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Self and Other: An fMRI Study of Referential Processing and Retrieval

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SELF AND OTHER:
AN fMRI STUDY OF REFERENTIAL PROCESSING AND RETRIEVAL

A Thesis Submitted to the
Yale University School of Medicine
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Abstract

Self and Other: an fMRI study of referential processing and retrieval.

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The self-reference effect has often been used as an indicator of how the brain processes information about one's self. Using fMRI, we studied the neural correlates of the self-reference effect during both encoding and retrieval by means of a unique paradigm of stimuli presentation. Changes in BOLD signal during self-referential processing were compared with those observed during mother-referential processing, and conjunction analysis of these two conditions resulted in joint activations of the superior fontal, inferior frontal and posterior cingulate gyri. Areas of the anterior cingulate gyrus and the visual word form area were observed for self-referential processing and not for mother-referential processing. During retrieval, hippocampal deactivation was observed for all memory tasks vs. the non-memory control task. Furthermore, the hippocampi deactivated less during the recall of self-referenced vs. mother-referenced items. Given that there was no significant difference between mean response times and recall accuracy between these conditions, the differences in deactivation are discussed as a way in which the recall of self-referenced material may be neurofunctionally special.

Subjects in this study also performed a social attribution task in which they inferred mental states about geometric shapes. BOLD signal changes during this condition indicated activation of dorsomedial prefrontal cortices (DMPFC), bilateral ventral pathways including the fusiform face area, the amygdalae (right > left), bilateral superior temporal sulci (STS, right > left), anterior fusiform, and bilateral posterior cingulate gyri. In order to explore the areas of overlap between this more abstract social processing and the activations observed in the referential-processing task, an overlay map of these two tasks was created. Overlap was observed in the MPFC, the STS and posterior cingulate cortices.

These findings are discussed in the context of a relationship between theory of mind and theory of self, and possible implications for the study of neuropsychiatric disorders are explored.

Acknowledgements

Introduction

Studying the Self: Theoretical Models

The study of the human self, the search for the locus of consciousness, and the mind-brain duality are pervasive topics in psychiatry, psychology, neurology and philosophy (1).[1] The reasons for the perpetuity of interest in the self are varied; the self is in some ways the medium for psychiatry and psychology, and although on an individual level the self is often experientially concrete and intuitively obvious, it remains complex and elusive as a collective idea, well-concealed by the problem of subjectivity. How it is that a conglomerate of neurons can result in the experience of *being*, of having a self? What parts and functions of the human brain are essential to this experience? In short, a multi-disciplinary effort has long been concerned with delineating a model of the self.

In 1918, the renowned psychologist William James (drawing from Hume) wrote one of the first descriptions of a self-model. His account of the self has been so influential that traces of his ideas and language can be seen in most, if not all, recent work on the subject. For this reason, we begin by briefly summarizing James' model of the self.

James proposes that the self has two main aspects. In so doing, he succinctly describes one of the most difficult interfaces in psychology, that of consciousness and the self. He writes,

Whatever I may be thinking of, I am always at the same time more or less aware of *myself*, of my *personal existence*. At the same time it is *I* who am aware; so that the

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[1] Gillihan and Farrah reported that a May 2004 search of the PsycInfo database for the word "self" in the titles of journal articles returned more than 39,500 hits. The same search performed in January, 2006, as a part of the current study, returned 65,876 hits.

total self of me, being as it were duplex, partly known and partly knower, partly object and partly subject, must have two aspects discriminated in it, of which for shortness we may call one *Me* and the other the *I*. (2)

He goes on to further delineate what he means by "object" and "subject." The object, or Me, is comprised of the material Self, the social Self, and the spiritual Self. The self as subject, or the I, is comprised of the pure Ego.

Within the Me, the material Self, James first places the body, noting that "certain parts of the body seem more intimately ours than the rest" (3). To the body, he adds clothes, family, home and property, pointing out that when any of these are adversely affected, we react with a unique "instinctive impulse." For instance, with regards to one's immediate family, he says, "[w]hen they die, a part of our very selves is gone. If they do anything wrong, it is our shame. If they are insulted, our anger flashes forth as readily as if we stood in their place." Indeed, throughout his account, James points to the special "warmth" evinced by different things as an indicator or "herd-mark" of their belonging to the self.

The second subpart of the Me is the social Self, and James describes the social Self of his 19th century male as "the recognition he gets from his mates" (293). In a passage that is still poignant today, he writes:

No more fiendish punishment could be devised, were such a thing physically possible, than that one should be turned loose in society and remain absolutely unnoticed by all the members thereof. If no one turned round when we entered, answered when we spoke, or minded what we did, but if every person we met 'cut us dead,' and acted as if we were non-existing things, a kind of rage and impotent despair would ere long well up in us, from which the cruelest bodily tortures would be a relief; for these would make us feel that, however bad might be our plight, we had not sunk to such a depth as to be unworthy of attention at all (pp.293-4).

In James' model, your reputation or what others think of you actually comprises a part of you. The self is an entity that gains meaning and substance through the

process of interactions with others.

The spiritual Self is a person's "psychic faculties or dispositions... These are the most enduring and intimate parts of the self, that which we most verily seem to be" (p.296). James posits that the spiritual Self can be observed only through self-reflection: "our considering the spiritual self at all is a reflective process, it is the result of our abandoning the outward looking point of view, and of our having become able to think of subjectivity as such, *to think ourselves as thinkers.*"

The I, or "that pure principle of personal identity," is a more difficult aspect of self to delineate (p.330). James begins here by describing a sense of personal identity. "[T]he thoughts which we actually know to exist," he writes, "do not fly about loose, but seem each to belong to some one thinker and not to another" (p.331). A sense of continuity or sameness over time is a key component of this personal identity. "The distant selves appear to our thought as having for hours of time been *continuous* with each other, and the most recent ones of them continuous with the Self of the present moment, melting into it by slow degrees; and we get a still stronger bond of union" (p.334). Furthermore, "..the unity of all the selves is not a mere appearance of similarity or continuity...It involves a real belonging to a real Owner, to a pure spiritual entity of some kind. Relationship to this entity is what makes the self's constituents stick together as they do for thought" (p.337). James summarizes many thoughts on this Owner by saying that it is "a *Thought*, at each moment different from that of the last moment, but *appropriative* of the latter, together with all that the latter has called its own" (p.401). He wavers about the role of psychology in exploring or defining this Thought, suggesting that perhaps psychology should stop with the postulate that because there is so much *known*,

there must be a *knower*, and in effect, begin its work based on that assumption.

Antonio Damasio, an influential thinker working today, also posits an interesting model of the self. His theoretical work both informs and is informed by his neurocognitive research, as well as by his experience as a neurologist. Damasio's musings about the self begin at the level of a single-celled organism and progress to a well-developed model (4). He attributes a duality to consciousness as well as to self, and links the two causally. "Consciousness is not a monolith…It can be separated into simple and complex kinds, and the neurological evidence makes the separation transparent" (p.16). The simplest kind he calls "core consciousness;" this is the consciousness which "provides the organism with a sense of self about one moment—now—and about one place—here." The other kind of consciousness he calls "extended consciousness," which is the more complicated kind. It "places a person at a point in individual historical time, richly aware of the lived past and of the anticipated future, and keenly cognizant of the world beside it." This division of consciousness echoes James, who writes, "This is an abstract way of dealing with consciousness, in which, as it actually presents itself, a plurality of such faculties are always to be simultaneously found…the spiritual self in us will be either the entire stream of our personal consciousness, or the present 'segment' or 'section' of that stream…" (p.296).

Damasio links his concept of the self to his ideas about consciousness. From core consciousness comes a sense of self called the "core self." This self is "a transient entity, ceaselessly re-created for each and every object with which the brain interacts" (p.17). The "autobiographical self," on the other hand, is that aspect of the self that is linked to an idea of identity, "and corresponds to a

nontransient collection of unique facts and ways of being which characterize a person." This autobiographical self is the product of the extended consciousness. Both the core self and the autobiographical self are manifestations of a nonconscious representation of the state of the living body that Damasio calls the "proto-self."

Within Damasio's model, we find again that personal identity and a sense of continuity are essential to the self concept. "In all the kinds of self we can consider, one notion always commands center stage: the notion of a bounded, single individual, that changes ever so gently across time but, somehow, seems to stay the same" (p.134). Despite this insistence on continuity over time, Damasio also points to the transient nature of the self, just as James did with his concept of the Thought, which is at each moment different from the next. "Our sense of self," writes Damasio, "is a state of the organism, the result of certain components operating in a certain manner and interacting in a certain way, within certain parameters. It is another construction, a vulnerable pattern of integrated operations whose consequence is to generate the mental representation of a living individual being" (p.145). Damasio parses the question of the I in biological terms: "The riddle of the biological roots of the self can be worded like this then: What is it that provides the mind with a spine, is single and is same?" (p.135).

Vogeley and colleagues have taken a slightly different approach, and have formulated a self-model specifically designed to comport with the data and types of investigations being undertaken within neuroimaging (5). They organize the findings of their studies into three features of the self—agency, perspectivity and unity. The feeling of ownership and agency is "the experience of having my own

thoughts, memories, performing my own actions (p.353)." Perspectivity is the experience of having a body around which one's conscious states are centered; it is the "incorporation of my memories, thoughts and perceptions in my own body." The experience of unity is the feature of the self that depends on long-term autobiographical memory as the working "platform" for the individual. Vogeley's description of the self reflects ideas that James attributed to the *I*. Its utility lies in the fact that these features can be studied, to some degree, as separate cognitive functions, thereby providing a bridge between philosophy and the neurobiological investigation of the self.

Studying the Self: Neuroimaging

Recently these aspects of the self have become the focus of research within neuroimaging. Broadly speaking, neuroscientists are trying to understand how the brain functions as a mind. How does an individual come to have a self concept, and how does an individual access, use, and modulate that self concept in both short and long-term ways? What are the neural systems underlying the experiences of unity, agency, perspectivity; of the material Me, of the I? Do activities of the self recruit unique neural pathways? Some of the studies pertinent to these questions will be briefly reviewed here, organized roughly around Vogeley's conception of the three aspects of the self. As will be seen, despite the variation in the experimental paradigms, many of the brain areas of interest involve the cortical midline structures, namely the medial prefrontal cortex, the anterior and posterior cingulate gyri, the retrosplenium and the precuneus (6, 7).

A number of imaging studies have explored the first feature of Vogeley's

self, the experience of ownership or of agency. Ruby and Decety used positron emission tomography (PET) to look at the differences between imagining one's self performing an action and imagining another person performing that same action (8). They reported that imagined self action activated the left inferior parietal lobe, posterior insula, post-central (somatosensory) gyrus and bilateral inferior occipital gyrus, with strong left-hemispheric activation predominating. They interpret the activation of the left inferior parietal lobe as playing a crucial role in programming the self's movements. These areas that are activated by both imagining and performing an action have been termed "mirror neurons," and much current research is focused on the role of mirror neurons in learning, in modeling ideas about other people, and in the self (9, 10).

The experience of perspectivity and of having a body has been studied through various perspective-taking tasks. Ruby and Decety again used PET to examine the differences between first- and third- person perspective taking (11). Subjects were asked to take either their own perspective or their mother's perspective in response to emotional or neutral situations. The authors reported significant activation in the right postcentral gyrus as the main effect of the first-person versus third-person comparison. The design of this study demonstrates the difficulty of forcing a specific task of social cognition. The third-person perspective tasks (i.e. answer the question as if you were your mother, choose the adjective that best describes how your mother would react) are still asking subjects to decide on *their own* opinion of how their mothers would answer; thus, it is not truly an exercise of taking another's perspective.

Vogeley and colleagues pursued the question of perspective-taking using

fMRI and a different design (12). In this study, subjects are asked to read short vignettes while in the scanner. In one condition, these stories are told in the third-person perspective, with a question following the story that asks, for example, "Why did the burglar do that?" In a second condition, the stories are told in the second-person perspective, with a question asking, "What do you think?" Another condition is told in the second-person perspective but asks a question about another agent in the story, creating a mixed theory of mind and self condition. The authors report the main effect of self as increased neural activity in the right temporoparietal junction, bilateral anterior cingulate cortices, right premotor and motor cortices and the precuneus bilaterally. This design seems to more accurately force subjects to actually take the third-person perspective, both because the longer narrative form enables the subject to more fully become a mental participant in the vignette, and because the questions were asked in a manner that was continuous with the narratives. This enabled the subject to stay "inside" the vignette, rather than requiring him or her to step back and decide something about the story from outside of it, i.e. it enabled the subjects to take on a certain perspective, and maintain it throughout the condition.

Many studies have examined how subjects view their own bodies in different ways than they view others' bodies. Evidence from neurological patients with the deficit termed asomatognosia prompted researchers to surmise that we identify our own body parts using a different brain area or method than we use to identify others' body parts. Patients with asomatognosia are unable to recognize their body parts as their own (usually hands and arms) but are able to recognize the ownership of other people's hands and arms. Within neuroimaging, many studies

on the self and the body have focused on self-face recognition versus non-self-face recognition (13-15). These studies have produced inconsistent results, probably largely because they employ different paradigms such as using morphed faces or non-morphed faces, and because they use different comparison tasks, such as unknown other, known other, and intimately known other. Gillihan and Farah conclude, "[i]n short, a clear pattern of anatomical localization has yet to emerge for self-face recognition" (1).

The experience of having a unified self-construct is an outcome that "relies basically on the availability of our individual personal history as the long-term memory platform" (5) (p.353). Many studies have investigated memory functions that relate to the self. Study designs that involve the recall of autobiographical material are often confounded by the fact that it is difficult to control for emotional valence, temporal remoteness, retrieval success, etc. Functional neuroimaging studies almost always use the subtraction method of analysis, where the activations of one task are subtracted from another. This method assumes that the two tasks compared only differ in one significant way. Thus, differences in emotional valence and temporal remoteness that occur as part of autobiographical memories act as confounders. Cabeza and colleagues recently introduced a "novel photo paradigm" that elegantly equated the autobiographical and control material to a significant degree. They controlled the nature of the autobiographical condition by providing undergraduate students with cameras and a list of locations on campus which they were instructed to photograph. Subjects were scanned while recognizing the photos they themselves had taken from among the photos taken by other students. The autobiographical condition elicited greater activity in the

medial prefrontal cortex (MPFC), the visual and parahippocampal regions, and the hippocampus bilaterally.

Most of the neuroimaging studies of the self look for neural activations that will be recruited during self tasks and not be recruited during other tasks. In short, there is an underlying belief that the self is "special" in some way. In a recent review article, Gillihan and Farah point out that it is very difficult to determine if "the self is special" because of the multiple meanings of both the term "self" and the term "special" (1). They review many of the different definitions of the self that are in use, the different ways that the self is "operationalized" in each study, and the different uses of the term "special" in neural circuitry. They define four criteria whereby a system can be considered special: 1) anatomy, (whether or not a system recruits a unique brain area; 2), functional uniqueness, (for example, faces are recognized in a more "holistic" manner than are objects); 3) functional independence (one system's operation does not depend on another's); and finally, 4) species specificity, (meaning that the system is unique to one species—for example, language). The authors conclude that "neuroimaging research has yet to include the needed controls to equate self- and non-self conditions in familiarity, affective associations, and other respects."

Another interesting issue that has arisen in regard to studies of the self within neuroimaging involves the resting state of the brain. Every functional neuroimaging study requires a "rest" condition. This rest condition is set as the baseline from which every activation is measured. Usually rest is "induced" by placing fixation marks on a blank screen to mark periods where subjects do not need to respond to a task. However, a meta-analysis performed by Wicker and

colleagues examined the activations reported by five studies wherein subjects had to direct their attention to stimuli external to themselves, for example, by performing attribution of intention tasks or perception of gaze tasks (16). The authors concluded that "medial prefrontal cortex exhibits a lower activity when the subject's attention is focused towards the external world than when the subject has to additionally refer to some internal states" (p.224). For instance, a study by Platek et al. reported "less deactivation" in the MPFC during a self-task than during the comparison task (17). When the authors contrasted resting state with other tasks they found that in all five experiments, regional cerebral blood flow (rCBF) was significantly higher during resting state than during the active condition bilaterally along the superior frontal sulcus, and the right anterior cingulate gyrus. Based on these results, the authors suggest that "resting state can be considered as an ultimate state of inspection of the self" (p.229). Similar conclusions were posited in two seminal papers by Gusnard et al., and have subsequently supported by other groups (18-21).

These findings correspond nicely with Damasio's description of the internal milieu of the self: "Under no normal condition is the brain ever excused from receiving continuous reports on the internal milieu and visceral states, and under most conditions, even when no active movement is being performed, the brain is also being informed of the state of its musculoskeletal apparatus" (p.150). James calls these continuous reports "the constant stream of thought...a teeming multiplicity of objects and relations" (p.224). In the face of this internal constant stream, we wonder how individuals learn to focus on, assign salience to, and incorporate information about the self.

Studying the Self: Disorders

In many neuropsychiatric, neurological and developmental disorders, patients seem to have difficulty assigning meaning to and incorporating the constant stream of input relating to the self. A prime example of this is schizophrenia, where researchers question the ability of individuals with schizophrenia to monitor their own thoughts, emotions, goals and actions, as well as their ability to recognize their own faces and voices (22-24).

Malaspina and colleagues performed a unique study of individuals with schizophrenia using PET to investigate neural activations during rest (25). They chose to focus on the resting state because, as mentioned previously, it is believed that brain activity during "rest" involves a constant monitoring of self thoughts, memories, goals, ideas and speech, as well as the retrieval and manipulation of episodic memories, implicit knowledge and emotional associations. In individuals with a subtype of schizophrenia, Malaspina et al. found lower rCBF (regional cerebral blood flow) in the dorsomedial prefrontal cortex (DMPFC), the anterior cingulate (AC) and the paracingulate cortices than in their control group, with more pronounced differences in these regions seen in the left hemisphere. The authors concluded that individuals with schizophrenia demonstrate significantly lower rCBF during the resting state than do normal controls, and that different subtypes of schizophrenia have different patterns of decreased rCBF. Based on the assumption that these areas indicate self-processing at rest, these findings support the hypothesis that the self model is impaired in schizophrenia.

Another example of a more focused impairment of the self-model in

schizophrenia occurs when individuals misattribute self-agency to an external source, resulting in the experience of "alien control" or other passivity experiences. Blakemore et al. explored the differences between passive and active movements in a PET study (26). They found that identical movements recruited different areas of the brain depending on whether the actions were attributed to self or to an external source, even when both actions were performed by the subject. Based on their findings, they agree with Spence and colleagues, who suggest that a parietal-cerebellar network may be over-active in schizophrenic patients, leading to the delusion of alien control and a deficit of the experience of ownership or agency (27).

Self-processing also seems to be altered in individuals who suffer from eating disorders. Studies have shown that the knowledge of one's body size is the product of higher-order cortical processing that is only partially explained by proprioceptive, visual, and other somatosensory input (28). It is suspected that this self-body processing system is impaired in people with body image distortion, as well as in some individuals who have undergone limb amputation. Many neuroimaging studies have explored these impairments in eating disorders (29). Wagner et al. focused on body image distortion in a recent fMRI study of 13 individuals with anorexia nervosa (30). In this study, subjects viewed pictures of themselves that had been morphed to varying degrees. Subjects with AN demonstrated hyper-responsiveness of the inferior parietal lobule (BA 40) and the anterior part of the intraparietal sulcus. The authors attribute these activations to differences in attention and in visuo-spatial processing, indicating that individuals with AN attend to and process their own body images differently than do normal

controls. Another study suggested that these individuals recruit the "fear network" of the amygdalae, fusiform gyrus, and the brainstem, in response to viewing pictures of themselves, thus indicating that their ability to associate emotional responses to information about themselves is abnormal (31).

Autism Spectrum Disorders (ASDs) are another group of disorders in which individuals demonstrate impairments of the self. ASDs include Autistic Disorder, Asperger's Syndrome and Pervasive Developmental Disorder not otherwise specified (PDD-NOS). Patients who meet diagnosis criteria for ASDs display a wide variety of aptitudes, impairments and characteristics. However, a triad of shared behavioral symptoms between these disorders is consistent, and includes: difficulties communicating; impairments of social function; and repetitive behaviors or obsessive areas of interest, first described as an "obsessive insistence on the preservation of sameness" (32). In 1968, Ornitz and Ritvo suggested that the inability of autistic individuals to adequately modulate sensory input results in an inability to develop a stable sense of self or others (33). Subsequent behavioral studies have attempted to demonstrate the ways in which this "sense of self" is or is not impaired.

One of the most well-established self-impairments in ASDs is that individuals with ASDs tend to use third-person pronouns to refer to themselves rather than first-person pronouns. In James' terms, the pronouns "he" or "she" refer to the self as Object, whereas the inability to use "I" or "me" suggests a deficit in the use of language appropriate to the self as Subject. Observations of this impairment have been reported by parents and clinicians for years, and was verified scientifically in a study by Lee et al (34).

Further examples of self-specific impairments in ASDs include difficulties or differences seen in self-recognition. Self-recognition in autistic children has been studied using variations of the self-recognition paradigm first designed by Gallup (37). Children placed in front of a mirror were observed while seeing themselves both with and without a rouge-mark on their face. Both Dawson and McKissick and Neuman and Hill note that while autistic children recognized themselves as often as did normal controls, their recognition was not accompanied by the same "coy behaviors" (like shrugging or changing facial expressions) as displayed by the normal controls (38, 39). Thus, though autistic children demonstrated intact self-recognition skills as measured rather crudely with this technique, self-recognition itself did not appear to carry the same emotional or social meaning for these children. Furthermore, it is highly possible that more subtle differences in self-recognition do exist between individuals with autism and typically developing children that were not appreciated in this task.

Another study showed that autistic adolescents tend to describe themselves using more self-as-object phrases (physical descriptors, or descriptions of activities) as opposed to psychological or social phrases (comparisons about personality, uniqueness, statements about agency) when compared with the control group (40). Millward et al. studied aspects of the self and memory in autistic children (41). A group of children with autism and a group of children matched for IQ and verbal ability were led on a walk which followed a scripted course of events: for example, going down the slide in the playground, then looking at the ducks in the pond, etc. Researchers found that autistic children had more difficulty remembering events experienced by themselves than they did events that they observed their peers

experiencing, whereas the opposite was true in non-autistic children.

On the other hand, individuals with ASDs sometimes demonstrate a very well-established sense of self. Some extreme examples of this are the insightful writing of Temple Grandin and Donna Williams, who have written numerous books describing their stories as individuals with autism (35 , 36).[2] Some individuals with ASDs are artists, and their work, most directly in their self-portraits and the way they talk about their work, can demonstrate a profound self-awareness.[3] Apart from artists and writers, stories told by people with an ASD or by their parents, teachers or clinicians, often give glimpses into the self-concept or self-esteem of individuals with ASDs.[4] Though these moments of self-awareness are expressed regularly in everyday lives, they might quite easily evade systematic measures of testing. As with many of the impairments within autism, it seems that impairments of the self will most likely prove to vary between individuals, as well as by developmental and verbal levels.

The Self Reference Effect

Perhaps the most well established phenomenon in the study of the self was developed in 1977 by Rogers and colleagues, who documented what is termed the "self reference effect" (SRE) (42). The SRE occurs when individuals readily remember a newly learned piece of information because they had somehow referenced the new information to their concept of self. Experimentally, this is

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[2] It should be noted that many people doubt the diagnosis of autism in the case of Donna Williams.
[3] To give just two examples, George Widener produces beautiful renderings of calendars and satellite maps etc. which can be seen online at www.georgewidener.com. Also, Richard Wawro produces wax crayon drawings. See his website, www.wawro.net.
[4] Please see the newsletter archives at the website www.asperger.org.

demonstrated when normal subjects are presented with lists of words and asked different types of questions about those words. One type of question is semantic, for example, "Does this word mean the same as brave?" Another type is self-referential, for example, "Does this word describe you?" The third type of question is phonetic, for example, "Which word is more rhythmic?" When normal subjects are then given a list of words comprised of both the adjectives they had been asked questions about and new adjectives, they will be able to recognize the words which were self-referentially encoded much more frequently than words encoded by any other method. This increase in memory is what is meant by the "self-reference effect" and it has been the subject of much research in the areas of memory and the self.

In a "meta-analytic integration of the SRE literature," Symons and Johnson attempted to determine if the self-reference effect is an actual phenomenon (43). Their analysis included 129 different studies, and considered aspects such as the nature of the comparison task, effect size, method of presentation of stimuli, age of subjects and memory load. In the end, the authors concluded that self-referential encoding *does* promote better recall on average than other types of encoding. However, the effect size varied widely. For example, one of the types of processing often used in SRE tasks is other-referential (OR) processing. In these conditions, subjects are usually asked if a word describes a certain person or not. Symons and Johnson demonstrate that in SRE studies that used an OR task, the effect size depended in large part on the degree of intimacy of the "other."

The meta-analysis also demonstrated that the effect size varied with age. Children showed less of an SRE than did adults, and undergraduates showed the

largest SRE when the comparison task was semantic, but not when the comparison task involved OR processing. Also, if the recall task was a surprise to the subjects, the SRE was more robust than if the subjects knew it was coming. The authors concluded that "the SRE appears to result primarily because the self is a well-developed and often-used construct that promotes elaboration and organization of encoded information."

Neuroimaging studies have attempted to identify the neural networks underlying this "often-used construct" by conducting different variations of the self-reference task. One of the first of these was conducted by Craik et al. in a PET study of 8 normal subjects (44). Four conditions were used: (a) *self* (How well does the word describe you?), (b) *other* (How well does the word describe Brian Mulroney?), (c) *general* (How socially desirable is this trait?), and (d) *syllable* (How many syllables does this word have?). Their results showed that self-related encoding yielded specific activations in the right frontal lobe. Because these areas had been shown to be involved in episodic memory in other studies, the authors concluded that "the concept of self involves both general schematic structures and further specific components involved in episodic memory retrieval."

An fMRI study by Kelley et al. used almost the same paradigm except that the *other* condition used George Bush, and the *control* condition asked subjects do determine if the adjective was presented in uppercase letters (45). Results showed that a separate region of the medial prefrontal cortex was selectively recruited during the *self* condition. The authors concluded that "these findings suggest that self-referential processing is functionally dissociable from other forms of semantic processing." The problem with these studies, it seems, lies primarily in the nature

of the *other* task insofar as the conditions *self* and *other* differ in intimacy: we would not expect a subject to have a Bush- or Mulroney-concept that was as well-developed as their self-concept. Thus differences seen between *self* and *other* activations can not be attributed to self-referential processing per se. Furthermore, using a control task that requires counting where the other conditions do not involve counting adds another confounding variable. One could also argue that encouraging subjects to evaluate the desirability of words within one condition might cause them to be more aware of desirability in the other conditions, particularly the *self* conditions.[5]

Lou et al. conducted an experiment that used a more intimately known other to study the retrieval of self-encoded adjectives (46). Subjects were shown lists of adjectives prior to scanning. They were instructed to rate the adjective according to how it best described them, how it best described the Danish Queen, and how it best described their closest friend. Subjects then underwent PET scanning, during which they were shown the adjectives again and asked to recall if the adjective had been characterized as describing self, Queen, and friend. A control condition was added where subjects decided if the adjective had an even number of syllables or not.

The authors reported that "activation increased in the left lateral temporal cortex and decreased in the right inferior parietal region with decreasing self-reference" (*self* > *best-friend* > *Queen* > *syllable*). Connectivity studies indicated that the right inferior parietal region (highest activity in self condition) was preferentially connected to the medial parietal cortex (MPC), leading the authors to

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[5] Other studies that use similar conditions include Fossati et al, 2003, though their focus was on contrasting the effects of positive and negative valence of words during both encoding and retrieval processes.

believe that the MPC was functioning as a "nodal structure in self representation."
They then used transcranial magnetic stimulation (TMS) over the area of the medial
parietal cortex and found that recall for self-encoded words decreased more than did
recall for the other-encoded words. Unfortunately, activation maps and z-scores
were provided for *self* and *Queen* comparisons, but not for *self* and *best-friend*
comparisons.

A more intimately-known other was used in another self-reference study
where subjects were asked to designate their own "close other" to be used in the
other condition (47). This study also included a social-desirability condition
(termed the *positive* condition) where the subject was asked to judge the desirability
of a trait based on what the "average person" would think. In the control task for
this experiment, subjects were asked to determine whether the adjective contained
two syllables. Interestingly, the results of this part of the experiment showed that
on *self* vs. *other* and on *self* vs. *positive*, no activations were seen when the
threshold was lowered to $P < .005$. Furthermore, activation of the MPFC was not
observed even when the threshold was lowered to and alpha value .01. This study
did not include a retrieval task.

Lastly, a small behavioral study has been conducted on the SRE in
individuals with ASDs (48). A group of 18 high-functioning autistic subjects was
compared with a group of 18 normal controls. Both groups underwent an SRE task
in which they were asked questions about adjectives. The questions were either
phonological (Does the word rhyme with _____?), *semantic* (Does the word mean
the same as _____?) and *self* (Does the word describe you?). During a subsequent
recall task, investigators found that individuals who had met diagnosis criteria for

an ASD recalled adjectives encoded in these three ways in a very different pattern

than did the group of normal controls. The normal controls identified 38.8%,

70.5% and 83.8% of the phonologically, semantically- and self-encoded words,

respectively. The subjects with ASDs recalled 58.5%, 77.9% and 77.8% of the

phonologically-, semantic-, and self-encoded words, respectively. Thus, the

subjects with ASDs remembered semantically-encoded words as well as they

remembered self-encoded words, and did not demonstrate the SRE seen in the

controls' responses.

It is difficult, based on behavioral data alone, to understand what this means.

Do people with ASDs not demonstrate a *self* vs. *semantic* SRE because they are

better at semantic encoding than normal controls? Do they use the same pathways

for semantic and for self encoding? These are the sorts of questions that

information from neuroimaging studies can help to answer.

The SRE in Neuroimaging: Clinical Utility

We have selected the self-reference effect as the focus for this study for four

main reasons. First, we believe that the SRE provides a quantifiable indicator of a

feature of the self that is inherently difficult to study, namely, the feature of having

a unified self-construct. Of course, one's ability to reference stimuli to one's self is

dependent on more than simply whether or not the subject *has* a self concept. The

subject must not only have a self concept, but they must also be able to access it in

ways that are compatible with the timing and format of the experimental conditions.

Nonetheless, it seems reasonable to conclude that a subject who demonstrates the

self-reference effect has and uses their self-concept in a way that facilitates

encoding and elaborating of new information, which is a different sort of information about the self than might be obtained using a self-esteem measure, etc.

Second, the adaptation of this task for neuroimaging carries the added benefit of combining a behavioral measure with functional data. In this way, inconclusive behavioral findings such as similar scores between self and other conditions can be explored neurofunctionally, and neurofunctional data can be interpreted in light of behavioral data. Furthermore, we feel that the designs of the tasks used in previous neuroimaging studies have not adapted the original SRE task in ways most conducive to producing the sustained, driven, and focused neural activity necessary for strong fMRI findings.

Third, there has not yet been a study that investigated the retrieval part of the SRE using an other-recall comparison task. All SRE paradigms necessarily involve two parts, an encoding portion in which the subjects are exposed to stimuli, followed by a retrieval task where subjects are asked to recognize the stimuli. The neuroimaging studies of the SRE to date have generally performed the "encoding" part of the task in the scanner, and the retrieval part of the task as a behavioral test outside of the scanner. We propose that both the encoding and the retrieval portions of the paradigm likely contribute to the behavioral results that have been observed. No neuroimaging study to date has compared the activation patterns that occur during the implicit recall of self-referenced and other-referenced stimuli.

Lastly, the self-reference effect was utilized because we believe that it has potential for use in studies of individuals with neurocognitive and developmental disorders such as schizophrenia, the eating disorders and the pervasive developmental disorders. The SRE as a well designed, normalized fMRI task could

provide researchers and clinicians with both behavioral and neurofunctional indices of an individual's ability to reference their self-concept. The use of an intimately known other in the comparison task also provides information about each subject's ability to engage in ToM processing, and facilitates comparison between self-processing and other-processing on a subject-by-subject basis. We believe that the recall portion of this experiment could be particularly useful in these disorders because the retrieval task involves an automatic or implicit activation of the self system as opposed to the active or directed involvement of self-processing. This implicit or automatic recruitment of self-processing more closely matches the impairments of social cognition and of self-processing seen in the daily interactions of individuals with disorders such as schizophrenia and autism.

Purpose and Hypotheses

The primary aim of this study was to establish the patterns of blood-oxygen-level-dependent (BOLD) activations that underlie self-referential processing and the retrieval of information that has been encoded via self-referential processing. By using a comparison task which forced processing of an intimately known other, we intend to demonstrate that the networks recruited during self-processing are largely the same as those recruited during intimate-other processing. We hypothesized that this common network would include areas that have previously been recruited during tasks that require social reasoning and the inference of mental states of others. These areas include the dorsomedial prefrontal cortices, superior temporal gyri and the posterior cingulate gyri. Based on the assumption that a person's self-

concept is a richer, more-detailed construct that is more frequently used and more elaborated than is one's mother-concept, we also hypothesized that stronger activations in these areas would be observed during self-processing than during mother-processing.

Furthermore, we anticipated significant differences between self and mother conditions during the retrieval task. We hypothesized that differences in activation would be observed in areas such as the DMPFC and the anterior cingulate cortices due to differing degrees of confidence between the recall conditions.

A second aim of this study was to compare the activation patterns observed during a well-established non-verbal social processing task known as the social attribution task (SAT). This task has been shown to recruit social networks without using words or concrete references to people by asking subjects to watch animations of moving shapes and to decide if they are all friends or not (49). The activation patterns recruited by this more abstract, non-verbal social processing task will be compared with the activation patterns seen in the self-referential and the intimate other-referential processing task in order to assess the effects of modality on the recruitment of social networks. We predict that both types of tasks will recruit similar areas, thereby demonstrating that the networks recruited during non-verbal abstract social processing are also utilized during more targeted, verbally-cued referential-processing.

Methods

Participants

20 healthy participants (11 females, 9 males, mean age ± s.d = 26.4 ± 3.9) were recruited via posters and newspaper ads from the Yale University community. Participants were screened for neurological and DSM IV Axis I psychiatric disorders through administration of the Adult Self-Report Inventory, and for family history of significant neurological or psychiatric disorders in first-degree relatives using an in-house self report survey (50). All subjects had normal or corrected-to-normal visual acuity, and scored in the normal range of the Benton Test of Facial Recognition (Benton 1994) (raw score range: 44-53 ; mean ± s.d. = 44.7 ± 2.7). All subjects gave written informed consent for this study and were paid for their participation in accordance with the procedures and protocols approved by the Human Investigations Committee at Yale University School of Medicine.

Of the 20 participants recruited, 3 were subsequently excluded from the study. One participant was found to have atypical structural variation of the hippocampus. Because the hippocampus is a region of interest in this study, and the region could not be aligned with other normal controls, this subject was excluded from the study. One subject did not perform the task as directed, rendering the functional data unusable. The third subject was an age outlier. Results reported here reflect data analyzed from the remaining subjects, comprised of 10 males and 7 females (mean age ± s.d = 21.5 ± 1.8). Decisions to exclude these subjects were made by the author prior to analyzing any functional data from these subjects.

Experimental Tasks

This study was designed to examine both the encoding and retrieval of self-referenced and other-referenced stimuli. Thus, each subject completed three experimental tasks: first, a referential processing task in which the subject was exposed to a list of adjectives; second, a ten-minute distractor task; and lastly, a "surprise" recognition memory task testing the subject's recall of the adjectives presented in the first task. All 17 subjects completed all three runs of the referential processing task. Six subjects performed a previously developed facial recognition task as the 10 minute distractor task between encoding and retrieval. At that point, the distractor task was changed from the facial recognition task to a 10 minute social attribution task in order to provide a complementary set of data derived from a more abstract type of social cognition. The remaining 11 subjects performed this previously developed social attribution task, the data from which is included in this study. Only 13 subjects performed the retrieval task inside the magnet as the decision to design an fMRI version of this task was not made until after the initial 4 subjects had already completed the experiment. Thus, the group data for the referential processing task is comprised of 17 subjects, the social attribution task data is comprised of 11 subjects, and the retrieval data is comprised of 13 subjects. All participants were trained for each experimental task by the author using written instructions and examples prior to entering the magnet. None of the subjects knew that they would be performing a recognition memory test. All stimuli were projected from behind the subject, and were viewed via a small mirror system mounted on the head coil above the subject's nose, and in this way appeared in an upright orientation.

Referential Processing Task

This task is a variant of the original self-reference task first described by Rogers et al. in 1977 (42). In Rogers' task, subjects were shown a series of adjectives and asked one of four questions about each word. The questions were designed to "force" different types of encoding, namely, *structural* ("Big letters?"), *phonemic* ("Rhymes with ____?"), *semantic* ("Means the same as _____?") and *self-reference* ("Describes you?"). Subjects were then asked to produce a written list of the adjectives they could recall having been shown.

We reasoned that thinking about a person over 15-20 seconds (rather than for 3-4 seconds) would cause a subject to interact with and to consider their self-concept or mother-concept in a deeper and more engaged manner. Thus, we chose a block-design for this study. An attempt was then made to design the stimuli in such a way that subjects would be forced to engage with the referential stimuli in a sustained and focused manner. Thus, in contrast to previous SRE experiments in which subjects were asked to respond to one adjective at a time, stimuli in the current study were presented in pairs; for example, in the Self condition, the subject was presented with two different adjectives and asked to choose the word that best described him or herself. It was surmised that forcing the subject to choose the best descriptor would be a more difficult decision requiring more sustained processing than simply deciding if a single word did or did not describe him or herself.

The three conditions included in this experiment were "Self," "Mother," and "Letter." The word pairs for each condition are presented in the Appendix. In the Mother condition, the subject was asked to choose from a pair of adjectives the

word that best describes his or her mother. This condition was chosen in order to force referential processing of an intimately known "other" that is as close to the self as possible without actually being the self.

The Letter condition served as the control condition, and subjects were asked to choose the word that contained the letter "A". They were asked to try to read both words during this condition, rather than simply scanning for the letter.

Each condition block began with a 3500ms prompt screen which presented the name of the task (either "Self", "Mother", or "A") to follow. Each prompt was followed by a block of 5 word-pairs. All words were presented side by side in lowercase letters in grey font on a black screen, and remained on the screen for 3500ms regardless of the response time of the subject. A black screen appeared for 500ms between each stimulus. For all three conditions, participants indicated their choice by pressing a button in their left hand to select the word on the left side of the screen, or a button in their right hand to select the word on the right side of the screen. Rest periods lasting 10s occurred between conditions and were comprised of two grey fixation points on a black screen. The fixation points were oriented on the screen to match the layout of the word-pairs.

The word list used was generated largely from a list of normalized adjectives with likeability ratings (51). In an attempt to balance the emotional valence of the stimuli, the list was divided into thirds, and the most and least likeable words were excluded. These words were then cross-referenced with frequency data compatible with a sixth grade reading level (52). Words that seemed out-dated or difficult were eliminated, and where possible, more appropriate synonyms found in a children's dictionary were substituted (53). Word

pairs were formed with similarly "likeable" words (based on Andersons' likeability ratings), and were counterbalanced for word length and number of syllables. Within each condition, each word was used twice, but appeared in a different pairing each time. Each condition was comprised of 45 word pairs (9 blocks of 5 word pairs), and each of the 3 functional runs contained 3 blocks of each condition. Blocks were counterbalanced for order of appearance within the runs. All aspects of the design and programming of this task were performed by the author.

Retrieval Task

In this task, subjects were again shown pairs of adjectives displayed visually in the same manner as in the referential processing task. However, there were only two prompts in this part of the experiment: either "Old", indicating that the subject was to choose the word that they recognized from the first three referential processing runs, or "A", indicating that the subject was again to choose the word that had the letter "A" in it. Each prompt was followed by a block of 7 word pairs. Unbeknownst to the subject, word pairs were grouped in blocks according to the condition in which the "old" word had first appeared. Therefore the "old" words in the "Mother Recall" task were comprised of an adjective taken from the Mother condition; likewise for "Self Recall" and "Letter Recall." The prompt for all of these blocks was simply "Old." Subjects were scanned during 2 runs of 8 blocks each (2 blocks each of Self Recall, Mother Recall, Letter Recall, and Letter), and indicated their choices using button boxes in the same manner as in the referential processing task. Pairs were presented for 3000ms and interstimulus time was again 500ms. This task was also designed and programmed by the author.

Social Attribution Task

The original social attribution task (SAT) was the work of Heider and Simmel (1944), and it was adapted to fMRI by Schultz et al (49). The Schultz version of this task was used in this study by permission or Robert Schultz.

The task employs short (approximately 15s) movies of simple geometric shapes—a diamond, a circle and a square—moving around a box. The box has one side that opens like a hinged door, and the shapes move in and out of the box in varied ways. In the "Social" condition, these mini-movie animations are designed so that the shapes are personified and follow a social script. For instance, the shapes can "chase" each other, play hide-and-seek or have a fight. The subject watching these movies is asked to decide whether the shapes are "all friends, or not all friends." The control condition for this task is called "Bumper Cars" and uses the exact same triangle, circle and square moving in and around the same hinged box. However, in this condition the shapes come into contact with each other and diverge from that contact to varying degrees and with different velocities. The subject is asked to imagine that the shapes are bumper cars, and to decide by watching how they bounce off each other if the bumper cars are the same or different weights. Thus, subjects have a social context in mind while viewing the first set of movies, and a physical context in mind while viewing the second set.

Subjects were presented with a prompt question, either "Bumper cars...Same weight?" or "People...All friends or not all friends?," followed by the 15s movie. Subjects were asked to answer the prompt question as soon as the movie was over, but not before. Each condition consisted of 10 movies, presented alternately over 2 runs.

Behavioral Tests

Follow up questionnaires were mailed to all study participants after all fMRI data was collected. Participants were given a list of the pairs of words they had seen in the magnet, and asked to rank the desirability of each word in each pair. This was done in order to obtain an individual-by-individual opinion of the emotional valence of each word, and to determine the degree to which subjects might be simply selecting words they liked best to describe themselves or their mothers.

Subjects were also given lists of the same pairs they had seen in the magnet and asked again to choose the word that best describes them and the word that best describes their mother (essentially repeating the mother and self conditions of the referential processing task). This was done in order to indicate how consistent over time subjects' answers and ideas about themselves and their mothers were.

Finally, participants also filled out the Rosenberg 10-item self-report inventory of self-esteem and a 25-item mother-specific variant of the Inventory of Parent and Peer Attachment to provide a rough measure of the variance between subjects of how positively they feel about themselves and their relationships with their mothers (54). Participants were also asked to indicate if they felt that their relationship to their mother or their understanding of themselves had "altered greatly" since the time that they had undergone the MRI portion of the experiment. These questionnaires were selected and distributed by the author, and were scored and processed by the author and one research assistant.

Data Acquisition

The referential processing and retrieval tasks were programmed and presented using E-Prime software, version 1.1, and run on a PC desktop computer. The SAT task was programmed and presented using PsyScope version 11.1 (freeware) and run on a Macintosh G3 computer. Images were back-projected onto a screen near the end of the MRI gantry, and subjects viewed the screen via a mirror mounted on the head coil. Subject's heads were immobilized using foam wedges and a strip of tape across the forehead. Responses and response times were collected automatically via fiber-optic button boxes.

Imaging was performed on a Siemens Trio 3 Tesla scanner with a standard quadrature head coil. Structural inplane images were collected using the following pulse sequence: TR (time to repetition) = 300ms, TE (time to echo) = 4. Thirty-four axial slices were collected at a slice thickness of 4mm each. 3D structural images were collected with an MP Rage sequence (TR = 2530, TE = 3.66, TI = 1100, flip angle = 7, yielding 1 mm^3 voxel size). Functional data was collected with TR = 1950 ms, TE = 25, flip angle = 60. The functional voxel size was 4 mm^3. 34 slices were collected. Each slice was 4 mm thick and was acquired in the same location as the inplane structural scans.

All scans except for those of 4 subjects were organized and conducted by the author and one of the laboratory research assistants, as well as a scanner technician. The four remaining subjects were acquired at the behest of the author by one of the research assistants.

Data Analysis

All data analysis was performed using Brain Voyager QX Software, version

1.4 (Brain Innovation, Maastricht, Netherlands). Functional runs were pre-processed using 3-dimension (3D) motion correction and spatial smoothing. The motion correction process used a Levenberg-Marquardt 6-parameter rigid-body function, which rotates all collected volumes as needed to match a given reference volume – in this case, the first volume of the first functional run. Furthermore, a standard of 2mm of motion in any plane was set as the limit of acceptability (all subjects met this criterion). Spatial smoothing was also performed on all subjects' data. Spatial smoothing, designed to increase the signal to noise ratio, is based on the assumption that a voxel which contains errant activation is more likely to be surrounded by areas of low activation than is a voxel containing "real" activation. In studies involving multiple subjects, spatial smoothing is also important to increase the accuracy of between-subject anatomical registration and to reduce any effects of noise spikes. Data was smoothed using a Gaussian kernel with a full-width half-maximum value of 2 pixels (8mm). Linear drift is a gradual change in the mean MRI signal intensity that happens over time throughout the scanning session. These drift effects were corrected for using a standard temporal filter function. Subject data was coregistered with the individual's high-resolution 3D anatomical data set.

The 3D image was then transformed into standardized 3D Talairach coordinate space (Talaraich and Tournoux, 1998). This was completed in two steps: first, the 3D image was rotated into the ACPC plane; next, the 6 planes defining the edge of the cortex were identified and used as boundaries for the Talairach coordinate scaling. Functional data was re-sampled to $3mm^3$ when it was transformed into 3D Talaraich coordinate space.

A protocol file was written for each functional run for each subject in order to model the expected time course response to the experiment. Though this experiment is a block-design study, individual stimulus response latencies were used because this more accurately modeled the mental processes during each block, resulting in a mixed-block design (see Figure 1). The Boynton hemodynamic response was applied to the design in order to model the temporal shift of the BOLD response (55).

A general linear model (GLM) that compared each task condition within each of the three different experimental conditions (encoding, retrieval and SAT) was computed to fit the time series data for each voxel location. Next, group composite t-maps were created for specific task contrasts using the beta weights for the GLMs. All group data used a random effects model so the data would be generalizable to the population. Statistical significance was evaluated using the false discovery rate (FDR) procedure, which sets the number of false positives to a specific extent, and simultansoulsy controls for multiple comparisons (56). In this study, we set the FDR to 5%, which is theoretically equivalent to commonly accepted alpha ratio of .05. For the comparisons of Self and Mother conditions, we explored the data with an uncorrected alpha of .001, as there were no regions that survived the more rigorous FDR = .05 threshold. For display purposes, figures of these comparisons are shown at $p < .01$, unless otherwise specified. The author performed the majority of the data processing. The SAT task and 4 subjects from the other two tasks were processed by one of the laboratory's research assistants.
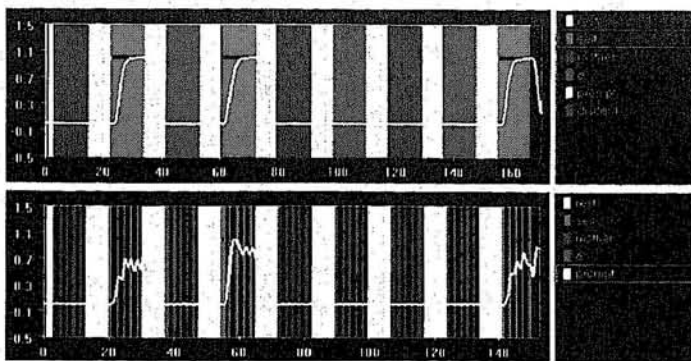
Figure 1. The top image in this figure depicts the time course of one run of this study as a normal block-design. The bottom figure shows the mixed-block design; the stimuli are still presented in blocked groups, but they are individually coded to the response latency for each stimulus. The notched shape of the BOLD signal in the mixed-block design more accurately models the changes in signal seen in this experiment.

Results

PART I. REFERENTIAL PROCESSING

Behavioral Results

Analysis of variance (ANOVA) tested whether the three encoding conditions (Self, Mother and Letter) differed significantly in terms of mean response time. Response times were significantly different for the three conditions ($F[2,50]=17.97$, $p < .0001$). Posthoc pairwise analyses showed that response times for Mother and Self conditions did not differ significantly ($t[16]=0.19$, p=.85), but that response times for each of these were significantly longer than for the Letter task (Self vs.Letter, $t[16] = 8.38$, $p <.0001$); Mother vs. Letter $t[16] = 8.12$, $p <.0001$). Behavioral results are presented in Table 1.

Table 1. Reaction Times: Referential Processing Task (n=17).*

Condition	Mean Response Time (ms)	± SD
Self ("Choose the word that best describes you...")	1965	± 487
Other ("Choose the word that best describes your mother...")	1971	± 481
Letter ("Choose the word that has the letter "A" in it...")	1312	± 302

* Mean response times of Self condition and Other condition did not differ significantly. Posthoc pairwise analysis showed that response times for Self and Other did not differ significantly. Significant differences ($p < .0001$) were found between Self and Letter and between Mother and Letter.

fMRI Results

Figure 2 shows statistical parametric maps for the contrast Self vs Letter (Figure 2a) and Mother vs. Letter (Figure 2b). The similar activation patterns recruited during both self- and mother-referential processing when compared to baseline can be seen by comparing these two figures. Figure 2c shows the activation maps for a conjunction analysis. The conjunction analysis displays only those areas that are activated by *both* tasks (i.e. it excludes activations that are present for Self vs. Letter but not for Mother vs. Letter, and vice versa). Areas activated include the bilateral frontal, left inferior frontal, left posterior and anterior cingulate gyri. Table 2 shows the Talairach coordinates, approximate Brodmann's area, *t* scores and alpha values for the peak activations from this comparison.
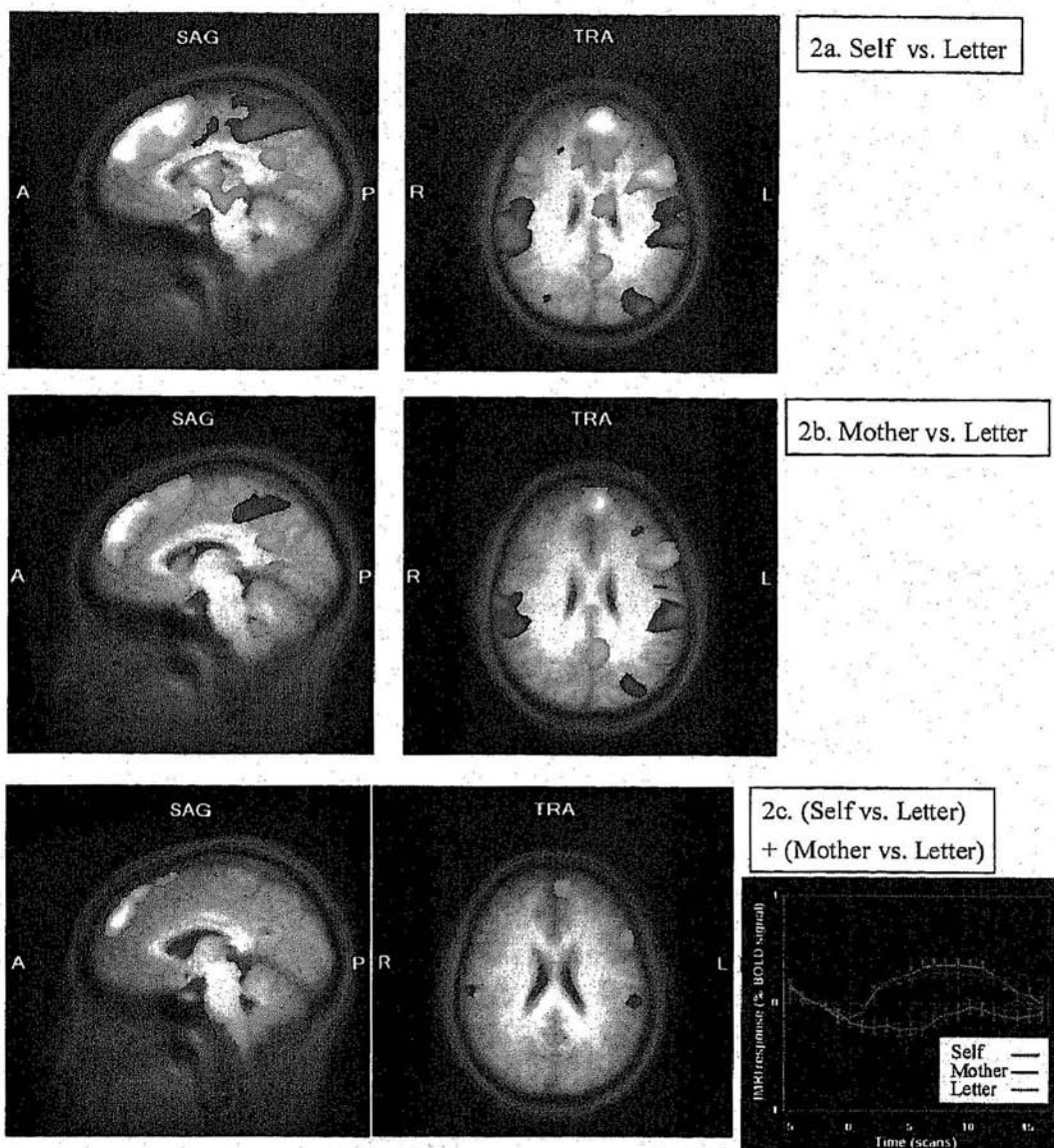
Figure 2a-c. Referential Processing. Composite t-maps displayed on averaged structural brain, n = 17. False discovery rate of .05 (FDR) was utilized in all comparisons in this figure.

2a. Statistical activation maps in sagittal and axial views showing activations for Self in red and for Letter in blue.

2b. Maps showing activations for Mother in red and for Letter in blue. FDR was utilized. Comparison between figures 2a and 2b demonstrate the degree to which self- and mother-referential processing recruit the same areas.

2c. Maps showing activations for the conjunction analysis (Self vs. Letter) plus (Mother vs. Letter). This comparison provides a more stringent way to demonstrate those areas that were activated in both the Self and the Mother tasks. Shared areas of activation are seen here at the left superior frontal gyrus, the left inferior frontal gyrus and the left anterior and posterior cingulate gyri. Time course for the peak voxel of activation from the left superior frontal gyrus is shown, indicating the percent change in BOLD signal over time. See Table 2 for coordinates and *t*-scores of peak activations.

Table 2. Peak Brain Regions Activated during Both Self and Mother Conditions (Conjunction Analysis).

| Brain Region | BA | Talaraich Coordinates | | | T score | P value |
		x	y	z		
Bilateral MPFC	9	-6	50	28	9.41	6.34×10^{-8}
Left DLPFC	45	-54	23	16	8.81	1.55×10^{-7}
Left DLPFC	44	-45	17	13	8.42	5.49×10^{-7}
Left MPFC	8	-6	44	43	8.38	3.03×10^{-7}
Left VLPFC	47	-42	23	-8	7.48	1.0×10^{-6}
Left posterior cingulate/precuneus	23	-3	-49	22	5.21	8.6×10^{-5}
Right DLPFC	6	15	26	49	5.17	9.4×10^{-5}

Figure 3 shows statistical parametric maps for the contrast Self (coded in red) vs. Mother (coded in blue) from the referential processing task. Red areas thereby represent those activations that are specific to self-referential processing, and are not recruited during mother-referential processing.

Figure 3a shows a region in the superior frontal gyrus on the left, and regions of the anterior cingulate and medial frontal gyri on the right. The activation on the left is the strongest activation seen in this contrast. The peak of this activation in the group data is located in white matter. However, when the data was explored on a subject-by-subject basis, activations appeared to source from the superior frontal sulcus (SFS). The depth and location of sulci in the frontal lobes varied widely between subjects, and likely accounts for the appearance of the location of the activation in the group-averaged map. Figure 3b shows an activation of the left lateral temporal region, possibly the visual word form area of the fusiform gyrus. In order to better determine if this area is indeed the visual word form area, it is displayed above coronal and sagittal slices in the same planes

from a different contrast, (Prompt + Letter) vs. rest, in Figure 3c. This figure was

selected as a basis for comparison because we would expect the visual word form

area to be activated while subjects were reading the prompts and looking for the

letter "a" when compared with rest. Thus, the contrast (prompt + Letter) vs. rest

provides a good localization of the visual word form area in this subject group, and

the peak is both very large and its location is consistent with a recent meta-analysis

on this area (57).

Though not shown here, this GLM for Self vs. Mother also depicted blue

activations (i.e. activations for Mother) in the temporal poles and the left

subcallosal gyrus. However, these activations were not present in a Mother vs. Rest

contrast. Thus, the presence of the blue on the Self vs. Mother map indicates a

relative difference between the two conditions, and does not indicate a real

activation for mother-referential processing. The Talairach coordinates,

approximate Brodmann's areas, t scores and alpha values for all of the significant

peaks for this comparison are shown in Table 2.

Table 3. Regions of Peak Activations from Referential Processing Task: Self vs. Mother Comparison.

| Brain Region | BA | Talaraich Coordinates | | | T score | P value |
		x	y	z		
Left superior frontal sulcus	9	-18	29	19	5.22	8.3×10^{-5}
Right anterior cingulate	32	12	35	13	4.45	.0004
Right cingulate gyrus	32	6	35	28	3.94	.001
Left fusiform gyrus	20	-36	-43	-8	4.78	.0002
Right fusiform gyrus*	20	-36	-48	-14	8.47	2.6×10^{-7}
Right temporal pole (STG)	38	25	14	-26	-4.72	.0002
Left temporal pole (STG)	38	-30	5	-19	-4.34	.0005
Left subcallosal gyrus	11/1	-3	26	-8	-3.88	.001

* This activation is from a different statistical map of the contrast (Letter + Prompt vs. Rest). It is included here in order to provide a comparison for localization purposes of the visual word form area of the fusiform gyrus.
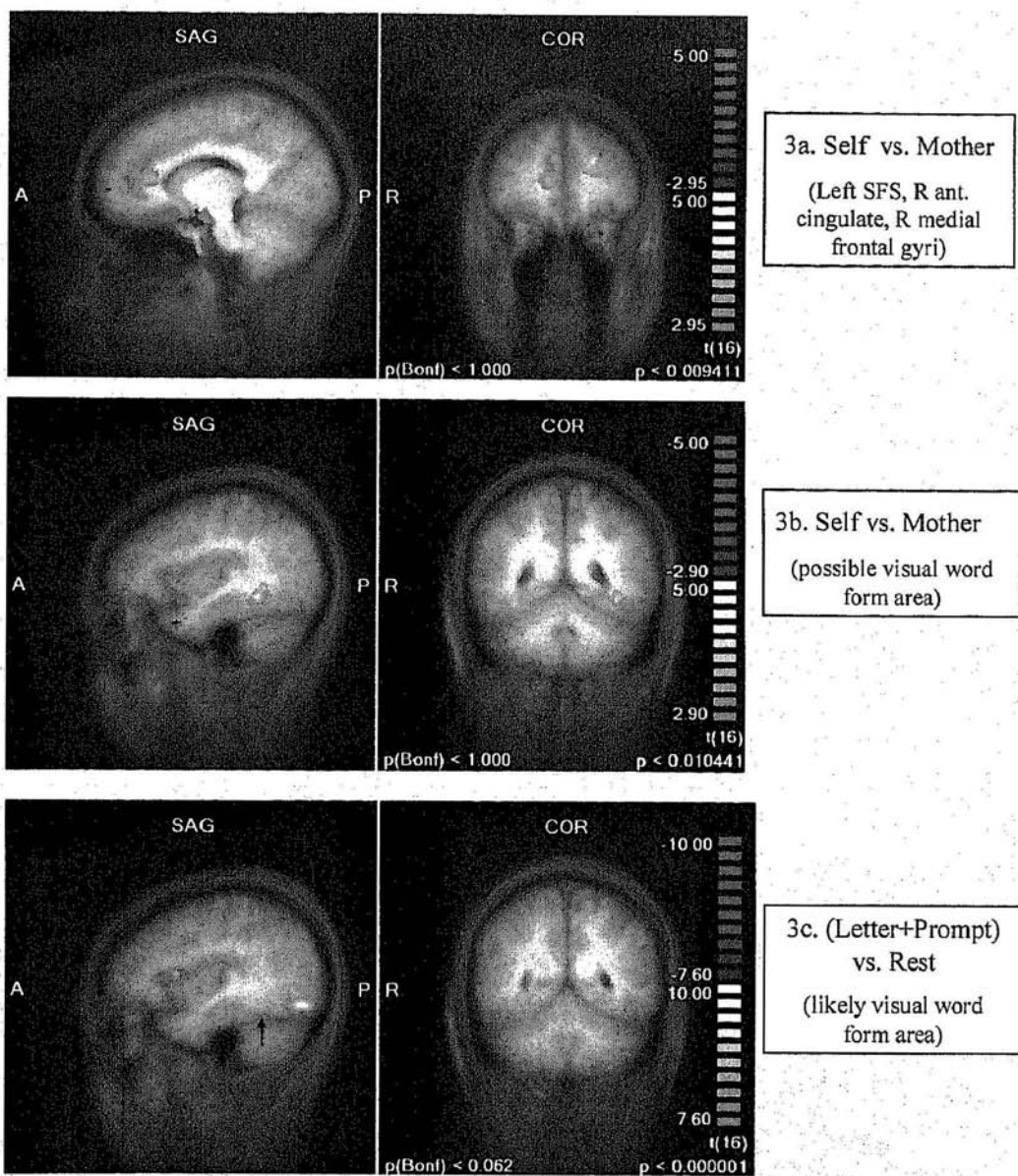
Figure 3a-c. Referential Processing, Self vs Mother comparisons, n = 17.

3a. Statistical activation maps in sagittal and coronal views showing activations for Self in red and for Mother in blue. Activation shown in the sagittal plane corresponds to the activation seen on the right side in the coronal view. P value was set to $< p = .01$.

3b. Maps showing activations for the same comparison, Self vs. Mother, in a different plane, $p = .01$. The activation of interest is shown in red, indicating positive activation for self-referential processing.

3c. Maps showing activations for a different comparison, this time (Letter + Prompt) vs. Rest. The Letter and Prompt parts of the experiment involve reading and identifying word forms without any referential processing. The activation seen in the coronal image corresponds to the activation indicated by the arrow in the sagittal plane. The p - value indicated was used in order to view the area of interest as a distinct region. Figure 3c is provided for comparison with figure 3b in an attempt to identify the visual word form area. See Table 3 for coordinates and t-scores of peak activations.

PART 2. SOCIAL ATTRIBUTION TASK

fMRI Results

Figure 4 shows statistical activation maps for the social attribution task, comparison SAT vs. Bumper Cars. This comparison resulted in a widely distributed set of significant activations. Peak areas included in this network are bilateral MPFC, bilateral ventral pathway including the fusiform face area, the amygdalae (right > left), bilateral superior temporal sulcus (STS) (right > left), and bilateral precuneus. Table 4 contains the coordinates, *t*-values and alpha values for these peaks.

Figure 5 combines activation maps from the referential processing task and the SAT in order to show areas of overlap. Thus, Figure 5 is not a statistical conjunction or contrast analysis but is more simply an overlap display tool. The conjunction analysis of (Self vs. Letter) + (Mother vs. Letter) from the referential processing task shows areas common to both self- and mother-referential processing, and are shown in red in this figure. The comparison SAT vs Bumper Cars shows areas recruited during a more abstract social processing task, colored blue in this figure. Areas of overlap between the referential-processing and the abstract social processing tasks are shown in purple, and include bilateral MPFC, bilateral inferior frontal gyri, posterior cingulate, left STS. These comparisons involve different number of subjects (referential processing, n = 17, SAT, n = 13). We took advantage of the larger number of subjects in each group for creating figure 5; instead of showing only those subjects in common for both sets of analyses, the larger samples were chosen so as to increase the precision of our

estimate of the locations of these activations in the general population. Only

positive activations are shown. The plane of each view is shown in single Talairach

coordinates on the images themselves.

Table 4. Regions of Peak Activations from SAT Task: SAT vs. Bumper Car Comparison.

| Brain Region	BA	Talaraich Coordinates			T score	P value
		x	y	z		
Right STG (post.)	22/39	45	-43	10	14.66	4.3×10^{-8}
Right STS (ant.)	22/28	57	-7	-11	13.92	7.1×10^{-8}
Left STG (post.)	22/39	-48	-52	16	13.17	1.2×10^{-7}
Right STS (post.)	22/39	54	-4	-14	12.88	1.5×10^{-7}
Right STS (mid)	22/21	51	-31	1	12.41	2.1×10^{-7}
Left middle temporal gyrus	39	-39	-67	10	11.92	3.1×10^{-7}
Right STS (horizontal post.)	21/37	-51	-52	7	11.51	4.3×10^{-7}
Right fusiform gyrus	20	33	-37	-16	9.01	4.0×10^{-6}
Right DMPFC	9	11	53	28	8.45	7.0×10^{-6}
Left fusiform gyrus	2	-33	-37	-8	7.02	3.6×10^{-5}
Right precuneus	7/31	6	-58	31	6.85	4.5×10^{-5}
Right amygdala	--	24	-7	11	6.56	6.4×10^{-5}
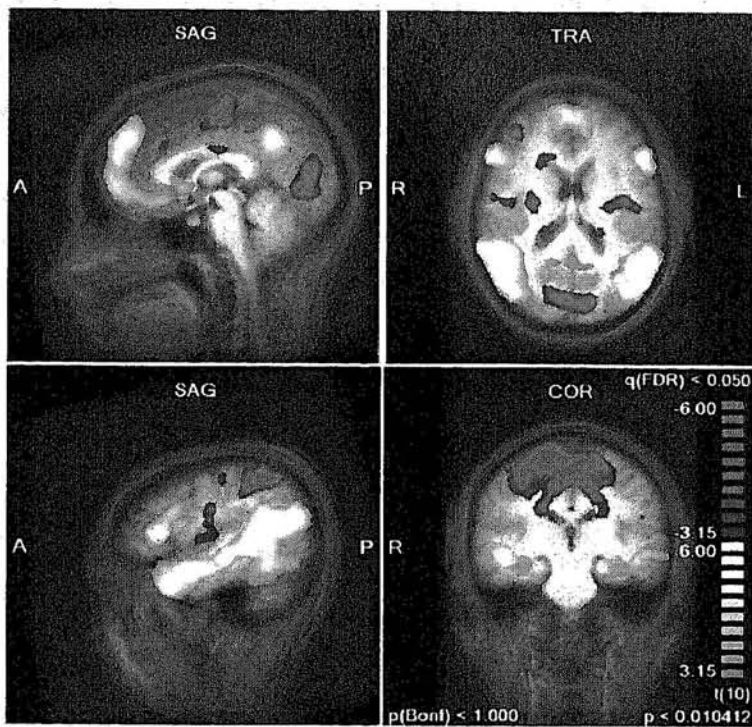
Figure 4. SAT Task, comparison SAT vs. Bumper Cars, n = 11. FDR < .05.

These statistical activation maps show a widely distributed set of significant activations recruited during the social processing of abstract shapes. Peak areas of activation include bilateral MPFC, bilateral ventral pathways including the amygdalae, bilateral STS, anterior fusiform and bilateral precuneus/posterior cingulate. See Table 4 for coordinates of peak activations.
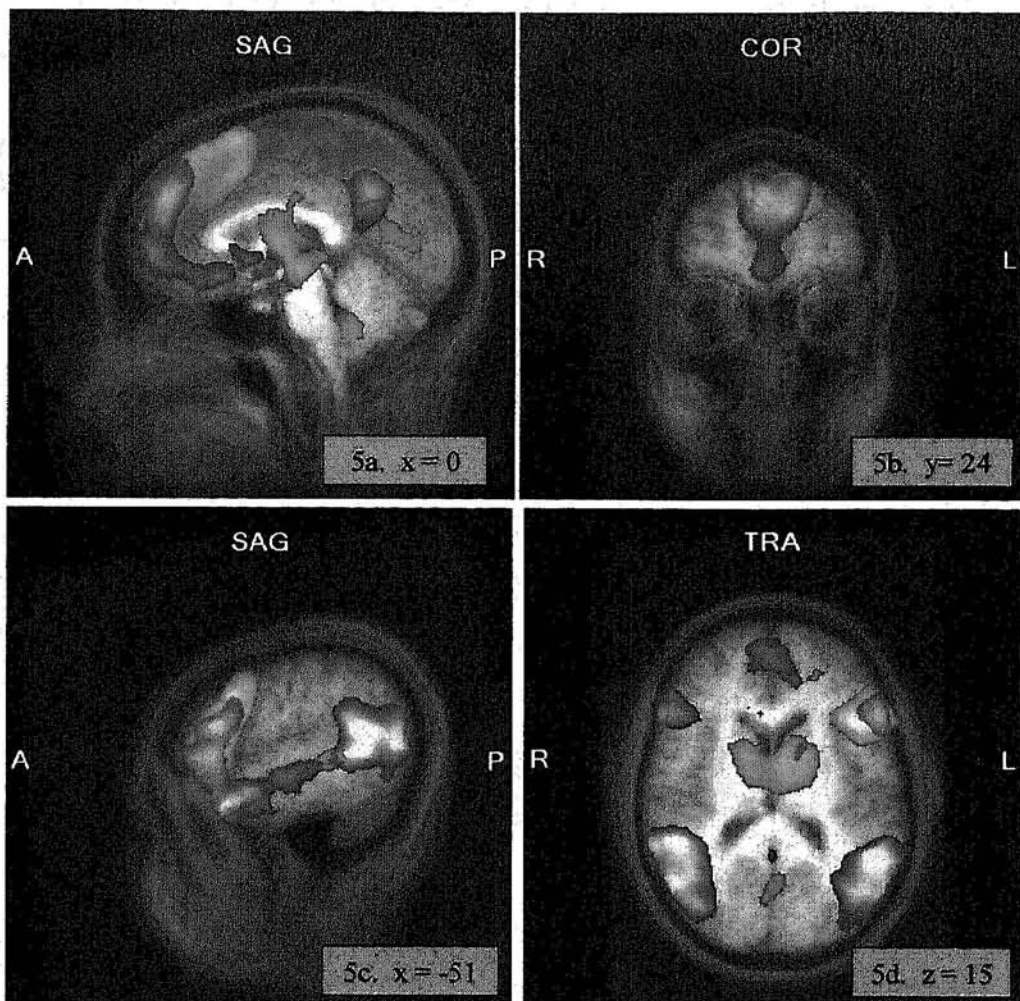
Figure 5. Social Processing Overlay. Referential Contribution: (Self vs. Letter) + (Mother vs. Letter) shown in red, n=17. SAT Contribution: SAT vs. Bumper Cars shown in blue, n=13. Slice in plane indicated by single Talaraich coordinates on each image.

5a-b. Sagittal and coronal images display areas of overlap (purple) in the MPFC and posterior cingulate/precuneus. Purple areas are recruited during both abstract (SAT) social processing and during referential processing.

5c-d. Sagittal image showing large area of overlap over left STS. Axial view of overlaps at bilateral STS and MPFC.

	Referential Processing Task
	SAT
	Overlap

PART 3. RETRIEVAL

Behavioral Results

Two separate analyses of variance (ANOVA) tested whether the three

retrieval conditions (Self Recall, Mother Recall, and Letter Recall) differed significantly in terms of task accuracy and mean response time. Task accuracy was significantly different for the three conditions (F[2,38]=69.07, p <.0001). Posthoc pairwise analyses showed that accuracy on the Mother and Self conditions did not differ significantly (t[24]=0.49, p=.63), but that performance on each of these was significantly better than on the Letter task (Letter Recall vs. Self Recall (t[24]=11.27, p <.0001; Letter Recall vs. Mother Recall (t[24]=8.75, p <.0001).

The second ANOVA revealed significant overall differences in mean response time (F[2,38]=10.30, p =.0003). As with response accuracy, there were no significant differences in mean response time between the Mother Recall and Self Recall conditions (t[24]=0.14, p=.89), but there were significant differences between Letter Recall and Mother Recall (t[24]=3.71, p =.001) and between the Letter Recall and Self Recall (t[24]=3.99, p =.0005). Thus, no significant differences were seen in either accuracy or response latencies during retrieval of self- and mother-referenced stimuli, but significant differences were seen in both accuracy and response time when self and mother retrieval conditions were compared with letter-referenced retrieval. These results are presented in Table 5.

Table 5. Reaction Times and Accuracy: Retrieval Task (n=13).

Condition	Mean Response Time*		Mean Score[†]	
	(ms)	± SD	%	± SD
Self Recall	1662	± 269	91.5	4.2
Other Recall	1677	± 293	90.6	7.1
Letter Recall	2123	± 319	65.3	7.2

* Mean response times of Self condition and Other condition did not differ significantly. Posthoc pairwise analysis showed that response times for Self and Other did not differ significantly. Significant differences ($p < .0001$) were found between Self and Letter and between Mother and Letter.

[†] Posthoc pairwise analysis showed that mean recall accuracy scores for Self Recall and Mother Recall did not differ significantly. The differences between the mean scores for Self Recall and Letter Recall, as well as for Mother Recall and Letter Recall, both reached significance ($p < .0001$).

fMRI Results

Figures 6 and 7 display statistical activation maps for the retrieval tasks. The contrast is a conjunction analysis of (Self Recall vs. Letter) + (Mother Recall vs. Letter) in order to show the areas being recruited for memory vs. non-memory tasks. Activations are shown in red, and deactivations are shown in blue. Areas of activation include the left middle frontal gyrus/DMPFC, right insula, and the left inferior and superior frontal gyri. Areas of deactivation include bilateral hippocampi, right postcentral gyrus, right anterior cingulate, right precuneus and right posterior cingulate cortex. The event averaged time course for the peak voxel of the deactivations are shown in figures 6 and 7. All three conditions show less activity compared to baseline rest, such that Letter Recall shows the most deactivation and Self Recall shows the least. The Talairach coordinates, approximate Brodmann's areas, t scores and alpha values for the peaks of this conjunction analysis are shown in Table 6.

Table 6. Regions of Peak Activations from Retrieval Task: (Self Recall vs. Letter) + (Mother Recall vs. Letter).

| Brain Region	BA	Talaraich Coordinates			T score	P value
		x	y	z		
Left DLPFC	9	-45	20	28	8.36	2.0×10^{-6}
Right insula	13	33	23	4	9.77	4.6×10^{-7}
Left VLPFC	13	-39	23	10	6.69	2.2×10^{-5}
Left DMPFC	8	-2	17	49	6.62	2.5×10^{-5}
Left hippocampus	27/28	-27	-16	-11	-6.86	1.7×10^{-5}
Right hippocampus	27/28	24	-16	-14	-6.65	2.4×10^{-5}
Right STG (post.)	22/39	51	-25	19	-6.40	3.4×10^{-5}
Right anterior cingulate gyrus	32	6	41	4	-6.58	2.6×10^{-5}
Right precuneus	7/31	3	-40	43	-6.63	2.4×10^{-5}
Right posterior cingulate	23	12	-52	16	-4.67	5.4×10^{-4}
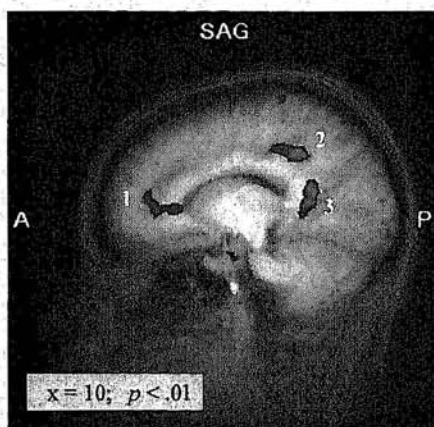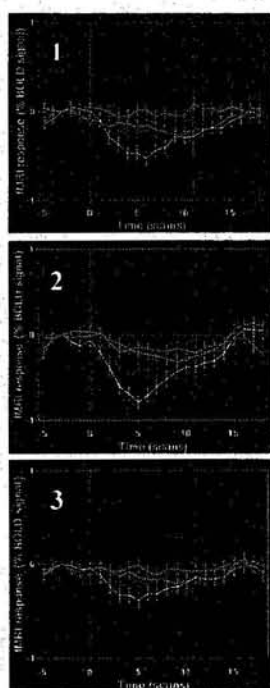
Figure 6. **Retrieval Task: (Self Recall vs. Letter) + (Mother Recall vs. Letter). Composite *t*-maps displayed on average structural brain, n = 13. Alpha value <.01.**

Sagittal view showing activations common to both Self Recall and Mother Recall in comparison to the Letter task. Areas of the anterior cingulate, mid-cingulate and posterior cingulate gyri are shown as deactivations in blue. Time course averages for these three areas are displayed, showing the differing degrees of deactivation between conditions.

——— Self recall
——— Mother recall
············ Letter recall
——— Letter
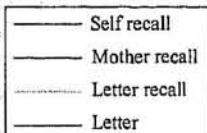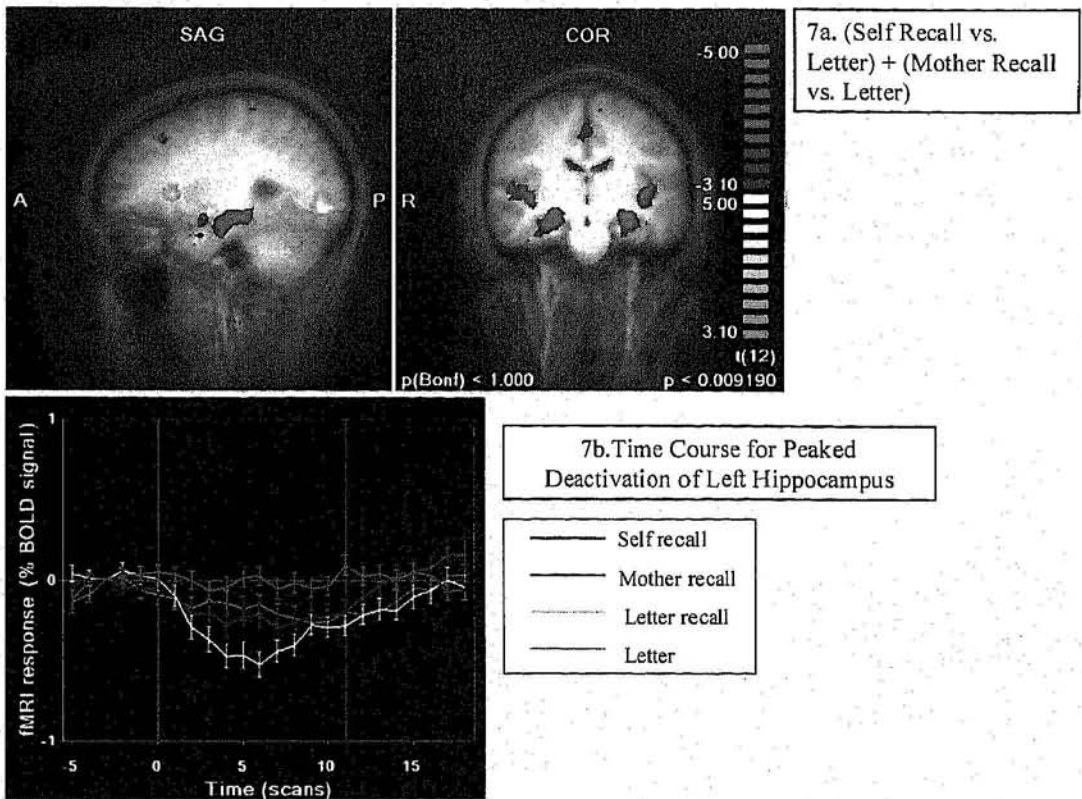
Figures 7a-b. Retrieval Tasks. Conjunction analysis, (Self Recall vs. Letter) + (Mother Recall vs. Letter). n = 13, $p < .01$.

7a. Statistical activation maps in sagittal and coronal views displaying bilateral deactivation of the hippocampi during memory tasks. The comparison task used is the original Letter task, and is not a recall task.

7b. Event time-course showing the percent change in BOLD signal of the peak voxel for each recall condition. The Letter Recall task is shown, and was not a part of the above conjunction analysis.

Discussion

In this study, a series of experiments were conducted in an attempt to determine the neural substrates recruited during self-referential processing. This was accomplished by comparing relative changes in BOLD signal during tasks that involved self-processing and tasks that involved processing related to an intimately known other. For this purpose, the well-known SRE paradigm was adapted to

promote sustained, focused cognitive processing for use in a block-designed fMRI study. The retrieval portion of this study was also designed to occur in the fMRI scanner, and was the first to compare Self and Other during the retrieval of self- and other-referenced stimuli. The comparison task in these parts of the experiment was the subject's own mother. This comparison was selected in an attempt to equate the degree of intimacy between the self task and the other task.

Lastly, within the same scanning session, subjects performed another well-studied task, the social attribution task, and these results were compared with the results of the referential processing task. The aim of this comparison was to determine the effects of modality (verbal and specific vs. non-verbal and abstract) on the recruitment of brain regions for social processing.

The results of this study confirmed our predictions: self-referential and mother-referential processing recruited highly similar networks which included peaked activations at bilateral dorsomedial frontal and dorsolateral frontal cortices, the left medial and ventrolateral prefrontal cortices, as well as the left posterior cingulate gyrus/precuneus (see table 2 and figure 2). Signal strength in these areas between the self and mother conditions was not significantly different. Furthermore, the more abstract social processing involved in both the SAT task and referential processing task recruited several areas in common: bilateral DMPFC, left posterior cingulate cortex, bilateral ventrolateral prefrontal gyri, left superior temporal sulcus (STS), and the temporal poles (left > right) (see figures 4-5).

Significant differences between self-referential and mother-referential processing in this task were observed as relative activations of the superior frontal sulcus, a region of the anterior cingulate gyrus (ACG) and a region of the fusiform

gyrus believed to be the visual word form area (see table 3 and figure 3).

Based on recall accuracy and response latencies for the retrieval portion of this experiment, no significant self-reference vs. mother-reference behavioral effect was observed. However, consistent with our hypotheses, memory was biased in favor of the recall of both self- and mother-referenced items compared to the Letter Recall task (see table 5).

The fMRI data from the retrieval task showed relative deactivations when the recall conditions were compared with the non-recall Letter task. Areas that deactivated included the right anterior cingulate gyrus, the right precuneus, the right posterior cingulate gyrus, and both hippocampi. All of these regions displayed the same graded degrees of deactivation; Self Recall < Mother Recall < Letter Recall. The results of these findings and the implications for future research are discussed below.

Self- and Mother-Referential Processing

Referential processes about one's self or one's mother seem to engage a similar but not identical neural network. The conjunction analysis (Self vs. Letter + Mother vs. Letter) resulted in a set of strong activations that were recruited for *both* the self-referential processing task and the mother-referential processing task. This network of regions included the superior frontal gyrus, inferior frontal gyrus, and posterior cingulate gyrus. It is not surprising that these areas have been identified by past research as key components of the "social brain."

The social brain is one of the terms used to describe the network of cortical regions that are activated during social perception and cognitive social tasks so important to human interaction and survival (58, 59). In a recent review of the

social brain literature, Adolphs proposes a three-part organization of this system. Social cognition begins when higher-order sensory cortices receive information about social stimuli (60). This perceptual representation is then associated with an emotional response, cognitive processing, and behavioral motivation, and recruit regions in the amygdala, striatum, and orbitofrontal cortex. Higher cortical regions are again involved as an internal model of the social environment is constructed, and internal representations of other people, and of their social relationships with one's self, are maintained. The areas of the cortex usually ascribed this latter function are the left prefrontal and right parietal cortices, as well as the ACG (inclusive of the medial surface of the superior frontal gyrus, immediately dorsal to the ACG) and posterior cingulate gyrus.

"Theory of Mind" regions were recruited by both self- and mother-referential processing in this study; and it is one of the major findings of this work that almost all of the neural networks recruited for self are also recruited during mother-referential processing. These results are similar to those reached by Ochsner and colleagues, who studied self- vs. "close other"-referential processing and found no statistically significant differences between those two conditions (47).

The shared nature of these regions indicate that—for the most part—self-referential processing is not subserved by its own unique neural system, as has been previously suggested (44, 45).

It is interesting to note that, within social cognitive neuroscience, the debate about "shared" and "special" neural substrates, occurs in different ways. An example of this is the "fusiform face area" (FFA) which, when first identified, seemed to be recruited specifically for face perception (61-63). Further studies

have suggested that the FFA is in fact activated during the visual recognition of any object for which the subject has a significant degree of expertise (1, 64-66). In response to these results, facial recognition abilities are now considered to result from a domain-general process (i.e., recognition based on expertise processing of cars, faces, etc.) rather than a domain-specific process (i.e., uniquely part of social cognition and nothing else). Thus, the recruitment of the fusiform face area during recognition no longer belongs exclusively to the realm of social cognition.

In a recent review, Apperly, Samson and Humphrey suggest that this pattern of discovery has been the norm rather than the exception within cognitive neuroscience. They suggest that up to this point in time, there are no functions within the social brain that have yet been shown to be part of "domain-specific or modular processes" (67). They make their case for this argument by reviewing the literature on one of the most-studied aspects of social cognition, namely, reasoning about beliefs. Though they conclude that evidence to this point does not support the claim that belief reasoning is a domain-specific process, they still believe that it is a domain-specific process. The problem rests in the methods used for studying these types of tasks, and they posit that progress in this area will depend on the development of more sensitive comparison and control tasks.

In reply to this article, Stone and Gerrens agree that evidence to this point does not support the social cognition's claim to domain-specific processes (68). However, they believe that the evidence for domain-specific processes in the social brain are lacking because they in fact do not exist. They suggest that it is time to "abandon the quest for the neural substrate of the fabled ToM module" and to focus instead on the domain-general and species-unique ability of metarepresentation.

In this context, the results reported in this study need to be carefully explained. We have shown that self- and mother-referential processing recruit largely the same areas, prompting us to disagree with the notion that referencing the self results in an entirely different neural pattern than does mother-referential processing. We claim that some of the areas that have previously been described as special to the self are in fact common to referential processing tasks when the conditions are equated for degree of intimacy. However, both types of referential processing in this task are firmly grounded in social cognition. In this way, the move from "special" to "shared" is not as dramatic as was seen in the case of the fusiform face area.

Furthermore, it is possible that the same sorts of "base-level" cognitive tasks required during referential processing could be common to other sorts of processing not directly linked to ToM or social cognition. Further research in this area would, as Apperly, Samson and Humphrey suggest, require carefully selected comparison tasks. Thus, an interesting aim of future work would be to demonstrate those areas within referential processing that are used in non-social referential processing. One possible way to test this hypothesis would be to borrow from the FFA literature and to generate an appropriate list of words that would enable the referential-processing task to be used for items that the subject has expertise in, such as birds or sports cars.

A further note is warranted on the lateralization of the peaks common to both self- and mother-referential processing. The peaks for all of these activations (superior frontal gyrus, inferior frontal gyrus, and posterior cingulate gyrus) were located in the left hemisphere. Even when the threshold was dropped, these areas

remained strongly lateralized on the left side. Left PFC activation has been shown in ToM tasks in which subjects listen to stories that require taking another's point of view (69). Ochsner and colleagues also reported left PFC activation for both self and other conditions in a task that involved looking at photos and attributing emotion to self in response to the photo, or to the person in the photo (70). The left-laterality of prefrontal cortex and superior frontal gyrus also coincides with the hemispheric encoding/retrieval asymmetry (HERA) model (71). In this model, left prefrontal cortex is recruited during encoding; right prefrontal cortex is more strongly recruited during retrieval. Left MPFC or superior frontal gyrus has also been implicated in recall tasks as opposed to recognition tasks (72). Recall tasks use cues that contain very little information, requiring the subject to augment that information themselves, whereas recognition tasks use very rich cues which only need to be "recognized." In the case of the referential processing task, we would argue that the task is rather like a recall task; a subject looks at a pair of words, and in trying to decide which word best describes her mother, she is having to produce more information from her memory and ideas about her mother. She is recalling her mother-concept in response to a cue that does not inherently carry information about her mother-concept. Thus, the left lateralization of the MPFC activation in this study coincides with the results reported by Cabeza et al.

Self-Referential Processing

Although the network recruited by self-referential processing in this task was highly similar to that recruited by mother-referential processing, three regions displayed significant activations in the Self vs. Mother comparison.

Northoff et al. have suggested that the processing of self-referential stimuli is comprised of 4 sub-processes termed representation, monitoring, evaluation and integration (6). The orbitomedial prefrontal cortex (OMPFC), they suggest, plays a central role in the continuous representation of self-referential stimuli. These stimuli are monitored in the supragenual portion of the anterior cingulate, and evaluated in the DMPFC. Stimuli can then be integrated into the emotional autobiographical context of one's own person. Our findings only correspond to this model in part, as we did not find that self-processing preferentially recruited areas of the OMPFC or of the posterior cingulate gyrus. We suggest that the differences between our findings and those reported by Northoff and colleagues can be explained by the fact that their model was based on a review of studies that did not, for the most part, use an intimately-known other as a comparison task. Thus, we suggest that the sub-processes and areas delineated in the model are most likely common to the processing of both self- and other-referenced stimuli. However, our results do show preferential activation in the superior frontal sulcus (BA 9) and the anterior cingulate gyrus for self vs. other processing, and these areas likely represent regions that are activated preferentially during self-referential processing.

The strongest activation that was distinct for self-referential processing was an area that sources from the left superior frontal sulcus in the left medial prefrontal cortex (see figure 3a). In Northoff's model, this corresponds to the region responsible for the continuous representation of self-referential stimuli. Further contrasts involving this region showed that, in this study, this area was activated during both Mother vs. Rest and Self vs. Rest comparisons. Thus, we conclude that this area is recruited during both mother-referential and self-referential processing,

but that the activation during the self condition is stronger than during the mother condition. The event time course for the region also indicates that this is the case. As stated in our hypotheses, we expected to see some areas that were driven more strongly during self-referential processing, based on the assumption that one's self-concept contains more information and is more elaborated than is one's mother-concept.

Other studies have shown that the anterior cingulate gyrus can be anatomically subdivided into regions which function in distinct ways (73). The region activated in this study has been termed the "affective" (as opposed to "cognitive") division of the anterior cingulate gyrus (74). According to Bush and colleagues, the affective division of the anterior cingulate gyrus is involved in assessing the salience of emotional and motivational stimuli, and in the regulation of emotional responses. For instance, during a modified Stroop task using emotional and neutral words, the affective division of the anterior cingulate gyrus is preferentially activated during the emotional word task.

Given the affective specificity of this area, it seems plausible that the processing of self-referential stimuli may be more emotional than the processing of mother-referential stimuli. We suggest that subjects find the process of consulting their self-concept inherently more affective; i.e., one's self-concept may have inherent emotional salience above even that of one's mother-concept. This concept echoes Damasio's view of the self as an evolutionarily necessary construct (4). In other words, it would likely be advantageous for survival if information and stimuli from and about one's self carried added import or salience. We would also suggest that this emotional salience is not necessarily experienced by the subject as an

emotion. In this way, the salience is perhaps registered in the "protoself" of the individual – i.e., the processing is taking place at a preconscious level. If one's self-concept is truly inherently more emotionally salient, the activation of the anterior cingulate gyrus in the self condition would be considered neuroanatomically "special."

The second area shown to activate preferentially in the self task was the visual word form area. The visual word form area is a region of the fusiform gyrus that has been repeatedly shown to be involved in the pre-lexical processing of words and pseudo words (57, 75, 76). Given that the response latencies between the Self and Mother tasks were not significantly different, it is remarkable that the visual word form area was activated more for Self than for Mother. This is a difficult finding of which to make sense. Perhaps words register more strongly when they are referenced to the self; just as the fusiform face area is activated more strongly for emotional faces than for neutral faces, even if subjects spend longer looking at the neutral faces. Further testing might address this question by attempting to increase and decrease the emotional valence of the words for both self and mother conditions. Although some studies have looked at these variables, none have selected the visual word form area as an a priori region of interest. It is also possible that the preferential activation of the visual word form for self-referential processing is only seen when subjects are forced to choose between paired adjectives, and thus would not have been seen in earlier work.

A second possible explanation for the relative activation of the visual word form area is that knowledge about the self is more immediately obvious or accessible than knowledge about an other; thus, while trying to decide which word

best describes him or herself, the subject spends more time deliberating over the stimuli, paying more visual attention to the words on the screen, to their meanings and differences, than to the particulars of his or her self-concept. One possible way of testing this hypothesis would be to develop a task where subjects "learned" concepts of invented characters to varying degrees of intimacy (through narratives, videos, over the course of different time-frames, etc.). The referential-processing task could then be used to compare the referential-processing of more- and less-intimately known characters without that intimacy being dependent on "self" or "non-self" per se.

Referential Processing and Social Attribution

The Social Attribution Task (SAT) required subjects to observe geometric shapes moving on a screen and to answer questions about the "friendliness" exhibited by the shapes. This task requires inferences about the mental states of the shapes, whereas the control task (Bumper Cars) requires inferences about physical properties of the shapes. When these two conditions were directly compared, the condition that required mental state inferences resulted in significant activations of the MPFC, amygdalae, fusiform gyri, STS, STG and the posterior cingulate gyrus/precuneus (see table 4 and figure 4). These results are consistent with previous findings, and represent recruitment of traditional ToM areas, as well as recruitment of areas used to recognize biological movement (49).

This data set was overlaid onto the statistical map of the shared activations recruited during both self- and mother-referential processing. Overlap between the SAT task and the referential-processing task was seen in the MPFC, bilateral inferior frontal gyri, left STS and posterior cingulate gyrus (see figure 5).

These areas of overlap are interesting because they show the regions common to two very different tasks within a single group of subjects. The SAT involves visual stimuli without verbal labels or words, and may entail more abstract social processing than that produced by the referential processing tasks. The inferences made about the mental states of the geometric shapes are presumably based on ideas about mental states of people in general, built on years of personal experience. Subjects attempt to make decisions based on the friendliness of these personified shapes. In the referential processing task, subjects are consulting the concepts of themselves and their mothers—concepts comprised of intimately known details that have been constructed and changed over time—in order to answer questions about how best to describe themselves or their mothers.

As can be seen in the overlay map, areas recruited for abstract social processing are also used during tasks of specific referential processing. These findings are consistent with our hypothesis, which predicted that the networks recruited during non-verbal abstract social processing would also be utilized during more targeted, verbally-cued referential-processing. Again, we see that within social cognition, the same regions of the brain are recruited for different types of social processing. With regards to domain specificity, we suggest that the network seen in the overlay between these two tasks represents a network that is specific to social cognition. Further testing with this hypothesis in mind would be needed to support this conclusion, and tasks that are not social but that do drive this network would point to the idea that social cognition does not involve domain-specific processes. On the other hand, it would be very interesting to determine if other tasks of social processing also recruit these regions, and to attempt to determine

which sub-processes within these different tasks are driving the shared network.

Retrieval of Self-Referenced Items

The behavioral results of this study showed no significant difference of recall accuracy or response latency between the Self Recall and Mother Recall conditions. Thus, in this comparison, we found no behavioral self-reference effect as it has classically been defined. The results from this study coincide with the findings of Bower and Gilligan who also reported no significant difference in recall between self and mother conditions (77).

We did, however, find significant differences in recall accuracy and response latencies when comparing the Letter Recall task with either the Self Recall or the Mother Recall task. Thus, our results show both a self-reference and a mother-reference effect in comparison to the control task, coinciding with the idea that using a self-concept or an other-concept during encoding facilitates recall as an extension of the depth of processing paradigm (78). In this way, these results support the theories of Rogers, who first posited that the self was a "superordinate schema." However, we agree with Aron and colleagues, who posited in 1991 that information about an intimate other may be nearly as well known and well elaborated as information about the self (79). In view of the similarities seen between self and mother conditions in the referential-processing functional data, we surmise that these behavioral similarities between self and an intimately known other exist because both the self the intimately known other function as superordinate schemas. The neurofunctional results of the retrieval task, however, indicate that the retrieval of items that were referenced to these superordinate schemas may not result in exactly the same retrieval processes.

Many of the significant changes in BOLD response seen in the retrieval part of this study are "deactivations." The term deactivation in neuroimaging studies is used primarily as a descriptive term of relative difference. For instance, if condition A and condition B both result in activations, and the signal for A is stronger than it is for B, the relative difference between the two conditions could be called a deactivation for B. The magnitude of the deactivation would be the difference in signal strength. In this example, both A and B trend up from baseline, but the term deactivation is still used.

In this study, we have attempted to use the term deactivation only for relative differences in BOLD signal that drop below the baseline. This information can not be determined from looking at the statistical t-maps of a single contrast, but requires multiple contrasts against other conditions (usually against rest) and the additional data of beta-plots or event time courses. Thus, the magnitude of a deactivation in this study will be determined in reference to baseline; a large deactivation will fall further below baseline than will a "smaller" deactivation. Even within these constraints, it is important to remember that all activations and deactivations are the result of comparisons, and that the baseline itself is not inherent to the data-set, but, like the model for the BOLD signal, is applied to the data-set.

Significant deactivations by these criteria were seen when the memory tasks (Self Recall and Mother Recall) were compared to the non-memory Letter task in a conjunction analysis. Areas included the posterior section of the right superior temporal gyrus (STG), the right anterior and posterior cingulate gyri, and the right precuneus, as well as both hippocampi.

Previous studies have also shown deactivations in these areas (posterior and anterior cingulate gyri, the precuneus, inferior parietal, temporal and medial prefrontal cortices) that occur during cognitive tasks when compared with rest (19, 21). The idea (as was discussed earlier) is that these areas are constantly active in the passive state, and that activity of these regions constitutes the default mode of brain function. Deactivations are thus observed during explicit cognitive tasks when compared with rest as default processing is suspended in order to attend to the demands of the task.

In order to explore this hypothesis, Gould et al. studied task-induced deactivations during memory tasks of different levels of difficulty (80). They found that as task difficulty increased, the magnitude of the task-induced deactivations in the medial prefrontal/superior frontal gyrus, middle/posterior cinculate cortex and precuneus also increased. In other words, the more attention and focus required by a task, the greater the deactivation of the default activity in the brain.

Given that the magnitude of deactivations in these regions is directly correlated with task difficulty, the combination of the behavioral data and the functional results of this study are particularly interesting. No significant differences were seen in response times or accuracy scores between the Self Recall and Mother Recall conditions. Thus, we suggest that the degree of difficulty between these two tasks is not significantly different. Based on the findings of other studies, we would assume that the magnitude of deactivations in these regions for Self Recall and Mother Recall would be similar, and that the deactivations for both of these conditions would be less than the deactivation seen for the Letter Recall task. However, that is not the case. Anterior cingulate, posterior and mid-

cingulate cortices deactivated *less* for Self Recall than for Mother Recall despite the fact that these conditions did not differ significantly in behavioral markers of task difficulty. We suggest that this disjunct between degree of difficulty and degree of deactivation is a finding particular to the recall of self-referenced stimuli.

The lesser deactivation for the Self Recall condition could be explained in one of two ways, both of which are interesting in regards to the self-reference effect. First, it is possible that we do not have to work as hard to score as well when recalling self-referenced information. Thus, we do not have to "suppress" default brain activity as much. This is simply a re-iteration of Rogers initial theory of the self reference effect, this time based on neurofunctional data. The other possibility is that a smaller magnitude of deactivation is observed during the recall of self-referenced stimuli because those areas are actually being used for self-processing. This would support the ideas of Gusnard et al. that these areas are involved in self-processing at rest (18, 19).

The fMRI results for this task also showed deactivation of the hippocampi during the Recall tasks vs. the Letter task. Both the beta-plots and the time course for these activations, as well as comparisons of each task against rest, support the conclusion that the regions are truly deactivating. This is interesting because it is counter-intuitive, but nonetheless consistent with recent findings of other studies (81, 82). It has been speculated that the deactivation seen in the hippocampus may be an example of a case in which inhibition is used to create contrast. Astur and colleagues posit that the hippocampus is always "online" and performing many different tasks. Thus, inhibition of some signals will increase the contrast between the neurons of interest and neighboring neurons. Another possibility is that the

hippocampus does not increase its blood flow in the same way as do other brain regions; thus, the canonical modeling of the BOLD response in fMRI would not accurately represent the changes occurring during activation or deactivation (82). However, in a different study, Constable and colleagues found that the hippocampus reacts to vasodilators in the same way as other cortical regions, thereby suggesting that the vascular supply to the hippocampus does, or at least can, respond in a similar way to that of the cortex (83).

If it is indeed the case that, unlike the cortex, the hippocampus deactivates during focused activity, then the different degrees of deactivation seen in this study merit discussion. The time course for the peak in the right hippocampus showed less deactivation in the Self Recall condition compared to the Mother Recall or Letter Recall conditions. Direct comparison of Self Recall vs. Mother Recall revealed statistically significant relative activation, suggesting a real difference in deactivation between the self and mother tasks. This finding is particularly interesting given the similarity of the two tasks (Self Recall and Mother Recall), and the fact that the response latencies and accuracy scores of these two conditions did not differ to a significant degree. These data suggest that in the recall of self-referenced material, the self *is* meeting a criterion for "specialness", that is, the functional uniqueness of the hippocampus.

Theory of Self and Theory of Mind

At this point, we would like to propose another way in which the self might be considered special: namely, because of the role it plays in the development of the social mind.

In a recent review, Johnson and colleagues examine social cognition from a developmental perspective (59). They favor a developmental approach called "interactive specialization" (IS), in which the response properties of a specific region are partly determined by its pattern of connectivity to other regions and those regions' patterns of activity. In other words, the line between form and function in the brain is, to some degree, fluid throughout development. In terms of the social brain, this approach predicts the following: 1) during infancy the social brain network will not have clearly emerged; 2) the social brain will emerge as a whole (as opposed to emerging region by region) during infancy or early childhood; and 3) specialization within this network will occur so that different tasks produce different activation patterns of the same regions.

The IS approach to development is similar to the Hebbian learning rule: "nerves that fire together, wire together." In a review of data from the study of primates, Keysers and Perret propose a model that explains how monkeys learn to understand the actions of others (9). They observe that both infants and monkeys spend a lot of time watching themselves, be it while grasping an object or moving their toes. They propose that monkeys first "loosely" learn about their own actions from watching themselves; the process of receiving visual input about grasping an object couples together with the somatosensory information simultaneously produced by the grasping of an object. This association is honed as it is repeated, and the neural connections between the concordant areas become stronger as regions of neurons involved become more specific with use. A subset of the activated neurons involved in these actions eventually responds either to seeing the action *or* to doing the action (i.e. a "mirror neuron'). Thus, it is a series of

repetitions of cross-modal sensory information with different areas of overlap that result in learning. The authors argue that it is the different synaptic patterns impressed upon a subpopulation of these neurons in the course of Hebbian learning that results in the development of mirror neurons.

These connections between the development of social cognition and the self make intuitive sense, and given the data from this and other neuroimaging studies that show overlapping areas between self-processes and other-processes, some sort of developmental interplay seems plausible. Decety and Chaminade note that the self seems to be both "special and social" and surmise that the self-other interaction is the driving force behind self-development (84). In the same vein, Adolphs writes, "[i]f we understand other people in part by simulating processes within ourselves, the converse is also true: we understand ourselves in part by observing other people and their reactions to us" (60).

In what remains of this discussion, we propose that the theory of self (ToS) precedes ToM in normal development, eventually becoming an integral part of ToM. We suggest that there is a time early in development, most likely in utero and in very early infancy, where stimuli from one's self and stimuli from anything else are indistinguishable. This idea echoes that of the "protoconversation" proposed by Heinz Kohut (85). Kohut believed that the child must experience the caregiver for a period of time as an extension of the child's own self system. The caregiver facilitates this experience naturally by responding to and anticipating the child's expressions, by "fitting in" with them. In so doing, the caregiver is functioning as a selfobject to the child (86). From this protoconversation, the child evolves the ability to recognize self and nonself.

Incorporating mirror neurons into this concept is not difficult. The protoconversation would be the experience of stimuli prior to, and perhaps in the early stages of, the modeling of mirror neurons. Disruptions at different time points in this process would lead to different outcomes. For instance, because of their seemingly central role in social cognition, researchers are pointing to mirror neurons as possibly playing a role in the development of autistic disorders (9, 87, 88). Given these speculations, it would be helpful to better determine the nature of self-impairments seen in autism—both behaviorally and via neuroimaging—as well as to explore whether there are cohorts of individuals with ASDs who have different degrees of self-awareness or self-knowing.

ToS and ToM in Autism

Many cognitive theories have been suggested as researchers attempt to describe a paradigm that can most fully explain the behavioral characteristics seen in ASDs. Most of these theories focus on the difficulties that persons with ASDs have relating in the social world. For instance, Frith and Happé propose a theory based on a deficit in central coherence (89). They propose that "people with autism make relatively less use of context and pay preferential attention to parts rather than wholes." They favor this explanation because instead of only accounting for deficits, it at least in part also accounts for some of the cognitive strengths seen in ASDs.

Baron-Cohen also attempts to explain both the strengths and impairments in the ASDs, and has recently advanced the "empathizing-systematizing" (E-S) theory of autism (90). This theory attributes the social and communicative problems seen in ASDs to impairments in empathizing, which involves the ability to attribute

states of mind to others *and* to have appropriate emotional responses to those states of mind. The systematizing aspect of the model accounts for the cognitive strengths often seen in people with ASDs, described as "the drive to analyze systems and objects in order to understand their structure and to predict their future behavior."

Klin and colleagues also address the difference between the cognitive strengths and social impairments of individuals with ASDs. They introduce the term "enactive mind" (EM) in response to the discrepancy observed between autistic individuals' abilities to solve explicit social cognitive problems and their inability to meet the demands of everyday social situations. The EM approach focuses on the idea that, for individuals with autism, social stimuli do not carry appropriate salience. This lack of salience alters the process of early social cognitive development, leaving autistic individuals without the full repertoire of tools of social adaptation needed to function appropriately within ordinary social situations of daily life.

We suggest that many of the skills, ideas, beliefs and assumptions that are utilized in dealing with the external social world are also used when dealing with the internal world of one's own mind. In particular, the ability to recognize salient stimuli seems extremely important when one considers the constant stream of input involved in self-processing. The running commentary of one's opinions, worries and recollections, along with proprioceptive and other self-derived sensory information must be sorted out and ordered in real time, all the time. Thus, in the same way that many researchers place impairment in theory of mind (ToM) at the center of ASDs, we suggest that impairments in theory of self (ToS) play an important and interconnected role in the social deficits observed in ASDs.

Future Directions

This study has sought to underscore the role of the self in social cognition. Starting with James and his theoretical model of the self, the social self was portrayed as an integral part of one's self concept. The neurofunctional data from this study underscores this connection by demonstrating a striking degree of similarity between regions recruited in the self-referential *and* mother-referential processing conditions. Shared circuitry was also demonstrated across tasks in the overlay maps of the referential processing and social attribution tasks; subjects recruited similar brain regions when thinking about themselves, their mothers, and when inferring about the mental states of moving squares and triangles. These results demonstrate that there is a network involved in social processing that is not determined by the nature or presentation mode of the task, and this network is recruited by self processing and social processing in normal individuals.

The areas where significant differences in activation were observed for self vs. other comparisons invite further study. It would be interesting to determine if the affective division of the anterior cingulate gyrus is recruited for all types of self-processing or not. Further studies of the visual word form area of the fusiform gyrus and its relationship to different types of self-referenced stimuli may also add to our understanding of the affective nature of the self.

The differences seen in the hippocampus during retrieval of self-referenced items are quite intriguing. Though many previous studies have targeted autobiographical memory, the new findings about the nature of activations in the hippocampus in response to self-referenced stimuli warrant further, and in some cases, repeat investigation. As has been discussed, in all of these areas, the choice

of the control conditions will be pivotal.

One of the reasons we used the self-reference effect was because we believe it has potential for use in studies of individuals with neurocognitive and developmental disorders. The fact that the SRE provides information about both ToM processing and ToS processing lends itself to the study of disorders where social and self impairments have been observed. The addition of the retrieval task to the fMRI paradigm will facilitate the study of the implicit or automatic activation of self or other-referenced stimuli, more closely mimicking the implicit and automatic nature of social cognitive processes. We would be interested to see if individuals with schizophrenia, for example, demonstrate a behavioral self reference effect, as well as to determine if they recruit the same regions during self- and other-referential processing. Do individuals with eating disorders deactivate the anterior and posterior cingulate gyri and the precuneus regions of their brain during the recall of self-referenced stimuli?

The next step in the current project is to test this referential-processing task behaviorally with subjects who have ASDs and to re-design the task in response to the specific needs of this population. We propose that, as a group, subjects with ASDs will perform better on the Letter Recall task than normal controls, and that they will overall not show a recall bias to self-referenced or mother-referenced stimuli. Given our proposal that the development of a self-concept precedes the development of an other-concept, we suggest that the ToS and ToM impairments in individuals with ASDs could vary depending on the point at which normal development was interrupted. Thus, some individuals with ASDs will demonstrate impairments in both ToS and ToM, while others will have a more developed ToS,

but still show impairments in ToM. In other words, we propose that there are cohorts within the autistic population that self-reference to different degrees, and that these cohorts could be identified through the SRE task. Such a distinction would be important clinically as an autistic individual who is able to self-reference but has profound difficulties with other-referential processing tasks might benefit from cognitive therapy that focused more on thinking of others as he or she thinks of him or her self. On the other hand, an autistic individual who does not seem to have a well-integrated self concept might benefit from behavioral therapies that focus on the identification and integration of self-stimuli and understanding the meaning and source of self-thoughts.

In closing, we suggest that in the normal population, a common neural circuit is recruited for both self and other processing. However, in light of the findings presented here, as well as progress being made in the area of mirror neurons, future research that considers ToS and ToM as possibly dissociable areas of social cognition—especially in the area of development and the developmental disabilities—may prove fruitful. A task such as the version of the self-reference effect presented here enables researchers to correlate behavioral and neuroimaging data, and may prove to be a useful tool in exploring the role of the self in neuropsychiatric and developmental disorders.

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