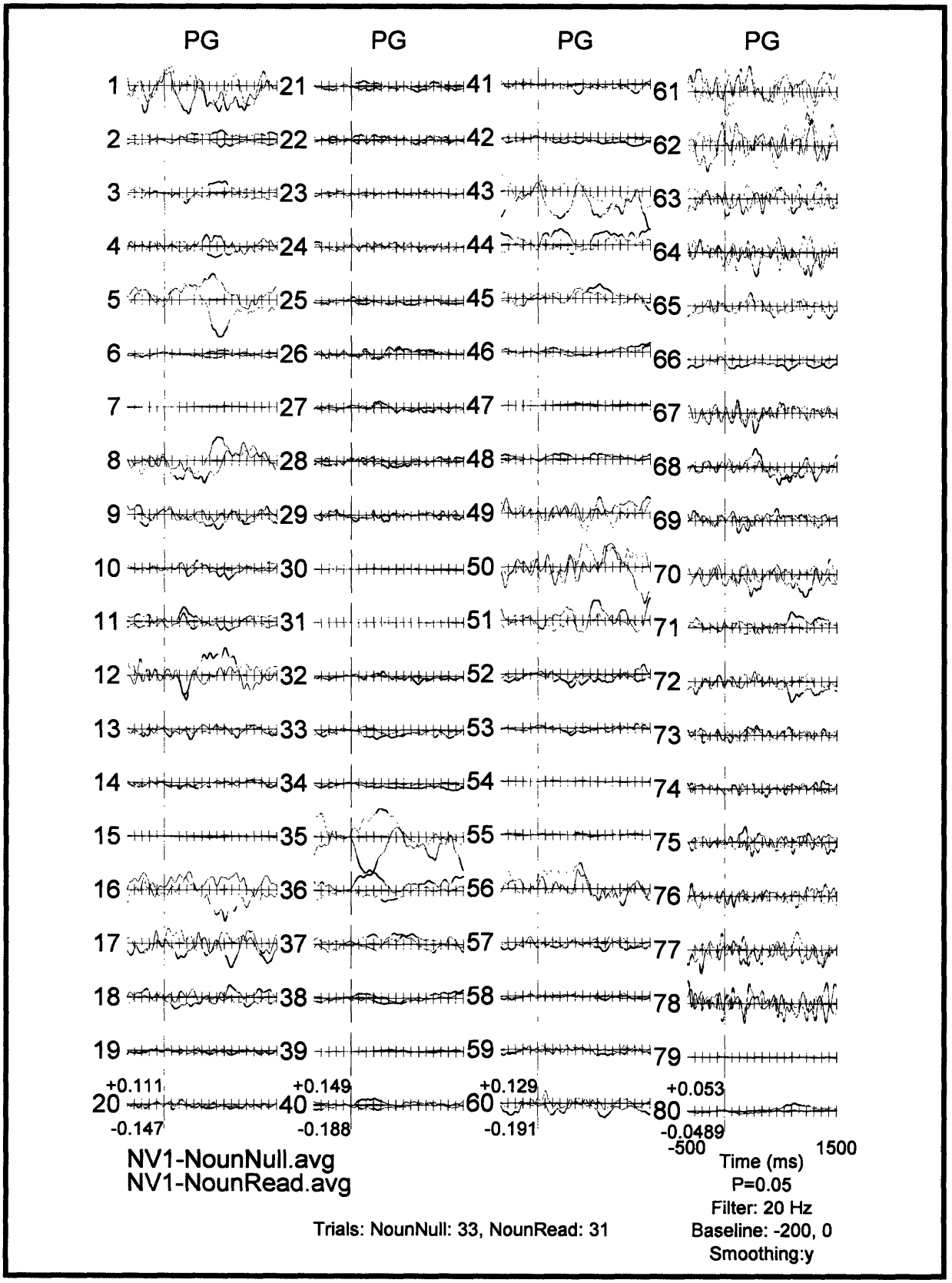


Figure 33: Intracranial E-phys Contrast: Noun Zero-Inflect V Noun Read

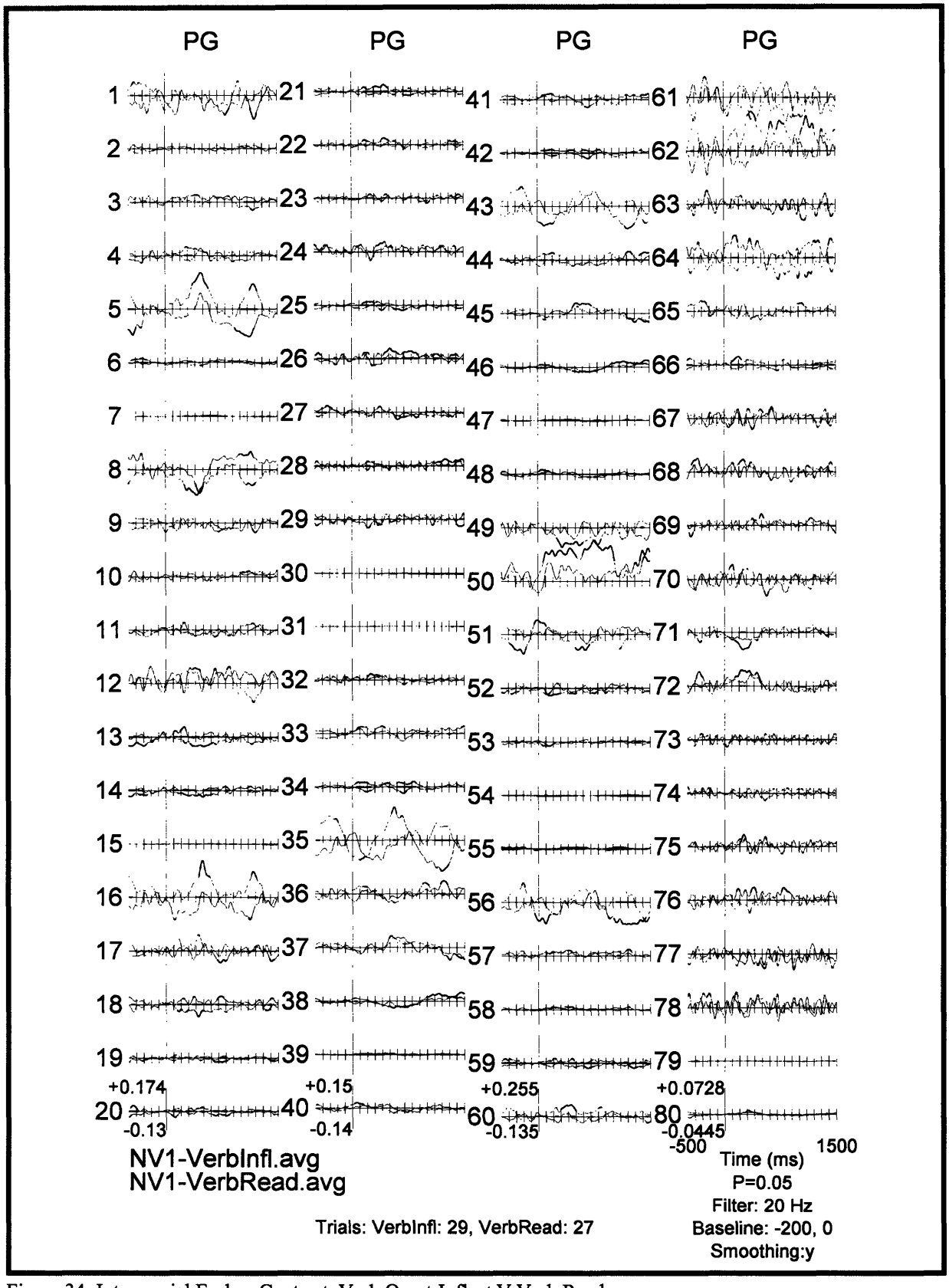


Figure 34: Intracranial E-phys Contrast: Verb Overt-Inflect V Verb Read

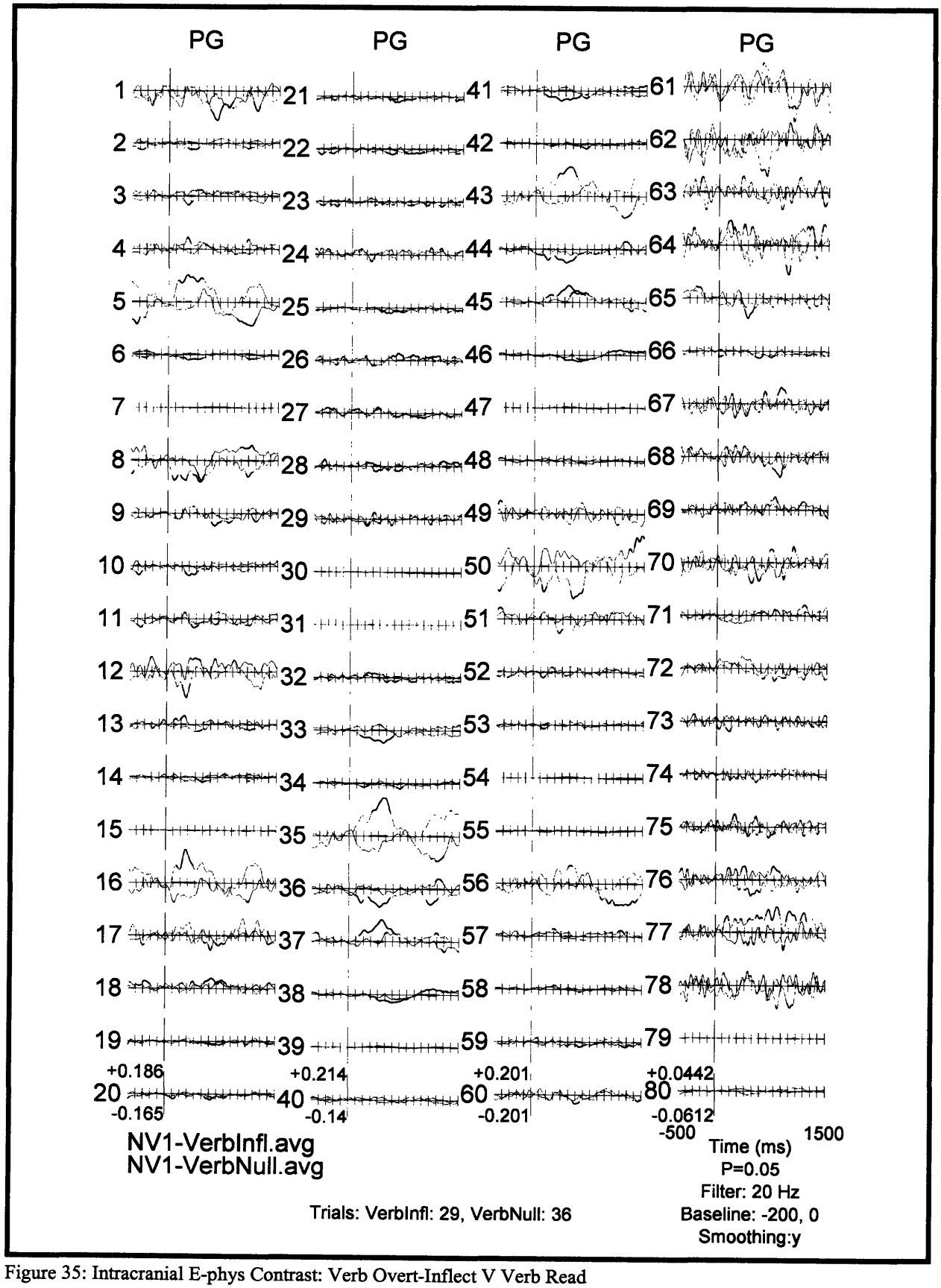


Figure 35: Intracranial E-phys Contrast: Verb Overt-Inflect V Verb Read

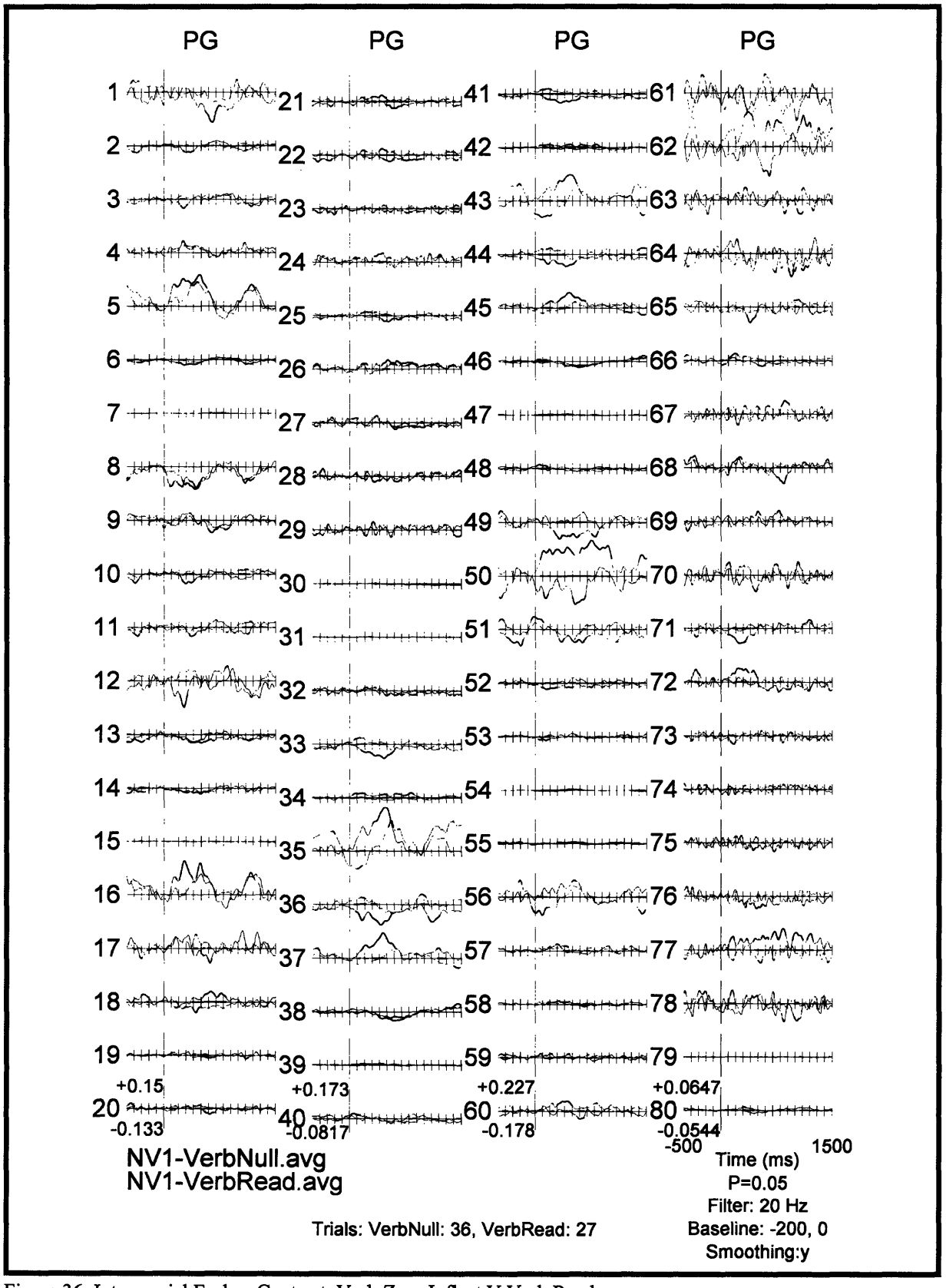


Figure 36: Intracranial E-phys Contrast: Verb Zero-Inflect V Verb Read

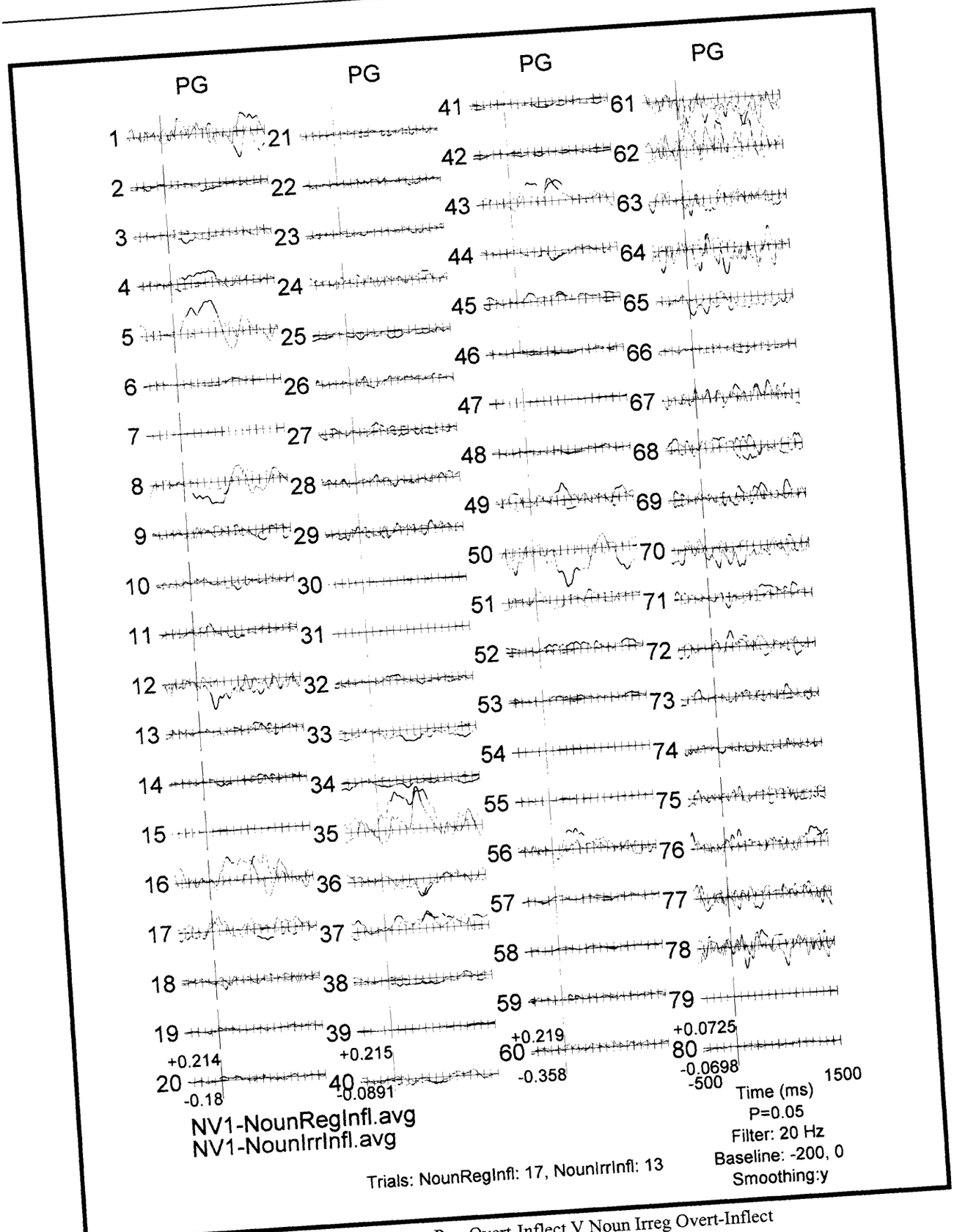


Figure 37: Intracranial E-phys Contrast: Noun Reg Overt-Inflect V Noun Irreg Overt-Inflect

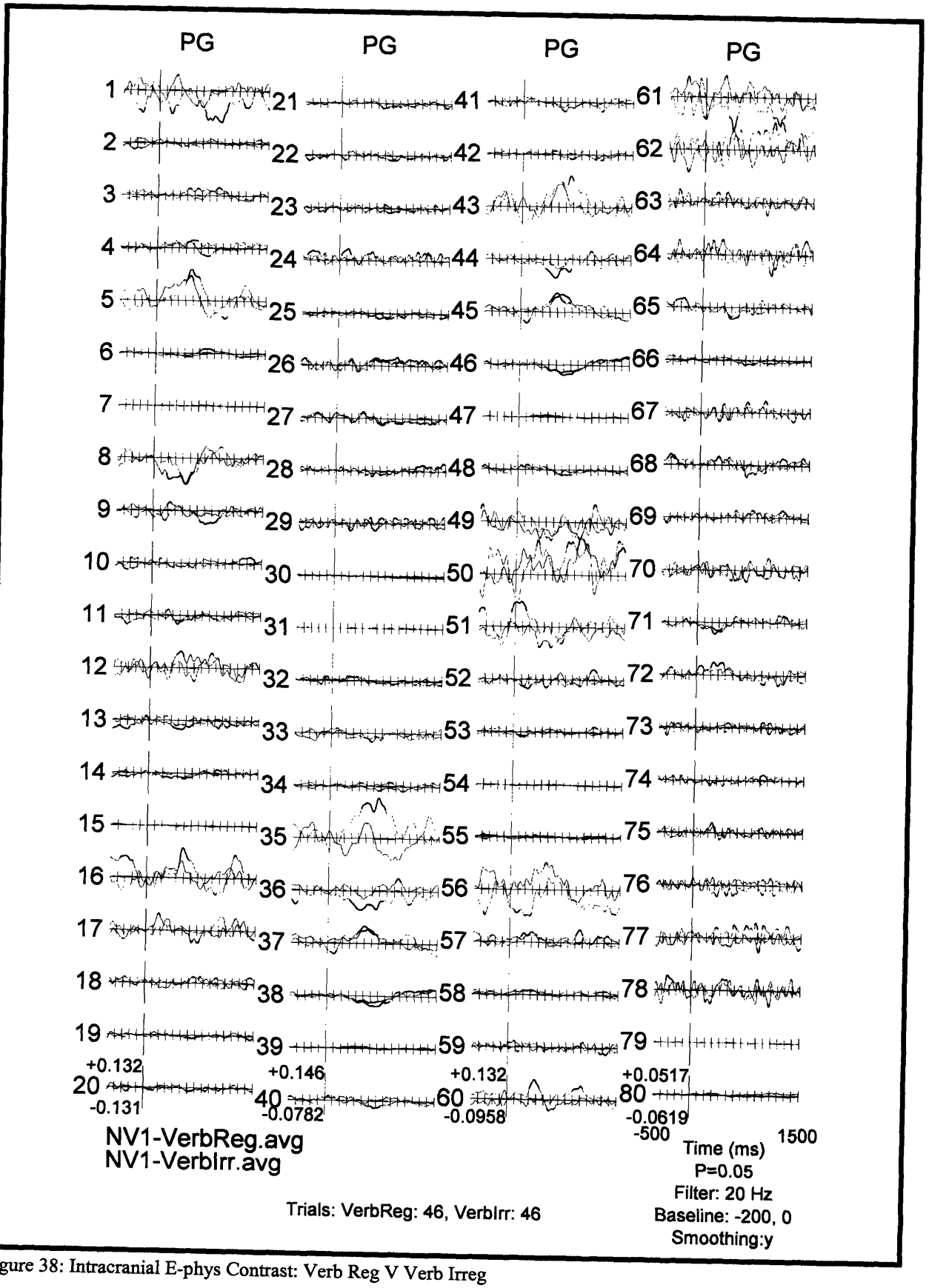


Figure 38: Intracranial E-phys Contrast: Verb Reg V Verb Irreg

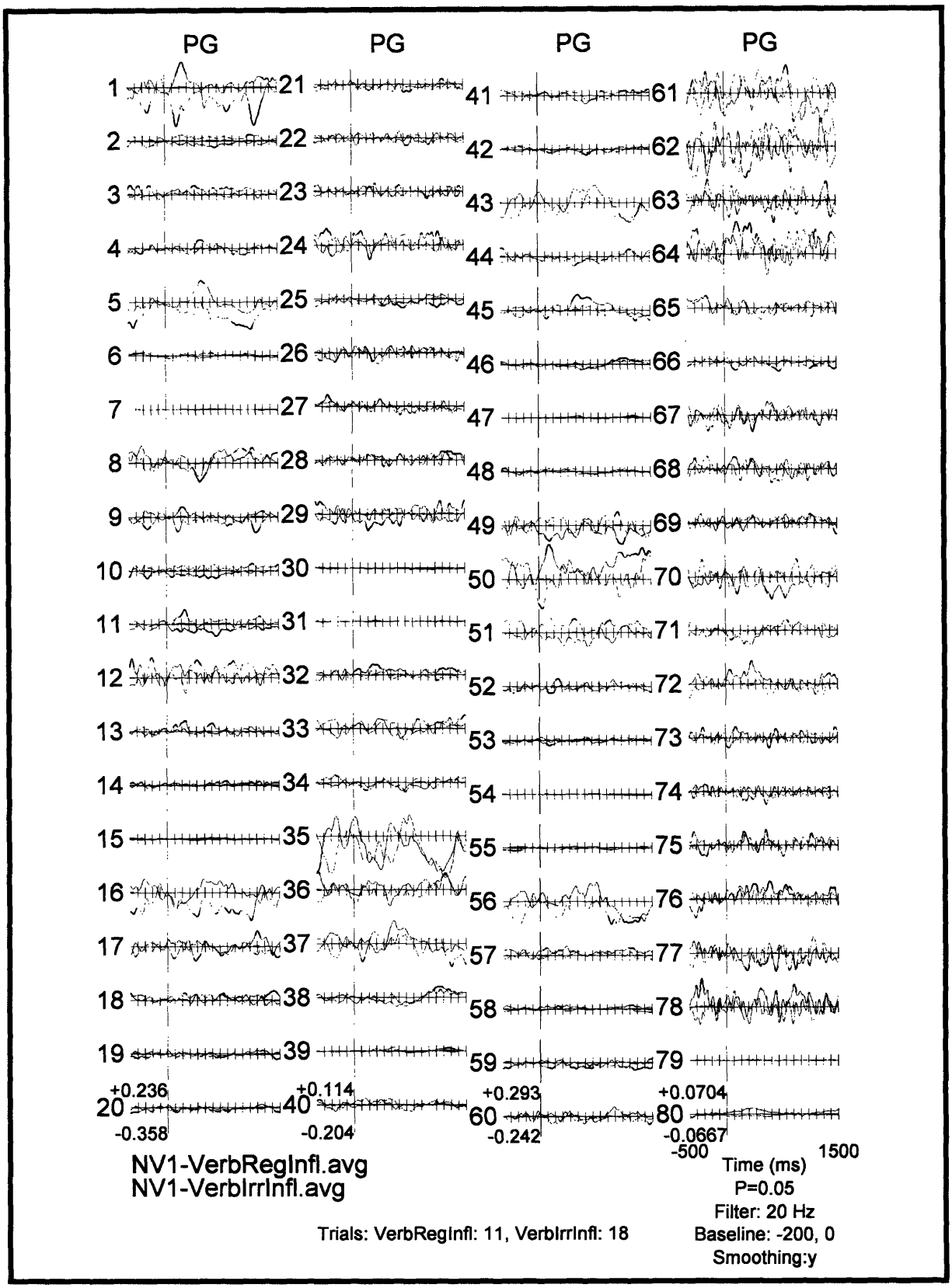


Figure 39: Intracranial E-phys Contrast: Verb Reg Overt-Inflect V Verb Irreg Overt-Inflect

9 FINDINGS: INFLECTIONAL MORPHOLOGY AND BROCA'S AREA

Affix-in' Broca's Convolution

9.1 Chapter Summary

Almost 150 years ago, Dr. Paul Broca diagnosed his patient's peculiar loss of speech, with intact comprehension, as stemming from destruction of the third frontal convolution of his left hemisphere. This would lead to the establishment of not only Broca's Area and Broca's Aphasia, but a whole movement, which continues today, of establishing correlations to implicate pieces of the brain in computing pieces of the mind. However, the nature of Broca's Area has had its own convolutions and evolutions over the years, with the current state including a growing split between those who think it computes grammar and those who think it has more domain-general responsibilities such as in working memory. Much of the confusion may result from tasks manipulating syntax, or structural flaws in sentences, which by nature co-vary with working memory and other general cognitive demands. My task – adding context-appropriate grammatical affixes to simple nouns and verbs – is a grammatical task and yet greatly reduces manipulation of general demands. My clear demonstration of Broca's activity supports returning to a view of abstract grammatical computation in Broca's Area.

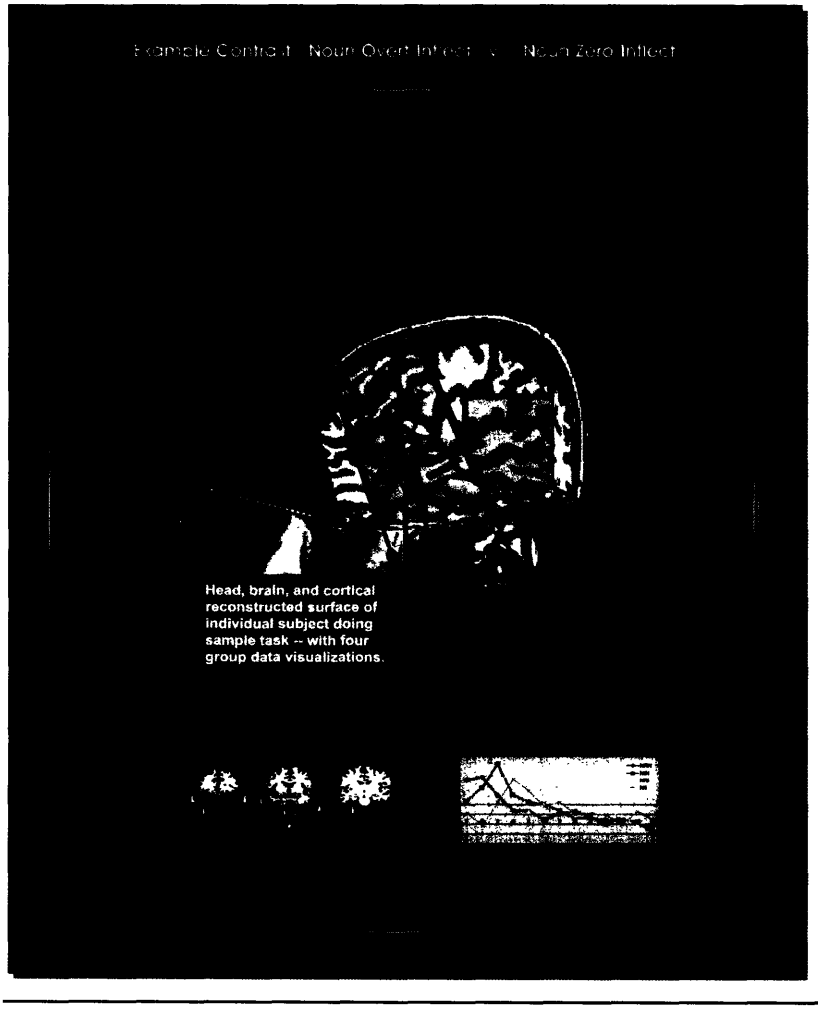


Figure 40: Cartoon depicting an example of the task, and fMRI results.
Individual subject performs task leading to example contrast, and that individual's actual brain registers the respective results in multiple views of the processed group data. Filmstrip-like timeline depicts what the subject sees over the course of two trials representing the two sides of the contrast. Strong and focal activation is seen in Broca's and directly-connected brain areas.

9.2 Running Title

"Broca's Area Revisited: A Central Role in Simple Verb and Noun Morphosyntax in Production"

9.3 Introduction and Literature

Broca's Area is the original and most popularly known example of brain-behavior correspondence, and yet after 150 years the specialized role in language of this cognitive organ remains unclear and is heavily debated. Patients with lesions to Broca's Area, still very common and devastating amongst the nation's seniors, were originally described as barely able to speak while nonetheless able to comprehend sentences spoken to them (Broca, 1861) – leading to a view that Broca's area handled *expressive* as opposed to *receptive* language (Wernicke, 1874), (Geschwind, 1970). This view, the Wernicke-Geschwind model, was challenged when Broca's aphasics were shown to be unable to comprehend sentences in which thematic roles (who did what to whom) could only be accessed through grammatical structure (e.g. "the boy who was hit by the girl is tall") (Caramazza & Zurif, 1976). This led to a view of Broca's involvement in the computation of *Grammar*, whether receptive or expressive (Caramazza & Zurif, 1976), c.f. (Dronkers, 2000). This is even reflected in the clinical and research terminology for Broca's aphasics – originally termed "non-fluent" aphasics, and since about 1970 also interchangeably referred to as "agrammatic" aphasics by many (and some taxonomies hold agrammatics as a subset of Broca's Aphasics).

Grammatical computation is what enables the infinite expressive power of Language, through the combination of memorized elements (e.g. words) to express novel ideas, and its evolutionary advent may be what differentiated human communication (Nowak, Plotkin, & Jansen, 2000), so identifying its neural mediator is central to the study of Language. (Linebarger, Schwartz, & Saffran, 1983) challenged the idea that Broca's aphasics were incapable of recovering grammatical structure, reporting such patients who could correctly reject sentences that were grammatically flawed in specific ways. Responses (e.g. (Zurif & Grodzinsky, 1983)) led to further refinements of what had come to be called the "syntactic

theory" of Broca's Aphasia (Caramazza, 1988), which led to honing of the questions (Berndt & Caramazza, 1999), and finally to a position that became the title of (Caramazza, Capitani, Rey, & Berndt, 2001): "Agrammatic Broca's aphasia is not associated with a single pattern of comprehension performance." Nonetheless, all these lesions studies still implicated Broca's Area in the knowledge or performance of aspects of language grammar.

Recent decades have brought the advent of functional neuroimaging to complement lesion studies, yet the computation of all or any part of grammar in Broca's Area has not been definitively confirmed. The neuroimaging work is reviewed in (Kaan & Swaab, 2002), whose conclusions include "Broca's area is only systematically activated when processing demands increase due to working memory demands or task requirements," as discussed in Section 4.4.

I believe one reason for the confusion lies in *tasks* that don't allow the separation of abstract grammatical manipulations from general working memory or task demands. Much good recent imaging work on grammar has focused on **syntax**, for instance in comparing syntactically complex to simple sentences in order to extract brain signals corresponding to syntactic processing. Sentences in experiments such as (Caplan, Alpert, Waters, & Olivieri, 2000) were well controlled: containing identical words and conveying the same overall meaning, yet with the complex sentences arranged with clauses nested within each other ("center-embedded" structure), compared to the simpler right-branching word order. Imaging the difference between such stimuli was intended to isolate syntactic differences and thus abstract grammatical processing, and indeed Broca's area was in many cases activated.

However, various critics note that less linguistically interesting factors may account for Broca's Area activations. For instance, general working memory demands increase for production or comprehension of the complex sentences (Just & Carpenter, 1992). The system could fail if it runs out of working memory, and thus the seeming grammatical difficulties in Broca's Aphasic may be attributable to the inability to temporarily store information as the patients attempt to produce or comprehend complex sentences. Likewise, functional activation of Broca's Area could result purely from the increased working memory demands for complex side of a *complex* vs. *simple* functional imaging contrast. (Just & Carpenter, 1992; Just, Carpenter, & Keller, 1996) pose the argument in terms of a truly domain-general working memory capacity, having failed to find evidence of distinct pools of memory for linguistic versus digit span tasks. Working memory is also implicated in Broca's activations by (Caplan,

1999; Stromswold, Caplan, Alpert, & Rauch, 1996) while their accounts lean toward a more language-related brand of working memory.

The manipulation of syntax usually results in "movement" of elements within the spoken ("surface") sentence structure relative to its actual meaning ("deep structure") (Bastiaanse & Thompson, 2003). The system could fail if, specifically, it loses the placeholder (or "trace") of the moved word, like a golfer losing the marker for his next putt. Grodzinsky and colleagues argue for a highly specific role for Broca's Area, namely that manipulation of traces is the only thing computed in Broca's Area, and Broca's Aphasia results from deletion of the traces (Grodzinsky, 1986a, 1986b). They clearly reiterate their very strong stance in a more recent paper: "Combinatorial aspects of the language faculty reside in the human left cerebral hemisphere, but only the transformational component (or algorithms that implement it in use) is located in and around Broca's area." (Grodzinsky, 2000) Finally, in a very recent paper, they pronounce that experiments designed to isolate transformations from other aspects of complex sentences have revealed "the neural reality of syntactic transformations." (Ben-Shachar, Hendler, Kahn, Ben-Bashat, & Grodzinsky, 2003)

A distinct theoretical account of what might co-vary with syntactic complexity and thus account for Broca's activation comes in Gibson's Dependency Locality Theory (Gibson, 1998), which describes and, crucially, quantifies the mental cost of integrating a word from the earlier part of a sentence with its partner in the later part, and of buffering it until then. The theory describes linguistic processes and incorporates some of the elements of Grodzinsky's principles, yet does not specify constraints on the working memory and schematic processing demands as necessarily grammar- or even language- specific.

Furthermore, it has been pointed out that processing the more complex sentences would involve higher "selection" demands (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) that could confound the signal from grammatical processing. Finally, whenever comparing two sentences it is very difficult to eliminate differences in articulatory complexity, or semantic processing. Broca's Area has been convincingly implicated in semantic processing and has long been associated with articulation and articulatory planning, especially given its anatomic proximity to the mouth and face region of the motor cortex.

Aside from manipulating syntactic complexity, sentences containing grammatical errors have long been used as another way to tease out grammatical processing. For instance, a recent fMRI study compared sentences containing misspelled words to ones containing misplaced words (Embick, Marantz, Miyashita, O'Neil, & Sakai, 2000). The syntactic errors were meant to ramp up syntactic processing centers (a very common paradigm), while the orthographic errors were meant to be surface-only errors and thus not invoke syntax. The authors showed activation throughout language areas for all conditions, with the greatest difference between grammatical and spelling errors in Broca's Area, which they interpret to indicate "that Broca's area is specifically involved in syntactic processing." This is an elegant manipulation because it focuses the contrast on a single or very few words and promises to isolate syntactic processing. However, Embick, *et al.* assert that the spelling-error sentences control for sentence processing and error detection, yet they do not account for the possibility that only the syntactic anomaly sentences will trigger "re-analysis."

Since our language system is trained on and designed for utterances that do make sense, it seems likely that laboratory sentences with bizarrely mutated syntax or semantics would primarily activate existing systems meant to deal with sentences that are mis-understood rather than mis-produced. The problem is, the re-analysis process may involve fully restarting the sentence comprehension process (Grodner, Gibson, Argaman, & Babyonyshev, 2003), potentially multiple times, and may require processing semantic, syntactic, and morphological clues in an unpredictable combination across subjects and stimuli.

Indeed, in the realm of electroencephalographic event-related potentials (ERP), a long tradition of studying errors has uncovered two major components of the scalp-recorded brain signal. Canonically, the N400 is associated with semantic processing (Holcomb, 1993; Kutas, Neville, & Holcomb, 1987), and the P600 is associated with syntactic processing (Hagoort, Brown, & Groothusen, 1993). However, this dissociation blurs when the violations depart from cleanly separated and simple laboratory examples. For instance, a recent ERP study included sentences intended to show a type of semantic violation, where the subject could not, based on its meaning, perform the actions of the verb ("For breakfast the eggs would only eat...") (Kuperberg, Sitnikova, Caplan, & Holcomb, 2003).[1] Instead of the hypothesized N400 the

[1] The reader is here invited to consider whether this very sentence itself caused a re-analysis event in the reader's mind. One may at first presume "the subject" is going to refer to an experimental subject in a study for instance. Note how in my meta-example the re-analysis will of course involve syntactic but also semantic and maybe pragmatic re-evaluation of the possible

authors found a strong P600, which they interpreted to index reanalysis of the anomalous sentence – presumably toward finding a missed potential reading that would restore sense to the sentence. Reanalysis has been shown to elicit a P600 (Friederici, Hahne, & Saddy, 2002) (Friederici, Pfeifer, & Hahne, 1993).

With only the grammatical side of the grammar-spelling contrast containing re-analysis, which may involve multiple readings of the sentence and buffering of possible meanings, one is again open to all the reservations from comparisons of full-blown syntactic differences, such as confounds of working memory, syntactic movement, dependencies, and basic articulatory and semantic differences.

All these factors could be involved in any subtraction of the brain signal for simple from complex or semantically from syntactically anomalous sentences, which may be a reason it has proven vexingly difficult to resolve the question of whether Broca's area responds to pure grammatical computations. Definitive assignment of a role in abstract grammatical processing to Broca's area may require a *model system* with the linguistic combinatorial processing required for syntax, and yet a greater degree of simplicity and a freedom from these other confounding factors. For these reasons, we chose to study a model system simpler than syntax but which still contains combinatoric grammatical processing, namely the system of inflectional morphology.

Grammar can be decomposed into syntax and morphology, with syntax concerning the construction of sentences from sequences of words, and morphology concerning the construction of words from elemental parts called "morphemes." Morphology literally means "shape," and applies because the shape or final form of the word is changed by the process, not just the location within the sentence. Morphology encompasses multiple domains, such as the forming of compound words or *deriving* nouns from adjectives, but *inflectional* morphology specifically refers to the affixation of morphemes to mark the grammatical role of the word in the specific context. For instance, the inflected (conjugated) verb form "walked" is minimally composed of the stem morpheme "*walk*" and the past-tense morpheme "*-ed*" and the inflected (number-marked, in this case plural) noun form "hawks" is minimally composed of "hawk" plus the plural morpheme "*-s.*"

meanings of individual words as well as phrases. In this case, even a more richly morphologically marked language would not disambiguate in real time at the surface structure level because the ambiguity has to do with the lexical semantics of "subject," but which would in all readings still in fact be the subject.

Such morphological patterns are highly productive and stereotyped, applying to tens of thousands of nouns and verbs equally and predictably. In languages other than English, such as Turkish, each given verb has a menu of possible forms numbering in the thousands – it is only the fact that the same patterns hold for most verbs that keeps the total from a combinatoric explosion that would overwhelm the language system. These patterns of how to apply inflections, which can be thought of as rules, therefore form a model system for the combinatorial rules that we know must exist to sequence our finite memorized menu of words into an infinite and unmemorizable set of possible sentences.

The other requirement for our model system to study grammatical processing in Broca's Area is that it allow sequestering of such processes from extralinguistic demands on working memory and other cognitive processes/systems. Whereas syntax involves sequences and relationships across many words, morphosyntax involves parts of a single word, and therefore the difference between a morphologically simple and complex word does not in itself demand significant generalized working memory. The type of working memory discussed by Caplan and colleagues also does not apply. There are no long-distance dependencies that differ between morphologically simple and complex words, and furthermore there is no movement and no traces to keep track of.

There has been some lesion work on morphosyntax, such as (Friedmann & Grodzinsky, 1997), and many descriptions of Broca's Aphasics include description of morphological deficits. There is little neuroimaging work focusing on inflectional morphology, and no intra-cranial electrophysiology.

My objective was to use this simplified but combinatoric grammatical system to investigate whether Broca's Area would respond to grammatical manipulations in isolation of as much other processing as possible. My hypothesis was that Broca's Area would be the common denominator and minimum activation in all the contrasts varying the inflectional task condition.

9.4 Methods

The methods have been discussed previously.

9.5 Results and Discussion

To identify the neural systems metabolically active during morphological inflection, I contrasted fMRI activation during **Overt-Inflect** and **Read** trials (**Figure 41**). This contrast should index most of the processes involved in grammatically inflecting words, of both syntactic and regularity classes. Broca's Area (BA44/45) was strongly activated in this contrast, within a highly circumscribed network including much of the inferior frontal gyrus (discussed below). All statistical activation maps in **Figure 41** are shown at $p<0.005$, uncorrected. The activation cluster with center of gravity in Broca's Area in **Figure 41a** is visible up to a threshold of $p<0.00001$, and the region is shown to be generally task-responsive to the Over-Inflection task (**Figure 41c**: Overt-Inflect>Fixation) up to a threshold of $p<0.000005$.[2]

The primary research question for this chapter can therefore be answered, namely that grammatical inflection was indeed sufficient to activate Broca's Area. My task conditions did not involve syntactic movement or long-distance dependencies, and did not increase working memory demands. Therefore, mediation of inflectional morphology by Broca's Area challenges the strong views that this region is only responsible for maintaining traces, or that it mediates only domain-general processing resources. Rather we back the position that one role of Broca's Area lies in the combinatorial, grammatical processing of word morphology.

To verify that Broca's Area was involved in the affixing of overt inflectional morphemes, I contrasted the metabolic activity for the **Overt-Inflect** trials with **Zero-Inflect**. These conditions were cued with highly similar frames (*Those are the___. / That is the ___.* for Nouns; and for Verbs: *Yesterday they___. / Every day they ____.*), and both provided contexts which unambiguously specified the tense or plurality required. The difference was that in

[2] Statistical thresholds are of the t-test for statistical differences in activity level for each voxel in the brain, considering all instances of the given trial type(s) on each side of the contrast. Because there are many voxels in the brain, a conservative approach would be to apply Bonferonni correction for independent tests by dividing the p-value by the total number of voxels to get the adjusted value, assuming that each voxel is entirely independent of all other brain voxels. Ignoring the fact that voxels represent arbitrarily-sized pieces of tissue whose neural interconnections and vascular co-dependence assures they are not physiologically independent, it is also difficult to determine the correct number of voxels to factor into the Bonferonni correction. Different analysis software packages apply the correction differently. Whereas SPM, a widely used toolset, has only one option, the FS-FAST toolset has no preset correction and therefore the flexibility to compute the correction based on types of analysis run. To avoid confusion and incompatibility of published "corrected" values, we chose to report pure uncorrected values. For sake of comparison, we could estimate the correction factor. Clearly, it must approximate the number of voxels included in the inflated cortical surface matrix, but even this is complicated by the partial contribution of underlying voxels and the complex intersection of the convoluted cortical ribbon with the cubic voxels, as well as smoothing in the original volume as well as on cortical surface.

English only the form in the **Overt-Inflect** condition (plural/past-tense) takes an overt, pronounced suffix. In the **Zero-Inflect** trials (not included in the contrasts in **Figure 41a**, only **Figure 41b**), the output form (singular/present-tense) is grammatically specified in context but is phonologically identical to the base form presented on screen. This contrast should more tightly index certain processes involved in grammatical inflection, such as the accessing and application of abstract grammatical features, the selection of correct inflectional morphemes, accessing and adapting their phonology, concatenation into a final morphological form, generating the final phonetic material, and readying for final articulatory output. These processes were shown to activate the entire circuit seen above, including Broca's Area (**Figure 41b, left**). This result verifies BA44/45 involvement in inflectional morphology, but does not differentiate between the application of abstract grammatical features (tense & number), and manipulation of phonological material.

To determine if Broca's Area was sensitive to manipulation of abstract grammatical features encoded by inflectional morphology, in the absence of phonological manipulation, I contrasted the **Zero-Inflect** trials with **Read** trials. In both conditions the subject covertly produced the phonetically identical form. The **Zero-Inflect** trials added unambiguous grammatical context and thus required specification of grammatical features (tense & number), accessing and selecting the morpheme (some theories support a "0" morpheme that is silent but marks the feature), and checking the final phonological/phonetic output against the grammatical context.[3] This hypothesized grammatical computation is clearly our most subtle. Since the contrast does not vary articulatory output, articulation theories of Broca's Area/Aphasia would hypothesize no Broca's Area activity. In fact, Broca's Area was strongly activated by this contrast (**Figure 41b, right**).

[3] The Read frame "repeat word: ___." was 2 words / 3 syllables long and the Zero-inflect frames were 2 or 3 words and 3 or 4 syllables. The Zero-inflect frame, when completed by the target form, formed a short sentence, so it is possible to argue that the Z>R subtraction includes some grammatical processing due to this minimal. However it is also true that subjects saw each type of frame 120 times, not including practice, so they became very used to them and in fact reported on debrief not reading the frames all the way through. In all frames, the first word was the disambiguating word, and the last word before the blank was identical within class ("they" for verbs and "the" for nouns). Subjects could therefore determine the response required by the first word of the frame. Also, any additional "syntax" in the Zero-Inflect frames certainly did not involve movement or a great deal of working memory. Finally, the whole experimental mission was to measure neural responses within a reduced model system for grammatical manipulations. Where words differ between the Zero and Overt frames they differ in exactly the variable being manipulated (plurality or past tenseness), and where the Zero frame adds a grammatical context over Read, it is also a manipulation of abstract grammatical features and not primarily semantics or extralinguistic features such as memory demands.

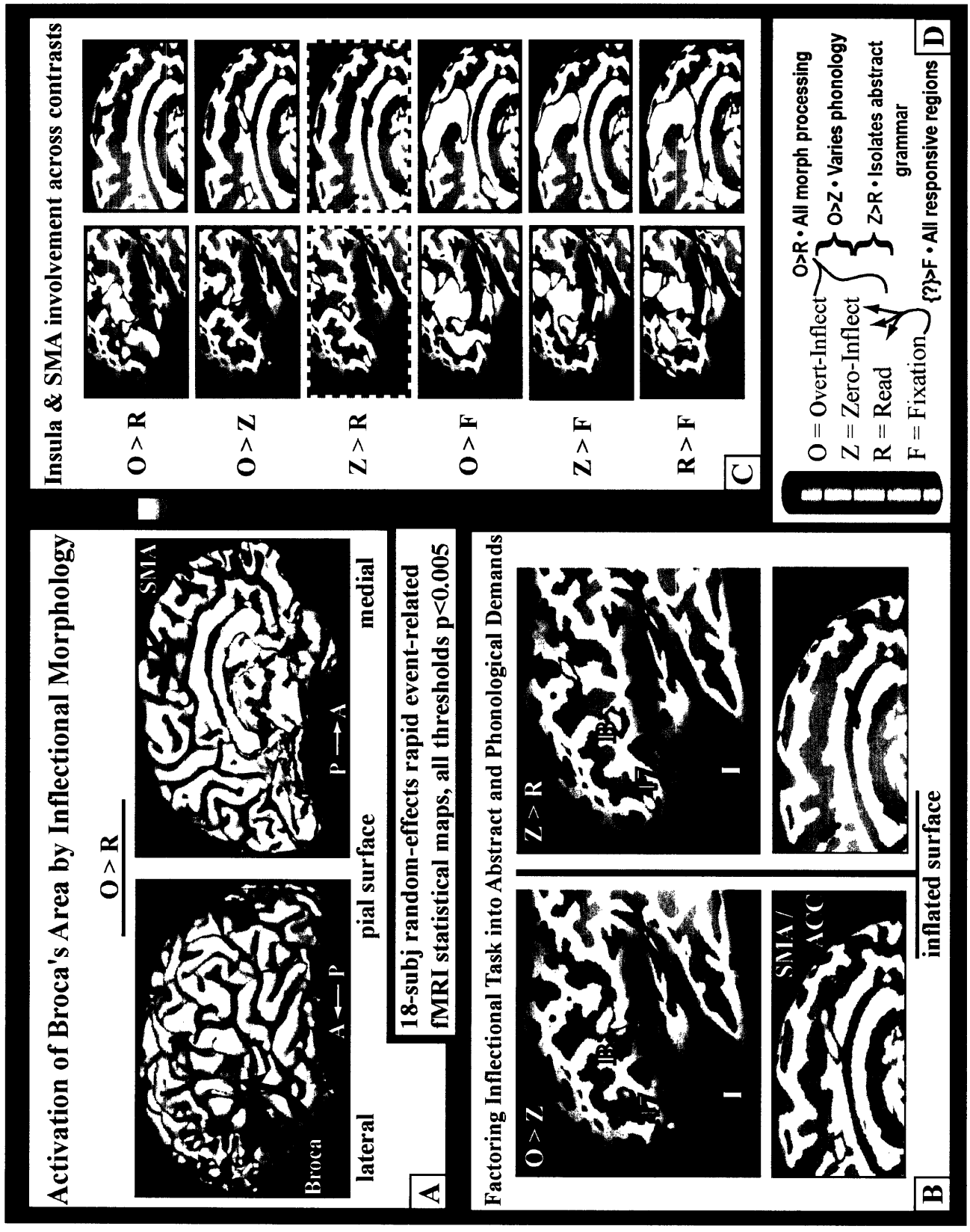


Figure 41: Broca's Area activation for grammatical inflection. Roles of BA47, insula, SMA.

Figure 41, Extended Caption: Broca's Area fMRI activation for grammatical inflection, and the roles of Broca's, BA47, anterior insula, and SMA. All images show color-coded statistical significance maps for the difference in metabolic activity level in cortical brain regions between task conditions denoted in each contrast. Random-effects average of functional data from 18 healthy volunteers mapped onto the anatomical brain surface of a single participant. **Panel D** decodes the condition labels for each contrast, depicting them on a "totem pole" schematic by hypothesized increasing demands for morphological processing. Contrasts used elsewhere in the figure are briefly explained. **Panel A** shows the primary contrast to index morphological processing (O>R), which compares all Overt-Inflect trials (subject is cued to produce plural forms of target nouns, and past-tense verbs) to all Read trials (subject is cued to read back the uninflected forms on screen). The lateral and medial pial surfaces of the left hemisphere are shown, and A(nterior) to P(osterior) direction labeled. Broca's Area (labeled) is strongly activated by noun and verb inflectional processing. Accompanying activations include the medial supplementary motor area (SMA) and much of the inferior frontal gyrus. The inflated brain surfaces in **Panel B** expose these areas and reveal activation of the anterior insula (marked with arrows and an "I"). The O>Z contrast keeps the cueing context highly similar but varies overt phonology and grammatical markings of the response. For this contrast, activation includes the SMA and anterior insula, whereas these regions are notably absent from the Z>R contrast, which varies abstract grammatical features but the phonological output is identical. This may indicate that insula and SMA involvement require phonological manipulation, while Broca's Area (labeled "B") and BA47 ("47") are sensitive to purely abstract grammatical manipulations. **Panel C** allows confirmation of this and comparison of our 4 major activation clusters for all the contrasts varying our Inflectional Task factor. Only Z>R, the one not varying phonology, fails to activate these regions implicated in motor planning/articulation of speech and apraxia of speech. The Z>F contrast (cued present-tense or singular production compared to fixation baseline) underscores that the insula and SMA are in fact active for the Zero-inflect condition but simply that, unlike Broca's Area, they are not significantly *more* active than for the Read condition. In the Z>R contrast especially, the medial activation extends in the Anterior Cingulate cortex. All maps were thresholded at $p<0.005$, uncorrected, yet the Broca's Area clusters in the O>R and O>F contrasts were visible up to respective thresholds of $p<0.00001$ and $p<0.000005$.

We examined the correspondence between the blood oxygen level dependent (BOLD) fMRI signal and neuronal firing in Broca's Area, in one of our epilepsy patients who completed the identical morphosyntactic experiment preoperatively and then during intracranial electrical recording. This patient was implanted with four penetrating 8-contact macroelectrodes, one of which directly traversed the anterior portion of Broca's area on the way to the cingulum. The within-subject fMRI results showed an activation cluster in Broca's Area for this patient,

convergent with results from the 18-subject healthy-volunteer study, and the BOLD-responsive brain voxels lay precisely where contacts 3-5 of the electrode were eventually implanted.. The time between the fMRI and electrophysiological recordings was 10 days, interceded by the surgical opening of the cranium and implantation of the electrodes. This "distracter task" should have served sufficiently to overwhelm effects of repetition priming between the two testing episodes!

The correspondence between the group and the patient's fMRI activation pattern can be seen in **Figure 42a** below. The patient showed an activation cluster in Broca's Area for the Overt Inflect task as compared to fixation. To verify the Broca's Area fMRI activation I looked for an implanted electrode that passed through this region of cortex. Having obtained the slice of the clinical MRI containing such an electrode, I searched for the corresponding slice in my functional data set. This slice revealed an activation cluster nearly exactly over an area that lay along the trajectory of the electrode implanted the day after the fMRI session took place. The region of correspondence was in the left inferior frontal gyrus, just anterior and subjacent to the core of Broca's Area, and passing near by the anterior insula **(Figure 42b)**.

Recordings from this electrode revealed task responsiveness only for the 3 or 4 channels penetrating the region of correspondence, and there was a clear inversion of the waveforms across these channels. This unambiguously indicated a source of electrical activity, at once confirming the result that Broca's Area and environs compute grammatical inflection, and showing a direct correspondence between fMRI BOLD and intra-cranial evoked potential neural signals.

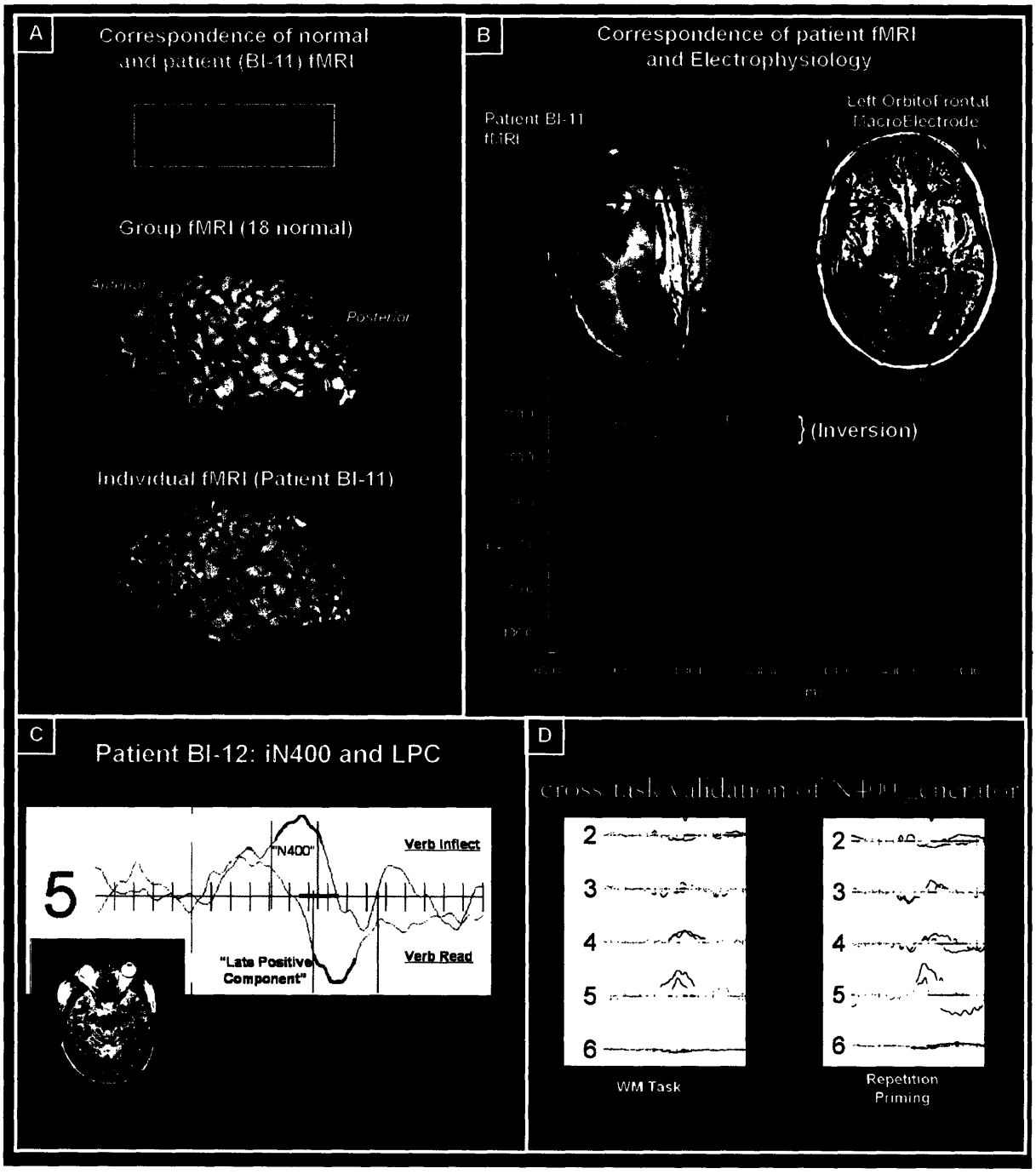


Figure 42: Intracranial electrophysiological confirmation of fMRI results

Figure 42, Extended Caption: Intracranial electrophysiology. Panels **A** and **B** go together, describing fMRI and Depth electrophysiology convergence in Patient BI-11 Broca's Area. Panels **C** and **D** go together, validating the Overt > Read contrast with iEEG components. **Panel A** depicts fMRI data for the contrast of Overt-Inflect trials against fixation trial, for the group average of the 18 healthy volunteers, as well as for Patient BI-11. Attention is called to activations shared in Broca's area and the anterior insula because this patient showed fMRI activation there and eventually had an electrode implanted through there. Also note the general correspondence of activated regions.

These clearly independent fMRI data sets are depicted as functional overlays on the same structural brain image, to facilitate comparison. **Panel B** shows first of all a slice-based depiction of BI-11 functional data, and a corresponding slice from post-implantation clinical MRI reveals electrode trajectory through this region. Beneath is shown the average voltage tracings from the channels along this electrode. The y-axis shows voltage, and the x-axis shows progression through time. Each colored line is a separate channel along this electrode. The channels in the region of the BOLD activation are electrically responsive to the task, other channels are not, and there is a clear inversion across the channels for contacts 4-5 and 5-6 indicating a source localization close to contact 5. Also, the tracings reveal time components of the signal, at 240ms, 380ms, and 525ms. **Panel C** depicts intra-cranial data from Patient BI-12. Average voltage tracings for both the Verb Overt-Inflect and Verb Read conditions are superimposed for this single channel, which represents recording from near the collateral sulcus of the temporal lobe. This region has been shown to be a generator of the N400, in MEG and fMRI studies, therefore the intracranial signals in this time range can be interpreted in terms of the scalp-recorded N400. We take the iN400 here to index general linguistic processing, not just semantic, and the Late Positive Component that follows it to index closure or task completion. In a contrast equivalent to Verb O>R, the Overt-Inflect trials show a much greater N400 than Read, and the Read show and earlier and greater LPC. These results converge with hypotheses that the Overt Inflect trials would require more processing in areas sensitive to the processing of this morphological task, and that the simple Read task is completed swiftly and clearly. **Panel D** provides within-subject evidence that this same channel responds according to an N400 pattern, and thus licenses our interpretation in **C**. Depicted are the tracings from the same channel as in **C** (#5) as well as neighboring channels, for two other cognitive paradigms performed by the same patient. The two tasks, one focusing on verbal working memory and one on repetition priming, shared a feature that some of the test stimuli were new to the subject in that session, and some had been seen before and so were "old." For both of these studies we see the contrast of New vs Old. In and only in channel 5, there is a strong difference in the waveforms near 400ms latency for the new vs old stims, thus showing that this focal region of the brain shows neural activity that indexes novelty effects and word processing with an N400.

Grammatically inflecting words also activated regions beyond Broca's Area. fMRI activity for the Overt Inflect condition as opposed to any other condition also included Brodmann Area 47 (BA47), anterior insula, and medial SMA, with occasional inclusion of the Anterior Cingulate.

The addition of inflectional morphemes, and accompanying manipulation of phonology, activated the anterior insula (**Figure 41b**: O>Z). This converges with the work of Nina Dronkers, who discovered a 100% correlation between aphasics who had significant lesioning of the insula and those with Apraxia of Speech (AOS). The net effect of AOS is difficulty and

slurring in speech production, and is thought to results from deficiencies in motor speech planning or articulation (Dronkers, 1996).

Broca himself might have anticipated the Dronkers lesion correlation between Broca's and the insula, or even the present functional co-involvement of the two. In the final footnote to his 1861 paper, he notes "It follows from this connection that a lesion that is spread, by way of this continuity, from the frontal lobe to the temporo-sphenoïdal lobe, or reciprocally, passes almost necessarily by the lobe of the *insula*" [Italics original] (Broca, 1861).

It turns out, Broca's hunch was correct in multiple ways. First of all, some insula lesioning was confirmed in his own original patient's brain (preserved in a museum in Paris since then), through a series of CT scans: (Castaigne, Lhermitte, Signoret, & Abelanet, 1980), and translated (Signoret, Castaigne, Lhermitte, Abelanet, & Lavorel, 1984). These scans offered low resolution compared to today's standards but nonetheless connected underlying insula damage to that more readily observed at the neocortical surface. Figure 43 shows a human brain dissection, revealing the cortex of the insula lying beneath classical language areas.

Figure 43: Human Brain dissection revealing insular cortex below left-hemi language areas.
(Image © 1995, Digital Anatomist, University of Washington, Seattle.)

Beyond sheer proximity, insula and Broca's Area might be expected to correlate both in terms of functional imaging of blood-related changes and in lesion studies, based on their underlying blood source. The regions lie in perfusion (blood irrigation) zones with a shared source: the Middle Cerebral Artery (MCA).

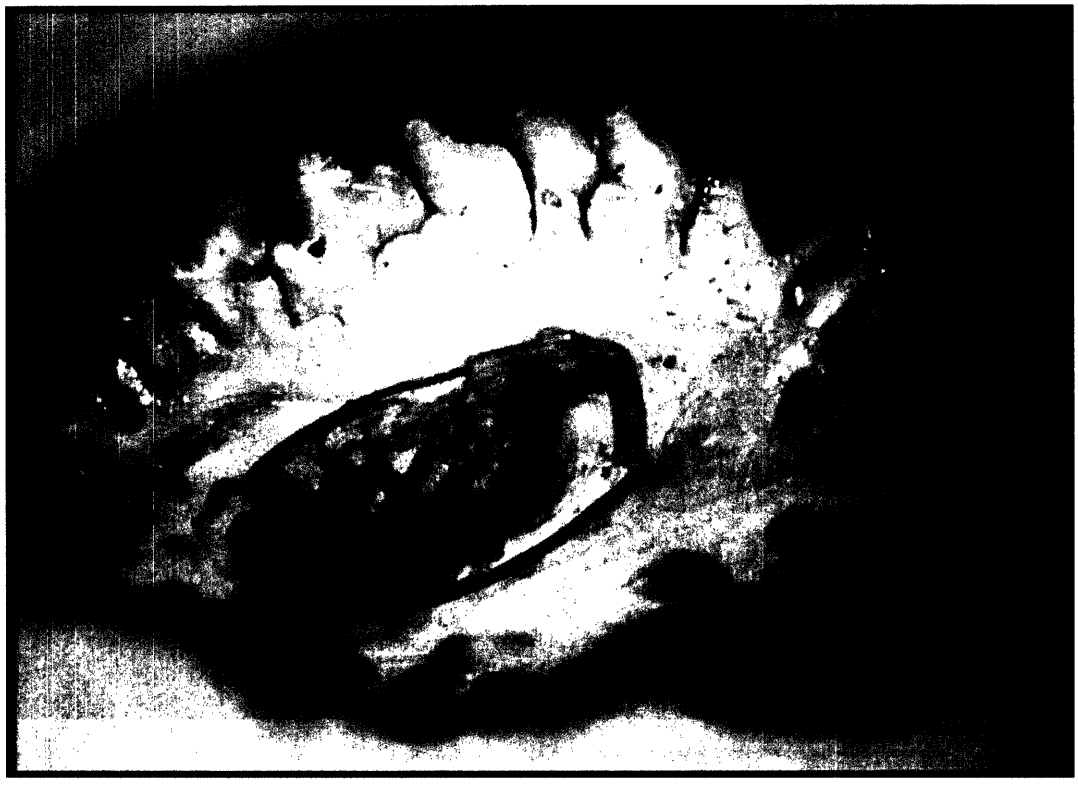


Figure 44: Sagittal resection of lateral left hemisphere, revealing MCA perfusion of insula. Univ Bristol

The MCA rises from the basilar artery and traverses the insular cortex before wrapping out through the Sylvian Fissure to fan out over much of the lateral frontal and parietal lobes. Cortical perfusion proceeds from out to it, with arterioles that creep along the cortical ribbon eventually branching and diving straight down through the cortex, providing capillary beds to feed the brain tissue. However, along the way all this blood supply comes through the insula region. Around this region, and with variability across patients, the lateral cortical supply branches – with the superior division of the MCA roughly covering Broca's Area and surroundings, and the inferior division providing flow to Wernicke's Area and environs. The branching of the superior division may come just before or after the branch that serves the insula, depending on the patient, but usually very near. Based on this cerebrovascular anatomy,

we should not be surprised to find that insula and Broca's Area damage often co-occur in embolic stroke.

A study of 21 stroke patients with resulting language difficulties, showed that 13 of them had >10% lesions to the insula, averaging 73% of this cortical "parcellation unit" destroyed by the stroke (Caviness et al., 2002). Related work on these data showed that the vascular etiology of such strokes could be reliably determined purely by the pattern of cortical damage (Sahin, 1998). All of the 13 insula-damaged in the Caviness, *et al.* study had been thus categorized as having infarction of the superior division of the MCA (with the worst being those with occlusions at the MCA stem before the inferior/superior divide), and there were no superior-division strokes without significant insula damage (all above 10% except one at 7%). Nine out of our 13 were left-hemisphere strokes, and all but 2 of these showed extremely poor performance (<65%) on reversible passive sentences (written and auditory combined), a hallmark of Broca's Aphasia. The others were the 2 with the smallest Broca's Area lesion.

This cerebrovascular framework not only shows why strokes that cause Broca's aphasia may usually include insula damage, but it shows that it may be difficult to infer the separable role of the insula from lesion studies. fMRI, although also dependent on blood, can localize and separate the source of neural metabolic activity even at two stops along the same arterial blood supply. Furthermore, where fMRI-based localization is doubted, a combined-methods approach such as the present one can offer independent verification, in this case electrophysiologically.

Interestingly, both the historically speech-centered focus of Broca's Aphasia, and the physical subjacency and vascular coupling of the motor-implicated insula to Broca's Area, may have fueled suspicions over time that Broca's aphasia may be mostly a motor/articulation problem and that Broca's Area itself may be simply a motor control area. This makes sense because Broca's Area abuts the part of motor cortex that controls the face and mouth, lending credibility to the lesion-based notion that it may be a specialized organ for complex control of the speech apparatus. However, the low effective "resolution" of lesion studies and vasculature-based co-occurrence of lesions in Broca's and insula may cloud the individual contributions of these regions, and meanwhile the confounding of many grammatical manipulations with basic articulatory demands makes these hard to factor apart.

With the resolution of fMRI, I was able to separate clearly the metabolic activity in Broca's Area from the insula. Having three different inflection task conditions allowed multiple

types of comparisons, and the nature of the conditions allowed factoring apart of articulatory planning from grammatical computation

As noted above, the combination of grammatical processing and phonological manipulations in the **Overt-Inflect Vs Zero-Inflect** contrast significantly involved the anterior insula (**Figure 41b, left**: O>Z), just as did **Overt-Inflect Vs Read** (**Figure 41c, top**: O>R). To determine the independent contribution of grammatical and phonological manipulations to insular activity, I subtracted the activity for **Read** trials from that of **Zero-Inflect**, thus varying grammatical context and adding at least the need to choose the correct morphological form, yet holding the phonological output constant. In this contrast, the insula activity disappeared (**Figure 41b, right**: Z>R). Meanwhile, the activation clusters in Broca's Area and BA47 remained, even though this is a very subtle contrast. Taken as a whole, this suggests that Broca's Area and BA47 are sensitive even to abstract grammatical computation, while the insula requires the *addition* or *manipulation* of phonological material.

My results converge with (Dogil, 2003), who showed anterior insula activity increases for repeating syllables of increasing phonological complexity. Dronkers had interpreted her perfect correspondence between insula lesion and apraxia of speech as implicating the insula in speech planning, because apraxia of speech is general described as a deficit of speech planning (Dronkers, 1996). Dogil, *et al*, however, showed their anterior insula activation only for overt and not covert speech, which they interpret to implicate the anterior insula in actual motor articulation and not speech planning. Drawing on Levelt's framework for speech production (Levelt, 1989, as discussed in (Dogil, 2002)), they suggest that the role of the insula should be pushed from Dronkers's "speech planning" to the "last stage of the transition between the higher cognitive (linguistic) and purely realizational motor processes." Namely, they conclude that the insula's role in apraxia of speech is in the "checking mechanism which transfers the phonetic code into the articulation module." (Dogil, 2003)

As mentioned, it is difficult to compare lesion and functional studies directly but it is possible that Dogil's anterior insula and Dronkers' more posterior insula regions are functionally segregated. Meanwhile, the present results confirm anterior insula involvement in the phonological aspect of production, except our task solely employs covert speech. This may refute the Dogil claim by showing that speech planning is sufficient to activate the anterior insula, which would again open up both speech planning and articulation as roles of the anterior

insula. Alternatively, it is possible that the present covert production task actually involves a hybrid process of "mental articulation" that goes beyond the speech planning that normally precedes articulation in conversational speech, and requires producing the articulation sequences. It may be the case that the present task, designed to approach natural speech events, picks up on this more than Dogil's repeated syllables and words.

Whether our anterior insula activation represents the speech planning or final articulatory sequence information to pass to primary motor cortex, it is important also to try to differentiate between *manipulation* of existing phonological material and the processing of *additional* phonology. Inflectional morphology often involves the binding together of multiple pieces of the final word, e.g. "dog" + "-s" or "cat" + "-s" and this addition may be accompanied by manipulation of the phonology of one or both of the morphemes according to phonotactic rules. In our examples, the first "-s" is pronounced as "*z*" and the second "*s*". Similarly, stem phonology can change, as in "house/houses." I sought to isolate the phonological change or customization of the given morphemes, from the articulatory or planning aspects of adding new phonological material.

To verify that anterior insula responds to any manipulation of phonological output, not only the addition of phonological and thus articulatory material, I separately contrasted only irregularly-inflected words for the Overt-inflect > Zero-inflect contrast (varies overt morphophonology). Most of the irregularly inflected stimuli changed rather than added phonology (e.g. stink/st*u*nk, man/m*e*n, as opposed to blink/blink*ed*, van/van*s*). I conducted a region-of-interest (ROI) analysis to measure averaged activity in all task-responsive voxels in the anterior insular, as defined functionally in the Read > Fixation reference contrast. The fact that the anterior insula showed significant increases even for these irregular inflections confirmed that they are sensitive to phonological/phonetic *manipulation* not just additional phonetic material.

The fact that matching Broca's Area and BA47 ROIs also showed significant but smaller increases, further confirms that their differential involvement does not require additional articulatory demands. Taken in light of the patterns discussed above (**Figure 41b, c**), their activity can be interpreted in terms of the increased abstract grammatical demands in applying past-tense or plural morphology, which, unlike present or singular, is marked overtly (regularly or irregularly) in English. Regularly and irregularly inflected verbs have previously been shown

to recruit different neural systems (Pinker, 1991, 1997), and further confirmation of this theory based on the present work will be reported elsewhere.

Figure 41c shows further that insula activation co-occurs in all cases with activation of the medial aspect of the supplementary motor area (SMA). This functional linkage has been documented elsewhere, and makes physiological sense not in terms of vascular coupling or cortical topography, but in underlying white matter connections. Fundamental anatomy as well as recent tractography show direct fiber connections between these regions. Figure below **Figure 45** below shows a coronal brain slice including the insula and SMA. It is clear to see that direct, "short-cut" white-matter connections through the corona radiate form a convenient bridge between the insula and the medial SMA, vastly shorter and more likely a route than the long way around the cortical ribbon through cortico-cortical interconnections. Further studies may more finely apportion phonetic and articulatory tasks to the SMA and anterior insula.

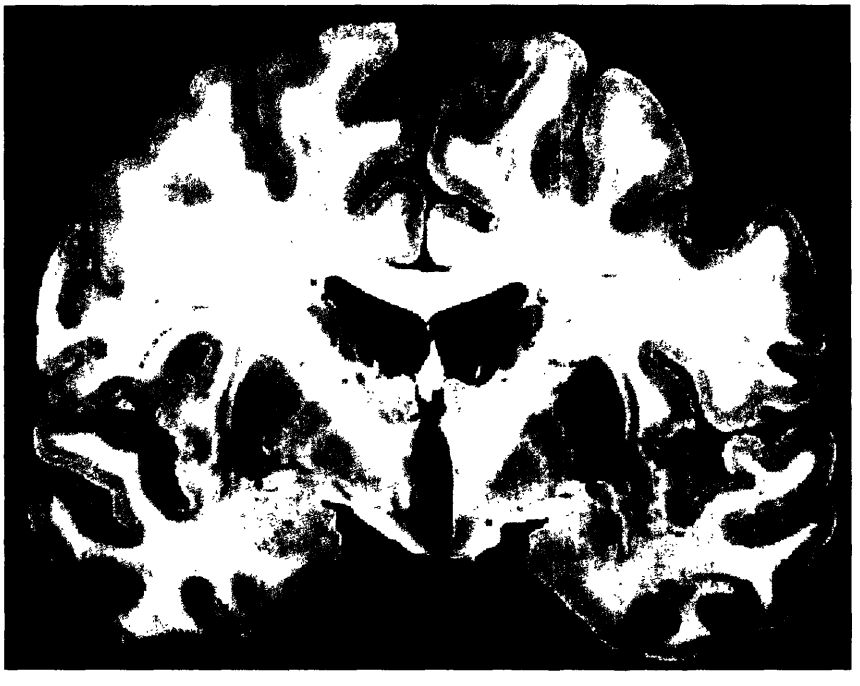


Figure 45: Human brain coronal slice, showing insula white matter connections to SMA, ACC

In summary, I found that cued pluralization of simple nouns and conjugation of simple verbs was sufficient to increase metabolic activity and electrical activity in Broca's Area. Since this task does not require sentential working memory, and the reported contrasts factor out the addition of articulatory complexity, Broca's Area is shown to subserve grammar-specific

processing and not only domain-general cognitive capacities. Furthermore, since the task does not vary nor even require movement or traces, the highly specific hypothesis that Broca's Area only computes these is also refuted. Inflectional morphology will continue to complement the study of syntax in the quest to understand the grammatical abilities of the human mind/brain.

The computation of language and specifically grammar in Broca's Area is extremely important to Cognitive Neuroscience, because it is a fundamental example of brain-mind linkage, and of modularity of mental processes. Furthermore, if grammatical computation is really carried out in Broca's Area, it gains a great evolutionary import since the evolution of the ability to manipulate representational variables and sequence stored concepts into new ideas may have been largely responsible for the rapid surge in evolution toward the complex minds and social structures we are equipped with as modern humans (Fitch & Hauser, 2004) (Nowak et al., 2000). One way or another it is important to determine the role or roles of Broca's Area as a cognitive organ within the brain.

Understanding Broca's Area and Aphasia is also important from the point of view of the thousands of patients each year who suffer strokes or other brain injuries and suddenly lose the ability to speak with and understand family members, or live independently in society.

The position of this work is not that Broca's Area only computes language grammar – indeed it would be incredible if a few hundred million neurons had only one job. This work also does not assert that any of the grammatical processing that might be done in Broca's Area is only done in Broca's Area. Indeed our data clearly show morphological computation by a larger circuit including Broca's. Namely, while Broca's and BA47 show activity patterns including but not limited to isolated abstract grammatical computation, the SMA and anterior insula show *specificity* for overt phonological manipulation or the addition of phonological material for production.

What is Broca's role in language? Is it possible that morphology is not just one system that happens to drive Broca's Area, but rather a core of what Broca's area does in language comprehension and production? I do not have evidence to support such a broad claim, nor do I feel it is really necessary to seek a common denominator this early in understanding the cognitive neuroscience of complex traits such as language, so I will discuss the idea only briefly. Long-distance relationships in syntax, often looked to in understanding Broca's Area, are also dependent on any local markings on each word that determine what sentential roles the

word can play. A morphological deficit would lead to syntactic deficits, especially in morphologically richer languages. Perhaps the inconsistency in Broca's functional activations in syntax studies comes from variability in the degree to which the morphological system is taxed and can be tapped for the required information. At risk of sounding like I have become convinced that my small plot of land is really the center of the universe, I would point out that the assertion that handling of traces and movement is all Broca's does seems just as strong a position as fingering morphology. Also, the ability to support movement in the surface structure and decode traces is somewhat related to morphology, especially in languages other than English. Simply put, a word whose internal morphological structure (e.g. endings) determines precisely what features it possesses (case, number, etc) is much less likely to become lost and uninterpretable no matter where in the surface structure it moves to. Similarly, a trace is more likely to be matched to the correct word, the more the role of that word is unambiguously specified by the morphology. Nonetheless, I will have to leave this idea open and highly speculative until I can inspect a wider range of evidence.

What is the role of Broca's Area in cognition, generally? Language evolved recently. Also, humans seem to be the only species with language capabilities anywhere near the level of complexity we enjoy. Therefore, we must think of language specialization in the brain in terms of what evolutionarily old capacities and skills were enhanced and recruited as the language faculty coalesced. In this perspective, the central role of the inferior frontal gyrus in so many parts of language should make us suspicious that this region has a history of processing information of a type or in a way that was necessary for proto-language and language.

We should look beyond language, therefore, for other drivers of IFG activity. Studies of music have shown Broca's activation (Maess, Koelsch, Gunter, & Friederici, 2001), and even the imitation of finger movements have lit up this region (Iacoboni et al., 1999). Sign language activates Broca's Area, and again finger movement more than hand and arm movement has been proven to be the strong activator of this region (Tanaka & Inui, 2002). So, what do the future tense, finger movements, and a fugue have in common? Again, I hesitate to speculate, especially since if evolution was powerful enough to fashion all of language from basic pre-existing principles, it may have been equally effective at progressing toward highly specialized skills related to music or social cognition of gesture in a totally independent way. That is to say that while these may have a common denominator across time, in shared cognitive ancestry,

music, language and imitation would not necessarily require a contemporary common denominator of a single type of processing.

With these caveats, I will briefly speculate that perhaps Broca's area specializes in processing signals that are particularly rich in the time dimension, and rely for their meaning or relevance on relationships along that time dimension. Music can be separated from noise because the sound at a given point in time bears a systematic relationship to the sounds immediately and distantly before and after it (musical syntax). Perhaps, also, a timeslice of sound can be decomposed into parts that themselves promise inter-relationships with each other and with future sounds – a musical morphology? Without the ability to keep track of very precise and complicated spatial relationships, in time, hand gestures would blur and be irreproducible. It is not enough to know the end state of the hand nor which fingers crossed which others at some point – one needs to remember at exactly what point the movements took place. Perhaps, then, Broca's Area involvement in these tasks has to do with extracting meaning from gesture, specifically by holding onto representations of intermediate states and crucially their relationships through time.

The most well-known visual area, V1, is so named because it has long been thought that all visual information goes there first among all regions of the cortex. However, recent work has shown that a blurred image goes quickly and directly to the frontal lobes while information is routed through V1 for detailed analysis (Bar, 2003). The original work by Hubel and Wiesel that characterized V1 was of course in terms of analysis of details of line segments (Hubel & Wiesel, 1959). It is possible, I think, to pitch V1 not in terms of an order of operations in all visual processing but rather in terms of a specialization for high spatial frequency information. We can think of visual discriminations that require high spatial frequency information as necessarily going through V1 (V_{HSF}?) while quick determination of predator existence or motion, for example, may not need to. V1 then becomes an specialist in the brain, a sub-organ that is recruited for such tasks. This may intersect with the debate over how far "back" in the visual stream mental imagery is able to stimulate. In this perspective, it would be a matter of whether the items being pictured internally were of sufficient detail or if the task required inspecting a remembered image for details (such as the location of the date on a U.S. 1-cent coin), that would determine whether V1 would be activated by the mentally-generated images.

Perhaps, then, one could draw a parallel here and investigate Broca's Area as specializing in "high temporal frequency" information.

Again, this is pure speculation, but it does seem that the sundry tasks attributed to Broca's Area rely on complex and potentially long-range temporal relationships. Clearly, it is of no use to know what words were said but not in what order, and the same goes for sentences. The ability to represent intermediate states and gestures abstractly, with variables, would be very useful here, as would memory buffers to hold onto them before integration. Perhaps some day an integrated theory of the special contributions of Broca's Area will exist. Meanwhile, I intend to push beyond this experiment to explore the computation of abstract grammar and grammar-like systems.

Future experiments will include investigation of the human mind during the act of coding software or reading others' code; and the processing of structural versus stylistic punctuation errors in sentences.

Convergent evidence from rapid event-related fMRI and intra-cranial *in vivo* electrophysiology demonstrated a correspondence between the fMRI BOLD signal and electrical discharges within populations of neurons. This type of cross-validation of results will help lend credibility to further fMRI studies, and also adds strength to the particular conclusions about Broca's Area. The electrophysiological data gathered not only confirmed results directly, but in some cases confirmed results tangentially and in other cases added completely new information. **Figure 42c** shows an example of an orthogonal confirmation of the fMRI results, namely that the N400 was much greater for the **Overt-Inflect** condition than for the **Read** trials, while the late positive component (LPC) was sooner and more pronounced for **Read**. Interpreting the N400 as such was licensed by previous results showing the implanted region is a generator of the scalp N400 and by strong repetition priming modulation of this component for the same electrode in the same patient on two other cognitive studies performed by other lab members. Taking the N400 to index general processing of linguistic stimuli, and the LPC to index "closure," these results were interpreted to ratify the idea that in task-related regions the overt-inflect condition requires more processing and the Read condition is done quickly, decisively, and fairly automatically.

Future patients will allow more and better investigation of the neuronal underpinnings of language, and the neuronal underpinnings of the fMRI signal.

9.6 Chapter Conclusions

Broca's Area is centrally involved in the abstract grammatical processing necessary for conjugating English verbs and pluralizing nouns, in covert production. Morphosyntax, as a model system, promises to allow neuroimaging studies of grammatical processing in a simpler and more constrained system than sentence syntax. Here it has allowed us to defend returning to the position that Broca's Area does have a specialized role in Language grammar processing. From the literature and from my data, Broca's Area seems to be a cognitive organ with many functions, and the position of this chapter is neither that only Broca's Area processes grammar nor that only grammar is processed in Broca's Area. It is sufficient that I have shown that one of the roles of Broca's is the computation of abstract grammar, in order to refute claims that it only has domain-general roles such as working memory.

The anterior insula and the supplementary motor area (SMA) co-activate in these tasks, and conspicuously are activated in every contrast except the one that does not change or add overt phonology. The position of this chapter is that this indicates the anterior insula and SMA process some aspects of the motor or pre-motor aspects of speech, notably without the need for out-loud speech since this study includes none.

Intra-cranial electrical recordings confirmed Broca's involvement in our task, and cross-validated fMRI localization results.

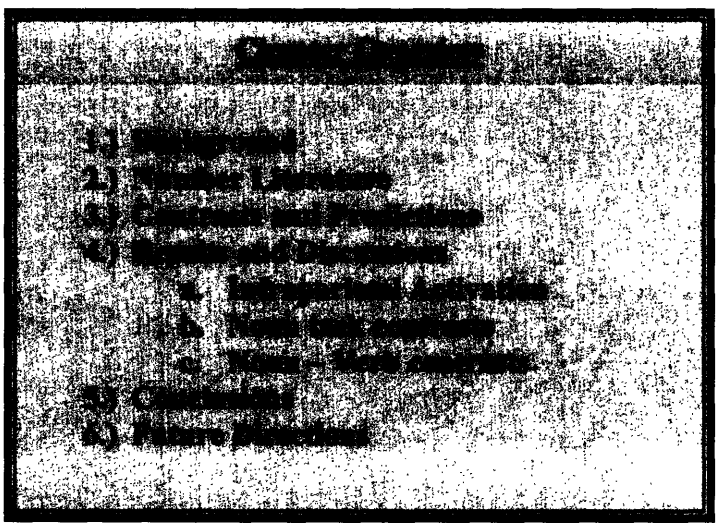
Broca's area has many roles, outside of language, and perhaps one common denominator is processing that relies for meaning on complex temporal sequence information.

10 FINDINGS: NUMERICAL PROCESSING

10.1 Chapter Abstract

Morphology of Nouns in English involves marking of features denoting number only. As such, noun (more selectively than verb) morphological processing might activate brain regions responsible for processing number. English verb morphology marks number but it is not manipulated in this study. Literature on numerical processing is discussed, largely implicating the intraparietal sulcus (IPS). Appropriate noun and verb contrasts maps from the current data are shown, demonstrating IPS activation. These results are discussed in the framework of numerical calculation, suggesting that the numerical aspect of noun morphology may drive some of the observed BOLD activity.

Figure 46: Comparison of Noun and Verb IPS activation for respective inflection processing.



10.2 Background

The cognitive processing of numbers and numerical quantity has long been a topic of study. Recent literature has implicated the intraparietal sulcus (IPS) in processing of numerical tasks such as simple arithmetic or comparison of pictured quantity. Interesting cognitive research has focused on mental processing of number quantity not in terms of the numbers themselves but abstract representations of number. The concept of abstract quantity intersects with this dataset in that morphology can mark grammatical number in most languages, and thus should be considered in interpreting some of the effects observed here.

Morphology of nouns and morphology of verbs are quite different in the features that can be assigned to words that are members of these grammatical categories, or are being used as such. In fact, one of the ways nouns versus verbs can be described categorically, across languages, is in terms of the features they are able to support, or the types of information they are able to receive and convey. In English, for instance, nouns can receive only number information, in the form of the singular/plural feature. English verbs can convey number, person, and tense; and sometimes mood or aspect. English noun morphology is considered to be quite impoverished, for instance lacking case structure prevalent in so many of the world's languages. Yet this impoverishment can perhaps be leveraged in this experiment, in that we have a constrained (e.g. one-word) model system that undergoes combinatorial processing but only varies in number. We can contrast this with a system (i.e. verbs) that is similar but varies more features and therefore is not as dominated by processing number.

The *task* (morphological processing) may be categorically similar between nouns and verbs, but the *task set* for nouns should be dominated by the numeracy discrimination. That is to say, we could entertain a conjecture that over the course of development in an English-only speaker, the language system optimizes such that when *noun* morphology must be computed for production, the cognitive set is one in which discrimination of singular from plural concepts dominates. According to this conjecture, this state could be contrasted to one that would be more efficient for *verb* morphology, in English, in which grammatical number is just one feature that must be determined, along with tense and person (and potentially mood and aspect). Task, set, and task and set switching may be slippery concepts, whose operating definitions

sometimes seem to overlap and collide, and furthermore this framing of the difference between noun and verb morphological processing is only conjecture. However, it is clear that English noun morphology differs from verb in being concerned *only* with the grammatical number subset of feature calculations. With the further consideration that in the verb task for this study the number feature was held constant (perhaps marked by zero affix) with only tense varied, our noun-verb contrast could reasonably be hypothesized to show some neural difference based on the neural correlates, loosely, of number versus time processing.

It is of course possible that every English noun has a zero affix for all features that exist in all languages, or indeed that every noun includes zero affixes for many features no longer or not yet used in any extant language, but it seems reasonable to take a more parsimonious model for purposes of building an interpretation of the present data. Furthermore, the noun-verb difference in *overt* morphology would still be constrained to the features marked in English, and these may drive most of the neural contrast.

Within this context, namely a different subset of cognitive processes recruited for noun versus verb morphology, one might expect a pronounced difference in the morphological processing neural correlates between nouns and verbs. They exhibit different low-level morpho*phonological* features in that the morphologically complex form for nouns is marked with an "-s" and verbs are marked with "-ed" (for regularly inflected words). Here we see they require assignment of different morpho*syntactic* features (number versus at least tense, person, and number). If the commonality really only lies in an artificial construct labeled by linguists with the word "morphology" and thus, self-referentially, is cached only in language, there might be little to bind together the neural arrays responsible for the respective processing. Adding to this the real processing differences, in number-focused versus more multifaceted calculations, should drive the neural activation loci apart. Our data, in fact, do show evidence of neural differences for noun versus verb morphological processing. It is these differences that must be inspected with relation to existing numeracy literature. However, we have seen from our previous discussion of morphosyntax and of noun-verb differences that there is a strong similarity in the results of noun-only and verb-only contrasts that isolate the respective morphological processing. It may be that the amount of abstract number processing required for grammatical number assignment is small, and/or that the amount of the overall noun morphological processing attributable to processing of the number feature (as opposed to e.g.

morpheme selection, binding, production) is small. In such a context, the hypothesized model becomes one in which there indeed is a shared common process for morphological processing in general, but with specific processing "out-sourced" to supporting expertise centers. Like the EU assigning orange production to Spain even though other countries are only slightly less good at producing oranges, the system may have evolved to borrow the specialized number-processing skills of the IPS for number-related calculations in language.

10.3 Number Literature

Neural processing of number has been investigated for decades, but one of the strongest advocates of a category-specific modular view of numerical processing is Stanislas Dehaene. In (Dehaene et al., 1996) he and colleagues implicate the intraparietal sulcus in a task manipulating arithmetic but not loading working memory (a confound with previous studies). Their comparison of digit pairs draws on overlearned stimuli and processing without long-distance working memory demands, much like the present morphosyntax study draws on simple ecologically normal sentence-like frames and simple words without the long-distance dependencies of varying sentences from normal discourse. In a 1999 study, his colleagues replicated the intraparietal sulcal activations (Chochon, Cohen, van de Moortele, & Dehaene, 1999), and this time controlled comparing and multiplying digits with simple naming of the digits. This is even more highly similar to the current study, involving repeating (naming) of nouns, as well as overt and null-marked inflection of them. They found bilateral intraparietal sulcal activations again. Furthermore, the right was more active for simple comparison of digits, while the left was more active for multiplication of digits.

(Naccache & Dehaene, 2001) showed the neural equivalent of repetition priming (repetition "depression" of fMRI signal) in the intraparietal sulcus, even when the prime and target differed in representation ("one" versus "1"). This suggests that numerical representation is abstract in nature in this region. Dehaene and colleagues have also consistently but less focally found activity in prefrontal cortices for numerical tasks. These activations have been somewhat modulated by their manipulations of working memory demands.

Earl Miller and colleagues (Nieder & Miller, 2003) focused more specifically on the prefrontal cortex (PFC) involvement in number tasks. Their paradigms differed drastically in

that first of all they used monkeys and secondly they did single-unit recordings. Some of the complexities in comparing these data are similar to those involved in comparing the fMRI and Intracranial experiments in this thesis, plus the cross-species comparison. However, the salient findings are that prefrontal single units mediate numerical processing, and that the representation was shown to be an abstract one as well.

In summary, recent literature points to intraparietal sulcus (IPS) and probably PFC involvement in abstract manipulations of numerical quantity.

10.4 Contrasts and Predictions

The contrasts in the current study that manipulate quantity and require differential responses accordingly are those that vary noun morphological inflection. Producing plural versus singular should involve more numerical processing, and producing plural or any number-unambiguous form versus repeating a word without determined number information should categorically recruit number processing centers.

Therefore, Intraparietal Sulcus activity should result from the **NounOvertVnounRead** contrast, the subtraction of ["Those are the ___." / "a dog"] minus ["repeat word:___" / "a dog"]. Also we might predict IPS activity for **NounOvertVnounZero** which is a tighter contrast of the noun plurals minus their singulars: ["Those are the___." / "a dog"] minus ["That is the ___." / "a dog"]. Both conditions in this contrast require determination and assignment of grammatical number but only one requires selecting, binding, and production of an overt number morpheme.

The story is more complex when we consider comparing nouns to verbs, within this framework. In this case we are considering contrasts that compare noun to verb morphological processing such as **VerbOvertVnounOvert** (past tense production compared to plural) or the meta-comparison between **NounOvertVnounRead** and **VerbOvertVverbRead**, the morphologically complex minus putatively uninflected forms for each class.

Our neural predictions are based on number computation being necessary for both nouns and verb, and verbs also requiring assignment of other features. In both cases, there should be shared computation of other elements of morphological production such as generalized articulatory planning and production. (Our neural predictions are also predicated, of course, on an optimism that separable elements of mental computation will somehow separate

in their brain correlates, and do so in a way that fMRI can pick them up). We therefore predict that a subset of the active regions for verb morphology would be active for noun morphology. The most interesting part of this subset of active regions should be driven by processing of grammatical number. Since we assume the streamlining of resources in noun morphology toward number calculation to result in a relative increase in corresponding activity, we predict that contrasts between noun and verb inflection conditions should reveal the region(s) involved in number processing. So far our prediction is that areas in common but more active for nouns should be implicated in number processing, with no predictions about areas active only for nouns. Areas active only for verbs may be involved in computing verb-only features such as tense. Some differences, with no prediction about direction of effect, would also be predicted in areas subserving articulatory and pre-articulatory processing to account for noun-verb morphophonological differences, though these may be too subtle for fMRI resolution.

As for the areas we expect to be in activated common, we must inspect our assumptions further. On the model that there is a core unitary process or at least neural processing complex for morphology, generally, with some processing outsourced to expertise centers such as numeracy in IPS, our contrasts should yield mostly overlapping regions with relatively small differences due to feature computation. This core morphological processing complex might for instance compute grammatical class independent features, select among alternative morphemes, take care of morpheme binding, make phonotactic adjustments based on stem and affix phonology, orchestrate articulatory planning, etc. We have already seen from discussion of general morphological computation across nouns and verbs that the neural processing is not co-segregated with noun-verb access/storage. However, if we do not assume a core unitary process for grammatical inflection we would predict a fairly large non-overlap here, which we could state from the point of view that the noun or verb-specific featural computation differences should be dominant. Thus the prediction would be fewer overlapping fMRI voxels and more emphasis on differences in featural expertise areas like the IPS. In either case, the areas more active for nouns than verbs should be considered for computation of grammatical number, whereas the areas active only for verbs and not nouns should be considered as candidates for the computation of verbs-specific features such as tense and person.

10.5 Results and Discussion

The contrasts discussed above showed some of the hypothesized activity in the Intraparietal Sulcus (IPS). The fMRI Contrast Statistical Maps in Chapter 6 only demonstrate this weakly as they were thresholded at $p<0.01$ and much of the activation for this contrast (of only 17% compared to 17% of the total data) is not visible at this threshold. The same 18-subject random-effects activation maps, thresholded at $p<0.05$ and represented on an averaged brain surface are presented here.

The contrast **NounOvertVnounRead** compares brain activity for the noun task that requires most numerical computation (Inflect) compared to the Repeat task which may not require any numerical computation.

Figure 47: NounOvertVnounRead at $p<0.05$ on average brain surface

As seen above, the intraparietal sulcus is clearly activated. Furthermore, along with a tiny activation cluster in the middle portion of the superior temporal sulcus, it is the only region active outside of the Broca's Complex activations discussed in the previous chapter.

Because this morphological manipulation of nouns requires selection of the correct numerical quantity, access and affixing of the correct number feature (e.g. plural), and production of a form conveying meaning including number, it is reasonable to conclude that number processing may be partly driving the IPS activations seen in the contrast **NounOvertVnounRead**. This would fit with the story of Dehaene and colleagues, in that IPS is

activated. However it can not be determined from these results if numeric processing is responsible for the activation.

One potential worry is that comparing to the Repeat condition involves a large cognitive difference and may involve a different state or strategy for producing the required output (overtly inflected versus repeated verbatim). A more minimal contrast and more specific manipulation of number results from the contrast of Overtly Inflected nouns versus Zero-Inflected nouns. That is to say, comparing the overtly-inflected plural to the form which is unambiguously singular given the grammatical context even though the singular inflection is not overtly marked. The repeat condition can be thought of as a *reading* task, not an inflection task, on some models, so it is unclear what is contrasted here.

Thus the contrast **NounOvertVNounZero** is a better comparison for number. The context frames are highly similar ("That is the___." versus "Those are the__.") and both tasks may require: determining of the correct number, selection and access of the number feature (singular or plural), selection and affixation of the correct morpheme, and production and monitoring of the correct form. Note that these may not be the processes actually implemented but they provide a framework for demonstrating the similarity of the tasks. The main difference between the two tasks in this contrast is that the Overt Inflect actually requires the plural form and this means accessing the abstract representation for "plural" or "many", as well as the corresponding morpheme.

The contrast actually shows a very strong IPS activation, as seen in the **NounOvertVnounZero** CSM rendered at $p<0.05$ on the canonical average brain inflated surface below:

Figure 48: NounOvertVnounZero - demonstrating IPS activity

On one hand, this contrast is between two tasks that clearly involve judgment of number and therefore should show less of a difference in the number-processing area. Yet on the other hand, on the model that greater demands may result from the larger number, it makes sense to see this strong activation. This is somewhat homologous to the strong activations in all our Broca-related areas, in the previous chapter, for the same contrasts. In fact, to continue this homology, there is a hint of greater superior IPS activation for the **NounOvertVnounRead** as opposed to **NounOvertVnounZero**. However, interpreting this in terms of subcomponents of IPS function is not possible from the power of the current data.

To further disentangle the IPS activity, we must compare noun to verb morphological inflection. The verb task varies tense, a type of time information, while the noun task varies number information. Therefore, we would expect IPS area to be less active in the verb task, its role here includes processing number. Accordingly, below is the comparison of homologous contrasts in nouns and verbs: **NounOvertVnounZero** is on the left, showing strong IPS activity. The identical data representation parameters yielded the map on the right, for **VerbOvertVverbZero** – showing no IPS activity at all.

Figure 49: Double comparison - Inflect > Zero for Nouns (A); Verbs (B).

The striking selectivity to the noun task is further evidence that observed IPS activity may be related to number processing. The noun-specific nature of the observed IPS activity also comes through in the direct comparison between verb and noun inflection. In the contrast below, blue marks the regions significantly more active in the Noun Overt-Inflect versus Verb Overt-inflect conditions. Here again the Intraparietal Sulcus shows much of the activity.

Figure 50: VerbOvertVnounOvert

So far, the activation patterns observed here correspond well to predictions based on work by Dehaene and colleagues. Another feature highly relevant in this pattern is that the IPS activation is highly lateralized. As seen below, the activation is almost entire in the left hemisphere. Note that the strong left IPS activation for the comparison of **NounOvert** over the fixation intervals between trials, can also be seen at the $p<0.01$ threshold of the CSMs in Chapter 6, and the sulcal nature of the activation is even more pronounced there rendered on an individual subject's brain.

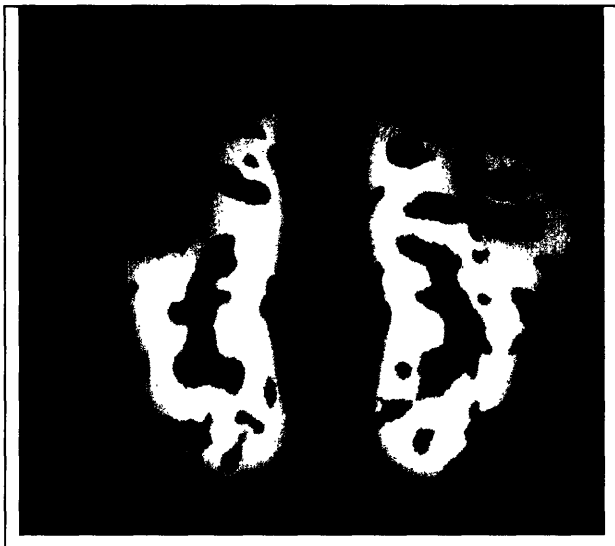


Figure 51: Posterior view of NounOvert VnounZero - showing left-lateralize IPS.

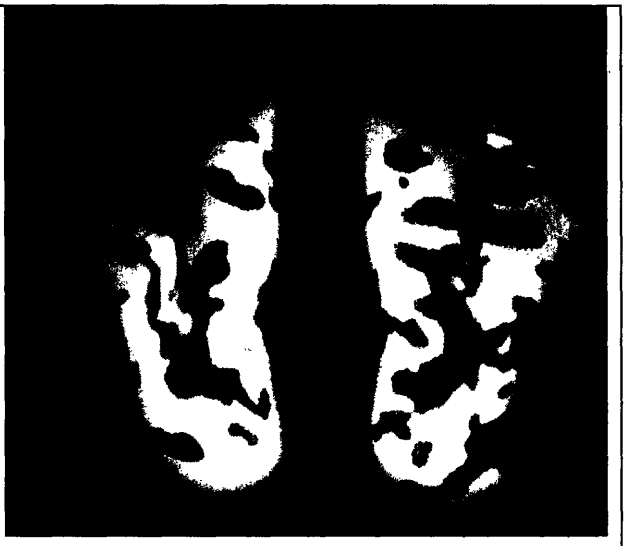


Figure 52: Posterior view of NounOvertVfixation - also left-lateralized IPS activity

Dehaene and colleagues noted that their IPS activity was left-lateralized for multiplication, but right-lateralized for simple comparison and bilateral for subtraction. Again, we cannot know if the IPS activity here is related to number at all, or perhaps just visual attention to verbal task, somehow more salient for Nouns. However, assuming there is a relation, the question becomes whether the left-lateralization is related in only a simplistic way to the general left-lateralization of the language-related activity in our task, or if the abstract nature of the number judgments calls on the left IPS. Just as (Dehaene et al., 1996) concluded that different arithmetic operations could draw on different but related neural resources, perhaps a relevant dimension for abstract representation of number is whether it is verbally encoded.

No claim is being made here, nor any suggestion, that number judgment is the only thing that neural assemblies in the Intraparietal Sulcus do! This would be a preposterous claim, and is the territory of only the most staunch and naïve localizationalist viewpoint. It is entirely unnecessary for a matrix of (hundreds of millions of) neurons have **only** one function simply in order to have that function at all. It is always possible for the system to develop 100% specialization, either in evolutionary or developmental timeframes, but is not necessary. It is important, in the context of a neuroimaging thesis, to make this point. Otherwise one is open to criticisms that working toward brain-task localization is neo-Phrenology. The important difference is that the eventual goal is not a better address in the meat of the brain for a little piece of the mind, but rather the goal is to use the crude evidence of a separation or specialization in brain-space to guess at such distinctions in function-space. The true goal is to unpack cognitive architectures and show what types of information are processed how. Localization only serves as a hint. The exception to this is for medical and not cognitive research, where, simply speaking, knowing what is normally where helps you know where to go when it is broken. In this framework, localization within actual brain space can be both diagnostically and prognostically relevant. (Polling a stroke patient's specific language, or numerical, abilities for example in the ambulance on the way to the hospital informs doctors where the embolus might be lodged. Confluent knowledge of cerebral specialization for important tasks and neurochemical receptor statistics for the region could allow performance-enhancing drugs.)

10.6 Future Directions

In future variants of this study, inserting a single block of arithmetic tasks will act as an independent localizer of numerical processing. Thus, within the same subject population, I will be able to compare IPS activation and state whether the noun morphology IPS region is identical to that subserving the more classical manipulations of number. Furthermore, within noun tasks, one in which the plural is obligatorily produced for all target stimuli could be compared to one in which the subject must produce the correct form as prompted by cues such as "one", "nine", "that", "many", "a", "all" etc. Finally, the verb task could be modified to

include both tense and number ("they walk", "he walks") to see if IPS activity comes in for the **VerbOvertVverbZero** contrast. Finally, conducting any of these experiments in MEG as well as fMRI would yield timecourse information on a global scale within the whole brain, and conducting the experiments in intra-operative epilepsy patients with implanted electrodes would give unambiguous localization and timecourse information. Timecourse information becomes particularly important if indeed the IPS activity in the noun morphological processing CSM shown here relates to number. The reason is, it might allow one to distinguish a model in which Broca's area initiates and emcee's the entire process of morphological inflection, calling on IPS for numerical judgment in midstream; versus a model in which Broca's acts to **collect** all the information necessary (such as number from IPS, and maybe tense from somewhere else) and mediates the final steps toward concatenation of morphemes and production of the morphologically correct form.

10.7 Chapter Conclusions

The Intraparietal Sulcus (IPS) may compute the number feature involved in English noun morphology, and this IPS involvement is strongly left-lateralized. The IPS, however, is likely involved in number-independent aspects of this task, and further research is required to ascertain whether the correlation between activity and number-related task manipulations is causal.

11 APPENDIX A: SCIENTIFIC COMMUNICATIONS

11.1 Section Abstract

Subsets of this work have been summarized in abstracts submitted for presentation at recent and upcoming scientific conferences. These abstracts as well as an example poster are presented in this section as a digest of only some of the ideas and results addressed in the thesis.

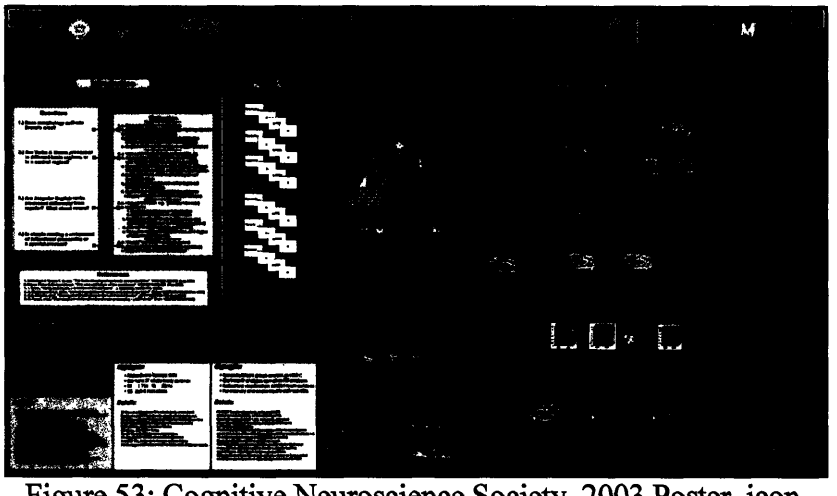
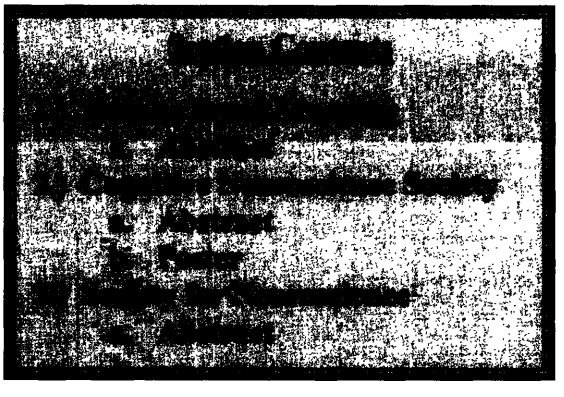


Figure 53: Cognitive Neuroscience Society 2003 Poster, icon.



11.2 Section Description

Much of the work contained in this Thesis document has been discussed, at least schematically, in abstracts submitted to professional scientific conferences. These form convenient summaries and distilled versions of many aspects of the present research. Reproductions of these abstracts and one poster are presented here. These provide a record and chronicle of the scientific communication released into the public domain during the course of the research program represented by this thesis document.

Note that many more results and conclusions are discussed in the body of the thesis than could possibly have been covered given the brevity of form and generality of audience for these abstracts.

For each of the three conferences there is an information section followed by a reprint of the abstract. In the case of the Cognitive Neuroscience Society 2003 conference, which has already passed, a reprint of the entire poster is also included. The other 2 conferences are upcoming. The contributions of the various authors are also noted.

11.3 Organization for Human Brain Mapping, Annual Meeting 2003

11.3.1 Meeting and Abstract Information

Meeting Information	
Conference:	Organization for Human Brain Mapping Annual Meeting
Known As:	Human Brain Mapping (HBM)
Date:	June 18-22, 2003 (Satellite Sessions June 17th + 18th)
Location:	New York City, USA (Marriott Marquis Hotel, Times Square)
Attendance:	1,600 posters. [registrant numbers unknown]
Attendees:	All brain imagers: both methods-centric and CogNeuro types
Topics Covered:	New methods in brain imaging, analysis techniques, all manner of research employing brain imaging. A more technical crowd than CNS, but very broad-reaching in recent years. All major topics in Cognition covered.
Series Number:	9th Annual Conference
Submission Deadline:	January 17, 2003, 5PM (CST)
Abstract Restrictions:	500 Words. Figures allowed. Web submission allows minimal formatting.

Session Information	
Session Type:	Poster
Scheduled Session:	June 22nd, 10:30am-11:30am. Poster 1354.
Session Theme:	Development & Aging, Language and Sensation & Perception
Session Title:	Language
Session Duration:	Posters are up for two days. Presenters by posters during 2 sessions.

Author Contributions	
Ned T. Sahin	Design of Expt, all scanning, all analysis, all data visualization, all abstract writing figure creation and layout, administration of submission.
Eric Halgren	Advisor for neuroimaging. Data interpretation. Guidance in analysis.
Anders Dale	Expt design, for scanner. Acquisition & analysis suggestions.
Evelina Busa	Reconstruction of subject cortical surfaces: a step in data analysis.
Steven Pinker	PhD Advisor. Expt design and refinement. Data interpretation. Shaping and guiding ideas and clear language for communication.

11.3.2 CONFERENCE ABSTRACT

(see following page)

Note: This work won a competitive $500 travel award from the Organization for Human Brain mapping, based on the content of the abstract.

Inflectional Morphology of Nouns and Verbs Shows fMRI Activation of Broca's and Related Areas

Ned T. Sahin[*†‡], Eric Halgren[†‡], Anders Dale[†‡], Evelina Busa[†], Steven Pinker[*]

[*] Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology
[†] Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging, Massachusetts General Hospital
[‡] Departments of Neurology and Radiology, Massachusetts General Hospital

Abstract submitted for presentation at the 2003 Human Brain Mapping annual conference, New York City.

Introduction: Does morphological inflection of words activate the traditional sentence-syntax brain system (Broca's and related areas)? What are the functional subcomponents of this system? Do noun-pluralization and verb-conjugation involve the same core brain processes, or are they processed differently?

Rapid event-related fMRI measured brain activity in 16 volunteers producing inflected or uninflected forms of nouns and verbs. Brain signal increase between production of uninflected and inflected forms was restricted to BA44/45 (core Broca's), BA47, anterior insula, and SMA. This syntax-system activation showed high similarity for nouns and verbs, and persisted with small variation in contrasts varying morphosyntactic information while keeping output phonology identical. Our results demonstrate inflectional morphology as a viable system for investigating grammar generally, suggest a centralization of inflectional processing for nouns and verbs, and may help unravel component functions of activated regions.

Methods: Sixteen native-primary English-speaking right-handed healthy adults (12M/4F) gave written informed consent for this study. Structural (3D MP-RAGE,1x1x1.33mm) and functional (gradient-echo EPI,3.1x3.1mm in-plane) MRI data were collected on Siemens Magnetom Trio 3T whole-body system. 25 axial 5mm slices were collected with 0.5mm skip at TE 30ms per 1.75s TR (full-brain). Stimulus presentation (rear-projection) was synchronized precisely to scanner TTL pulse.

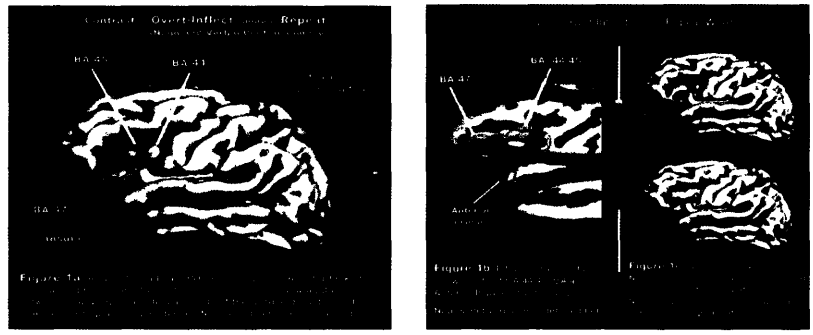
Materials: Subjects were cued visually by sentence frames to produce silently the correct forms of target words. A 2x2x3 design varied grammatical-class, regularity, and inflectional-task. Frames for each task were controlled for structure, syllables, length; were fixed throughout experiment while target words varied and appeared randomly (**Table 1**). 120 noun and 120 verb targets (60 regular/irregular matched pairs) were controlled for item and stem frequency, syllables, length. Optimized jittering of the 240 3.5s frame-target trials yielded 3-run set, which was repeated (reshuffled, counter-balanced) thrice.

	Verb Trials	Noun Trials	Time
"Overt-Inflect" condition	Yesterday they___, ↓ to run ↓	These are the___, ↓ a child ↓	650ms 1100ms 250ms 1500ms
"Zero-Inflect" condition	Every day they___, ↓ to walk ↓	That is the___, ↓ a man ↓	650ms 1100ms 250ms 1500ms
"Repeat" condition	repeat word: ___ ↓ to refuse ↓	repeat word: ___ ↓ an elf ↓	650ms 1100ms 250ms 1500ms

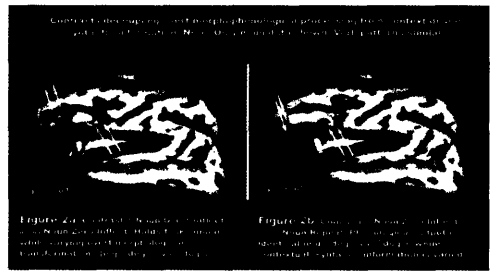
Table 1: Frames, targets and timings for the three task conditions.

Results: Subtracting activity for the *Repeat* condition from *Overt-Inflection* condition (e.g. "dogs" minus "dog", "walk*ed*" minus "walk") activated Brodmann's areas 44/45, 47, anterior insula, and SMA (**Figure 1a**). Separability of lateral activation clusters is demonstrated in **Figure 1b** . Splitting the data (**Figure 1c**) yields similar patterns for noun-only / verb-only versions of the same contrast.

Subtracting *Zero-Inflect* condition from the *Overt-Inflection* condition further controls task conditions and isolates morphosyntactic transformation. **Figure 2a** shows super-threshold activation for this contrast. Finally, **Figure 2b** contrasts *Zero-Inflect* with *Repeat*: in which the output is identical ("dog" versus "dog", "walk" vs "walk"), but the *Zero-Inflect* is in grammatical context. BOLD activity indicates similar processing to overt inflection.



All data shown: Random-effects group average (16 subjects) fMRI t-test significance statistical maps ($p < 0.01$, except noted), robustly normalized to common spherical space and rendered mathematically on inflated or pial surface of 40-brain canonical average brain. FS-FAST software, MGH.



Conclusions: Inflectional morphology is shown to activate a full complement of brain areas traditionally associated with syntactic processing. Noun-pluralization and verb-conjugation show highly similar activations despite apparent differences in cognitive tasks, suggesting large overlap of underlying neural processing. Manipulations holding task and response largely constant but varying grammatical context also activate Broca's and related areas, decoupling functional role from motor/articulative processing. We believe inflectional morphology, as a system simpler than sentence syntax, viably supports some investigation of the neural basis of grammar. Further analyses and experiments may unravel the role in morphosyntactic production of Brodmann's 44/45, 47, anterior insula, and SMA.

Figure 54: Abstract submitted for the Human Brain Mapping Annual Meeting, 2003.

11.4 Cognitive Neuroscience Society, Annual Meeting 2003

11.4.1 Meeting and Abstract Information

Meeting Information

Conference:	Cognitive Neuroscience Society Annual Meeting
Known As:	"CNS" or "Cognitive Neuroscience"
Date:	March 30th – April 1st, 2003
Location:	New York City, USA (Marriott Marquis Hotel, Times Square)
Attendance:	1,700 registrants (2003)
Attendees:	Experimental psychologists, cognitive neuroscientists, some technical folk
Topics Covered:	All topics of cognition, emotion, and behavior. Strong empirical, especially imaging flavor.
Series Number:	10th Annual Conference
Submission Deadline:	November 1st, 2002.
Abstract Restrictions:	250 words (body text).

Session Information

Session Type:	Poster
Scheduled Session:	April 1, 2003, 10:30am-12:30pm. Poster # 189.
Session Theme:	All themes mixed throughout conference.
Session Title:	None. Clustered with other Language posters, though.
Session Duration:	Posters could be left up all day.

Author Contributions

Ned T. Sahin	Evolution of expt design; All: fMRI scanning, analysis, data visualization; drafting of abstract, administration of submission.
Steven Pinker	PhD Advisor. Extensive editing of abstract.
Andre van der Kouwe	Technical assistance throughout project, particularly with choose scanner pulse sequences and parameters.
Doug Greve	Coding of software used at MGH for fMRI analysis. Support in setting up my analysis stream, and decisions on parameters.
Anders Dale	Expt design, for scanner. Acquisition & analysis suggestions.
Eric Halgren	Advisor for neuroimaging. Data interpretation. Guidance in analysis.

This was the first communication of data from this work. At the time of the abstract our conclusions were very tentative. However, by the time of the conference our interpretations had matured greatly. The poster reprint which follows the abstract shows many of the later directions our analysis has taken.

11.4.2 CONFERENCE ABSTRACT

Dissection of the Components of Inflectional Morphology Using Event-Related FMRI

Ned T. Sahin[1,2], Steven Pinker[1], Andre van der Kouwe[2], Doug Greve[2], Anders Dale[2], Eric Halgren[2]

1. Department of Brain and Cognitive Sciences, MIT
2. MGH/HMS/MIT Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging

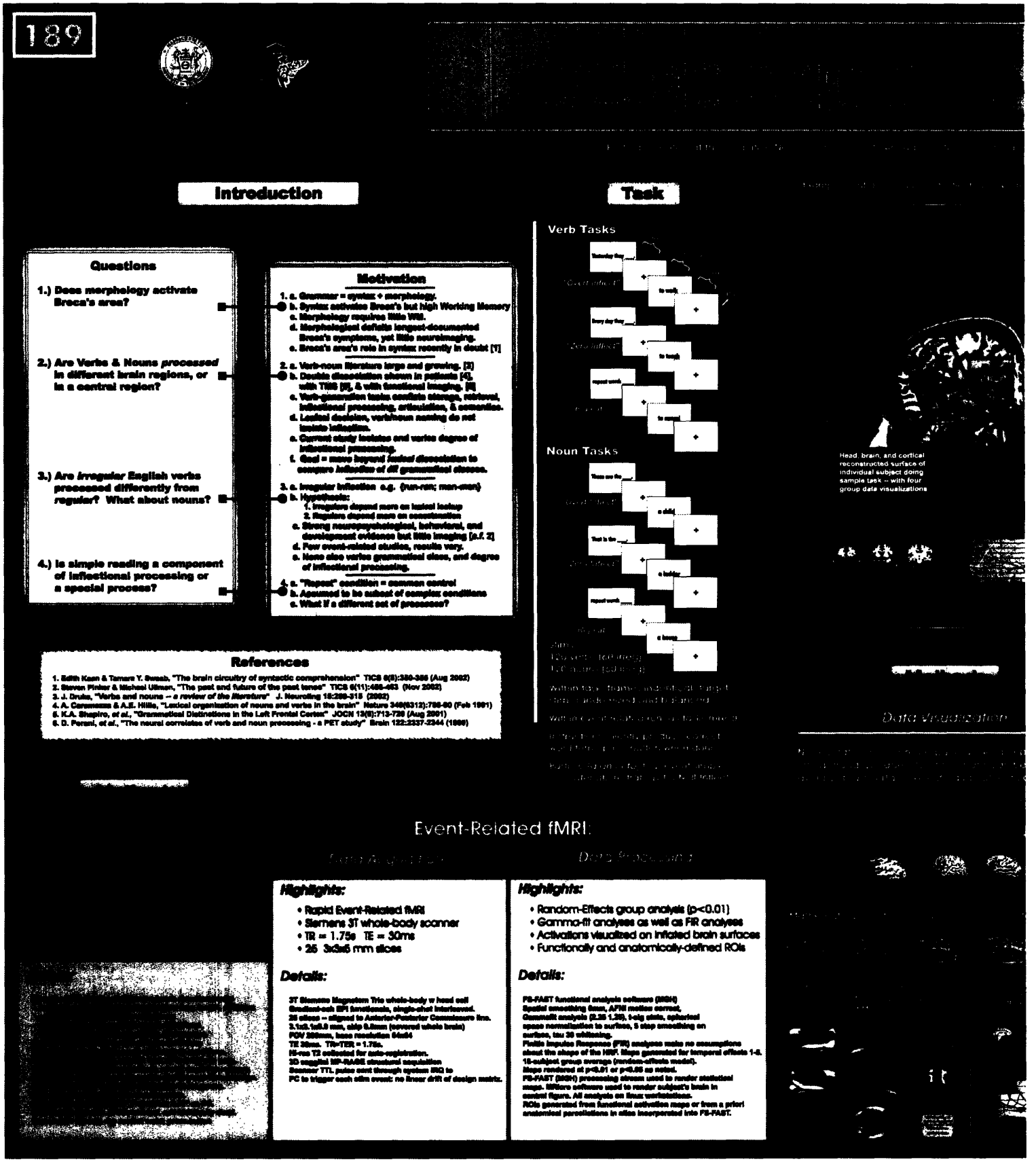
The application of neuroimaging to inflection promises to elucidate grammatical processing using a simpler system than syntax, and to identify possible differences between regular and irregular morphology.

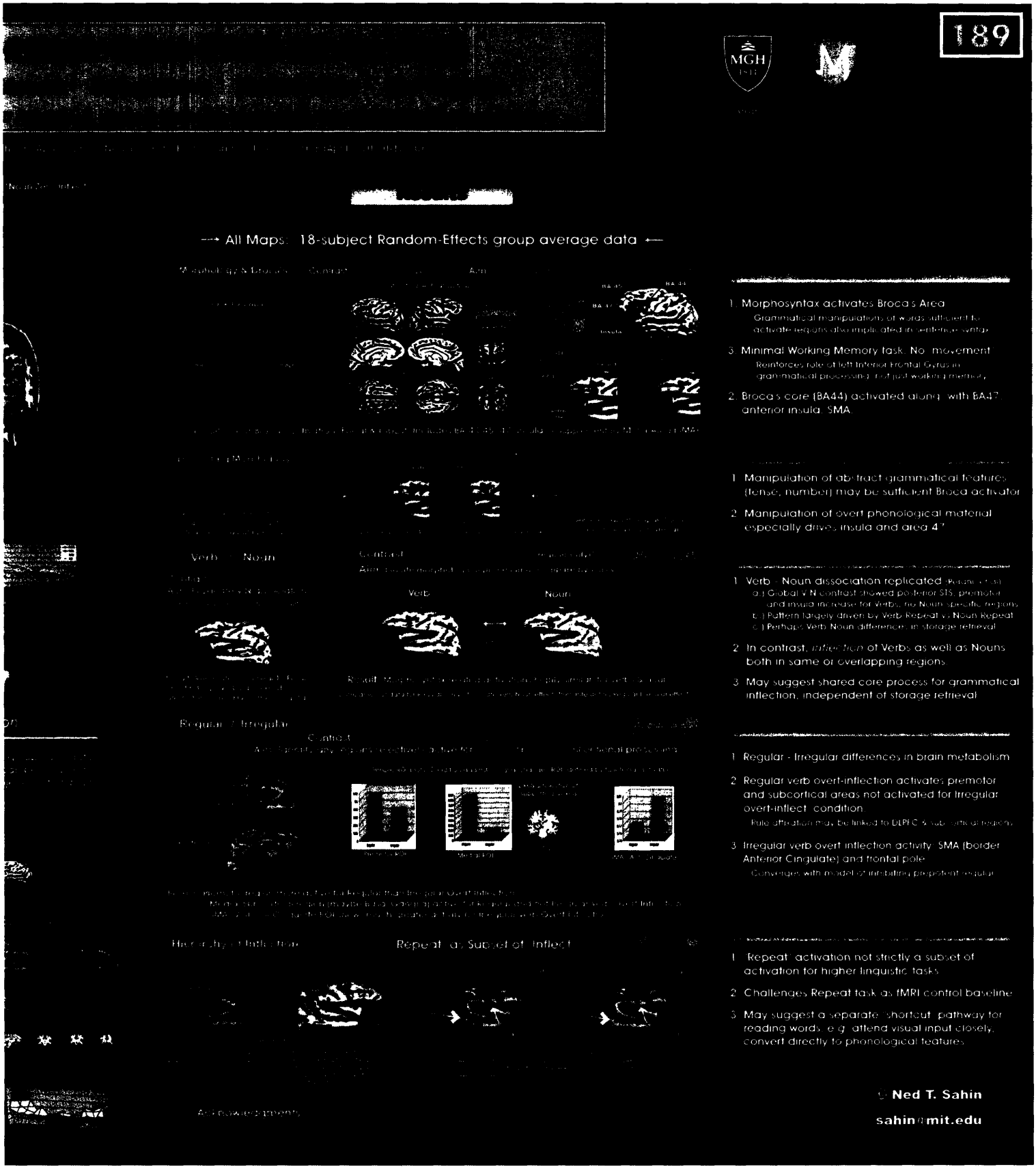
We systematically analyze the neural substrates of components of inflection, including the processing of morphosyntactic features, morphophonological changes, inflections specific to syntactic categories, and the discrimination of regular from irregular forms. Adults were scanned in a Siemens 3T fMRI in a rapid event-related design. Subjects were cued by sentence frames to generate correct forms of target words silently, as in [Everyday they ____.] ... [to walk]; [Yesterday he ____.] ... [to eat]; [That is the ____.] ... [a dog]; or [Those are the ____.] ... [a mouse]. In other trials they were cued with [repeat word ____]. A factorial design varied Verb/Noun, Regular/Irregular, and Overt Inflection/Zero Inflection/Repetition, and controlled items for frequency and length.

Subtractions of Repetition from Inflection suggest that left BA 44 (Broca's), 47 (ventrolateral prefrontal), and supplementary motor area (SMA) are engaged by inflectional processing, and that repetition may be handled by a distinct shortcut strategy involving left occipital, parietal, and superior temporal areas. Subtracting Zero from Overt inflection shows related 44, 47, and SMA activation, implicating these areas in overt morphophonological changes. These patterns are similar in nouns and verbs, though verbs engage frontal areas more in repetition, and nouns engage parietal and temporal areas more in zero-inflection. As in earlier studies, regular-irregular differences were significant though complex.

11.4.3 POSTER

(See following pages)


189
Introduction
Task
Questions
1.) Does morphology activate Broca's area?
2.) Are Verbs & Nouns processed in different brain regions, or in a central region?
3.) Are irregular English verbs processed differently from regular? What about nouns?
4.) Is simple reading a component of inflectional processing or a special process?
Motivation
1. a. Grammar = syntax + morphology.
b. Syntax activates Broca's but high Working Memory
c. Morphology requires little WM.
d. Morphological deficits longest-documented Broca's symptoms, yet little neuroimaging.
e. Broca's area's role in syntax recently in doubt [1]
2. a. Verb-noun literature large and growing. [2]
b. Double dissociation shown in patients [4], with TMS [5], & with functional imaging. [6]
c. Verb-generation tasks confuse storage, retrieval, inflectional processing, articulation, & semantics.
d. Lexical decision, verb/noun naming do not isolate inflection.
e. Current study isolates and varies degree of inflectional processing.
f. Goal = move beyond lexical dissociation to compare inflection of all grammatical classes.
3. a. Irregular inflection e.g. (run-ran; man-men)
b. Hypothesis:
1. Irregulars depend more on lexical lookup
2. Regulars depend more on concatenation
c. Strong neuropsychological, behavioral, and developmental evidence but little imaging [a.f. 2]
d. Few event-related studies, results very.
e. None also varies grammatical class, and degree of inflectional processing.
4. a. "Repeat" condition = common control
b. Assumed to be subset of complex conditions
c. What if a different set of processes?
Verb Tasks
Noun Tasks
Head, brain, and cortical reconstructed surface of individual subject doing sample task -- with four group data visualizations
Data Visualization
References
1. Edith Kaan & Tamara Y. Swaab, "The brain circuitry of syntactic comprehension" TICS 6(8):350-356 (Aug 2002)
2. Steven Pinker & Michael Ullman, "The past and future of the past tense" TICS 6(11):456-463 (Nov 2002)
3. J. Druks, "Verbs and nouns -- a review of the literature" J. Neurolng 18:289-315 (2002)
4. A. Caramazza & A.E. Hillis, "Lexical organization of nouns and verbs in the brain" Nature 349(6312):788-90 (Feb 1991)
5. K.A. Shapiro, et al., "Grammatical Distinctions in the Left Frontal Cortex" JOCN 13(6):713-720 (Aug 2001)
6. D. Perani, et al., "The neural correlates of verb and noun processing - a PET study" Brain 122:2337-2344 (1999)
Event-Related fMRI
Highlights:
• Rapid Event-Related fMRI
• Siemens 3T whole-body scanner
• TR = 1.75s TE = 30ms
• 25 3x3x5 mm slices
Details:
3T Siemens Magnetom Trio whole-body w head coil
Gradient-echo EPI functionals, single-shot interleaved.
25 slices -- aligned to Anterior-Posterior Commissure line.
3.1x3.1x5.0 mm, skip 0.5mm (covered whole brain)
FOV 200mm, base resolution 64x64
TE 30ms. TR=TER = 1.75s.
Hi-res T2 collected for auto-registration.
3D sagittal MP-RAGE structural acquisition
Scanner TTL pulse sent through system IRQ to PC to trigger each stim event: no linear drift of design matrix.
Highlights:
• Random-Effects group analysis (p<0.01)
• Gamma-fit analyses as well as FIR analyses
• Activations visualized on inflated brain surfaces
• Functionally and anatomically-defined ROIs
Details:
FS-FAST functional analysis software (MGH)
Spatial smoothing 6mm, AFNI motion correct,
Gammafit analysis (2.25 1.25), t-sig data, spherical
space normalization to surface, 5 step smoothing on
surface, iau 20 whitening.
Finite Impulse Response (FIR) analyses make no assumptions
about the shape of the HRF. Maps generated for temporal offsets 1-8.
15-subject group average (random-effects model).
Maps rendered at p<0.01 or p<0.05 as noted.
FS-FAST (MGH) processing stream used to render statistical
maps. MRIcro software used to render subject's brain in
central figure. All analysis on linux workstations.
ROIs generated from functional activation maps or from a priori
anatomical parcellations in atlas incorporated into FS-FAST.


189
MGH
→ All Maps: 18-subject Random-Effects group average data ←
1. Morphosyntax activates Broca's Area
Grammatical manipulations of words sufficient to activate regions also implicated in sentence syntax
3. Minimal Working Memory task. No movement
Reinforces role of left Inferior Frontal Gyrus in grammatical processing (not just working memory)
2. Broca's core (BA44) activated along with BA47, anterior insula, SMA
1. Manipulation of abstract grammatical features (tense, number) may be sufficient Broca activator
2. Manipulation of overt phonological material especially drives insula and area 47
Verb - Noun
Contrast
Verb
Noun
1. Verb - Noun dissociation replicated
a.) Global V-N contrast showed posterior STS, premotor and insula increase for Verbs, no Noun-specific regions
b.) Pattern largely driven by Verb-Repeat vs. Noun-Repeat
c.) Perhaps Verb-Noun differences in storage retrieval
2. In contrast, inflection of Verbs as well as Nouns both in same or overlapping regions
3. May suggest shared core process for grammatical inflection, independent of storage retrieval
Regular - Irregular
Contrast
1. Regular - Irregular differences in brain metabolism
2. Regular verb overt-inflection activates premotor and subcortical areas not activated for Irregular overt-inflect condition
Rote affixation may be linked to DLPFC & subcortical regions
3. Irregular verb overt inflection activity: SMA (border Anterior Cingulate) and frontal pole
Converges with model of instability-prone regular
Hierarchy: Little Now
Repeat as Subset of Inflect
1. Repeat activation not strictly a subset of activation for higher linguistic tasks
2. Challenges Repeat task as fMRI control baseline
3. May suggest a separate "shortcut" pathway for reading words, e.g. attend visual input closely, convert directly to phonological features
Ned T. Sahin
sahin@mit.edu

11.5 Society for Neuroscience, Annual Meeting 2003

11.5.1 MEETING AND ABSTRACT INFO

Meeting Information	
Conference:	Society for Neuroscience Annual Meeting
Known As:	"SfN" or "Neuroscience"
Date:	November 8-12th, 2003
Location:	New Orleans, Louisiana, USA
Attendance:	26,000 in 2002. 29,000 in 2001.
Attendees:	All types of researches of the Neurosciences, all levels.
Topics Covered:	Every field and subfield of the Neurosciences, from molecular to genetic to computational to cognitive.
Series Number:	33rd Annual Conference
Submission Deadline:	May 19th, 2003
Abstract Restrictions:	2200 characters, including title, authors, affiliations, and everything else.

Author Contributions	
Ned T. Sahin	All fMRI expt implementation, interpretation. Re-coding expts for depth recording, patient interaction, interpretation of depth data.
Eric Halgren	Offered the opportunity to do depth recordings. Close advising in background, technology, scientific approach to depth electrophysiology
Istvan Ulbert	Assistance in processing and interpretation of intracranial EEG data.
Chungmao Wang	Telemetry recording at hospital, explanation of procedures.
Don Schomer	Director of EEG lab at the patient's hospital
Julian Wu	Neurosurgeon. Implanted the electrodes.
Steven Pinker	PhD Advisor. Guidance in all aspects of fMRI experiment.

Supplementary Key Words:

1.) Language
2.) Cognition
3.) EEG
4.) Imaging

Primary Theme: Cognition and Behavior
↳ **Primary Sub-Theme:** ↳ Human Cognition and Behavior
↳ **Primary Topic:** ↳ Language

Secondary Theme: Neurological and Psychiatric Conditions
↳ **Secondary Sub-Theme:** ↳ Epilepsy
↳ **Secondary Topic:** ↳ Human and Animal Studies

11.5.2 CONFERENCE ABSTRACT – SOCIETY FOR NEUROSCIENCE 2003

CONVERGENT EVENT-RELATED fMRI & DEPTH ELECTROPHYSIOLOGY IN BROCA'S AREA DURING NOUN AND VERB GRAMMATICAL PROCESSING

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We found evidence that Broca's area processes inflectional morphology of both nouns and verbs, using depth electrodes in an epileptic patient, and fMRI in the patient as well as 18 normal volunteers.

The relation between inflectional morphology (e.g. verb conjugation) and syntax is debated; and Broca's area has lately been implicated in memory demands in processing sentence syntactic structure. Furthermore, nouns vs. verbs have been implicated in dissociable neural systems, but most studies discuss word storage or access, not processing. We investigated the role of Broca's area in morphology, without sentential working memory, and whether processing of nouns and verbs relies on a single common system.

Subjects viewed simple context "frames" cueing them to produce silently the ensuing target word in the *Inflected* (plural/past), *Uninflected* (singular/present) or simply *Repeated* form. Whole-brain random-effects fMRI (n=18) showed $p<0.01$ activations only in BA44,47,SMA, insula: for *Inflected* > *Repeated* words. *Uninflected* > *Repeat* (identical phonology but manipulation of abstract grammatical features) selected BA44 activity; while phonological manipulation in *Inflected* > *Uninflected* increased 47, insula. Noun and verb-only versions of these contrasts were highly similar.

Both fMRI and evoked potentials (EP) were measured for our task in an epilepsy patient implanted with intracranial depth electrodes. EP unambiguously confirmed a neural main effect of inflection in ~BA47, with component peaks at 240, 380, 520ms. An F2 region, also activated in the patient's fMRI, peaked at 250, 360, 500ms. Convergent electrical and hemodynamic measures yielded localization and timecourse information for grammatical processing of words.

Support Contributed By: NIH HD 18381 & NS18741

Note: This work won a competitive $750 travel award from the Boston Area Neuroscience Group (BANG), based on the content of the abstract and a cover letter.
This submission was chosen for a slide presentation rather than a poster at the Annual Meeting of the Society for Neuroscience.

12 APPENDIX B: SUBJECT INFORMATION AND POST-TEST DE-BRIEF FORMS

12.1 Subject Information Form

Subject Information Form
Ned T. Sahin
Pinker Lab
MIT Brain & Cognitive Sciences Dept

Today's Date: ___/___/_____
mo day full year

Subject ID: _STRUCT_01____

Last Name: _____

First Name: _____ Preferred Name: _____

MIT Department: _____ Year:_____

MIT ID Number: _____ SSN: _____

E-Mail: _____

Race: *(circle one)* American Indian/Alaskan Asian Pacific Islander
Black/African American White More than one race

Are you of Hispanic origin, regardless of race? **Yes** or **No**

Gender: **M** or **F** DOB: ___/___/_____ Weight: _____ **(LB)**

First Language: _____ Primary Language: _____

Other Languages: 1. _____ **(School or Family)** 2._____ **(School or Family)**

Handedness: **RIGHT** |or| **LEFT** |or| **AMBIDEXTEROUS**

Phone: _____

Experiment: _STRUCT_01_____ Experimenter: _____Ned T. Sahin_____

Campus Address: _____

Mailing Address: _____

Subject Signature: _____ Date: ___/___/_____

Experimenter Signature: _____ Date: ___/___/_____

Part II:

1.) What is your general level of stress today (relative to usual levels)?

1	2	3	4	5	6
(no stress)	(little stress)	(some stress)	(medium stress)	(high stress)	(frazzled)

2.) How alert do you feel today (relative to baseline alertness)?

1	2	3	4	5	6
(zombie)	(barely alert)	(somewhat alert)	(alert)	(highly alert)	(super alert)

3.) What is your general level of alertness?

1	2	3	4	5	6
(zombie)	(barely alert)	(somewhat alert)	(alert)	(highly alert)	(super alert)

Part IV: [Note time of scan: _____]

1.) How many hours did you sleep last night? _____
2.) What time did you go to sleep? _____ Wake up? _____
3.) During the past month, how many hours of sleep did you average per night? _____
4.) Have you been sleep deprived in the last week? _____
5.) How much coffee have you had today (# cups)? _____
6.) How many hours ago did you have your last cup? _____
7.) Average cups per day past week? _____
8.) Average cups per day last month? _____
9.) How many cigarettes have you smoked today? _____
10.) How many hours ago did you have last cigarette? _____
11.) Average cigarettes per day past month? _____ Years smoking? _____
12.) How much alcohol have you consumed in the past 24 hours?
    a. Beer: _____
    b. Wine: _____
    c. Other (specify): _____
13.) What is your average weekly consumption of alcohol?
    a. Beer: _____
    b. Wine: _____

c. Other (specify): _____

14.) Have you had any illnesses in the past month? _____

15.) Are you ill today (enter "2"), been feeling better for the past day or two ("1"), or have been better for at least 1 week ("0")? _____ (0,1, or 2)

16.) Have you used any drugs or medications in the past 24 hours? _____

a. Drug name: _____ amount/dose _____

b. Drug name: _____ amount/dose _____

c. Drug name: _____ amount/dose _____

d. How many hours ago did you last take the drug? _____

17.) Have you used any recreational drugs not listed above in the last 24 hours?

a. When? _____ (this and all information is confidential)

18.) Female subjects:

a. When was the first day of your last menstrual period? ___/___/____

b. Pregnant? _____ Test administered recently? _____

SahinLab Subject Information Sheet, version 4.5. 20-January-2003.

12.2 Subject De-Brief Form

Since subjects were usually tired after the scanning and because many questions on this form are open-ended, the author asked the questions verbally and recorded subject answers. Therefore this form served more as a structured interview template than a written questionnaire. Furthermore, some questions were of interest to the author mostly as the study was refined based on the first few (pilot) subjects, so not all questions were asked of all participants.

---

fMRI Study of Language
Ned T. Sahin, 2002
MGH + MIT
Post-Exam Debriefing Questionnaire

Project: __NV_Infl_01__

Subject: _____

Date: _____

1. Did you find the experiment too fast?
2. What strategies did you use to complete the task?
3. Did they change over time?
4. Did you get tired of the task?
5. How difficult did you find the task?
6. Did you ever get confused on the tenses?
    a. For instance, every day they ___ (walked).
7. Did you feel like you got enough practice on the task?

   Were you unclear on any of the instructions?
8. Is the sentence framing more natural than cues like "past" ?
9. Did you find yourself reading the sentences all the way through the experiment, or did you start stereotyping them?
10. Was there too much time staring at fixation between trials?
11. Were the words to big on the screen? Too small?
12. Were you scanning your eyes across to read them, or maintaining fixation?
13. How did you synchronize the button press to the voice in your head?
14. Did your mind wander?
15. What was your attention level in the first block of the experiment?
16. What was your attention level in the last block?

17. Did it help to have me check in with you between each block?
18. If we scored your actual performance, where would your accuracy be (%) ?
19. What kinds of 'errors' did you make? [Over-regularizations? Wrong tense?]
20. Did you find the nouns harder or the verbs?
21. Did you realize that you were basically dealing with two sets of words – nouns versus verbs?
22. Did you notice any other categories or patterns in the stimuli (be honest)?
23. Did you fall asleep during the first part of the scan – with no task?
24. Did you fall asleep during the second part – when you had to do the task?

    (NB: much more important for the science to be honest than try to give 'right' answer. You will still be paid! ☺)
25. How was the transition from no-task to task periods?
26. Were you comfortable in the scanner?
27. When were you most comfortable?
28. Least?
29. Do you feel you moved a lot?
30. During the noisy parts of the scan, or the quiet times in between?
31. Was there anything about the structure of the task that you think got in the way of your performing the task? Try to think about this a bit.

Perform task: (to verify comprehension and correct performance of task)

		[subject response]
Every day they ___.	(to walk)	_____
Yesterday they ___.	(to sing)	_____
That is the ___.	(a house)	_____
Those are the ___.	(a woman)	_____
repeat word: ___	(to swim)	_____
repeat word: ___	(an apple)	_____

13 APPENDIX C: FMRI PULSE SEQUENCE PARAMETERS

fMRI scanning is done somewhat differently at each research site. There are many free parameters that must be set whenever designing a new study. Likewise when comparing data across studies it is important to know exactly how the data were collected, in order to know how to compare them. For instance, the Echo Time (TE) in the EPI sequence will strongly affect how much the signal drops away in areas such as the orbitofrontal cortices. These regions are notorious from an MR physics standpoint because the interaction of air in nasal sinuses with tissue boundaries leads to magnetic field properties that can render nearby brain areas invisible to fMRI. These regions are also widely implicated in many cognitive tasks, however, so their absence in plots of fMRI results may be of great importance. For instance, a meta-analysis of studies of Executive Function in the frontal lobes may yield inconsistent results or a model that places processing of one set of tasks in the orbitofrontal cortices and other tasks in other parts of the brain. However, knowing something as simple as the TE of the studies may explain much more reliably the variance in orbitofrontal activations.

In order to assure the greatest relevance and generalizability of this archival document, this appendix specifies in rigorous for each pulse sequence used all the parameters that can be accessed and altered from the scanner operator interface.

The parameters are all condensed into sets of tables, roughly broken down to mirror the "tabs" or "cards" in the graphical user interface (GUI) that are offered for each sequence. Note that each tab lists many inter-dependant parameters. Only those which can be set and which do not appear on any previous tab are shown in the tables below, for any given tab.

13.1 Scanner Sequences -- Summary

All sequences were run on a Siemens Magnetom Trio 3-Tesla whole-body MR system. These sequences were finalized March 23, 2003, specifically for use in this project.
Each scan sequence used in the study is summarized in this section, roughly in order. Then following sections present the details for each sequence.

Structurals:

1. Localizer 18Mar02 (duration = 09 sec)
2. Flat Sag 3D 18Mar02 (8:07)
3. Flat Sag 3D 18Mar02 (8:07)

For registration and reconstruction:

4. T1 EPI A-P 18Mar02 (0:04)
5. T1 EPI R-L 18Mar02 (0:04)
6. T2 Conv Andre 18Mar02 (1:35)
7. Field Map TE2.23 18Mar02 (2:00)
8. Field Map TE4.44 18Mar02 (2:00)

Functionals:

9. Functionals GrdEch 18Mar02 (6:26 each)
   (*9 Functional Runs*)

Timing

Structural	16:23	*Special*	5:43	*Functional*	57:54	Total	**80 minutes**

Reportable parameters for functional scans:

Slices= 25 Thickness = 5mm Skip = 0.5mm
FOV = 200mm Base Resolution = 64x64

(Voxels = 3.1 * 3.1 * 5 mm, skip 0.5 mm)

TR=1750ms Acquisitions = 220 per run 9 Runs

13.2 Structural Scans

High-Resolution T1 Structural Scans ("Flat Sag 3D 18Mar02") ***8 min 07 sec***

Tab 1: *Routine*

Slab Group	1
Slabs	1
Distance Factor	50
Position	isocenter
Orientation	Sagittal
Phase enc. dir.	A>>P
Phase Oversampling	0 %
Slice Oversampling	0 %
Slices per slab	128

FoV read	256 mm
FoV phase	100 %
Slice thickness	1.33 mm
TR	2530 ms
TE	3.26 ms
Averages	1
Concatenations	1
Filter	None
Coil	HE

Tab 2: Contrast

TI	1100 ms
Averages	1
Flip Angle	7 °
Reconstruction	Magnitude

Fat suppression	None
Water suppression	None
Magnitude Preparation	Non-sel. IR
Measurements	1

Tab 3: Resolution

Base Resolution	256
Phase Resolution	75 %
Slice Resolution	100 %
Phase Partial Fourier	OFF
Slice Partial Fourier	OFF

Filter	Raw Filter
On	(unchecked)
Interpolated	(unchecked)

Tab 4: Geometry

Multi-slice mode	Single-shot
Series	Interleaved

Tab 5: *System*

Note: Shim Mode set to **Standard**, not **Tune-up**

Tab 8: Sequence

Introduction	(checked)
Dimension	3D
Averaging Mode	Long Term
Asymmetric Echo	OFF

Bandwidth	200 Hz/Px
Echo Spacing	6.7 ms

RF Pulse Type	Fast
Gradient Mode	Fast
Excitation	Non-Sel.
RF Spoiling	(checked)

Note: Scan collected scan twice, for good structural reconstruction.

13.3 T1 EPI Scans

T1 EPI Scans (Sequence name: "T1 EPI A-P 18Mar02" and "T1 EPI R-L 18Mar02") ***04 sec***

Tab 1: *Routine*

Slice Group	1
Slices *	**25**
Distance Factor *	**10**
Position	isocenter
Orientation	Transversal
Phase enc. dir.	A>>P AND R>>L
Phase Oversampling	0 %

!

FoV read	200 mm
FoV phase	100 %
Slice thickness *	**5 mm**
TR	1280 ms
TE	39 ms
Averages	1
Concatenations	1
Filter	None
Coil	HE

Tab 2: Contrast

TI	1200 ms
Reconstruction	Magnitude

Fat suppression	Fat sat.
Magnitude Preparation	Slice-sel. IR
Measurements	1

Tab 3: Resolution

Base Resolution	64
Phase Resolution	100 %
Phase Partial Fourier	OFF

Filter	Raw Filter
On	(unchecked)
Interpolated	(unchecked)

Tab 4: Geometry

Multislice Mode	Single Shot
Series	Interleaved

Special Saturation	None

Tab 5: *System*

Note: Shim Mode set to **Standard**, not **Tune-up**

Tab 8: Sequence

Introduction	(unchecked)
Averaging Mode	Long Term
Multi-slice Mode	Single Shot

EPI Factor	64

Bandwidth	2442 Hz/Px
Echo Spacing	0.47 ms

RF Pulse Type	Normal
Gradient Mode	Fast

Note: This scan must be collected twice, with Phase Encode direction A>>P and R>>L. This is to cross-check for distortion correction.

* Asterisked fields must be same as functional scans.
Copy these fields, and also "Copy Parameters" (such as Shim and Field of View).

13.4 T2 Conventional Scan

T2 Conventional Scan ("T2 Conv Andre 18Mar02") ***1 min 35 sec***

Tab 1: *Routine*

Slice Group	1
Slices *	**25**
Distance Factor *	**10 %**
Position	isocenter
Orientation	Transversal
Phase enc. dir.	A>>P
Phase Oversampling	0 %

FoV read	200 mm
FoV phase	100 %
Slice thickness*	**5.00 mm**
TR	**364 ms**
TE	4.35 ms
Averages	1
Concatenations	1
Filter	None
Coil Elements	HE

Tab 2: Contrast

Flip Angle	25 °
Reconstruction	**Magnitude**

Fat suppression	None
Water suppression	None
Magnitude Preparation	None
Measurements	**1**

Tab 3: Resolution

Base Resolution	256
Phase Resolution	100 %
Phase Partial Fourier	OFF

Filter	Raw Filter
On	(unchecked)
Interpolated	(unchecked)

Tab 4: Geometry

Multislice Mode	Interleaved
Series	Interleaved

Special Saturation	None

Tab 5: *System*

Note: Shim Mode set to **Standard**, not **Tune-up**

Tab 8: Sequence

Introduction	(checked)
Dimension	2D
Averaging Mode	Short Term
Multislice Mode	Interleaved
Asymmetric Echo	OFF

Bandwidth	200 Hz/Px
Contrasts	1
Segments	1

RF Pulse Type	Normal
Gradient Mode	Fast
Excitation	Slice-sel.
RF Spoiling	(checked)

* Asterisked fields same as functional scans.

13.5 Field Map Scans

Field Map Scans
(Sequence name: "Field Map_2.23_17Mar02" & "Field Map_4.44_17Mar02") ***2 min***

Tab 1: *Routine*

Slab Group	1
Slabs	1
Distance Factor	20 %
Position	isocenter
Orientation	Saggital
Phase enc. dir.	A>>P
Phase Oversampling	0 %
Slice Oversampling	0 %
Slices per slab	104

FoV read	256 mm	
FoV phase	100 %	
Slice thickness	2.00 mm	
TR	9.0 ms	
TE	2.23 ms	4.44 ms
Averages	1	
Concatenations	1	
Filter	None	
Coil Elements	HE	

Tab 2: Contrast

Averages	1
Flip Angle	10 °
Reconstruction	**Magnitude**

Fat suppr.	None
Water suppr.	None
Magnitude Preparation	None
Measurements	1

Tab 3: Resolution

Base Resolution	128
Phase Resolution	100 %
Slice Resolution	100 %
Phase Partial Fourier	OFF
Slice Partial Fourier	OFF

Filter	Raw Filter
On	(unchecked)
Interpolated	(unchecked)

Tab 4: Geometry

Multi-slice mode	Interleaved
Series	Interleaved

Tab 5: *System*

Note: Shim Mode set to **Standard**, not **Tune-up**

Tab 8: Sequence

Dimension	3D
Averaging Mode	Short Term
Asymmetric Echo	OFF

Contrasts	1
Bandwidth	800 Hz/Px

RF Pulse Type	Normal
Gradient Mode	Fast
Excitation	Slab-sel.
RF Spoiling	(checked)

13.6 Functional Scans

Gradient Echo Functionals ("Functionals GrdEch 18Mar02") ***6 min 26 sec***

Tab 1: *Routine*

Slice Group	1
Slices *	**25**
Distance Factor *	**10 %**
Position	isocenter
Orientation	Transversal
Phase enc. dir.	A>>P
Phase Oversampling	0 %

FoV read	200 mm
FoV phase	100 %
Slice thickness*	**5.00 mm**
TR *	**70.09 ms**
TE	30 ms
Averages	1
Concatenations	1
Filter	None
Coil Elements	HE

Tab 2: Contrast

Flip Angle	90 °
Reconstruction	**Magnitude**

Fat suppression	Fat sat.
Measurements *	**220**
Pause after measure	0.0 ms

Tab 3: Resolution

Base Resolution	64
Phase Resolution	100 %
Phase Partial Fourier	OFF

Filter	Raw Filter
On	(unchecked)
Interpolated	(unchecked)

Tab 4: Geometry

Multi-slice mode	Single Shot
Series	Interleaved

Tab 5: *System*

Note: Shim Mode set to **Standard**, not **Tune-up**

Tab 8: Sequence

Averaging Mode	Long Term

Bandwidth	2232 Hz/Px
Echo Spacing	0.51 ms

(Special) --

Motion Correction	(unchecked)
Interpolation	K-Space
Filter Strength	1.0

Dummy Scans	**4**
Supermosaic Factor	1 * 1
Oscilloscope Trig	**First Slice**

* Asterisked fields are the parameters most often changed and adjusted by fMRI investigators in EPI sequences. These correspond to the primary settings and parameters highlighted in the fMRI methods chapter as interactively determined by the author.

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